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.....PROPERTIES OF α-(ALKYLTHIO)ACETALS.....

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DEGREE.....Ph.D.....YEAR GRANTED.....1968.....

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TO MY PARENTS

THE UNIVERSITY OF ALBERTA

THE PREPARATION, STRUCTURES AND SOME PROPERTIES OF α-(ALKYLTHIO)ACETALS

by

© MICHAEL JOHN BALDWIN, B.Sc.

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

JULY, 1968

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled THE PREPARATION, STRUCTURES AND SOME PROPERTIES OF α-(ALKYLTHIO)ACETALS submitted by MICHAEL JOHN BALDWIN, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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Date July 4 1968

ABSTRACT

Nayak, Sharma and Brown have recently reported that treatment of three methyl S-alkyl-4,6-O-alkylidene-3-O-methyl-2-thio-α-D-altropyranosides with powdered sodium metal, or bases, in refluxing 1,2-dimethoxyethane afforded olefinic products which were formed as a result of loss of the elements of methanol from the parent carbohydrates. No such eliminations occurred in molecules which lacked the C-2 alkylthio function.

In order to investigate the generality of this type of elimination process the syntheses of a number of simple analogs of the above carbohydrates were undertaken. These compounds were subsequently subjected to reaction with sodium metal in 1,2-dimethoxyethane.

Alkyl β-benzylthioethyl ethers and acetals of benzylthioacetaldehyde gave high yields of unchanged starting materials under these conditions.

A series of 3-alkylthio-2-methoxytetrahydropyrans were synthesized by the addition of alkanesulfenyl chlorides to 3,4-dihydro-2H-pyran. The resulting unstable 3-alkylthio-2-chlorotetrahydropyrans were treated with methoxide ion. Analysis of the crude reaction products indicated that they contained a mixture of cis- and trans-3-alkylthio-2-methoxytetrahydropyran in which the trans isomer was predominant ($\geqslant$95%). Heat, or exposure to acids, caused isomerization with an increase in the relative amount of the cis isomer. Purification of the products by distillation resulted in partial or, in some cases, complete thermal decomposition to produce 5-alkylthio-

3,4-dihydro-2H-pyrans in good yield. The conformational preferences of the 3-alkylthio-2-methoxytetrahydropyrans are discussed. Treatment of these compounds with sodium metal in refluxing 1,2-dimethoxyethane afforded unchanged starting material only. Several attempts were made to synthesize tetrahydropyrano[2,3-b]-1,4-oxathiane, a model compound, which would be of assistance in determining the preference in conformations of the 3-alkylthio-2-methoxytetrahydropyrans.

A mechanism is proposed for the addition of ethanesulfenyl chloride to 3,4-dihydro-2H-pyran. The n.m.r. spectrum, at -40°, of the crude mixture obtained from the above reaction supported the view that the product was trans-2-chloro-3-ethylthiotetrahydropyran in the preferred conformation having both the halogen and the alkylthio group axially disposed. The possibility that there had been initial formation of 3-chloro-2-ethylthiotetrahydropyran followed by its rapid rearrangement to 2-chloro-3-ethylthiotetrahydropyran was ruled out because of the stability of the former to distillation under vacuum. 3-Chloro-2-ethylthiotetrahydropyran was obtained as a mixture of cis and trans isomers by the addition of ethanethiol to 5-chloro-3,4-dihydro-2H-pyran in the presence of sulfur dioxide. It reacted with ethanesulfenyl chloride to afford diethyl disulfide and 2,3-dichlortetrahydropyran only.

In order to investigate a previously reported acid-catalyzed addition of trichloromethanesulfenyl chloride to 2,3-dihydrofuran, this reaction was carried out in the presence and in the absence of a few

drops of concentrated hydrochloric acid. A vigorously exothermic reaction occurred in both cases. Trichloromethanesulfenyl chloride did not add to 3,4-dihydro-2H-pyran under either condition.

A number of attempts were made to synthesize 3-alkylthio-2,4-dimethoxytetrahydropyrans. Addition of ethanesulfenyl chloride to 2-methoxy-5,6-dihydro-2H-pyran afforded 4-chloro-3-ethylthio-2-methoxytetrahydropyran in the preferred conformation having the halogen, alkylthio group and methoxyl functions equatorially disposed. Displacement of the C-4 halogen by methoxide ion, or by methanol in the presence of silver carbonate, failed to yield the desired product.

A further synthetic route to 3-alkylthio-2,4-dimethoxytetrahydropyrans was based on the addition of alkanesulfenyl chlorides to 4-methoxy-3,4-dihydro-2H-pyran. Several attempts were made to synthesize the latter compound but all met with failure. Distillation of 2,4-dimethoxytetrahydropyran from both phosphorus pentoxide and p-toluenesulfonic acid afforded unchanged starting material and 2-methoxy-5,6-dihydro-2H-pyran respectively. Treatment of 2,4-dimethoxytetrahydropyran with n-butyl lithium also gave unchanged starting material. The reaction of 3-bromo-2,4-dimethoxytetrahydropyran with powdered zinc in ethanol afforded a mixture of unchanged starting material and 2-methoxy-5,6-dihydro-2H-pyran. Similar reaction of 3-bromo-2,4-dimethoxytetrahydropyran with sodium sand in benzene resulted in the isolation of starting material only. Pyrolysis of 2-acetoxy-4-methoxytetrahydropyran, prepared by

acetylation of 2-hydroxy-4-methoxytetrahydropyran, resulted in extensive decomposition and attempts to prepare the carbonate ester of 2-hydroxy-4-methoxytetrahydropyran, and 2-chloro-4-methoxytetrahydropyran also met with failure. The conformational preferences of 3-bromo-2,4-dimethoxytetrahydropyran and 2-hydroxy-4-methoxytetrahydropyran are discussed.

The syntheses of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-α-D-altropyranoside and its β-anomer are reported. Treatment of these compounds and also methyl 4,6-O-ethylidene-3-O,S-dimethyl-2-thio-β-D-altropyranoside with sodium metal in refluxing 1,2-dimethoxyethane failed to yield olefinic products but afforded nearly quantitative recovery of unchanged starting materials. Reaction of the above carbohydrates along with methyl S-benzyl-4,6-O-benzylidene-3-O-methyl-2-thio-α-D-altropyranoside and methyl 4,6-O-ethylidene-3-O,S-dimethyl-2-thio-α-D-altropyranoside with sodium methoxide in d_1-methanol resulted in no deuterium incorporation and no production of olefinic materials. On the basis of the above data a mechanism is proposed to account for the results observed by Nayak, Sharma and Brown.

ACKNOWLEDGEMENTS

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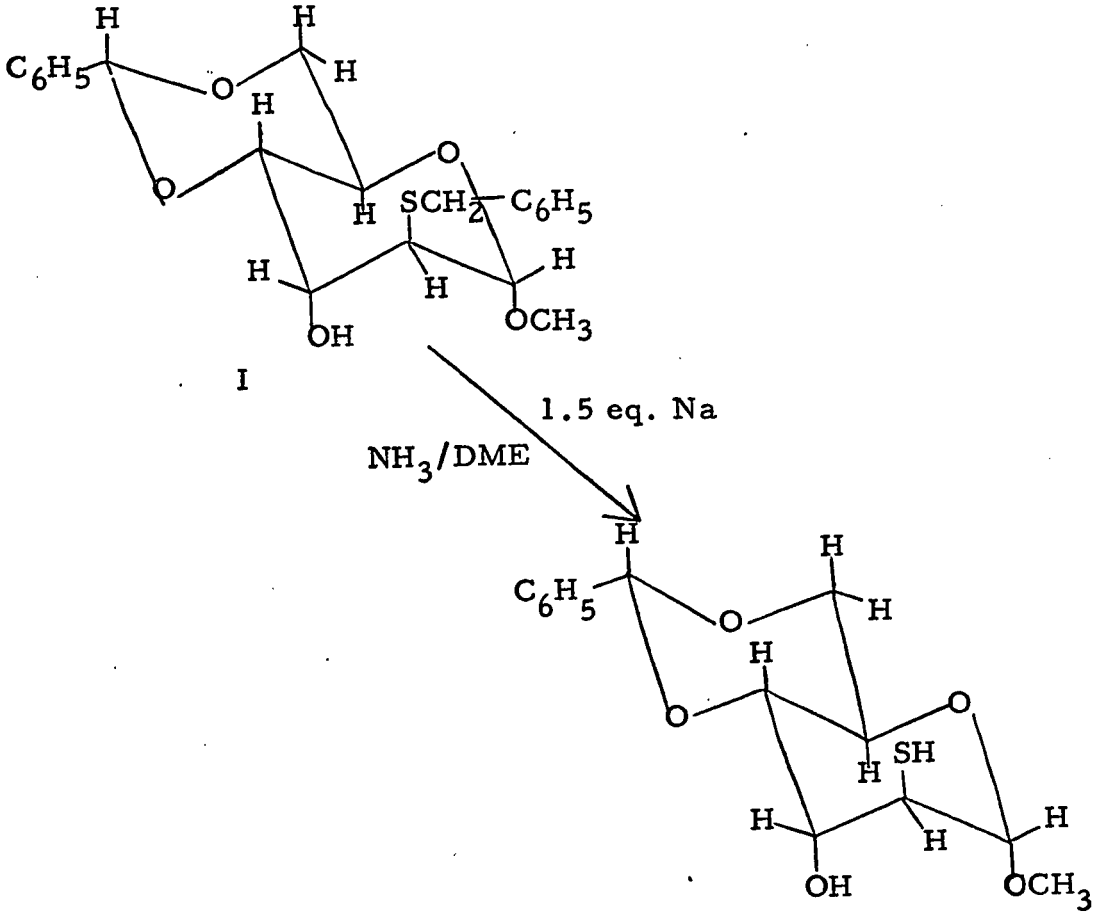
INTRODUCTION

