Tetrahedron Vol. 40, No. 10, pp. 1633 to 1660, 1984
Printed in Great Britain.

0040-4020/84 $5.00 + .00

TETRAHEDRON REPORT NUMBER 164

(7*S*)-7-DEOXY-7-SUBSTITUTED-ALKYLTHIO-LINCOMYCINS. S-ALKYLATION OF SULPHIDES BY AN ACTIVATED EPIMINE UNDER ACIDIC CATALYSIS: FORMATION OF α-ACETAMIDO-SULPHIDES

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(*Received in the UK 24 May* 1983)

CONTENTS

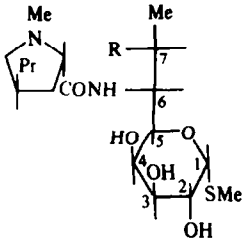
INTRODUCTION

The chemical modification of the structure of an antibiotic can be of importance in the advantageous alteration of such diverse biological properties as potency, spectrum of activity, absorption following oral administration, blood levels, distribution among body tissues, excretion, and the degree and manner of metabolism of the drug by the host.

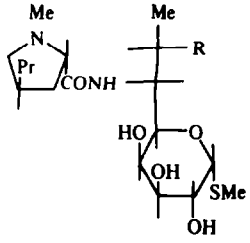
The clinically important antibiotic lincomycin† (**1**) exerts its antibacterial activity by the inhibition of protein synthesis at the ribosomal level.[1] Early work had demonstrated[2] that modifications of either substituent or stereochemistry at positions 1, 2, 3 or 4 of the pyranose ring of the carbohydrate fragment resulted in drastic reduction of antibacterial activity. However, modification of either substituent or stereochemistry at position 7 of the side-chain of the carbohydrate fragment[3a–c] resulted in at least essential retention of this activity, and led in some cases to both increased potency and a broadening of the spectrum of activity. For example, inversion of the configuration of the 7*R*-hydroxy-group of (**1**) to 7*S*- (**2**) gave an analogue showing one half of the potency of the parent; the 7*R*-chloro-7-deoxy-compound (**3**) showed twice the potency of lincomycin, whereas the 7*S*-chloro-7-deoxy-compound (**4**) showed four times the potency together with a broadening of the spectrum of activity. Similarly, the 7*R*-methoxy-analogue (**5**)[3a] showed a modest increase in potency, whereas the 7*S*-methoxy-analogue (**6**)[3b] showed a four-fold enhancement of potency. Introduction of the more polar 2-hydroxyethoxy-substituent[3b] into the 7*S*-position resulted in a diminution of potency to 30% of that of lincomycin.

These structure-activity relationships may indicate that the integrity of the carbohydrate substituents at positions 1, 2, 3 and 4 is necessary for binding at the ribosomal level in order to inhibit protein synthesis in the bacterial cell, whereas modification at the 7-position enhances the ability of the analogue to penetrate into the bacterial cell, and thus to be present at higher concentrations in the ribosomal environment.

†Lincocin is the trade-mark of The Upjohn Company for lincomycin hydrochloride.
‡Cleocin HCl is the trade-mark of The Upjohn Company for (7*S*)-7-chloro-7-deoxylincomycin hydrochloride.



(1) R = OH (lincomycin)
(3) R = Cl
(5) R = OMe



(2) R = OH
(4) R = Cl (clindamycin)
(6) R = OMe

Metabolism of clindamycin in the host animal produces, *inter alia*, its sulphoxide in substantial amounts; this metabolite is only half as potent as clindamycin, and is unstable in aqueous solution, generating the sulphur-free "clindamycose", of very low antibacterial activity.[4] It was of interest to determine if the introduction of a second sulphide sulphur atom into the molecule in the 7*S*-position might both increase the potency and spectrum of antibacterial activity and alter the metabolism of the drug.

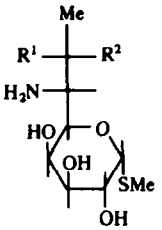
The subject matter of this report concerns an investigation of methods for the introduction of such 7*S*-alkylthio-substituents into the lincomycin structure.

DISCUSSION

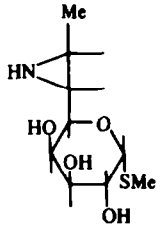
Both hydrogen sulphide and alkanethiols are known[5] to effect ring-opening of simple epimines to yield α-amino-thiols and -sulphides. Epimino-sugars have been suggested as useful intermediates for the synthesis of a variety of α-substituted amino-sugars, although, unlike epoxy-sugars, they have been shown not to undergo ring-opening with alkoxide ion.[6]

Hydrazinolysis of lincomycin cleaves the amide bond, generating the free amino-sugar methyl thiolincosaminide (**7**);[7] reaction with "triphenylphosphine dichloride" gives the 7*S*-7-chloro-7-deoxy-sugar (**8**),[8] from which the 6*R*, 7*R*-epimino-sugar (**9**) is formed readily with base. Reaction of this epimine with hydrogen sulphide in isopropyl alcohol gives the 7*S*-thiol (**10**).[8] However, under similar conditions, no reaction occurs between the epimine (**9**) and methanethiol, and thus does not afford an entry to the desired 7*S*-alkylthio-amino-sugars. Presumably, the initial step in the ring-opening of the epimine by hydrogen sulphide is the protonation of the epimino–nitrogen atom, resulting in the weakening of the C–N bond, and is followed by nucleophilic attack of the conjugate base. The acidity of the methanethiol must be reduced sufficiently from that of hydrogen sulphide that both the protonation of the epimino–nitrogen atom and the concentration of the conjugate base are suppressed to an extent inadequate for reaction to occur.

In the investigation[3b] of the introduction of 7*S*-alkoxy-substituents into the sugar fragment, and in the expectation that an electron-withdrawing substituent on the epimino–nitrogen atom should increase the ease of ring-opening reactions, the *N*-acetylepimine (**11**) had been made, but it was inert to hot methanol. However, rapid reaction occurred in methanol in the presence of acetic acid,



(7) R^1 = OH, R^2 = H
(8) R^1 = H, R^2 = Cl
(10) R^1 = H, R^2 = SH



(9)

even at room temperature, to give a methoxyamide, distinguished from the known 7*R*-methoxy-compound,[3a] and giving a dominant ion (**12**) in the mass spectrum. In view of the known 6*R*-stereochemistry of the epimine (**9**), the structure of the methoxy-amide was defined as the 7*S*-(**13**).

The tetra-acetylepimine (**14**) reacted similarly with methanol in the presence of acetic acid to give the tri-*O*-acetyl amide (**15**), identical with the product of acetylation of (**13**). The requirement of the presence of acetic acid for the opening of the epimino-ring of the activated epimines must be that a protonated acylepimine is necessary further to weaken the N–C_7 bond permitting nucleophilic attack by the alcohol. Similar reactions occurred with higher alcohols to give the corresponding 7*S*-alkoxy derivatives but, even with ethanol, competitive ring opening by acetate ion occurred to give the 7*S*-acetate (**16**). Exclusive nucleophilic attack of the epimine at C-7 is in conformity with the well-established unfavourable interactions involving S_N2-reactions at C-6 occasioned by *galacto*-stereochemistry.[9] Deprotection of the acetylated sugar gave the free amino-sugar, which was converted into the corresponding analogue of lincomycin[3b] by condensation with 1-methyl-*trans*-4-propyl-L-proline *via* its mixed anhydride from isobutyl chloroformate.

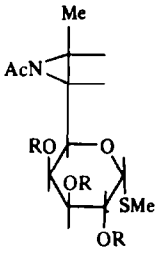
Pearson[10] has shown that the nucleophilic reactivity of a thiol is *ca* 10^6 times that of the corresponding alcohol, and 10–10^2 times that of acetate ion. Ring-opening of the acetylated epimine (**14**) in the presence of methanethiol and acetic acid, therefore, would be expected to occur more readily than with methanol and to yield the 7*S*-methylthio-derivative (**17**). In the event, use of a large excess of methanethiol in an equal volume of methanol as solvent gave the methoxy-derivative (**15**) as sole product. Conducted in a sealed tube at 100° in methanethiol–acetic acid in the absence of diluent, the acetoxy-derivative (**16**) was the sole product. This failure of methanethiol to effect ring-opening of the activated epimine in the presence of acetic acid suggested that, on the theory of soft and hard acids and bases,[11] the hard electrophilic centre of the protonated *N*-acetylepimine reacted readily with the hard alcohol but not with the soft thiol.

In the light of this failure to introduce the desired methylthio-substituent, and the desire to introduce a 7*S*-sulphide grouping, the reaction of the acetylated epimine with 2-methylthioethanol–acetic acid was investigated in the expectation of generating the 2-(methylthio)-ethoxy-product (**18**).[12] The reaction yielded a major and two minor products, identified as the 2-hydroxyethylthio-derivative (**19**), the methylthio-derivative (**17**), and the known 7*S*-acetate (**16**): there was no indication of the formation of the expected (**18**). X-ray analysis of the crystalline methylthio-compound (**17**) demonstrated the structure to be that shown.

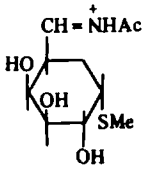
The course of the reaction, therefore, must be as indicated (Scheme 1); nucleophilic attack of the sulphide sulfur atom at C-7 of the protonated epimine yields the sulphonium ion, which collapses by nucleophilic attack of acetate ion (see later) mainly at the methyl group adjacent to the positively charged sulphur atom to give (**19**); attack at the more hindered α-methylene group gives (**17**) as the minor product.

Reaction with symmetrical dialkyl sulphides[12]

Reaction of the epimine (**14**) with symmetrical dialkyl sulphides in the presence of acetic acid occurs quite generally to yield the 7*S*-alkylthio-derivative. However, although the yield of the methylthio-derivative (**17**) using dimethyl sulphide is almost quantitative, the utility of the reaction



(11) R = H
(14) R = Ac



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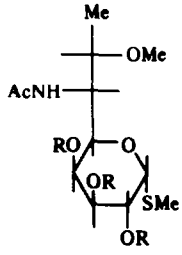
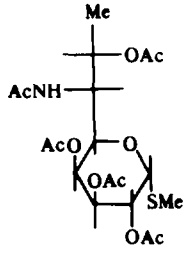


(13) R = H
(15) R = Ac



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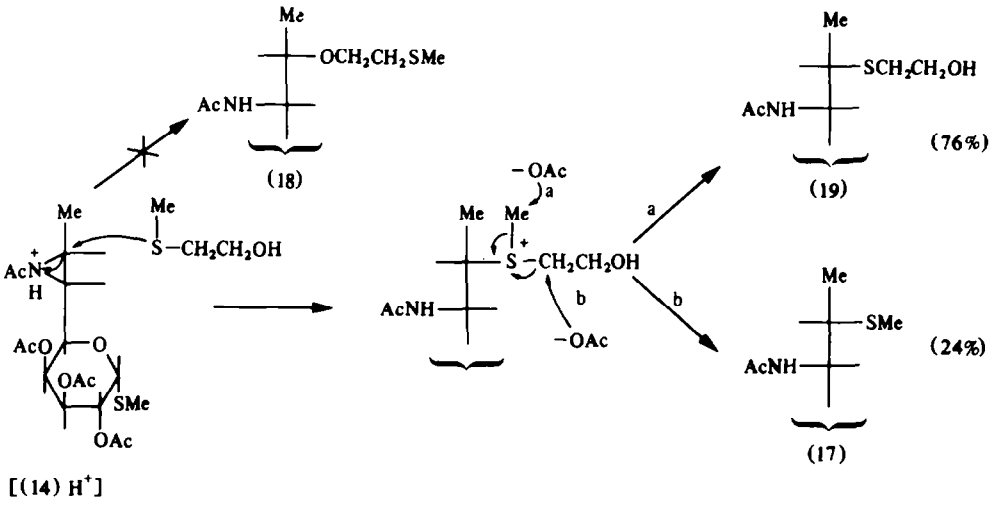


Scheme 1.

diminishes rapidly as the steric hindrance imparted by bulkier alkyl groups reduces the nucleophilic reactivity of the sulphide sulphur atom, and allows ring-opening by acetate ion to become more dominant. With diethyl sulphide, the yield of the 7-ethylthio-product was 61%: with di-n-propyl sulphide, the yield of n-propylthio-product had decreased to 18.5% and, with di-t-butyl sulphide, the yield of t-butylthio-product was only 2.5%.

In the case of reaction with diallyl sulphide, the acidity of the proton on the α-methylene group of the intermediate sulphonium salt was shown by the formation of both the 7-allylthio-[(**20**), minor] and the 7-propenylthio-[(**21**), major] products (Scheme 2).

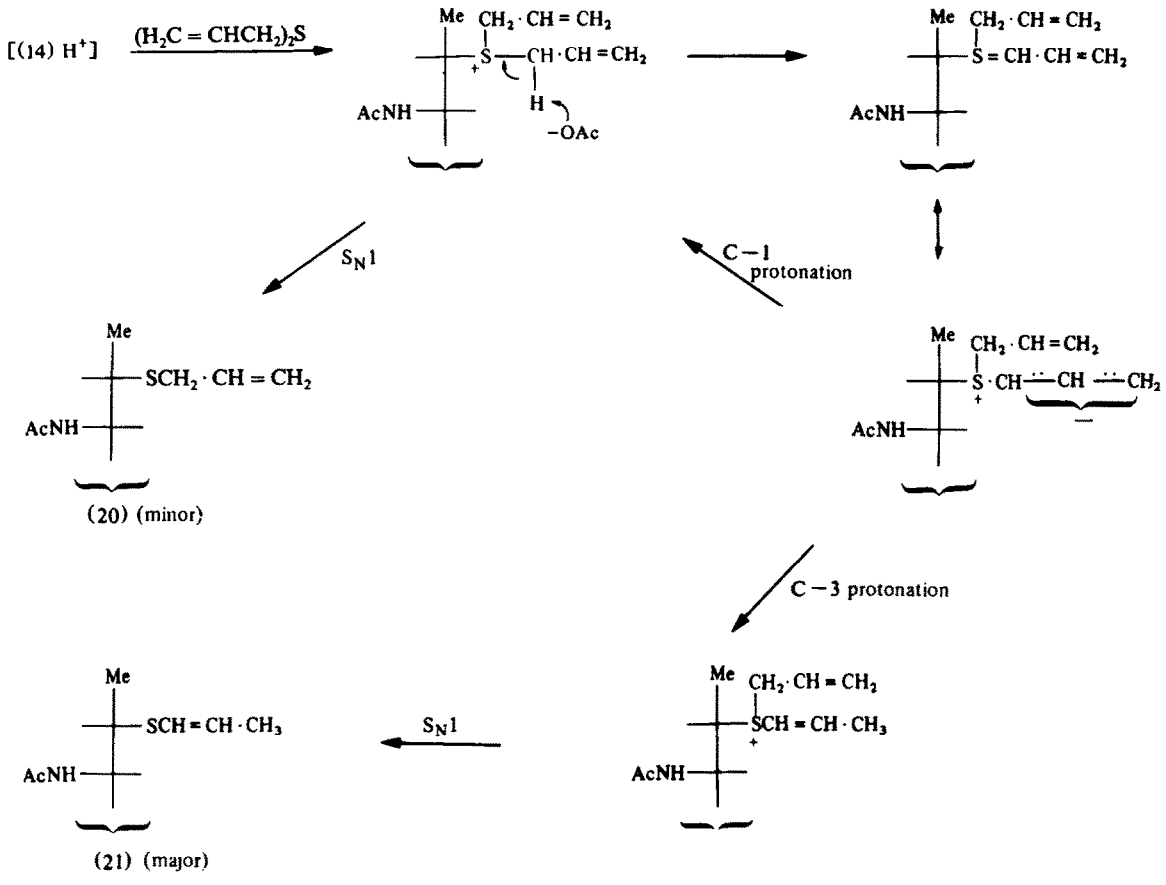
In all cases of these reactions with sulphides in which 7-acetate is formed, the acetoxy-group has the 7*S*-configuration, and no 7*R*-acetate[3b] was detected. Therefore, presumably because its attack is too hindered, no displacement of sulphide by attack of acetate ion at C-7 in the intermediate sulphonium salt occurs.

Reaction with alkyl methyl sulphides[12]

The rapidly diminishing yield of the 7-alkylthio-product noted with dialkyl sulphides, as steric hindrance decreases the nucleophilic reactivity of the sulphide sulphur atom, should be ameliorated by the use of alkyl methyl sulphides. Thus, methyl propyl and methyl isopropyl sulphides gave the propylthio- and isopropylthio-sulphides in improved (*ca* 30%) yield, together with the methylthio-compound, but competitive ring-opening by acetate ion still predominated. Similar yields of cyclopentylthio- and cyclohexylthio-products were obtained when the reaction was extended to the use of cycloalkyl methyl sulphides.

With t-butyl methyl sulphide, an 80% yield of the methylthio-compound resulted, with no formation of the 7-t-butylthio-product. This, taken together with the results of the reaction with diallyl sulphide, suggested that substituents exerting less steric hindrance about the sulphide sulphur atom, but capable of yielding stabilised carbocations by heterolytic scission of the carbon-sulphonium sulphur bond, could be of utility in the generation of particular thio-substituents in this reaction. This was borne out by the introduction of the 7-phenylthio-substituent in *ca* 70% yield using benzyl phenyl sulphide, and of the 7-benzylthio-substituent in similar yield using dibenzyl sulphide.

The methyl thioglycosidic group of the penta-acetate of methyl α-thiolincosaminide is not subject to sulphonium salt formation in methanol solution in the presence of an excess of alkyl iodide.[12] In view of the noted ready collapse of the intermediate sulphonium salts at C-7 containing a substituent subject to heterolytic bond scission, *S*-alkylation of the readily-available 7-benzylthio-compound to form a sulphonium salt in which the newly introduced substituent would not be capable of carbocation stabilisation, should allow the use of this benzylthio-compound as an intermediate in the introduction of a variety of thio-substituents. In the event, quantitative recovery of the benzylthio-tetra-acetate from its solution in acetonitrile in the presence of an excess



Scheme 2.

of methyl iodide indicated that severe hindrance of approach to the 7-sulphide sulphur atom exists. Further examples of this hindrance are discussed below.

Reaction with symmetrical dialkyl disulphides, diallyl disulphide, and diethyl trisulphide[12]

Dialkyl disulphides appear[13] to exist in the linear form R–S–S–R rather than as the branched form R–$\overset{\overset{S}{\|}}{S}$–R. The reduced nucleophilic reactivity imposed by the higher alkyl groups in the dialkyl sulphides should be alleviated in the corresponding dialkyl disulphides. However, early work by Hilditch and Smiles[14] had shown the reaction between alkyl halides and dialkyl disulphides to be slow, but to proceed with the ultimate formation of a trialkylsulphonium salt, and the rate of methylation of diethyl sulphide by methyl fluorosulphate has been found[15] to be one hundred times greater than that of diethyl disulphide. Helmkamp[16] showed that trimethyloxonium trinitrobenzenesulphonate effects the ready methylation of dialkyl disulphides to yield alkylmethyl(alkylthio)sulphonium salts which react in solution with iodide ion to yield dialkyl sulphide, dialkyl disulphide, and iodine, implying that the sulphur–sulphur bond was cleaved as a consequence of nucleophilic attack of iodide ion on the sulphenyl sulphur atom. Similarly, from a study of the ^{1}H NMR spectra of dimethyl sulphide, $MeS{\cdot}\overset{+}{S}Me_2$, and mixtures of the two, Kice and Favstritsky[17] found that an extremely rapid reaction occurs between the two, the Me_2S being an excellent leaving group, expelled as the neutral dimethyl sulphide, following nucleophilic attack at the sulphenyl sulphur atom. Calculation showed that this displacement by the nucleophile at the sulphenyl sulphur atom occurs at least 10^9 times faster than the analogous displacement on sp^3 carbon in the reaction between methyl iodide and dimethyl sulphide.

Hence, it was envisaged that, if the nucleophilic reactivity of a dialkyl disulphide were greater than that of acetate ion, the reaction with the activated epimine should generate the di-

alkyl(alkylthio)sulphonium salt which should collapse to give the alkylthio- and not the alkyldithio-derivative (Scheme 3).

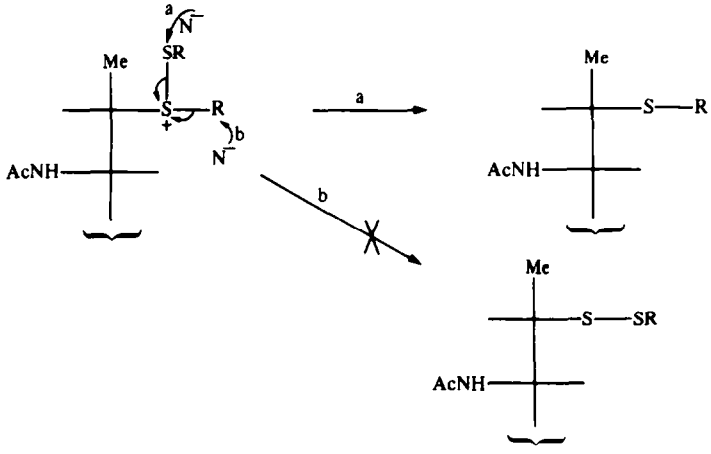
In the event, reaction between the acetylated epimine and dimethyl disulphide in the presence of acetic acid gave the expected 7-methylthio-compound in 82% yield: the only other product was the 7-acetate. Significantly improved yields of 7-alkylthio-products were formed from di-isopropyl and di-n-butyl disulphides; the 7-benzylthio-product was formed in the same yield from both dibenzyl sulphide and disulphide, and demonstrates that nucleophilic attack on the sulphenyl sulphur atom takes precedence over heterolytic scission to the carbocation.

However, two disulphides were investigated in which the reaction followed a different course. With di-t-butyl disulphide, the 7-thio-product was not identical to the 7-t-butylthio-derivative formed in extremely poor yield from di-t-butyl sulphide, but was the 7-t-butyldithio-product. This alternative and exclusive mode of collapse of the dialkyl(alkylthio)sulphonium salt must be attributed to the extreme crowding between the carbohydrate side chain and the $Bu^t-\overset{+}{S}$ group, the steric hindrance to the approach of a nucleophile to the sulphenyl sulphur atom occasioned by the second t-butyl group, and the relief of steric strain in the salt by heterolytic bond scission to give the stabilised t-butyl carbocation.

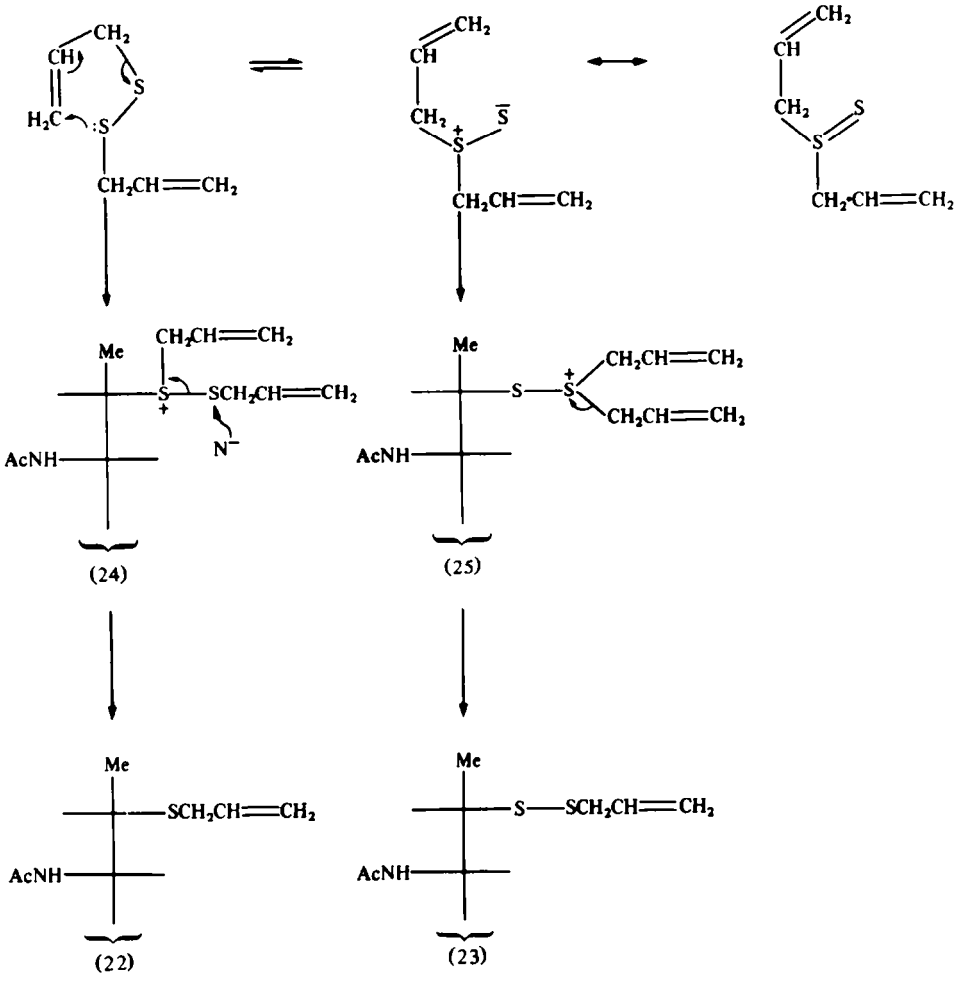
With diallyl disulphide, both the 7-allylthio-(**22**) and the 7-allyldithio- (**23**) products were formed in approximately equal yield. Of the three factors determining the collapse of the sulphonium salt intermediate from di-t-butyl disulphide, only the stabilisation of the carbocation is shared by the corresponding intermediate from di-allyl disulphide, and cannot explain the formation of both the allylthio- and allyldithio-substituent. However, in an investigation of the thermal rearrangement of α-substituted allylic disulphides to their more stable isomers, Höfle and Baldwin[18] have presented evidence for the intermediacy of a thiosulphoxide (the unstable branched form of a disulphide) by a [2, 3]-sigmatropic rearrangement. Invoking this concept permits the rationalisation of the results (Scheme 4).

The enhanced nucleophilicity of the canonical form of the thiosulphoxide in which a negative charge resides on the terminal branched sulphide sulphur atom, relative to the linear disulphide, presumably leads to the more rapid reaction of this intermediate than of the linear disulphide with the protonated acetylated epimine; hence, the formation in this reaction of approximately equal amounts of allythio- and allyldithio-products is not in itself indicative of the position of equilibrium between linear and branched forms of the disulphide.

Two other points of interest arise in the collapse of the two thiosulphonium salt intermediates in this reaction. The lack of formation of propenylthio-derivative, which was the major product of the reaction with diallyl sulphide, must reflect the extreme rapidity of the reaction involving nucleophilic attack on the sulphenyl sulphur atom in the ion (**24**) remarked upon above, which must not allow a longevity of this salt adequate for significant abstraction of a proton before collapse to allylthio-product. Secondly, the formation from the corresponding thiosulphonium salt (**25**) of the allyldithio-derivative implies that, extremely rapid as the attack of nucleophile on the



Scheme 3.



Scheme 4.

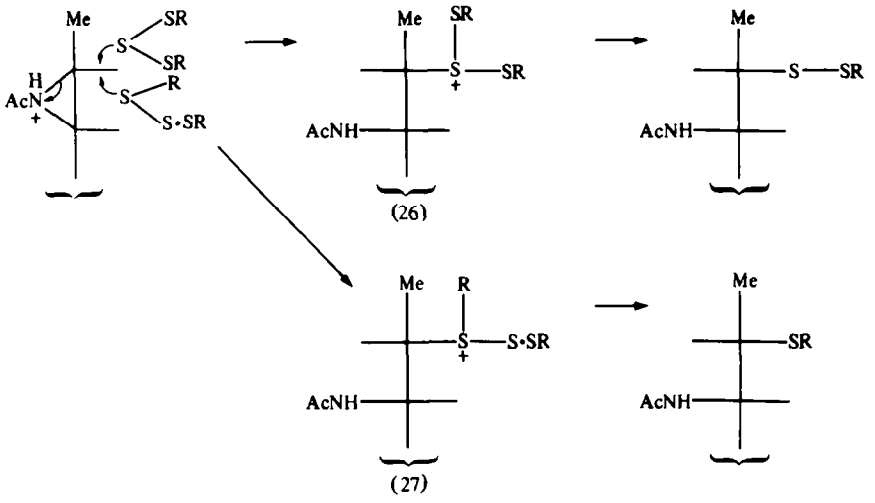
sulphenyl sulphur atom in such salts is in general, steric hindrance at C-7 must prevent effectively the approach of a nucleophile to the sulphenyl sulphur atom, and so promote collapse by generation of the allyl carbocation.