A. THE PROBLEM

Nayak and Brown (1) recently reported the selective reductive cleavage of the benzylthio C-S bond in the presence of the benzylidenedioxy C-O bond of methyl S-benzyl-4,6-O-benzylidene-2-thio-α-D-altropyranoside (I) (Chart 1). Treatment of I with 1.5 equivalents of sodium metal in a mixture of liquid ammonia and 1,2-dimethoxyethane (DME), 6:5 v/v, afforded a 71% yield of methyl 4,6-O-benzylidene-2-thio-α-D-altropyranoside (II).



I II

CHART 1

Subjection of methyl S-benzyl-4,6-O-benzylidene-3-O-methyl-2-thio-α-D-altropyranoside (III) to similar reaction conditions (2)

yielded, not the expected methyl 4,6-O-benzylidene-3-O-methyl-2-thio-α-D-altropyranoside (IV), but rather a mixture of three olefinic products (Chart 2).

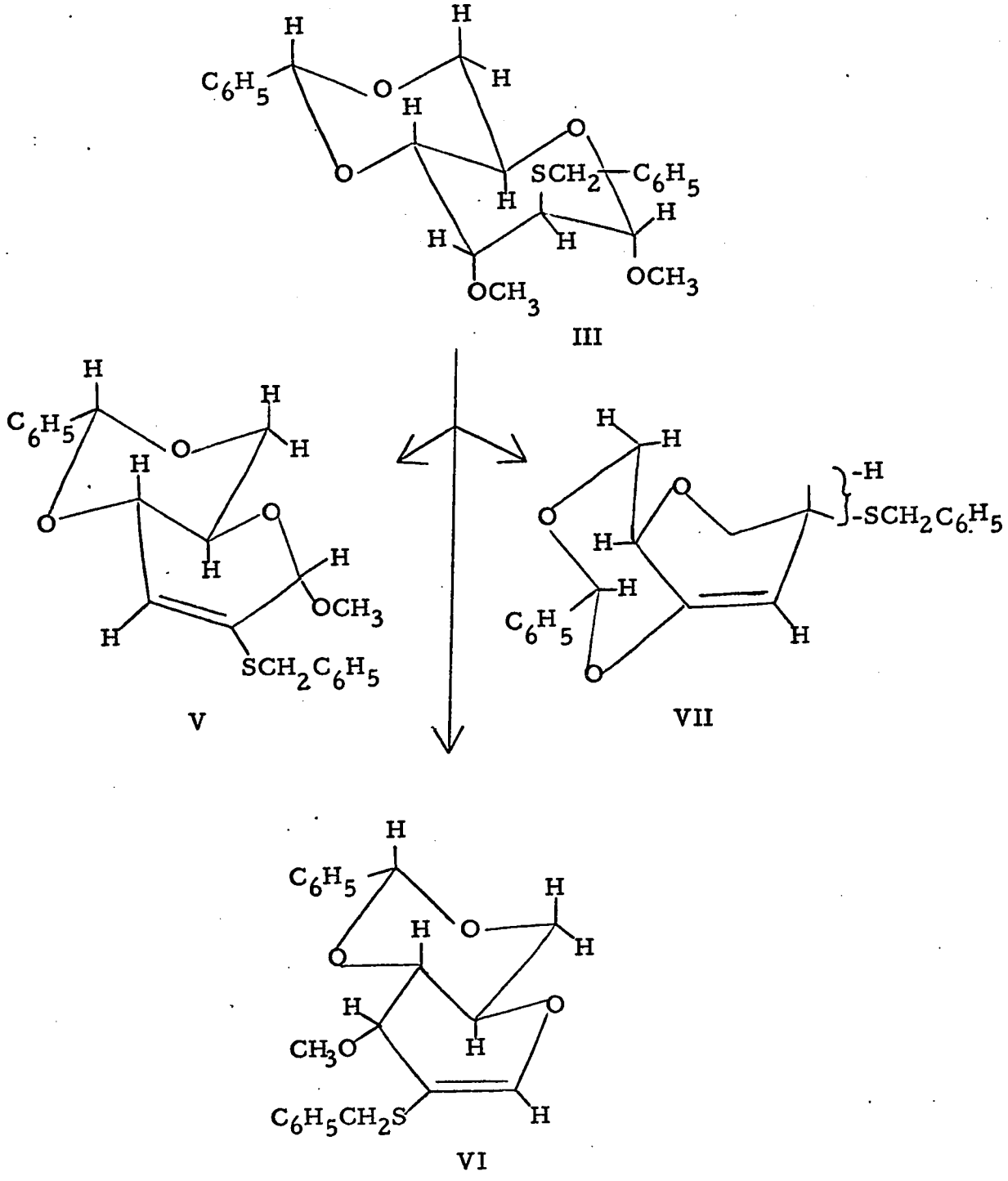


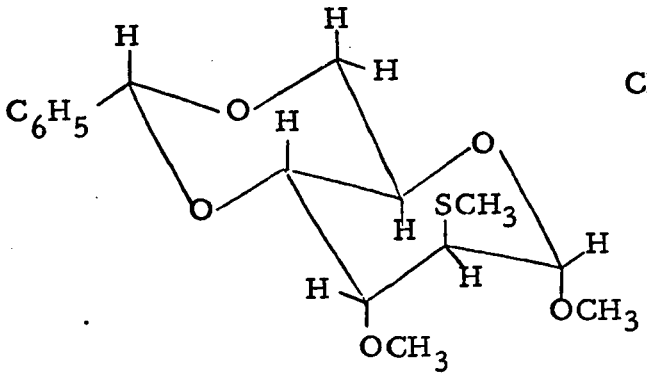
CHART 2

Two of these were identified as methyl S-benzyl-4,6-O-benzylidene-2,3-didehydro-3-deoxy-2-thio-α-D-erythro-hexopyranoside (V) and S-benzyl-4,6-O-benzylidene-1,2-didehydro-1-deoxy-3-O-methyl-2-thio-D-ribo-hexopyranose (VI). Positive identification of the third product proved impossible. Structure VII was proposed on the basis that desulfurization of VII (contaminated with V) with deactivated Raney Nickel gave a mixture of methyl 4,6-O-benzylidene-3,4-didehydro-2,3-dideoxy-α-D-glycero-hexopyranoside and methyl 4,6-O-benzylidene-2,3-didehydro-2,3-dideoxy-α-D-erythro-hexopyranoside.

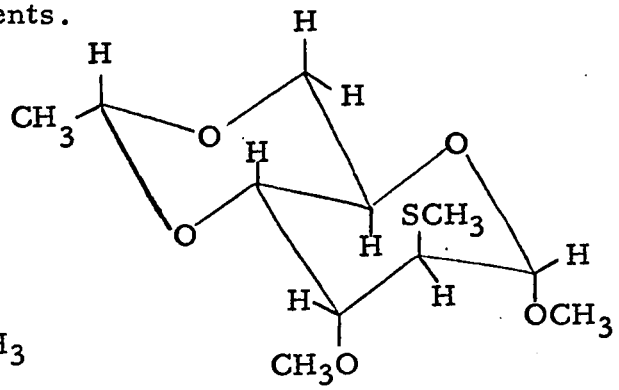
Similar results were obtained if III was treated either with one equivalent of sodium metal in refluxing DME alone, or with a variety of bases in DME.

It is thus apparent that in the case of III, elimination of methanol, rather than reductive cleavage of the C-S bond is preferred.

Further work by Nayak, Sharma and Brown (2,3) showed that methyl 4,6-O-benzylidene-3-O,S-dimethyl-2-thio-α-D-altropyranoside (VIII) and methyl 4,6-O-ethylidene-3-O,S-dimethyl-2-thio-α-D-altropyranoside (IX) also underwent similar elimination reactions on treatment with either of the above reagents.



VIII



IX

The objectives of the current investigation were:

(i) to subject a number of model compounds of the sugars III, VIII and IX to treatment with sodium metal in refluxing DME in an attempt to discover the generality of the observed elimination reactions and the factors which control such a reaction. For such a study, the syntheses of a number of β-alkylthioethyl ethers, alkylthioacetaldehyde acetals and simple pyran analogs of the sugars would be necessary.

(ii) to prepare a β-analog of the sugars III, VIII and IX for treatment with sodium in DME to determine whether 1,3-diaxial interaction present in the α-anomers had a bearing on the base catalyzed elimination observed.

B. LITERATURE SURVEY

It was felt necessary to review the available information concerning the cleavage of sulfides by alkali metals in both liquid ammonia and ethereal solvents, as well as that on elimination reactions involving loss of a leaving group β to a sulfur atom. Such information might be of assistance in the understanding of the problem in general.

1. THE CLEAVAGE OF C-S BONDS BY ALKALI METALS IN LIQUID AMMONIA

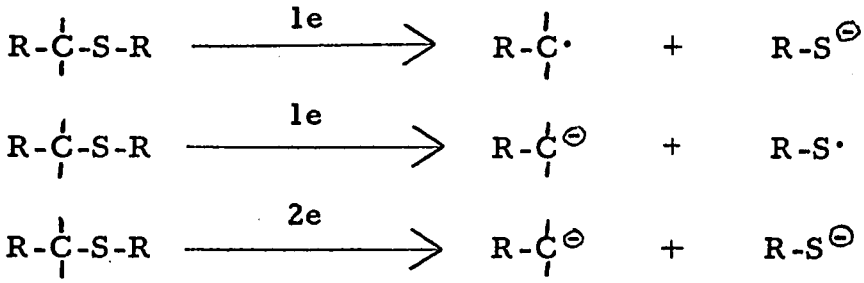
(a) The nature of the reducing species

It is well known that solutions of sodium metal in liquid ammonia display a blue coloration, conduct electricity and deposit the metal unchanged on evaporation of the solvent (4). The conductivity data of Kraus (5) and magnetic susceptibility measurements of Freed (6) and Huster (7) showed the presence of paired and unpaired electrons in solution. A number of solution theories have been proposed to explain the rapidly expanding volume of physical data obtained from such solutions (8-10) but will not be considered here.

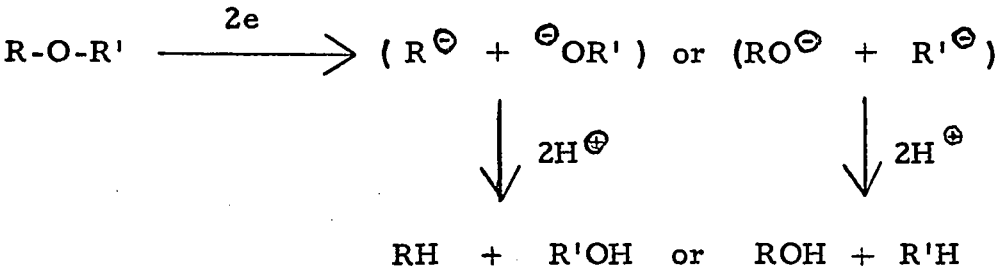
For the purposes of a reduction mechanism it is sufficient to employ the generally accepted premise that solutions of sodium in liquid ammonia contain solvated electrons which, during the reduction process, are donated to the reducible molecule. Birch (11)

differentiates two types of reduction process in which the rate determining step is either a one electron or a two electron addition. A one electron addition process would lead to the formation of an anion-radical or an anion and a radical, whereas a two electron addition would yield a di-anion or two anions.

Thus for the reductive cleavage of a carbon-sulfur bond three mechanistic possibilities arise whose rate determining steps are as follows:



Birch favors the initial production of two anions because of the comparison of sulfide cleavage with the cleavage of ethers. In the fission of ethers by such a process the direction will be decided by the transition state which has the lower energy.



Since RH is generally a much weaker acid than ROH, then the greater part of the energy will be required to form the carbanion $R^{\ominus}$ or $R'^{\ominus}$. In a particular series the R group containing electron

attracting groups (which would stabilize a carbanion) should appear as RH if in fact anions are intermediates. Experimentally this is found to be the case. Reduction of propylene oxide yields 2-propanol (12). Reaction proceeded via formation of the more stable primary carbanion. Similarly, the cleavage of a number of substituted di-aryl ethers led to phenolic products whose formation was compatible with di-anion intermediates (13-15).

(b) Carbon-sulfur bond cleavage in simple aliphatic and aromatic systems

The first published report of the cleavage of a carbon-sulfur bond by sodium in liquid ammonia appeared in 1923 when Kraus and White (16) treated diphenyl sulfide with two equivalents of the metal and obtained benzene and sodium sulfide as sole products.

Eight years later, Williams and Gebauer-Fülnegg (17) repeated this work but, even after several attempts, were unable to duplicate the results. In their hands the reaction yielded thiophenol and aniline only. They further showed that simple aliphatic sulfides are cleaved by an excess of sodium in liquid ammonia affording mercaptans and alkanes. n-Propyl sulfide gave high yields of propane and sodium n-propyl mercaptide. Corresponding results were obtained with ethyl and n-heptyl sulfides. On the basis of these results the authors proposed the following overall stoichiometry for the reduction process.

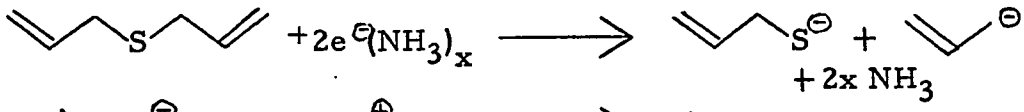
$$R_2S + 2\,Na + NH_3 \longrightarrow RSNa + NaNH_2 + RH$$

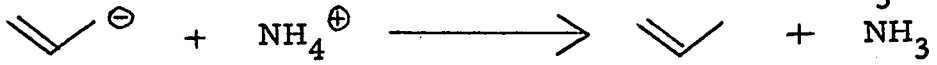
R = alkyl

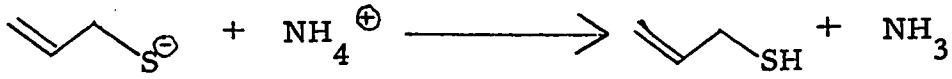
Treatment of ethyl, n-propyl and isoamyl disulfides under similar reaction conditions gave almost quantitative yields of the corresponding sodium alkyl mercaptides only, indicating the greater ease of cleavage of the S-S versus the C-S bond.

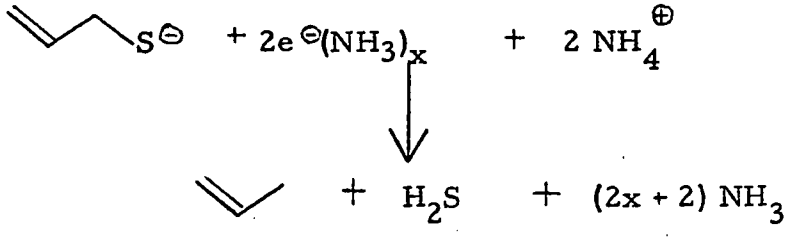
In 1954, Krug and Tocker (18) studied the effects of different metal ammonia systems on the C-S bond. In the presence of ammonium sulfate as a proton source and with two equivalents of sodium they found that n-propyl, n-butyl and n-hexyl sulfides remained unchanged, whereas if lithium replaced sodium, reduction did occur, giving low yields of alkyl mercaptans. In contrast to these observations, allyl sulfide was found to reduce almost completely in the presence of either sodium or lithium metals and ammonium sulfate yielding allyl mercaptan and small amounts of hydrogen sulfide. They proposed the following equations to explain their observations.