The formation of the t-butyldithio- and allyldithio-compounds are specific examples of exceptions to the course of reactions between disulphides and the protonated activated epimine. Little is recorded in the literature of the products of *S*-alkylation of trisulphides; if, in the ring-opening of the epimine, the central sulphide sulphur atom is the more nucleophilic, an alkyl(dialkylthio)sulphonium salt (**26**) should result in which again the reactivity of the symmetrical sulphenyl sulphur atoms should lead to the generation of a disulphide. Greater nucleophilicity of the terminal sulphide sulphur atoms of the trisulphide, however, would generate a di-alkyl(alkyldithio)sulphonium salt (**27**) which would collapse to the sulphide (Scheme 5).

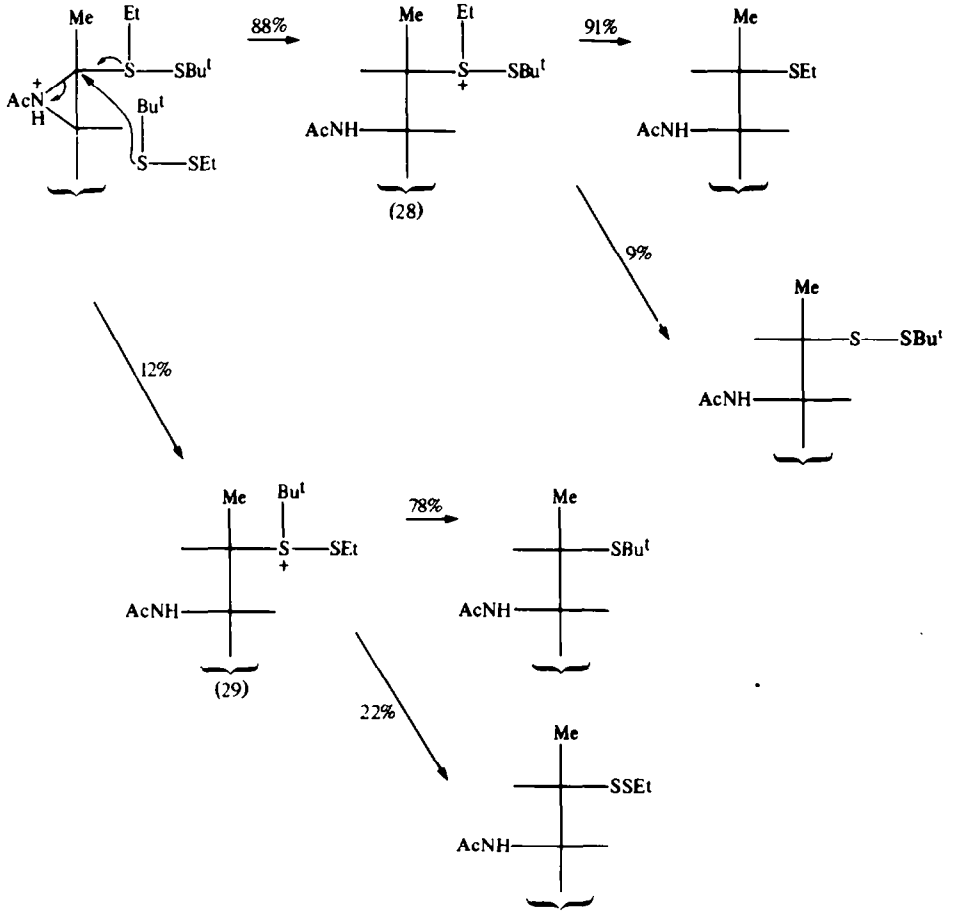
From the reaction with diethyl trisulphide, only the 7-ethylthio-derivative was formed. The inductive effect of the alkyl substituents in a trisulphide, therefore, increases the nucleophilicity of the terminal sulphur atoms relative to the central sulphur atom.

In order to investigate further the competing factors in the collapse of the intermediate thiosulphonium salts formed from dialkyl disulphides, the products of the opening of the acetylated epiminine with t-butyl ethyl disulphide were examined. The reaction would be expected to favour the formation of thiosulphonium ion (**28**) over that of (**29**) (Scheme 6), borne out by the analysis of the products.

In spite of the expected incipient instability of the alkyl t-butyl(ethylthio)sulphonium ion (**29**) owing to both the ability to generate the t-butyl cation and to the overcrowding occasioned by the t-butyl substituent, as discussed above, the proclivity of the sulphonium–sulphenyl



Scheme 5.



Scheme 6.

sulphur–sulphur bond to undergo cleavage predominates, in the absence of severe hindrance to the approach of a nucleophile, and results in the major collapse of the ion (**29**) to the 7-t-butylthio-compound rather than to the 7-ethyldithio-compound. Similarly, the hindrance to nucleophilic attack at the t-butyl sulphenyl sulphur atom in (**28**) demonstrated in the product of the reaction with di-t-butyl disulphide, would have been predicted to lead to the major collapse of the ion (**28**) to give the 7-t-butyldithio-compound; in the event, the formation of the 7-ethylthio-compound as the major product of the collapse of this ion reveals the propensity of such an ion to collapse by heterolytic scission of the sulphonium-sulphenyl sulphur–sulphur bond with the generation of the sulphenium cation Bu^tS^+, a course not adopted when the sulphonium sulphur atom also bears a t-butyl substituent.

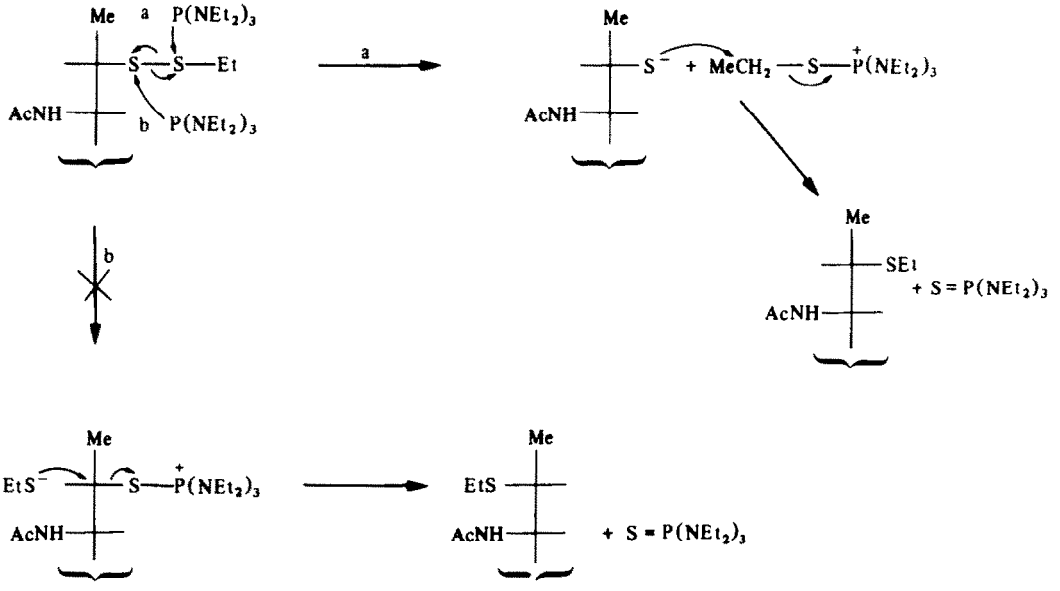
Treatment of the 7-ethyldithio-compound in benzene with tris(diethylamino)phosphine could generate either the 7*R*- or 7*S*-ethylthio-compound depending upon which sulphur atom of the disulphide is attacked by the nucleophilic phosphorus atom. In fact, only the 7*S*-ethylthio-derivative was formed, indicating again that the 7-sulphur atom in these thio-compounds is hindered significantly (Scheme 7).

Reaction with cyclic sulphides, and with sulphides bearing an additional nucleophilic sulphur substituent[19,20]

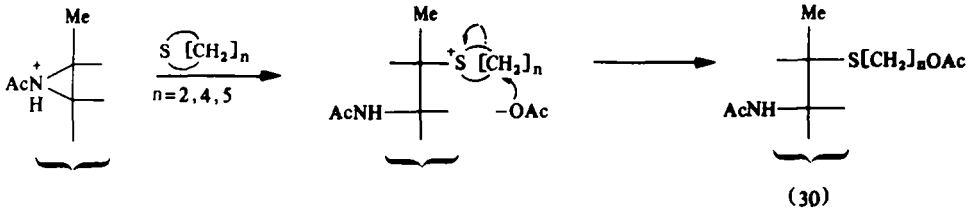
Although the reaction between the activated epimine and hydroxyethyl methyl sulphide allowed the introduction of the 7-(2-hydroxyethyl)thio-substituent, collapse of the intermediate sulphonium salt by nucleophilic attack at both carbon atoms α- to the positively charged sulphur atom decreased the yield of the desired hydroxyethylthio-compound. On the assumption that acetate ion was the nucleophile occasioning the collapse of such sulphonium salts to sulphide, the possibility of using cyclic sulphides in the reaction with the activated epimine was investigated, since greater nucleophilic reactivity of such a sulphur atom relative to a linear sulphide could be expected and, also, the intermediate sulphonium salt, being symmetrical, would collapse to a single product.

Reaction with the three-, five-, and six-membered thiiran, thiolan, and thian proceeded as expected to give the ω-acetoxy-alkylthio-products (**30**) (Scheme 8).

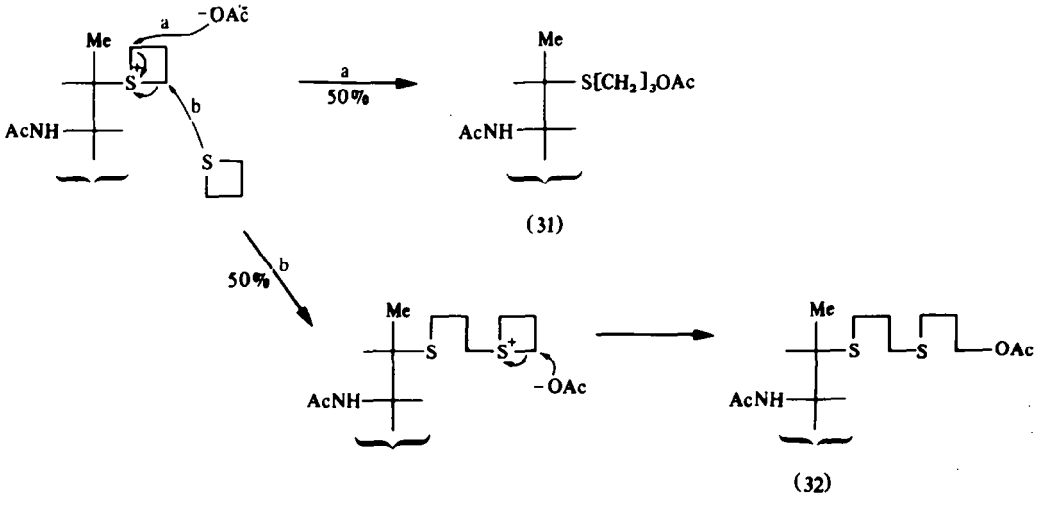
However, with the four-membered thietan, the expected 7-(3-acetoxypropyl)thio-product (**31**) was accompanied by an equivalent yield of the 7-[3-(3-acetoxypropylthio)propyl]thio-compound (**32**) (Scheme 9). Evidently, the intermediate sulphonium salt in this case suffers attack by both acetate ion and thietan, although neither the factors which limit the nucleophilic attack of reagent to the initial sulphonium salt, nor those which restrict this mode of attack in the cyclic series to thietan, are understood.



Scheme 7.



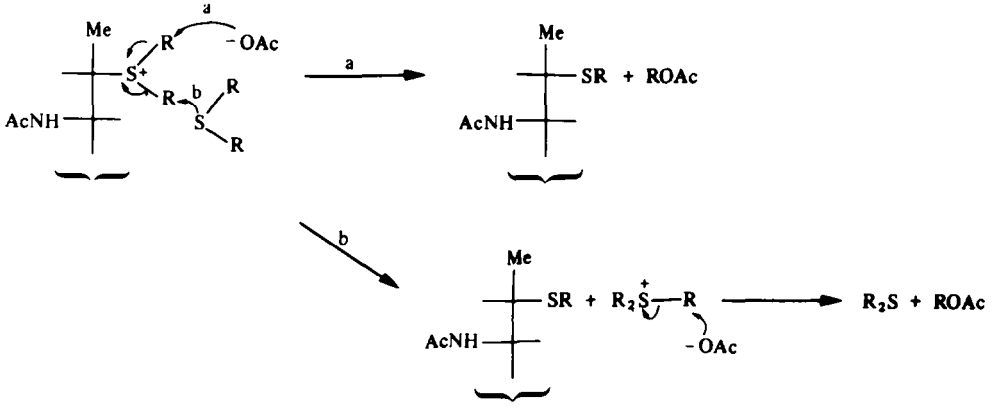
Scheme 8.



Scheme 9.

Ethyl acetate had been identified as a product of the reaction between the activated epimine, acetic acid, and diethyl sulphide,[12] and the initial assumption was that attack on the α-carbon atom by acetate ion as nucleophile generated the sulphide product. However, in the light of the above demonstration that a sulphide sulphur atom can be involved in this initial displacement, there is no evidence as to which direct course such a reaction follows (Scheme 10).

The relative reactivities of nucleophiles in displacements at α-carbon atoms of sulphonium salts are not well documented. In an examination of the transference of methyl groups from substituted dimethylphenylsulphonium salts to various nucleophiles, Coward and Sweet[21] found the relative reactivities to be in the order $NCS^- > R_2NH > HO^-$, and considered sulphonium salts to be extremely resistant to attack by oxygen nucleophiles; the same order of reactivity has been reported by Schlenk *et al.*[22] in enzyme-catalysed reactions of methyl group transference from analogues of



Scheme 10.

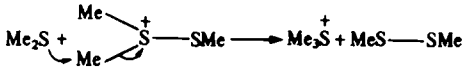
the biological *trans*-methylating agent *S*-adenosyl-L-methionine involving acetylserotonin *O*-methyltransferase, histamine *N*-methyltransferase, and homocysteine *S*-methyltransferase. Although, as mentioned earlier, Kice and Favstritsky[17] found an equilibrium to be established very rapidly between dimethyl sulphide and the dimethyl(methylthio)sulphonium ion, Caserio *et al.* found no reaction to be discernible on the ^{1}H NMR time scale between dimethyl sulphide and the trimethylsulphonium ion;[23] however, an irreversible reaction occurred on long contact between dimethyl sulphide and the dimethyl(methylthio)sulphonium ion[24] (Scheme 11).