1. $M + x\ NH_3 \longrightarrow M^{\oplus} + e^{\ominus}(NH_3)_x$

2. 

3. 

4. 

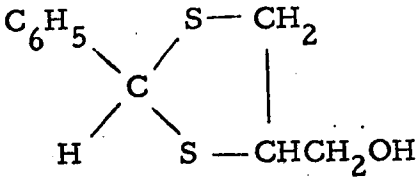
5. 

The greater stability of the allyl carbanion compared to that of the n-propyl, n-butyl or n-hexyl carbanions could account for the facile cleavage of allyl sulfide.

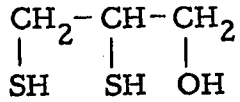
The high reactivity of allyl sulfides is parallelled by that of benzyl sulfides. Hesse and Jörder (19) report the synthesis of mercaptoacetaldehyde diethylacetal by reaction of bromoacetaldehyde diethylacetal with sodium benzyl mercaptide, and subsequent cleavage of the benzylthio C-S bond by sodium in liquid ammonia. The wide application of the benzyl group to protect mercaptans in natural product syntheses is discussed later (p. 14).

Adams and Ferretti (20) took advantage of the facile cleavage of aryl ethyl sulfides in the preparation of a number of di- and trimercaptoaromatic compounds. As an example, p-diethylmercaptobenzene was reduced by four equivalents of sodium in liquid ammonia to yield 1,4-dimercaptobenzene (98%).

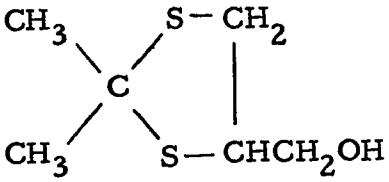
In 1966 Brown, Iqbal and Owen (21) carried out a more comprehensive study on the reductive fission of methyl sulfides, 1,3-dithiolanes and a 1,3-oxathiolane. Their interest had been aroused by the fact that sodium-liquid ammonia reduction of 2-phenyl-4-hydroxymethyl-1,3-dithiolane (X) gave high yields of 2,3-dimercaptopropanol (XI) (22), whereas 2,2-dimethyl-4-hydroxymethyl-1,3-dithiolane (XII), on similar treatment, yielded a mixture of 3-mercapto-2-isopropylthiopropanol-1 (XIII) and 2-mercapto-3-isopropylthiopropanol-1 (XIV) (23).



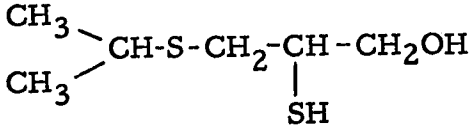
X



XI



XII



XIV

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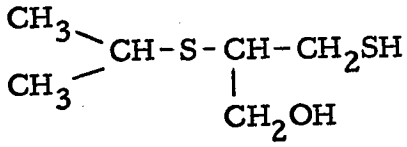
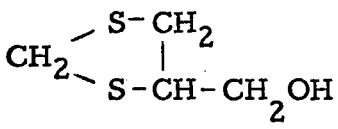
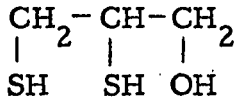
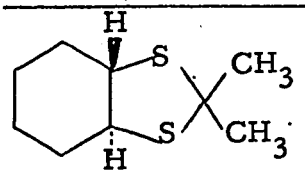
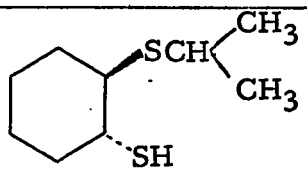
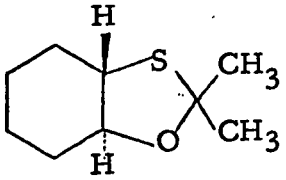
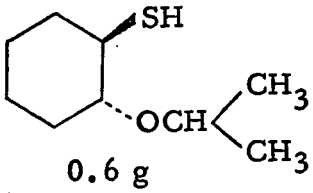
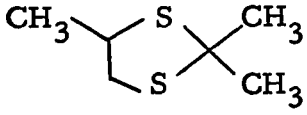
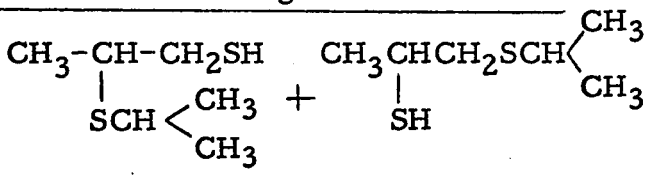


XIII

They also felt that the earlier work of Williams and Gebauer-Fülnegg (17) and of Krug and Tocker (18) was not dependable since products were not adequately analyzed or characterized. They, therefore, subjected a number of 2,2-dimethyldithiolanes and 2-alkylthioethanols to reductive cleavage. The results obtained are shown in Table 1. The fact that 2,3-dimercaptopropanol could be regenerated from its S,S-methylene derivative, but not from its S,S-isopropylidene derivative was explained by the difference in stability of the respective intermediate carbanions. In the series of 2-alkylthioethanols studied, only the methylthio- compound was cleaved. The isopropylidene derivatives of cyclohexane-trans-1,2-dithiol, 2-mercaptocyclohexanol and propane-1,2-dithiol gave, respectively trans-2-isopropylthiocyclohexanethiol, trans-2-isopropoxycyclo-

TABLE I *

Substrate	Products
 5.1 g	 2.8 g
 2.7 g	 1.2 g
 2.1 g	 0.6 g
 2.7 g	 1.1 g
$CH_3SCH_2CH_2OH$ 2.6 g	$HSCH_2CH_2OH$ 0.95 g
$CH_3CH_2SCH_2CH_2OH$	unchanged + trace of $HSCH_2CH_2OH$
$(CH_3)_2CHSCH_2CH_2OH$	no reaction
$CH_3SCH_2CH_2SCH_3$ 2.1 g	$HSCH_2CH_2SH$ 0.9 g

* Taken from reference 21

hexanethiol, and a mixture of 2-isopropylthiopropanethiol-1 and 1-isopropylthiopropanethiol-2 on reductive cleavage. In contrast to the last example, the partial cleavage of the isopropylidene derivative of 2,3-dimercaptopropanol occurred only in one direction, to give 2-isopropylthio-3-mercaptopropanol.

Assuming that cleavage proceeded via the generally accepted mechanism (11) to form an alkyl carbanion and a mercaptide ion as initial fragments, they concluded that the special lability of methyl and benzyl sulfides must be due to the relatively good stabilities of the methyl and benzyl carbanions, which must require less energy for their formation than would be necessary for an ethyl or isopropyl carbanion. This would also account for the observed direction of sulfide fission. They suggested that the oxathiolane underwent preferential fission of the C-S bond in $\begin{matrix}CH_3\\CH_3\end{matrix}>CH-S$ since the developing negative charge is accommodated better by the sulfur atom than by the oxygen atom.

Pinder and Smith (24) had previously reported that 2-methyl-2-phenyl-1,3-oxathiolane, on treatment with an excess of sodium metal in liquid ammonia containing ether as cosolvent and methanol as a proton source, yielded ethylbenzene as sole product. Although Brown and coworkers (21) make no reference to this work it is readily explained since the cleavage of benzyl ethers by sodium and liquid ammonia is a well known reaction (25, and references cited therein).

(c) Carbon-sulfur bond cleavage in natural product syntheses

The observation, in 1935, by Sifferd and du Vigneaud (26) that the benzylthio C-S bond could be readily cleaved by sodium in liquid ammonia has led to the extensive use of the benzyl group as a protecting group for mercaptans in natural product syntheses, especially those of sulfur-containing amino acids and peptides (25a, and references cited therein). A considerable volume of work has been published by du Vigneaud and coworkers who have used the method in the synthesis of homocystine (27), glutathione (28), isoglutathione (29) and more recently the cyclic polypeptide oxytocin (30, 31).

Tarbell and Harnish (32) have reviewed a variety of methods for the cleavage of a carbon-sulfur bond.