Competition between nucleophiles in the collapse of a sulphonium salt has been reported by Ramirez *et al.*[25] The main pathway of decomposition of *S*-methylmethionine sulphonium salts in neutral and basic aqueous solutions gives homoserine *via* intramolecular attack by carboxylate ion on the adjacent methylene group, but degradation to methionine becomes important when the carboxylate anion concentration is suppressed by lowering the pH, intermolecular attack by liberated dimethyl sulphide now occurring on one of the sulphonium methyl groups (Scheme 12).

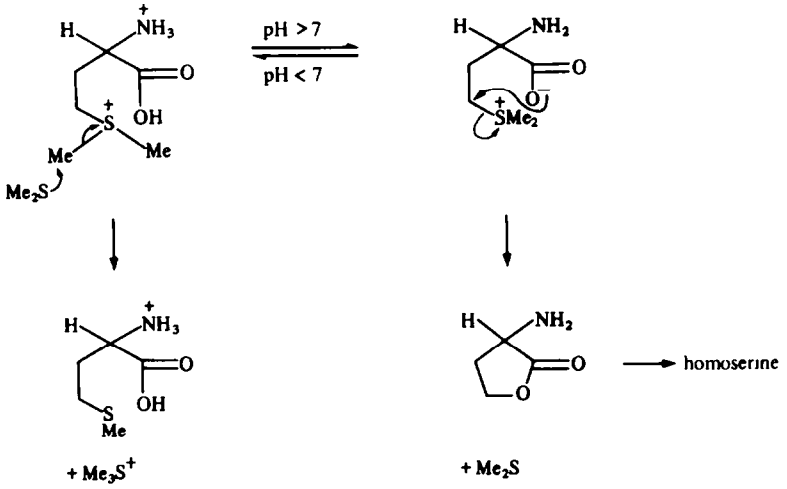
It was of interest, therefore, to examine the possible role in the collapse of sulphonium salts, generated by the reaction between the epimine and a sulphide bearing a second nucleophilic thio-substituent, of neighboring group participation. First chosen was a second methylthio-substituent in a series of α,ω-bis(methylthio)alkanes.

With 1,2-bis(methylthio)ethane, the only product, apart from a trace of the 7-acetate, was the known 7-methylthio-derivative [(**17**), 93%]. The failure to generate the 7-[(2-methylthio)ethyl]thio-derivative (**33**) shows that MeS-3 participation completely outweighs the intermolecular attack of a nucleophile. Similarly, with 1,4-bis(methylthio)butane, the major product (78%) was the 7-methylthio-derivative, showing MeS-5 participation also to be an efficient process; however, a small yield (5%) of the 7-[(4-methylthio)butyl]thio- product (**34**) was present, indicating that MeS-5 participation did not circumvent completely collapse by intermolecular nucleophilic attack. By means of the reagent 1,3-bis(methylthio)propane, MeS-4 participation was shown to be relatively ineffective, the minor product (19%) being the 7-methylthio-derivative; the resulting longevity of the initial sulphonium ion must thereby be sufficiently great that the major collapse is occasioned by intermolecular nucleophilic attack to give the 7[(3-methylthio)propyl]thio-derivative [(**35**), Scheme 13].

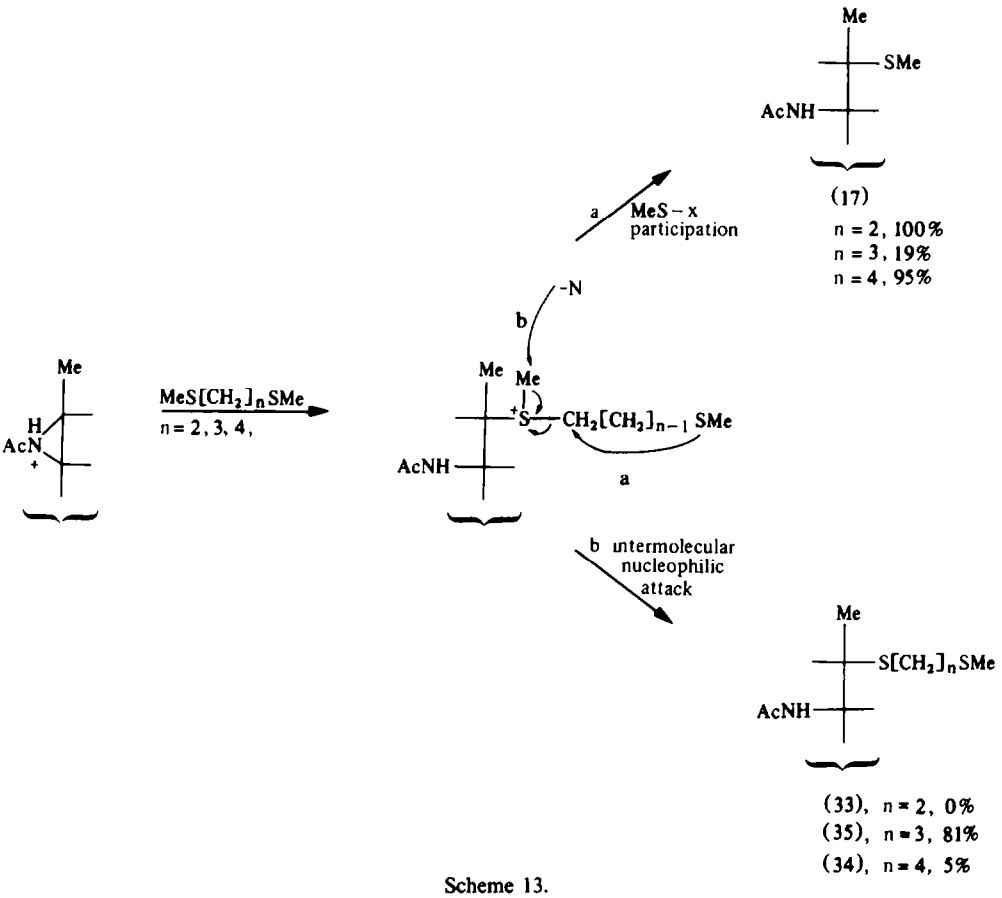
Since, surprisingly, the nucleophilicity of simple thiols had been found to be inadequate to effect reaction under these conditions with the activated epimine, it was of interest to determine the influence of a thiol group as a second nucleophilic substituent in a sulphide on the course of collapse of the corresponding sulphonium salt.



Scheme 11.



Scheme 12.



Scheme 13.

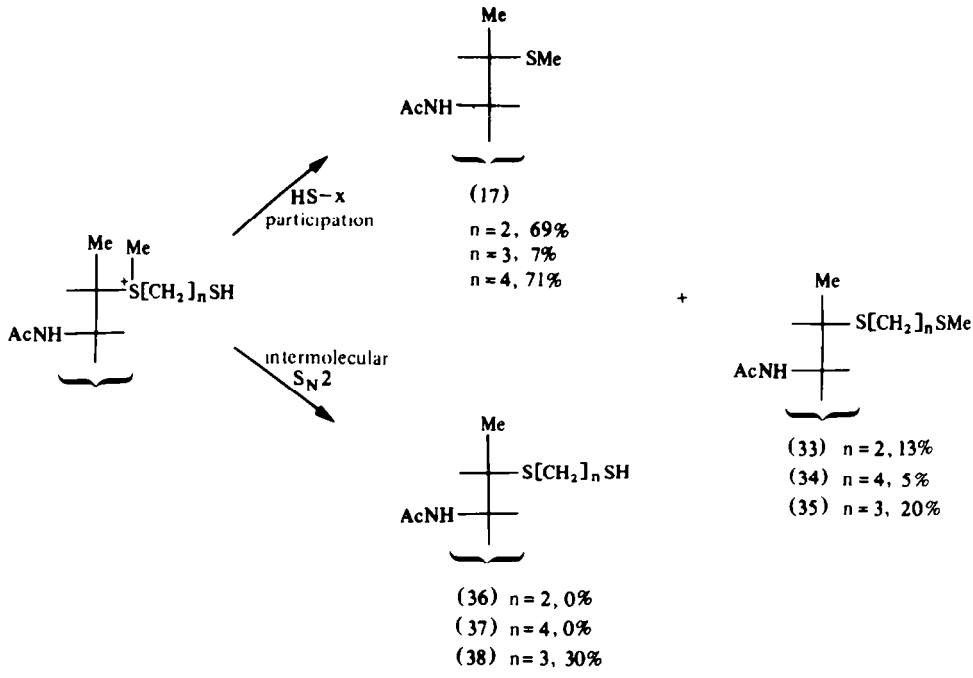
From the reaction with 2-(methylthio)ethanethiol, the major product (69%) was the 7-methylthio-derivative (**17**); no indication was found of the formation of the terminal thiol [(**36**), Scheme 14] that would have resulted from intermolecular nucleophilic attack on the methyl substituent of the sulphonium salt, showing HS-3 participation to be an efficient process. In addition, however, there was found (13% yield) the unexpected 7-[(2-methylthio)-ethyl]thio-derivative (**33**), which had *not* resulted from the ring-opening reaction of the epimine with 1,2-bis(methylthio)ethane. With the reagent 4-(methylthio)butanethiol, the 7-methylthio-derivative again was the major product (71%); again, the absence of the terminal thiol (**37**) demonstrated that HS-5 participation circumvented collapse of the sulphonium salt by intermolecular nucleophilic attack on the methyl substituent. Again, the unexpected formation of the terminal methylthio-product, the 7-[(4-methylthio)butyl]thio-derivative [(**34**), 5%] was found.

With the reagent 3-(methylthio)propanethiol, three products resulted, of which the 7-methylthio-derivative was the minor (7%), the major component now being the terminal thiol, the 7-[(3-mercapto)propyl]thio-compound [(**38**), 30%]; as with MeS-4 participation, HS-4 participation is inefficient. Again, a terminal methylthio-derivative, the 7-[(3-methylthio)propyl]thio-derivative [(**35**), 20%] was formed.

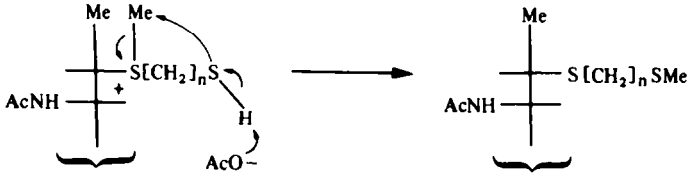
Thus, the formation of the 7-methylthio-derivative in all three cases, together with the formation of the 7-(3-mercaptopropyl)thio-derivative from 3-methylthiopropanethiol, are essentially consistent with the extent of HS-x participation predictable from the MeS-x results.

Since simple thiols had been shown not to take part in the ring-opening reactions of the activated epimine, two mechanisms for the rationalisation of the formation of the 7-[(ω-methylthio)alkyl]thio-products seemed attractive. The first involved nucleophilic attack by the thiol-group on the methyl substituent of the sulphonium sulphur atom, instead of the α-methylene substituent (Scheme 15).

Neighbouring-group participation of the ω-thiol group in the intermediate sulphonium salts leading to the collapse to the 7-methylthio-derivative involves a 3-, 4-, or 5-membered-ring



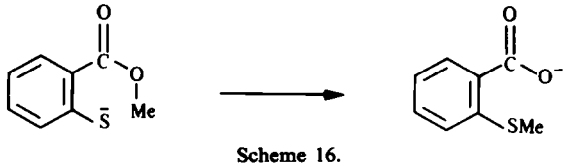
Scheme 14.



Scheme 15.

transition state in an *exo*-cyclic reaction. However, the alternative attack of the thiol-group on the methyl substituent of the sulphonium salt involves an *endo*-cyclic reaction, with a 5-, 6-, or 7-membered-ring transition state. Eschenmoser and his collaborators[26] have shown that, in the *S*-methylation below (Scheme 16), an entirely intermolecular transfer is involved, and stress the improbability of intramolecular endocyclic reactions involving ring-transition states of less than ten atoms because of the requirement of the back-side attack at the tetrahedral carbon atom. In general, such reactions fall into Baldwin's[27] class of disfavoured 5- to 6-*endo-tetrahedral* processes involving linear transition states with first-row elements. However, in the case of the second-row element sulphur, the larger radius and bond lengths may allow the assumption of a conformation in the transition state adequate for such an endocyclic reaction, and it was intriguing to see if the unexpected products of the ω-methylthioalkanethiol-epimine reaction provided such an example.

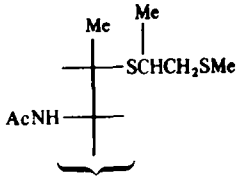
The second attractive rationalisation for the generation of these products involved the intramolecular attack of the thiol group in the intermediate sulphonium salt on the sulphonium-sulphur atom itself to give a 1,2-dithietan derivative, followed by migration of the methyl group



Scheme 16.

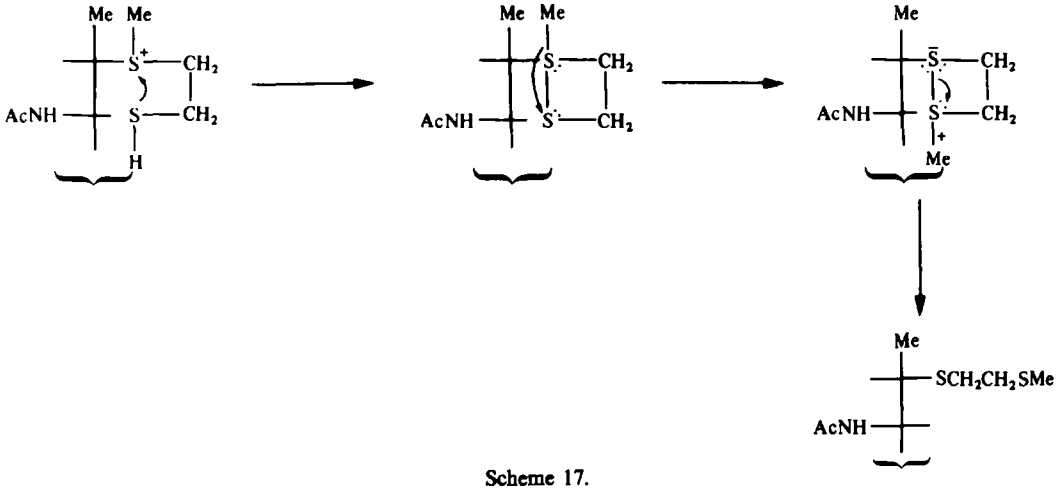
from the tetracovalent to the dicovalent sulphur atom, and, finally, scission of the sulphur–sulphur bond (Scheme 17).