2. THE CLEAVAGE OF CARBON-SULFUR BONDS BY ALKALI METALS IN ETHERS

(a) The nature of solutions of alkali metals in ethers

In 1959, Cafasso and Sundheim (33, 34) studied the properties of solutions of the alkali metals in DME. The solvent, after purification by an exhaustive distillation and drying procedure, was distilled into vessels containing freshly condensed alkali metal mirrors. Potassium, rubidium and caesium gave blue colored solutions whose physical properties resembled those of the corresponding metal-ammonia systems. Sodium, however, proved to be

insoluble.

The latter observation was confirmed by Down and coworkers (35) who obtained blue colored solutions of potassium and potassium-sodium alloy in DME, but found that sodium, lithium and calcium were insoluble. Slough and Ubbelohde (36) had reported earlier that a suspension of sodium metal in DME survived ultrasonic irradiation unchanged.

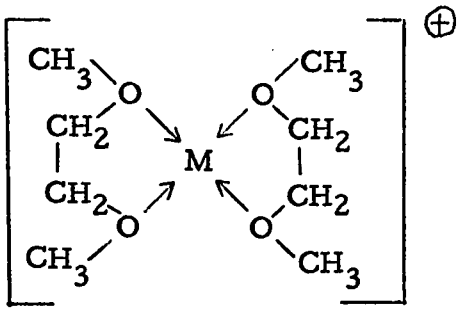
However, in 1964, Petrov and coworkers (37) found that if "very pure reagents" were used, both sodium and lithium would dissolve in DME to give blue solutions having an absorption maximum at 705 mμ. Unfortunately no experimental details were given to clarify what they meant by "very pure reagents".

In a study on the metalation and methylation of indene, Bosch (38) refluxed potassium metal in DME for periods of 3, 16.5 and 36 hours. After removal of unreacted metal by filtration, the residual liquid was refluxed with indene for one hour, then cooled and treated with an excess of methyl iodide. Work-up of the reaction mixture showed the product to contain 1-methylindene (2%) and indene (98%).

He further noted that after 16.5 hours of reflux, the mixture of metal and DME developed a small amount of sludge. After 36 hours of reflux a considerable amount of sludge accumulated. When this was isolated it proved to be strongly basic. The presence of such alkaline material was thought to account for the formation of the 1-methylindene under these conditions.

A similar alkylation experiment with lithium metal in refluxing DME indicated that methyl indenes were absent. The inference made was that lithium metal and DME do not react to form basic substances.

A large number of organometallic reactions involving the use of sodium in DME have been reported in the literature (39, and references cited therein). The efficacy of this solvent has been attributed (40) to its strong donor character, thereby reducing the energy of the metal ion by solvation.

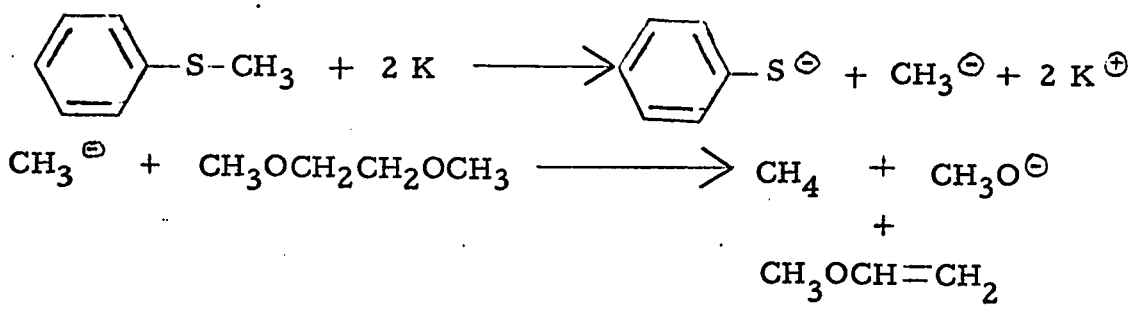


Agami has recently reviewed many aspects of the chemistry of DME extensively (40a).

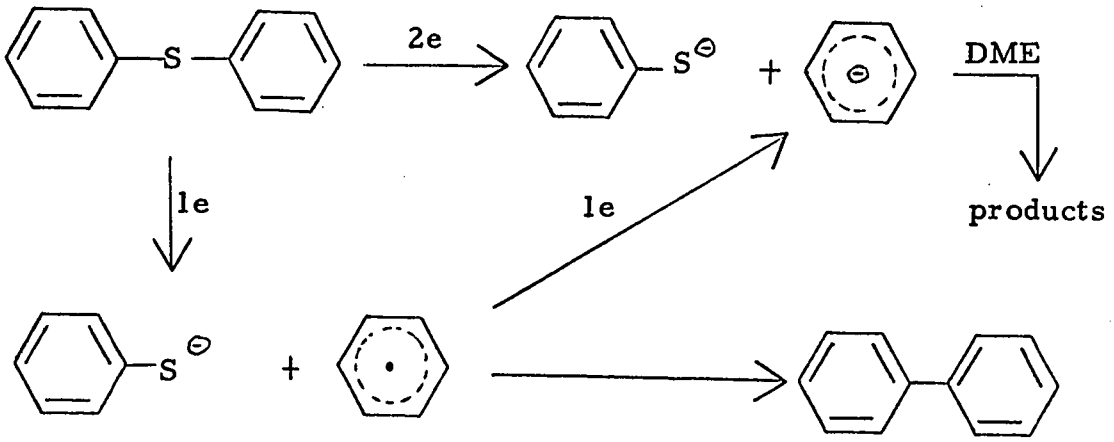
(b) Cleavage of simple aliphatic and aromatic sulfides

Little work has been reported to date on the cleavage of sulfides in ethereal solvents. Moses and Reid (41) showed that alkyl sulfides underwent little change on standing with sodium metal in dry diethyl ether for up to three months. Disulfides, however, were cleaved readily to yield mercaptans, with the exception of benzyl disulfide which in diethyl ether was cleaved extremely slowly even after standing in contact with the metal for several months.

In a series of papers Gerdil and Lucken (42-44) studied the cleavage of sulfides by potassium metal in DME. Methyl phenyl sulfide yielded, after hydrolysis of the reaction mixture, methane, vinyl methyl ether, benzenethiol, methanol, potassium hydroxide and trace amounts of ethylene. The following mechanistic route was proposed.



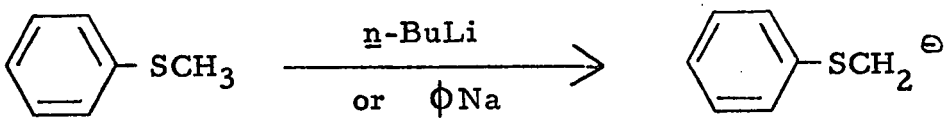
Diphenyl sulfide gave near quantitative yields of benzene and benzenethiol, along with a small amount of biphenyl. The latter was rationalized as arising via an initial one electron donation to the sulfide.



Finally, benzyl phenyl sulfide yielded mainly toluene and

benzenethiol, along with smaller quantitites of benzyl mercaptan, benzene and hydrogen sulfide.

Gilman and Webb (45) showed that treatment of methyl phenyl sulfide with one equivalent of sodium metal in diethyl ether at room temperature for 18 hours gave a 21% yield of thiophenol. Corresponding reactions using butyl lithium and phenyl sodium as metallating agents gave exclusive lateral metallation.

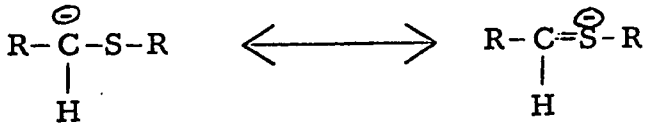


3. THE PREPARATION OF α,β-UNSATURATED SULFIDES VIA ELIMINATION REACTIONS

Comparatively few reports have appeared in which a base catalyzed proton abstraction from carbon adjacent to sulfur has led, via subsequent loss of a β-situated leaving group, to the production of α,β-unsaturated sulfides.