Both of these mechanisms involve transference of the methyl group from the sulphonium to the thiol sulphur atom. In an attempt to determine whether or not this were the case, the corresponding reaction with the unsymmetrically branched (2*RS*)-1-(methylthio)propane-2-thiol was conducted. The major product was the 7-methylthio-derivative; the structure of the minor product was demonstrated by X-ray crystallographic analysis to be (**39**), showing that no migration of the methyl group from one sulphur atom to the other had occurred.

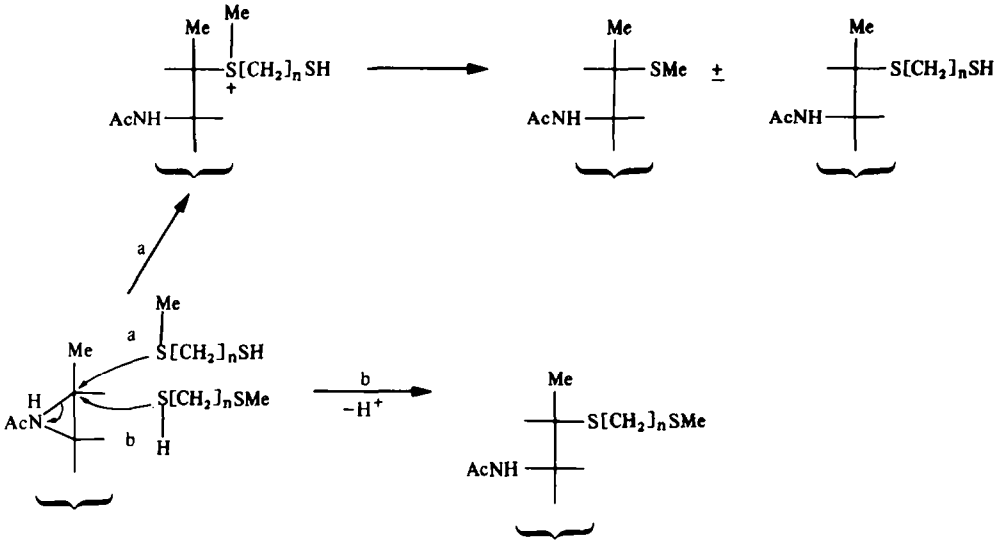


(39)

The formation of the 7-methylthio-compound and the one instance of the 7-(ω-mercaptoalkyl)thio-compound on the one hand and the 7-(ω-methylthio)alkylthio-compounds on the other from these reagents must thus be the consequence of the separate nucleophilic attack of the two different sulphur nucleophiles (Scheme 18).

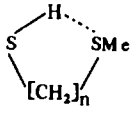


Scheme 17.



Scheme 18.

Although no enhancement of the nucleophilicity of such substituted thiols could be envisaged by any inductive effect of the methylthio-group operating through up to four carbon atoms, an electrostatic field effect acting through space might be operative; more conventionally, this effect of increasing the electron density on the thiol sulphur atom could be attributed to hydrogen bonding between the thiol and methylthio-groups[(40)]:

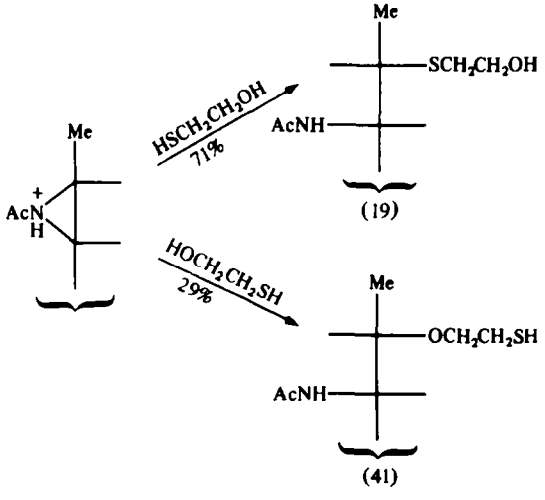


(40)

Hydrogen bonding between a hydroxy-group and a sulphide sulphur atom has been demonstrated in the series $HO[CH_2]_nSEt$[28] for $n = 2$ and 3, but not at greater separation, and in 2-hydroxyethanethiol,[29] by observations of the generation of a second hydroxy-group stretching band of lower frequency in the IR spectra. In order to examine the plausibility of this rationalisation, a thiol with an oxygen substituent as a proton acceptor was chosen.

The reaction between the activated epimine and 2-methoxyethanethiol gave the 7-(2-methoxyethyl)thio-derivative, demonstrating that the thiol group in such reagents indeed shows greater nucleophilicity than in the case of simple alkanethiols. With 2-hydroxyethanethiol, the known 7-(2-hydroxyethyl)thio-product [(**19**), 71%, Scheme 19] was obtained, together with the 7-(2-mercapto-ethoxy)-derivative [(**41**), 29%]. The β-hydroxy-substituent has thus made the thiol group 2.5 times as reactive nucleophilically as the hydroxy-group itself. This nucleophilicity of the thiol group, though enhanced, is still less than that of the methylthio-group in 2-hydroxyethyl methyl sulphide, with which no nucleophilic attack by the hydroxy-group is observed.

Similar reactions with 2-(benzylthio)ethanethiol and 2-(t-butylthio)ethanethiol gave the 7-benzylthio-(61%) and 7-(2-benzylthio)ethylthio-(39%) and 7-t-butylthio-(32%) and 7-(2-t-butylthio)ethylthio-(67%) compounds, respectively. An examination of the relative yields on a molar basis in these cases shows that, in the series $MeS[CH_2]_nSH$ (Table 1), the activation of the thiol group is greatest when the methylthio- substituent is in the γ-position, significant when in the β-position, and slight when in the δ-position, indicating that the hydrogen bonding is most effective in the case of the six-membered cyclic structure. In the series $RSCH_2CH_2SH$, the extent of alkylation of the thiol group relative to the sulphide group increases in the order $R = Me < CH_2Ph < Bu^t$ (Table 2), ascribable to the increased electron density on the sulphide sulphur atom from the greater inductive effects of the benzyl and t-butyl groups leading to the greater stabilisation of the hydrogen-bonded structure. In addition, the hindrance about the sulphide sulphur atom caused by the bulky alkyl group will, by rendering this atom less reactive nucleophilically, favour the competitive nucleophilic attack of the thiol group.



Scheme 19.

Table 1.

MeS $[CH_2]_nSH$	MeS : SH attack
n = 2	5.0 : 1
n = 3	1.9 : 1
n = 4	14.9 : 1

Table 2.

RS $[CH_2]_2SH$	RS : SH attack
R = Me	5.0 : 1
$R = CH_2Ph$	1.6 : 1
$R = Bu^t$	0.5 : 1

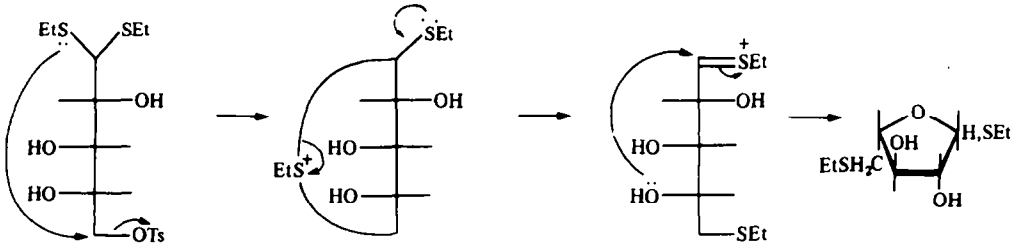
Reaction with mono- and di-thioacetals[30]

The failure[12] of methyl *N*-acetyl-2,3,4,7-tetra-*O*-acetyl-1-thio-α-lincosaminide to undergo *S*-methylation in the presence of methyl iodide, remarked upon earlier, the sole formation of *N*- and *O*-methylation products in the reaction under forcing conditions of methyl *N*-acetyl-3,4-*O*-isopropylidene-1-thio-α-lincosaminide with potassium t-butoxide and methyl iodide,[2] and the stability of the dibenzyl dithioacetals of carbohydrates during the standard conditions[31] of per *O*-methylation, implied that some factor inhibited the alkylation of the sulphur atom of mono- and di-thioacetals. However, the migration of alkylthio-groups of carbohydrate dialkyl dithioacetals to positions elsewhere in the molecule possessing good leaving groups is most plausibly rationalised[32] by participation of such alkylthio-substituents in the displacement of the leaving group. This generates an intermediate cyclic sulphonium salt, the collapse of which is assisted by the mesomeric effect of the second alkylthio-group; the resulting acyclic methylenesulphonium ion is then quenched by the attack of a nucleophile to give a sulphide. For example, the reaction of 5-*O*-*p*-tolylsulphonyl-L-arabinose diethyl dithioacetal in aqueous acetone gives an anomeric mixture of ethyl 1,5-dideoxy-5-ethylthio-1-thio-α- and β-L-arabinofuranosides (Scheme 20).

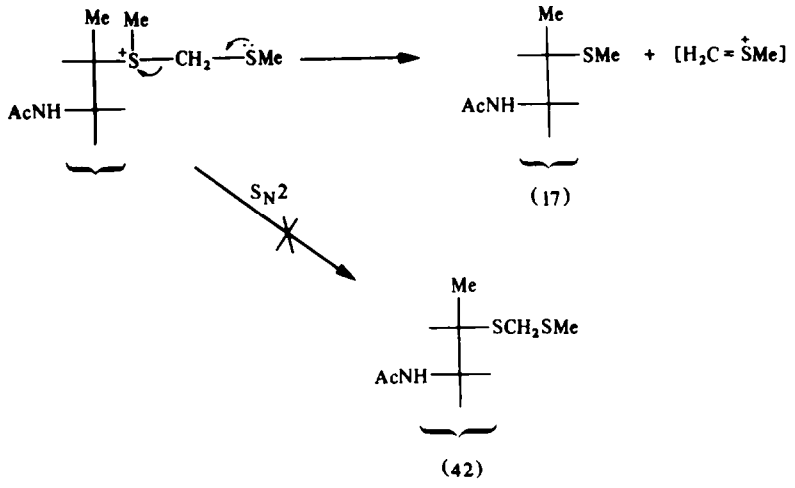
The reactivity of such methylenesulphonium salts toward nucleophilic attack seems to be well established: they are considered[33] to be intermediates in the Pummerer reaction, being quenched by the nucleophilic attack of acetate ion to give α-acetoxysulphides, and the quenching of the parent ion, $[MeS^{+}{=}CH_2]$, by alcohols is accepted as the mechanism of the formation of methylthiomethyl ethers as by-products in dimethyl sulphoxide-acetic anhydride oxidations.[34]

Although both mono- and di-*S*-alkylation of dithioacetals[35,36] and dithioketals[37] are known, generally these alkylations are conducted with the highly electrophilic Meerwein trialkyloxonium salts, or with methyl fluorosulphate. The ability of the activated epimine to effect alkylation of such dithioacetals was investigated with formaldehyde dimethyl dithioacetal. Apart from a trace of the 7*S*-acetoxy-amide, the 7*S*-methylthio-derivative [(**17**), Scheme 21] was formed in almost quantitative yield, with no indication of the formation of the (methylthio)methylthio-derivative (**42**) which would have resulted from intermolecular nucleophilic attack on the methyl group in the intermediate sulphonium salt, thus substantiating the mode of collapse of this ion by the mesomeric assistance of the heterolysis of the carbon–sulphur bond.

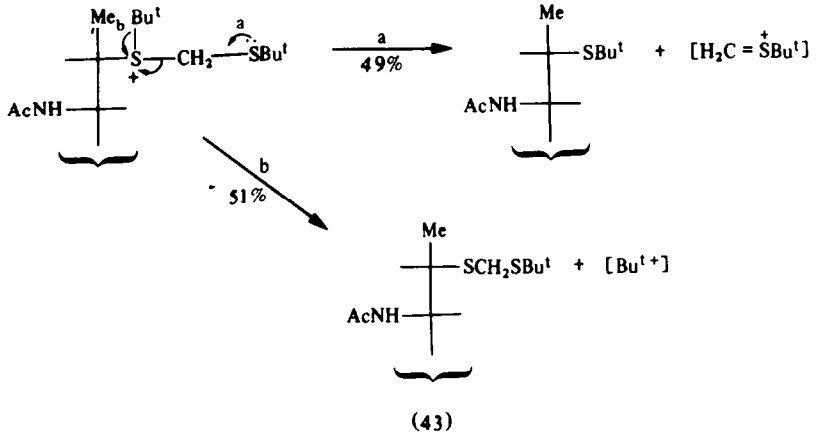
In the corresponding reaction with formaldehyde di-t-butyl dithioacetal, the 7*S*-acetoxy-amide was formed (19%, reflecting the lessened nucleophilic reactivity occasioned by the bulky t-butyl substituent) together with essentially equimolar amounts of both the 7*S*-t-butylthio- and 7*S*-(t-butylthio)methylthio-[(**42**), Scheme 22] derivatives. Thus, this intermediate sulphonium salt, unlike that in the dimethyl dithioacetal case, can collapse either by the heterolysis of the carbon–sulphur bond assisted by the mesomeric effect of the sulphide sulphur atom or by



Scheme 20.



Scheme 21.



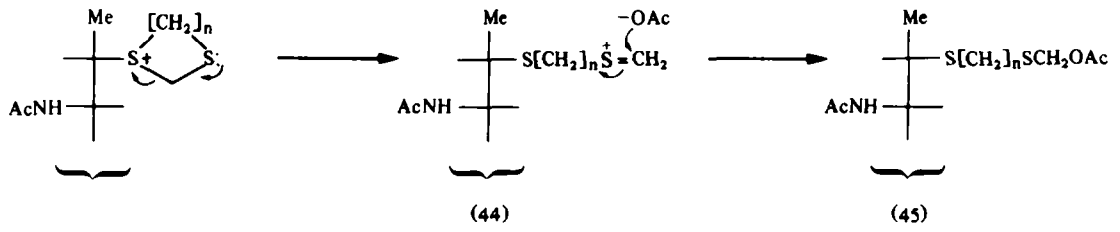
Scheme 22.

heterolysis of the carbon–sulphonium sulphur bond to generate the t-butyl carbocation. These two processes are seen to be favoured equally energetically.

In spite of the collapse of this sulphonium salt by two equally favoured routes, this reaction with formaldehyde di-t-butyl dithioacetal constitutes the most efficient method found for the introduction of the 7*S*-t-butylthio-substituent (cf from di-t-butyl sulphide, 2.5%; from di-t-butyl disulphide, 0%; from 2-(t-butylthio)ethanethiol, 18%; from t-butyl ethyl disulphide, 9.5%).

The major interest in alkylations of dithioacetals by the activated epimine lay in cyclic dithioacetals. The derived cyclic sulphonium salt would be expected to collapse, assisted again by the mesomeric effect of the sulphide sulphur atom, to give the new acyclic methylenesulphonium salt [(**44**), Scheme 23]. If this could be quenched by nucleophilic attack of acetate ion, it would generate an ω-(acetoxymethylthio)alkylthio-derivative (**45**) which, as an ester of a hemithioacetal, should be hydrolysed to the ω-mercaptoalkylthio-substituent which is not available in general via the reaction with the corresponding ω-(alkylthio)alkanethiol.

In the reactions with formaldehyde dimethyl and di-t-butyl dithioacetals, the fate of the methylenesulphonium ions was not determined, and there was a question of whether the sulphonium ion would indeed be quenched by acetate ion as nucleophile. Meerwein *et al.*[35] have shown that methylmethylenesulphonium hexachloroantimonate, $[MeS^{+}{=}CH_2]SbCl_6^-$, reacts readily with dimethyl sulphide to give the dimethyl(methylthiomethyl)sulphonium salt, $[MeSCH_2S^{+}Me_2]SbCl_6^-$. In the Pummerer reaction, acetate ion similarly is the only nucleophile



(44) (45)

Scheme 23.

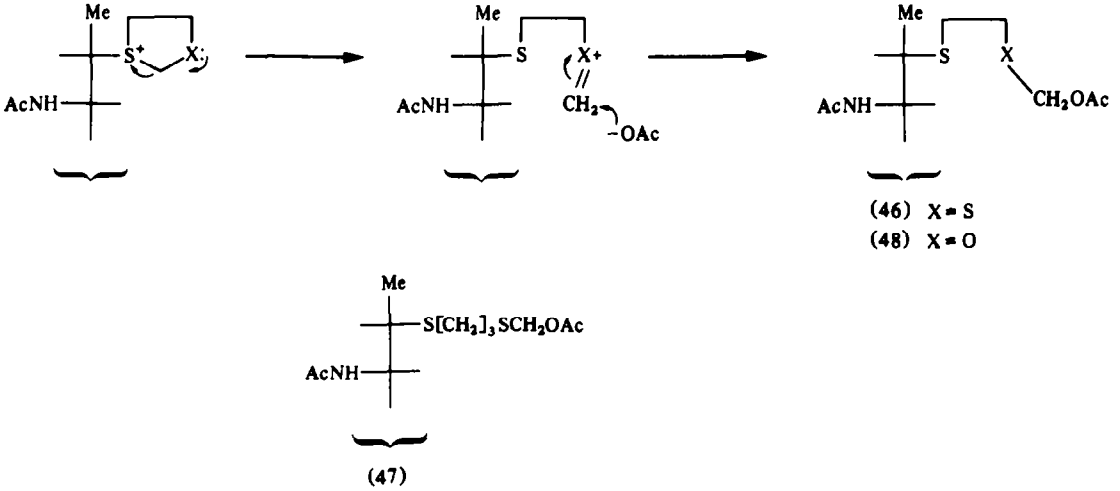
present by which the methylenesulphonium ion can be quenched, and it is present in large excess. In dimethylsulphoxide-acetic anhydride oxidations of alcohols, the formation of acetoxymethyl methyl sulphide as the Pummerer by-product always occurs; in those oxidations of alcohols in which the acetoxymethylthio-ether of the alcohol is formed, it is apparent that the alcohol and acetate ion compete as nucleophiles in the quenching of the methylenesulphonium ion. In the cyclic dithioacetal sequence, therefore, quenching of the methylenesulphonium salt by acetate ion would yield the desired acetoxymethylthio-derivative, but quenching by the large excess of cyclic dithioacetal would lead to product(s) useless in the present investigation.

In the event, reaction with 1,3-dithiolan gave the desired 2-(acetoxymethylthio)ethylthio-compound [(**46**), Scheme 24] in excellent yield. Similarly, the use of 1,3-dithian resulted in the formation in high yield of the 3-(acetoxymethylthio)propylthio-compound (**47**).

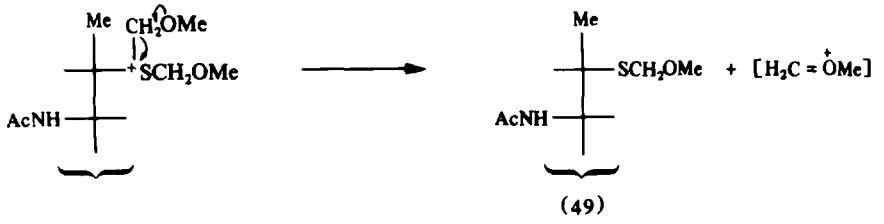
The relative rates of solvolysis of α-halogeno-sulphides and -ethers indicate that the stabilisation of the carbocationic center by oxygen is 10^2–10^3 times more efficient than by sulphur.[38] The corresponding alkylation of 1,3-oxathiolan by the activated epimine to generate the cyclic sulphonium salt would thus be expected to be followed by the even more ready generation of the acyclic oxonium salt which, on quenching by acetate ion, would yield the 2-(acetoxymethoxy)ethylthio-compound (**48**); this product was formed in excellent yield, and provided a much more efficient route to this acetate ester of the hemi-acetal derivative of the 2-hydroxyethylthio-compound (**19**) than resulted from the corresponding reaction with 2-hydroxyethyl methyl sulphide.

Reaction with acyclic methoxymethyl sulphides[30,39]

The same concept of assistance in the collapse of a sulphonium salt to a sulphide by the mesomeric effect of an oxygen substituent could be utilised in acyclic sulphides. For example, bis(methoxymethyl) sulphide gave the 7*S*-methoxymethylthio-derivative [(**49**), 63%] (Scheme 25). However, the nucleophilic reactivity of the methoxymethylthio-sulphur atom is lower than that of



Scheme 24.



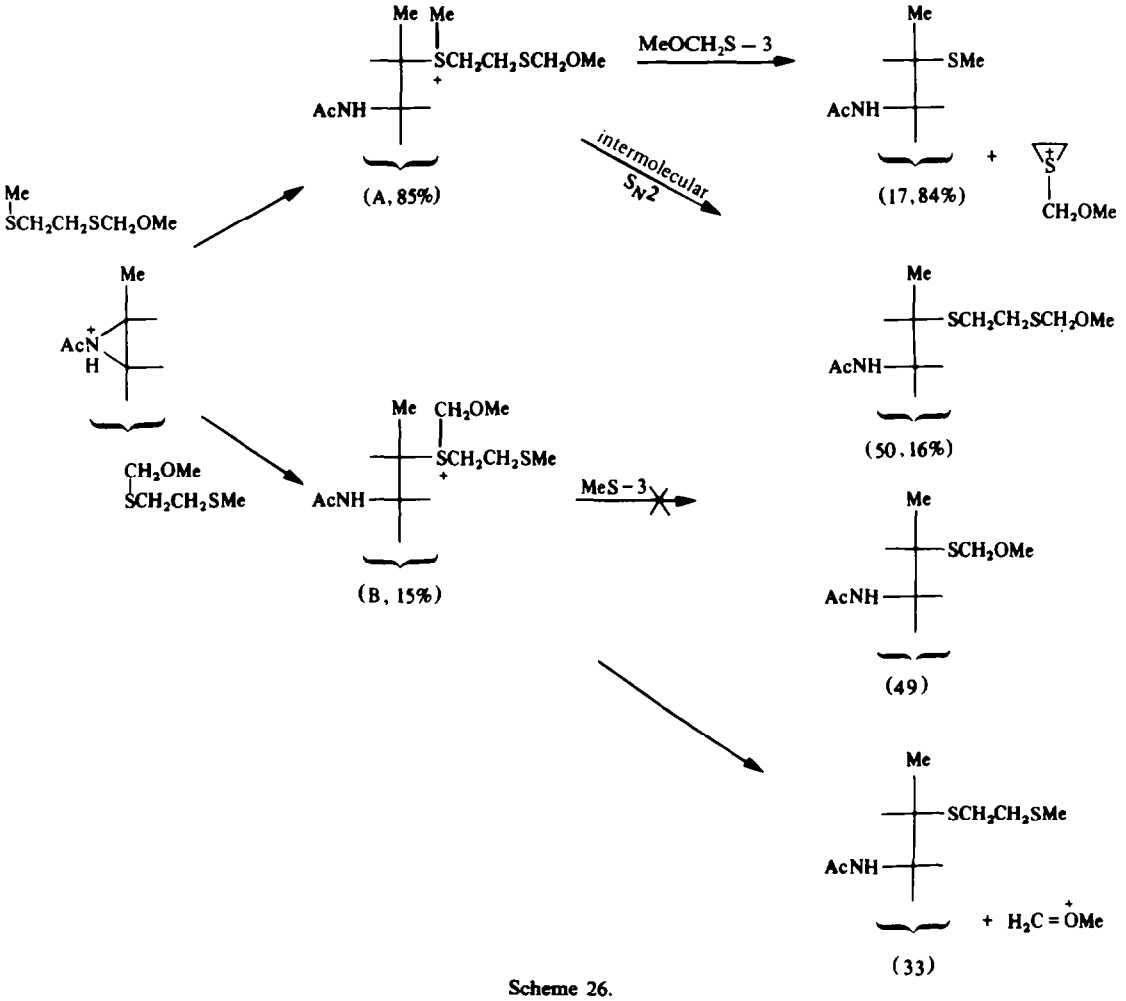
Scheme 25.

the methylthio-sulphur atom toward the initial alkylation by the activated epimine, as illustrated for the reaction with 1-methoxymethylthio-2-methylthioethane (Scheme 26).

From the formation of both (**17**) and (**50**) in the collapse of the ion (A), $MeOCH_2S$-3 participation is also seen to be considerably less efficient than MeS-3 participation using the reagent $MeSCH_2CH_2SMe$. Further, the collapse of the ion (B) to (**33**) with no indication of any MeS-3 participation to give (**49**), demonstrates the inefficiency of MeS-3 participation relative to the generation of the methyleneoxonium ion.

Relative nucleophilic reactivities of sulphides vs disulphides[39]

The literature[15] indicates that the rate of alkylation of a sulphide is about one hundred times greater than that of a disulphide. The reactions of both bis(methylthiomethyl) disulphide and bis(2-methylthioethyl) disulphide with the activated epimine demonstrated that the relative rates of alkylation of sulphide sulphur to disulphide sulphur are only approximately ten to one under



Scheme 26.

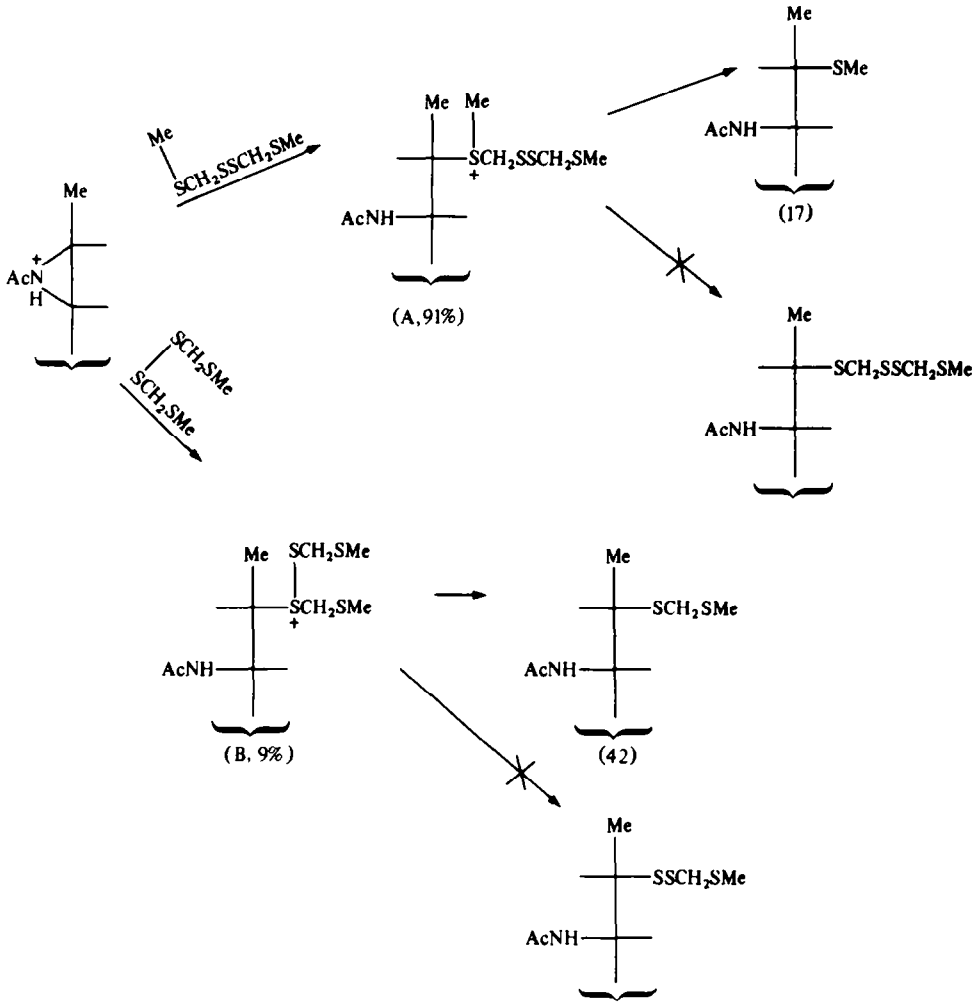
these conditions, but also gave further insight into the relative efficacies of the modes of collapse of sulphonium salts. The generation from ion [(A), Scheme 27] only of the methylthio-product (**17**) could be due to mesomeric assistance of collapse with the formation of $[CH_2 = \overset{+}{S}SCH_2SMe]$, to $MeSCH_2S$-3 participation, or to MeS-5 participation, but the formation from the ion (B) only of the methylthiomethylthio-derivative (**42**) is indicative, in a thiosulphonium salt, of the high reactivity toward nucleophilic attack of the sulphenyl sulphur atom's taking precedence over the ease of formation of the $[H_2C{=}\overset{+}{S}Me]$ ion.