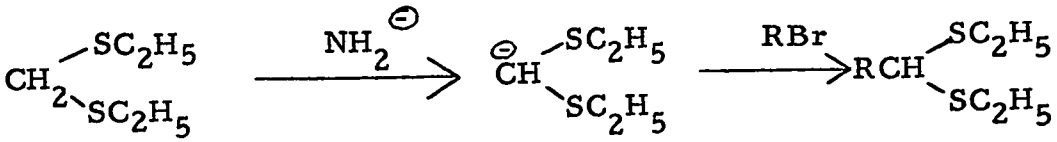
Nevertheless, the greater stability of a negative charge on carbon adjacent to sulfur, as opposed to a similar charge on carbon adjacent to oxygen, is a recognized fact and is demonstrated by the deuterium exchange experiments of Oae and coworkers (46). Treatment of α-deuteromercaptals and α-deuteroorthothioformates with either sodium ethoxide in ethanol or potassium t-butoxide in t-butyl alcohol resulted in facile exchange of hydrogen for deuterium, whereas the corresponding oxygen analogs underwent no exchange. Under more vigorous conditions the latter compounds experienced

considerable decomposition. These observations were attributed to the greater stability of the carbanion formed in the sulfur-containing compounds during the exchange process. Such stability is caused by the ability of sulfur to accept an electron pair into its 3d orbitals, thus giving rise to the following resonance structures.

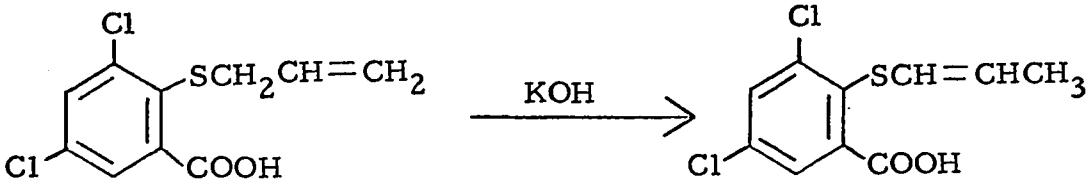


Such a possibility is not present in the case of oxygen.

Arens and coworkers (47, and references cited therein) have utilized such carbanion stabilization by sulfur in synthetic work. For example, when treated with sodamide in liquid ammonia, formaldehyde diethylthioacetal loses a proton and the resulting carbanion easily reacts with an alkyl bromide to yield the diethylthioacetal of a higher aldehyde.

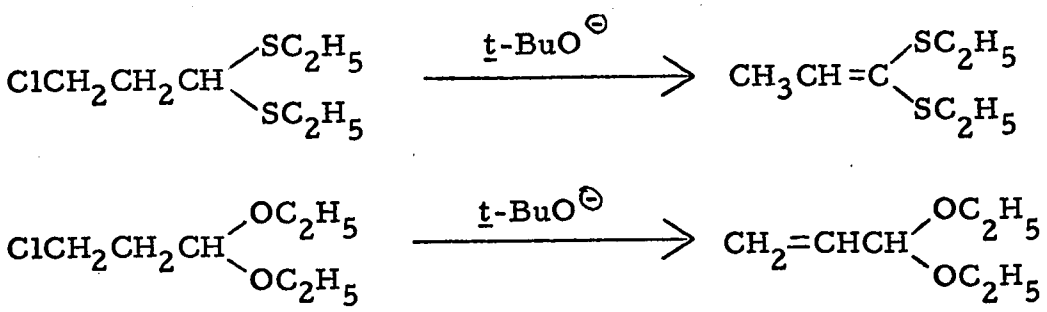


Tarbell and coworkers (48, 49) noted the isomerization of a number of allyl alkyl sulfides and allyl aryl sulfides under basic conditions. S-Allyl-3,5-dichlorothiosalicylic acid rearranged to S-propenyl-3,5-dichlorothiosalicylic acid on treatment with potassium hydroxide solution.



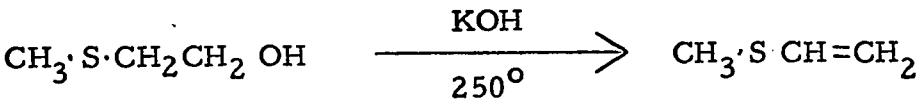
Reaction of allyl phenyl sulfide and allyl n-hexyl sulfide with alcoholic sodium ethoxide yielded phenyl propenyl sulfide and n-hexyl propenyl sulfide respectively. The corresponding oxygen analogs underwent no such rearrangements. The results were again explained by carbanion stabilization due to sulfur participation.

An analogous reaction was reported by Rothstein (50) who found that potassium t-butoxide treatment of β-chloropropionaldehyde diethylmercaptal afforded methylketene mercaptal, whereas β-chloropropionaldehyde diethylacetal under similar conditions gave acrolein acetal (51).



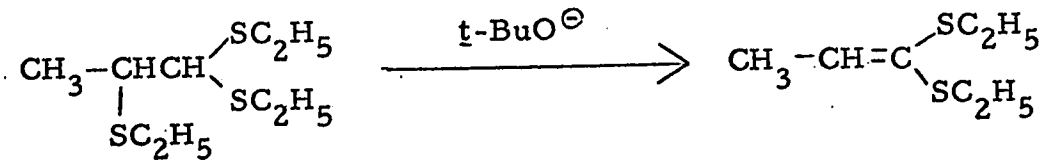
The following references serve to illustrate the simple β-eliminations reported to date.

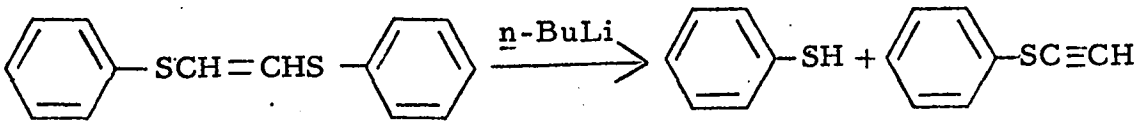
Doumani (52) and Arens (53) both observed the formation of methyl vinyl sulfide from the base catalyzed dehydration of 2-methylthioethanol at 250°.



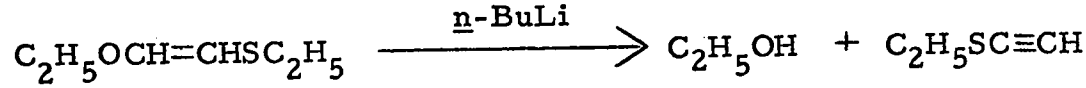
Rothstein (54) showed that 1,1,2-tris-(ethylthio)propane and potassium t-butoxide afforded methylketene diethylthioacetal, and Parham and Stright (55) effected the elimination of thiophenol from

cis- and trans-1,2-bis-(phenylthio)ethene with n-butyl lithium in ether at 0°.





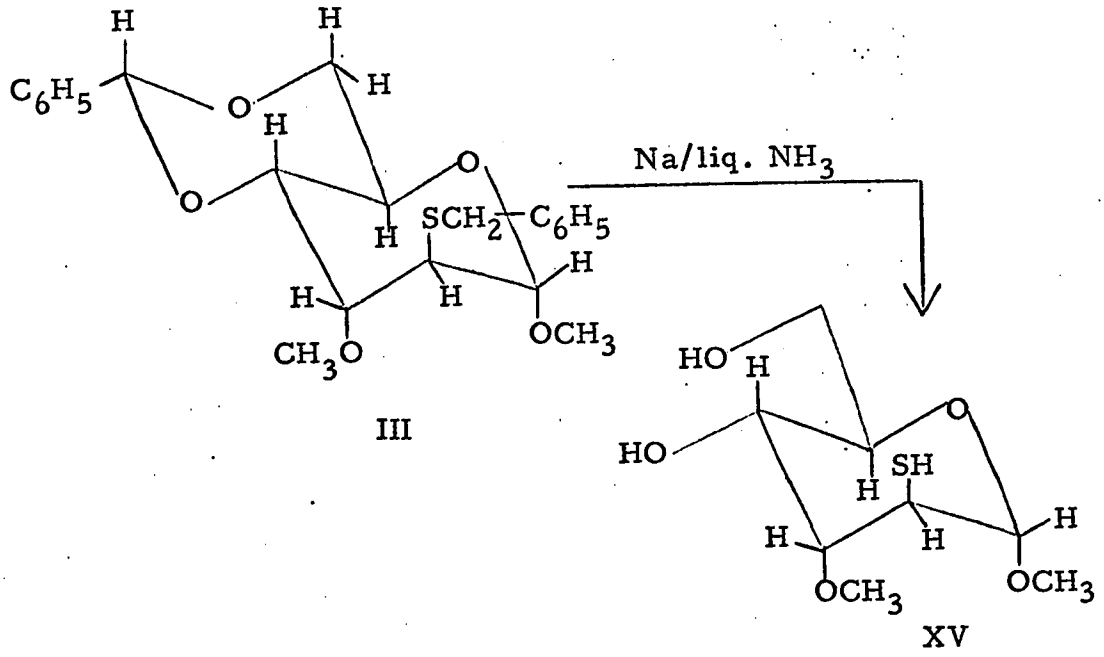
In an analogous reaction Arens and coworkers (47) found that ethanol can be eliminated from enol ethers by base if a β-alkylthio group is present.