The formation of twice as much (**51**) as of (**17**) from the ion [(A), Scheme 28] shows that $MeSCH_2CH_2SS$-3 participation is less efficient than MeS-3 participation (cf Scheme 13), while the formation of (**33**) and the absence of (**52**) from the collapse of ion (B) again shows that an unhindered sulphenyl sulphur atom of a thiosulphonium salt is extremely sensitive to nucleophilic attack, taking precedence over MeS-3 participation.

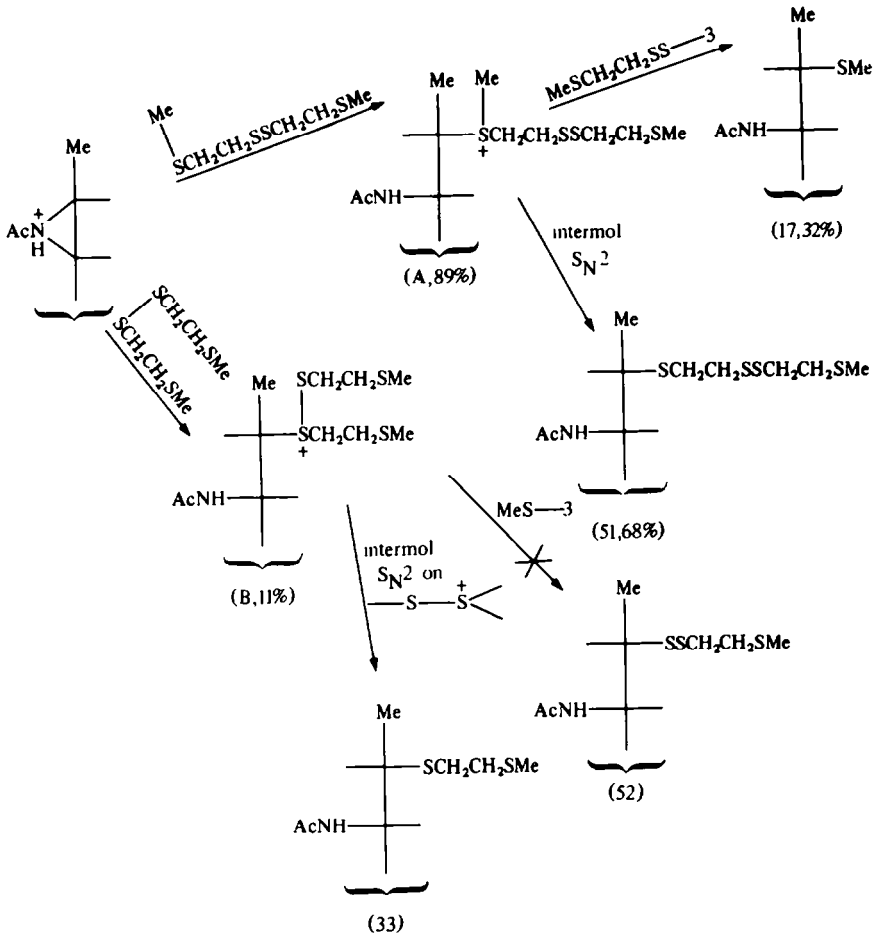
Relative efficacies of reactions involving MeS-3 and MeS-5 participation

In the section concerning the reaction of the activated epimine with α,ω-bis(methylthio)alkanes, the nature of the reaction products indicated that both MeS-3 and MeS-5 participation processes were efficient, with the MeS-3 somewhat favoured over the MeS-5 participation.

In the reaction between ω-halogenoalkyl sulphides and nucleophiles, the formation of the cyclic sulphonium salt has been found to be the rate-determining process, and this is followed by the rapid attack of the nucleophile to give the ring-opened product.[39,40] With ethyl ω-halogenoalkyl



Scheme 27.



Scheme 28.

sulphides, the rate of formation of the thiiranium salt is much less than that of the thiolanium salt, as shown by the inability[41] to isolate 4-chlorobutyl ethyl sulphide because of its ease of cyclisation.

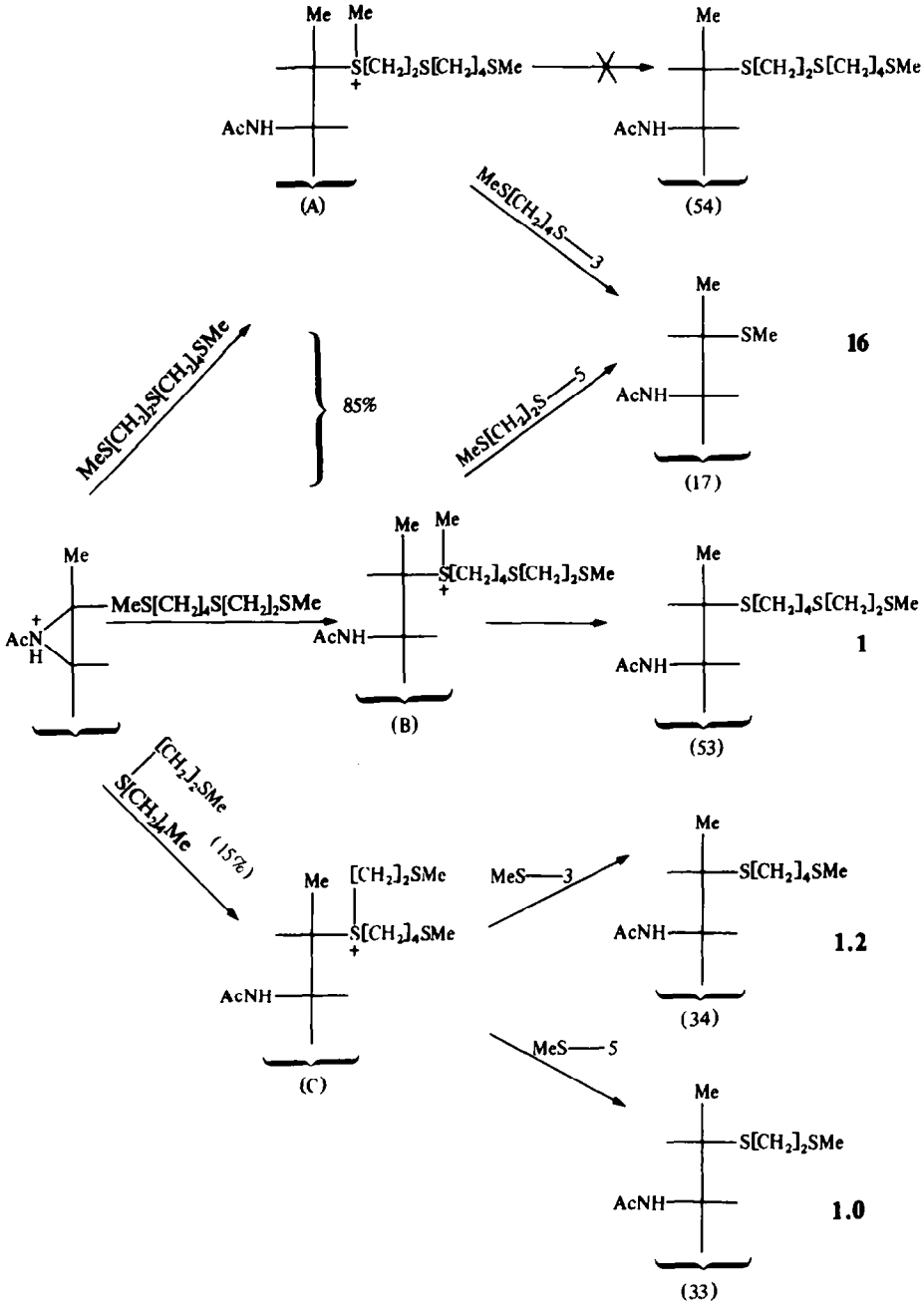
In view of the apparently equivalent efficacy of the MeS-3 and -5 participation processes in the present work, it was of interest to examine the fate of a sulphonium salt which could collapse by competitive MeS-3 and -5 participation. The reaction between the activated epimine and 2-methylthioethyl 4-methylthiobutyl sulphide is summarised in Scheme 29.

Although the formation of the 7-methylthio-compound (**17**) does not throw light on the relative efficacies of the participation processes by which this is formed from the ions (A) and (B), the formation of the tris-sulphide (**53**) and the lack of formation of the tris-sulphide (**54**) indicates that the $MeS[CH_2]_4S$-3 process from the ion (A) is more efficient than the $MeS[CH_2]_2S$-5 process from the ion (B). The products (**33**) and (**34**) formed by the collapse of the ion (C) again demonstrate clearly that the MeS-3 and MeS-5 processes are comparable in efficiency, with MeS-3 perhaps being favoured.

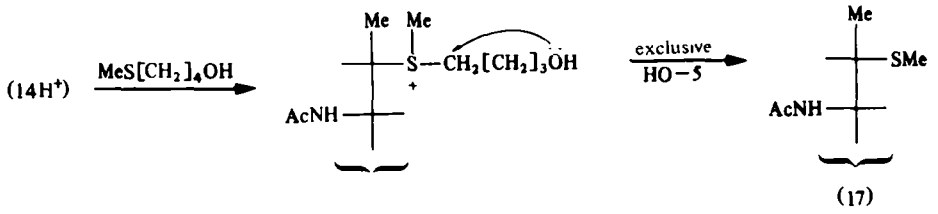
The balance between the enthalpy and entropy of activation must be considered in the ring-closure of 3- and 5-membered rings, the enthalpy term being unfavourable for the 3-membered ring, and the entropy term being unfavourable for the 5-membered ring.[40,42] Böhme and Sell[41] found that, in a study of ω-halogenoalkyl phenyl sulphides, and as opposed to the studies quoted above with ω-halogenoalkyl ethyl sulphides, the rate of closure to the 3-membered exceeds that to the 5-membered ring. Stirling and co-workers have suggested[43] that the magnitude of the unfavourable enthalpy term is decreased in a transition state, in which a significant degree of ring-formation is present, by the introduction into the molecule of a conjugative substituent which allows resonant interaction of the forming ring and that substituent, accelerating selectively the formation of the 3-membered ring. However, although the sulphonium ion may be considered to be such a

conjugative group during the formation of the transition state, it is also the leaving group in the reaction, and so cannot contribute to the enhanced stability of the product.

To further complicate the whole problem of neighbouring group participation, that of the hydroxy-group in the sulphonium salt intermediates is puzzling. The ratio of the ω-hydroxyalkylthio- (**19**) to methylthio- (**17**) products from the reagent 2-hydroxyethyl methyl sulphide, as pointed out earlier, is consistent entirely with intermolecular nucleophilic attack at the methyl and methylene positions α- to the sulphonium sulphur atom in the initial salt, and gives no indication of the involvement of hydroxy-group participation. However, in the corresponding reaction with 4-hydroxybutyl methyl sulphide (Scheme 30) only the product of HO-5 participation results. Comparisons of the rates of hydrolysis of ω-hydroxyalkyl chlorides in water, which indicate[40] that HO-5 participation exceeds HO-3 participation, are difficult because the basicity and nucleophilicity of the solvent are such that the rates of hydrolysis are high in the absence of



Scheme 29.



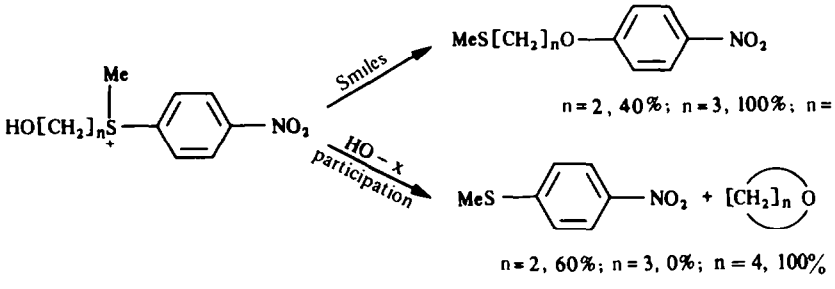
Scheme 30.

neighbouring group participation. In aqueous sodium hydroxide, the rate differences are small, but O^--3 anchimeric assistance is the greater.[44] In an examination of neighbouring group participation of the hydroxy-group in the Smiles rearrangement of (ω-hydroxyalkyl)methyl(*p*-nitrophenyl)-sulphonium perchlorates in aqueous alkali, Irie and Tanida[45] found the following (Scheme 31); although O^--3 and O^--5 participation resulted in the cleavage of the sulphonium salt to the *p*-methylthio-compound in both cases, the greater efficiency of the O^--5 participation prevented the occurrence of the Smiles rearrangement.

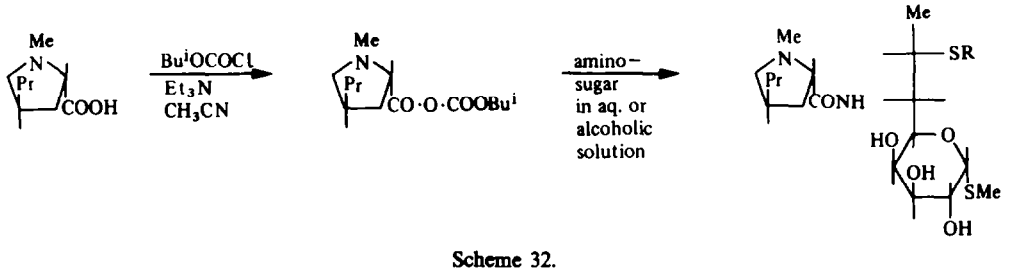
Conversion of the 7S-thio-substituted sugars into analogues of lincomycin

With few exceptions, all of the 7*S*-thio-substituted sugars obtained by the reactions mentioned were cleaved to the corresponding free amino-sugars by reaction with hydrazine hydrate under gentle reflux; this hydrazinolysis was necessary for the cleavage of the *N*-acetyl group. The free amino-sugars were condensed with 1-methyl-*trans*-4-propyl-L-proline, the amino acid fragment of lincomycin, via generation of the mixed anhydride from isobutyl chloroformate (Scheme 32). The products were purified as the free bases, and were converted into the hydrochlorides.

All of the analogues showed antibacterial activities at least equivalent to lincomycin both *in vitro* and *in vivo*. Most showed activity against Gram positive organisms of two to eight times that of the parent. The 7*S*-methylthio-, -(2-hydroxyethyl)thio-, and -(3-hydroxypropyl)thio-analogues also showed enhanced activity against certain Gram-negative organisms *in vitro*, but not at a level at which this activity was useful *in vivo*. The increase in potency of these analogues is ascribed to the increased ability of the analogues to enter the bacterial cell, resulting in higher concentrations of drug in the ribosomal environment. Differences of interest were also found in the extent of urinary excretion of the analogues, and in the degree of metabolism undergone *in vivo*;



Scheme 31.