4. THE REACTION OF METHYL S-BENZYL-4,6-O-BENZYLIDENE-3-O-METHYL-2-THIO-α-D-ALTROPYRANOSIDE (III) WITH SODIUM OR BASES IN DME

Since the work of Nayak, Sharma and Brown (1-3) formed the basis for the work described in this thesis, it was felt necessary to review their results in more detail as a preliminary to the discussion of those obtained in the current investigation.

Treatment of III with sodium in liquid ammonia alone afforded an 85% yield of methyl 3-O-methyl-2-thio-α-D-altropyranoside (XV).



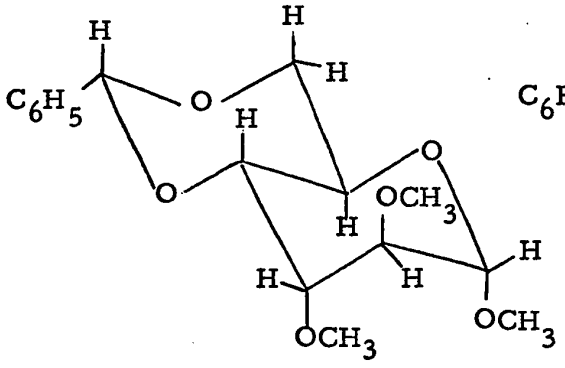
This result was not unexpected as Jamieson and Brown (56) had earlier described the preparation of several monomercaptomonosaccharides by reductive cleavage of S-benzyl-4,6-O-benzylidene-2 (or -3-)-thioglycopyranosides under similar conditions.

However, when III was allowed to react with sodium in liquid ammonia-DME mixtures, or in refluxing DME with either metallic sodium, metallic potassium, potassium hydroxide, sodium methoxide or sodium hydride, the formation of the three olefinic products V, VI and VII (Chart 1) was observed. VII was shown to arise via base catalyzed rearrangement of V.

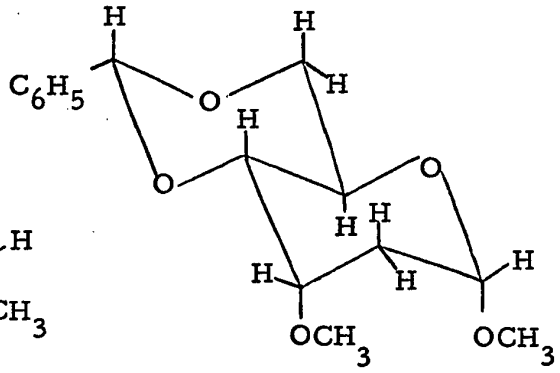
Of the metals, bases and solvent systems used above, sodium metal in refluxing DME proved the most efficient in promoting elimination, with overall yields of 75% or more. Potassium metal afforded a low yield of the 2,3-olefin (V) and caused extensive tar formation. Potassium hydroxide, sodium methoxide and sodium hydride gave somewhat higher yield of elimination products (20%,

30% and 50% respectively).

Only unchanged starting material was recovered when methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-altropyranoside (XVI) and methyl 4,6-O-benzylidene-2-deoxy-3-O-methyl-α-D-altropyranoside (XVII) were allowed to react with sodium metal in refluxing DME. Thus the presence of an alkylthio group on position 2 of the carbohydrate nucleus is a necessary factor for the above eliminations to occur.



XVI.



XVII

RESULTS AND DISCUSSION

A. THE PREPARATION OF ALKYL β-BENZYLTHIOETHYL ETHERS AND THEIR REACTION ON TREATMENT WITH SODIUM METAL IN REFLUXING DME

Since the elimination reactions observed by Nayak, Sharma and Brown (2,3) resulted in the formation of α,β-unsaturated sulfides via loss of methanol from the compounds III, VIII and IX having methoxy groups β to a benzylthio or methylthio function, then the simplest analog for such compounds would be methyl β-benzylthioethyl ether (XVIII). The preparation of this compound and benzyl β-benzylthioethyl ether (XIX) was therefore undertaken.

Brown and coworkers (2, 3) have also indicated that the highest yield of elimination products was obtained when powdered sodium/DME was used. For this reason such a system is employed in all attempted eliminations throughout the work.

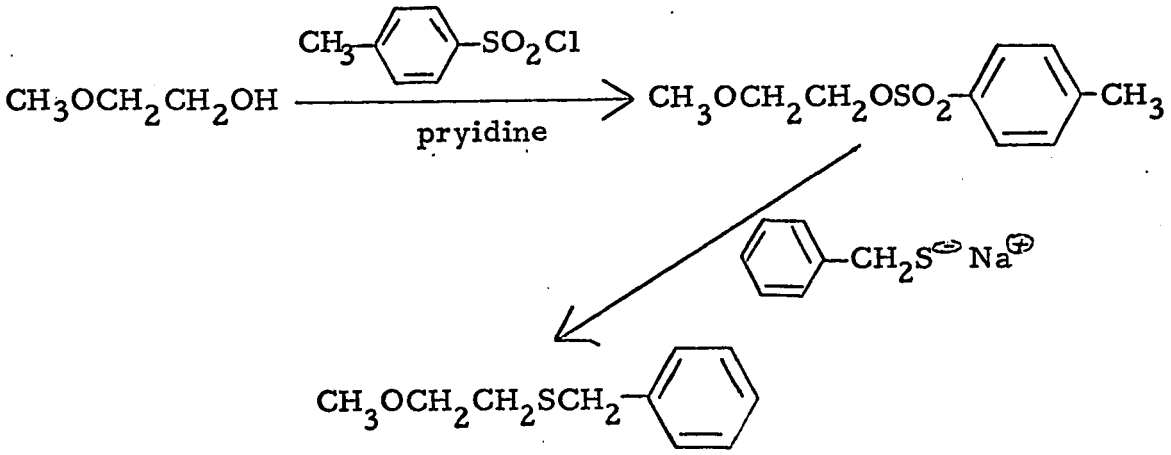
1. The preparation of methyl and benzyl β-benzylthioethyl ethers

The only simple alkyl β-benzylthioethyl ether whose preparation has been reported to date is ethyl β-benzylthioethyl ether. Rojahn and Lemme (57) reported the synthesis of this compound in 1925 in a study on the pesticidal properties of sulfides, but unfortunately their experimental details were not immediately available.

The syntheses of XVIII and XIX were achieved using modifications of published procedures. Gilman and Beaber (58), and, more recently, Drahowzal and Klamann (59), have reported the alkylation of mercaptans in high yield by treatment of their sodium

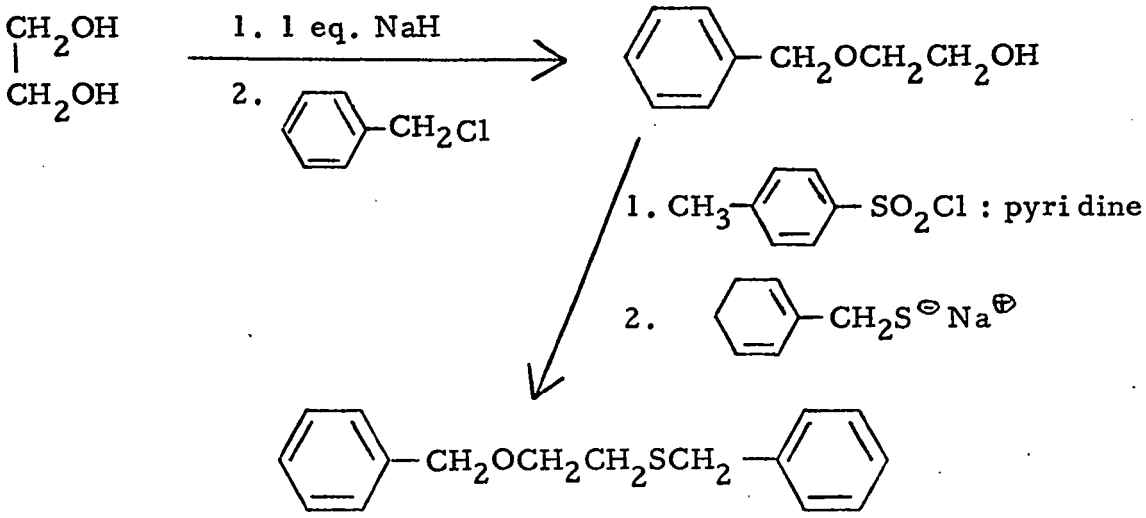
salts with the p-toluenesulfonate esters of alcohols.