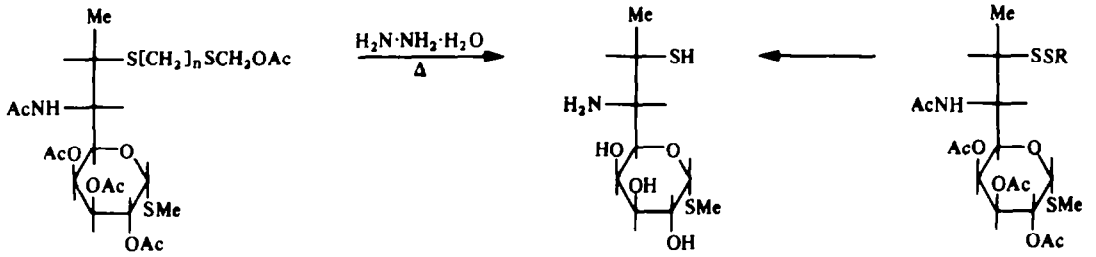


Scheme 32.

again, the presence of the 7*S*-(ω-hydroxyalkyl)thio-substituent decreased the extent to which de-*N*-methylation occurred.

The 7*S*-(dithioalkyl)-acetylated sugars could not be hydrazinolysed to the free amino-sugars, the disulphide linkage suffering reductive cleavage to the 7*S*-thiol amino-sugar (**55**) (Scheme 33). Remarkably, the compounds (**46**) and (**47**) yielded this same thio-substituted amino-sugar on hydrazinolysis. That this is a function of the generation of the free terminal thiol substituent is shown by the fact that the 7*S*-(2-alkylthio)ethylthio- and 7*S*-(2-benzylthio)ethylthio-acetylated sugars gave the expected amino-sugars on hydrazinolysis. Similarly, no cleavage of the 7*S*-thio-substituent to the 7*S*-thiol occurred with the corresponding 7*S*-(ω-hydroxyalkyl)thio-acetylated sugars.

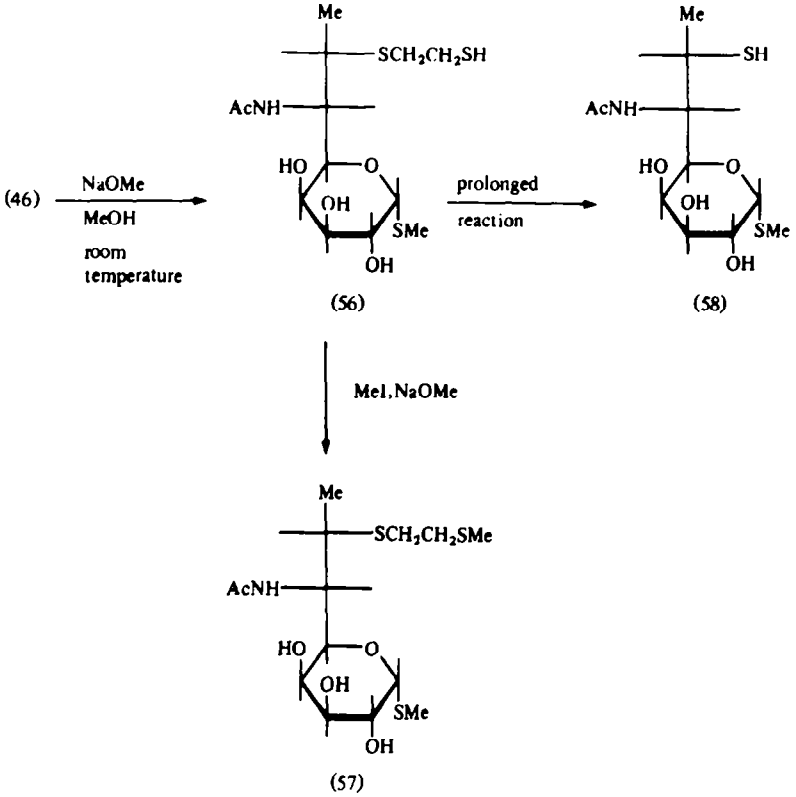
Zemplen de-esterification of the 7*S*-(2-acetoxymethylthioethyl)-thiotetra-acetate (**46**) in methanolic sodium methoxide generated rapidly the product (**56**) (Scheme 34), which was converted into (**57**) by methylation with methyl iodide. Indeed, this sequence presented the best method of introduction of this substituent, available otherwise, in low yield only, by the reaction of the



(**46**), n = 2
(**47**), n = 3

(**55**)

Scheme 33.



Scheme 34.

activated epimine with 2-methylthioethanethiol. If the base-catalysed hydrolysis of (**46**) were allowed to continue beyond the point of disappearance of starting material, a second product resulted, shown to be the thiol (**58**).

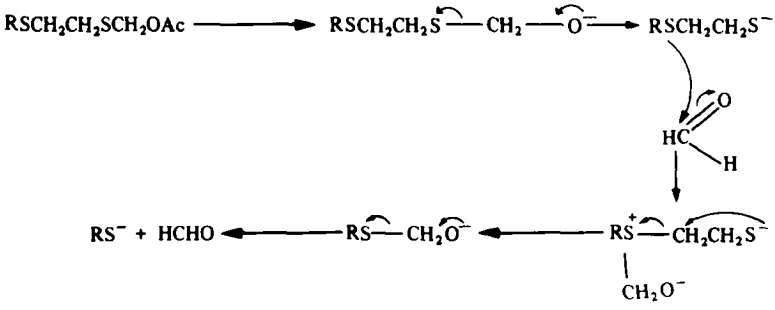
The nature of this cleavage of the $-SCH_2CH_2SH$ substituent to –SH, even under mildly basic conditions, is unknown. The apparently analogous compounds (2-methylthio)-[19,44] 2-(t-butylthio)-,[19] and 2-(benzylthio)- ethanethiols[19] are not degraded even under strongly basic conditions. In the hydrolysis of the 2-(acetoxymethylthio)ethylthio-derivative (**46**), formaldehyde is liberated, and it was considered that this might play the role indicated (Scheme 35) thus accounting for a ready S^--3 participation in a secondarily-formed sulphonium salt. However, no instability of 2-(methylthio)ethanethiol to base was found in the presence of added formaldehyde, and the instability of the corresponding sugar derivative remains unexplained.

Limitations of the nature of the acyl group in the activated epimine in reactions with sulphides for retention of stereospecificity

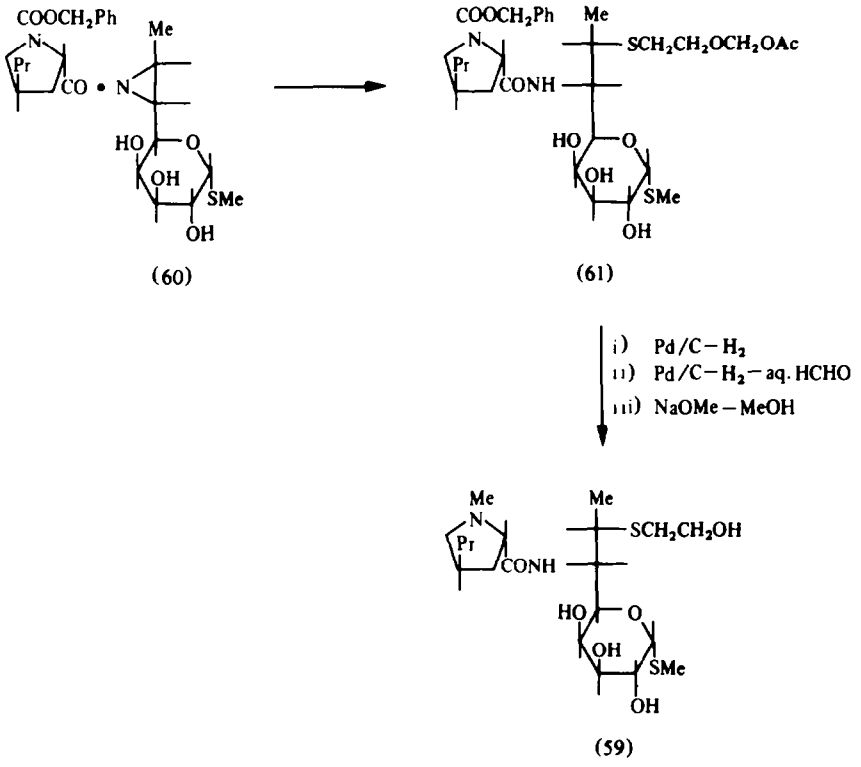
One of the analogues of major interest resulting from this investigation was the (7*S*)-7-deoxy-7-deoxy-7-(2-hydroxyethyl)thiolincomycin [(**59**), Scheme 36], derived, as indicated earlier, from the reaction between the acetylated epimine and 1,3-oxathiolan, followed by hydrazinolysis, and condensation of the free amino-sugar with 1-methyl-*trans*-4-propyl-L-proline. It was of interest, therefore, to see if an appropriate *N*-prolyl derivative of the epimine would serve as an activating group which need not be removed in the generation of the lincomycin analogue. Condensation of the epimine with 1-benzyloxycarbonyl-*trans*-4-propyl-L-proline by the mixed anhydride method gave the *N*-acyl derivative (**60**) which reacted with 1,3-oxathiolan and acetic acid to give the expected acetoxymethoxyethylthio-derivative (**61**). Hydrogenolytic removal of the benzyloxycarbonyl group, reductive methylation, and basic hydrolysis gave the desired product (**59**), isolated as the crystalline hydrochloride, identical with that obtained by the earlier route.

Since this protected proline derivative of the epimine functioned as desired, the possibility of using the 1-methyl-*trans*-4-propyl-L-proline itself in the same manner was examined. The *N*-propylprolylepimine underwent reaction with 1,3-oxathiolan–acetic acid, and mild hydrolysis of the acetoxymethoxy-product gave a syrupy free base, not distinguished by TLC or ^{1}H NMR spectrum (60 MHz) from the desired product, but the hydrochloride of which could be crystallized only in poor yield. The *in vitro* assay of unrecrystallised, lyophilised hydrochloride showed its antibacterial activity to be less than that of pure material. At 100 MHz, the ^{1}H NMR spectrum showed a doubling of the signals assigned to the 8-Me, SMe, SCH_2, OCH_2, and anomeric, protons. GC examination of the per-trifluoroacetylated free base showed it to be a 70:30 mixture of the required product and a second component, of longer retention time; both peaks gave identical fragmentation patterns by GC-MS.

Per-acetylation of the mixture of free bases, followed by extensive countercurrent distribution, gave an incomplete separation of the two components, but allowed the isolation of most of each as pure material. Zemplen de-esterification yielded the pure free base of the desired compound from the component of lower polarity; the minor component yielded a product of lower Gram positive antibacterial activity, and devoid of Gram negative activity. Hydrazinolysis of this material yielded an amorphous free amino-sugar, identified by its mass spectrum as containing the desired 7-(2-hydroxyethyl)thio-substituent which must, therefore, be of *R*-configuration.



Scheme 35.



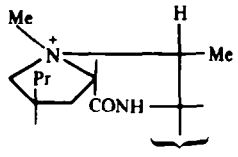
Scheme 36.

In no other case had there been found any 7*R*-product. The only difference between the reaction of the *N*-(1-methyl-*trans*-4-propyl-L-prolyl)epimine, and the reaction of the *N*-acetylepimine, and indeed, of the *N*-(1-benzyloxycarbonyl-*trans*-4-propyl-L-prolyl)epimine, with 1,3-oxathiolan, lies in the presence of a basic nitrogen function in the hygric acid derivative.

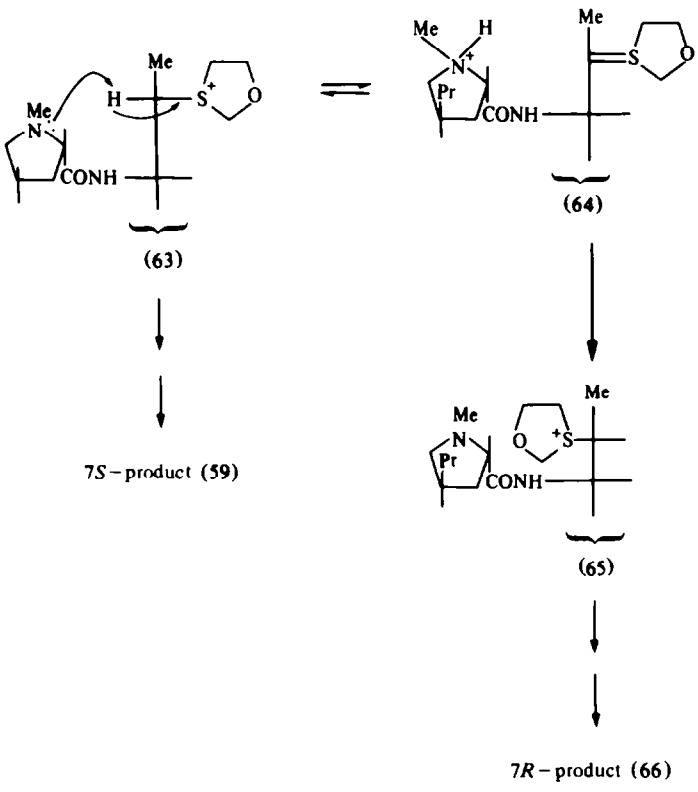
Competitive ring-opening of the activated epimine by this basic nitrogen atom would give the quaternary salt (**62**) in the 7*S*-configuration; nucleophilic attack by the 1,3-oxathiolan α- to the charged nitrogen function would then give the 7*R*-cyclic sulphonium salt (**65**), leading to the 7*R*-product (**66**). However, the transition state required for the formation of the cyclic quaternary ammonium ion (**62**), an endocyclic reaction, is five-membered, and affords another example of the disfavoured 5- to 6-*endo*-*tetrahedral* process.[27]

A preferred mechanism therefore (Scheme 37) is based on the ability of the basic prolyl nitrogen atom to remove the proton at C_7 of the initially-formed cyclic sulphonium salt (**63**) to give the ylide (**64**). Re-protonation of this ylide by the acetic acid present can occur from either side of the double bond to regenerate the original salt (**63**), from which will be derived the 7*S*-product (**59**), or to give the epimeric sulphonium salt (**65**), from which will be derived the 7*R*-product (**66**).

The stereospecificity of such reactions between acylepimines and sulphides would, therefore, be suspect if the acyl group contains a basic substituent, capable of generating an ylide from the initial sulphonium salt.



(62)



Scheme 37.

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