Consequently treatment of sodium benzyl mercaptide with the sulfonate ester of 2-methoxyethanol, prepared by the method of Tipson (60), gave the desired compound (XVIII).



XVIII

Similarly XIX was obtained, starting from 2-benzyloxyethanol. The latter was prepared by condensation of the monosodium salt of ethylene glycol with benzyl chloride (61).



XIX

The 60 MHz nuclear magnetic resonance (n.m.r.) spectrum of XVIII (CCl_4 solvent) is shown in Figure I. The singlet at τ2.77 (5H) was assigned to the aromatic protons of the benzylthio group, the singlet at τ6.31 (2H) to the methylene protons of the benzylthio group, the triplet at τ6.58 (2H: J = 7.0 Hz) to the CH_3-O-CH_2- methylene protons, the singlet at τ6.75 (3H) to the O-CH_3 group protons and the triplet at τ7.52 (2H: J = 7.0 Hz) to the S-CH_2 protons of the methoxy ethylthio group.

The 60 MHz n.m.r. spectrum of XIX (CCl_4 solvent) is shown in Figure II. The two low field singlets at τ2.81 (5H) and τ2.86 (5H) were assigned to the aromatic protons of the benzyloxy and benzylthio groups, the singlet at τ5.65 (2H) to the benzyloxy methylene protons, the singlet at τ6.40 (2H) to the benzylthio methylene protons and the two triplets at τ6.54 (2H: J = 7.0 Hz) and τ7.52 (2H: J = 7.0 Hz) to the remaining O-CH_2 and S-CH_2 methylene protons respectively.

Corroboration for these assignments was provided by the work of Dailey and Shoolery (62) who were able to establish a direct relationship between the chemical shift of methylene or methyl protons and the electonegativity of atoms to which such groups are attached. Since oxygen is more electronegative than is sulfur, the protons of alkylthiomethanes should be more heavily shielded than those of alkoxymethanes. Jackman (63) compared the observed shielding values in substituted methanes to those predicted by Dailey and Shoolery's calculations - Table 2. These values are in close

agreement with those found above.

TABLE 2

COMPARISON OF PREDICTED AND OBSERVED CHEMICAL SHIFTS IN SUBSTITUTED METHANES*

	Chemical shifts (τ values)	
Compound type	Calculated	Observed
C_6H_5-CH_2-OR	5.56	5.59
CH_3-CH_2-S-	7.58	7.61
CH_3-CH_2-O-R	6.84	6.63

* Taken from Jackman (63)

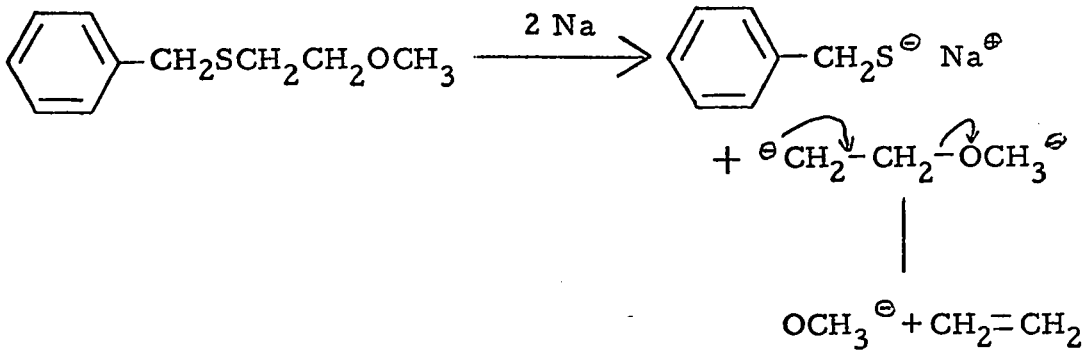
2. The treatment of XVIII and XIX with sodium in DME

XVIII and XIX were separately subjected to treatment with 1 equivalent of sodium metal in refluxing DME according to the method of Nayak, Sharma and Brown (2). After about one hour of reflux the reaction mixture became dark brown. Work up of the reaction mixtures after a 24 hour reflux period afforded a high yield of unchanged starting material along with a dark brown precipitate which gave a strongly basic solution in water. No sodium metal was recovered and no evidence could be found for the presence of benzyl vinyl sulfide which would have resulted if any elimination of the kind observed by Brown and coworkers (2, 3) had occurred. It therefore appears as though XVIII and XIX are stable under the conditions

employed.

In view of this, the disappearance of the sodium metal was surprising. Its possible loss by reaction with the solvent was eliminated since, in a control experiment, a suspension of the metal in DME alone was heated under reflux for 24 hours. No darkening of the solution occurred and when the latter was cooled it gave a quantitative recovery of unchanged metal.

The brown precipitate obtained from reaction of XVIII with sodium in DME was dissolved in water and the solution acidified. Evolution of hydrogen sulfide was observed. Extraction of this solution with ether, careful removal of the solvents and subjection of the residual oil to analysis by gas-liquid chromatography (g.l.c.) indicated the presence of a small amount of benzyl mercaptan. Such products would account for the somewhat less than quantitative recovery of starting material and could have arisen via a simple cleavage of the sulfide linkage as was observed by Gerdil and Lucken (42-44) (page 17) when they treated simple sulfides with potassium metal in DME. No evidence could be found for products which would have arisen via the alternative direction of sulfide cleavage.



In a further experiment XIX was treated with one equivalent of sodium metal in refluxing DME for 24 hours. When the reaction was completed the solution was quenched with D_2O. No deuterium incorporation could be detected in the recovered starting material on n.m.r. analysis.

B. THE PREPARATION OF BENZYLTHIOACETALDEHYDE ACETALS AND THEIR REACTION ON TREATMENT WITH SODIUM METAL IN REFLUXING DME

As no elimination was observed when the β-benzylthioethyl ethers XVIII and XIX were treated with sodium in DME, the syntheses of a number of acetals of benzylthioacetaldehyde were carried out. These compounds were then subjected to reaction as above.

Such acetals more closely resemble the structures of III, VIII and IX and might be expected to undergo elimination via the loss of a molecule of alcohol more readily than do XVIII and XIX, since it is known that the alkoxy groups of acetals are somewhat more labile than are those of simple ethers.

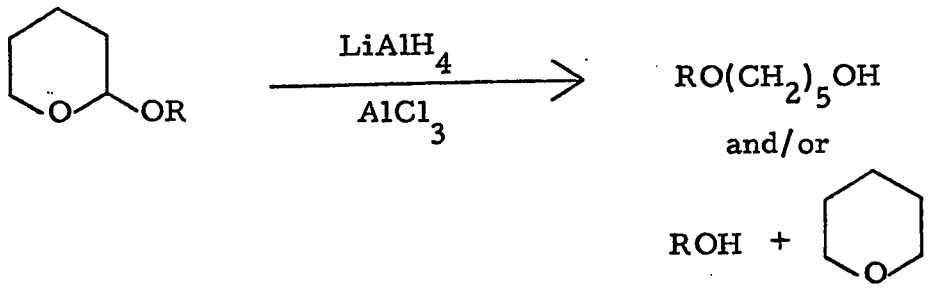
For example, substituted ethers can be readily prepared by the action of Grignard reagents on an acetal or ketal (64).

$$CH_3CH(OCH_3)_2 \xrightarrow{RMgX} CH_3\underset{\displaystyle R}{\underset{|}{C}}HOCH_3 + Mg(OCH_3)X$$

Simple alkyl ethers are unaffected by these reagents. Indeed, diethyl ether and tetrahydrofuran are the most commonly used solvents in

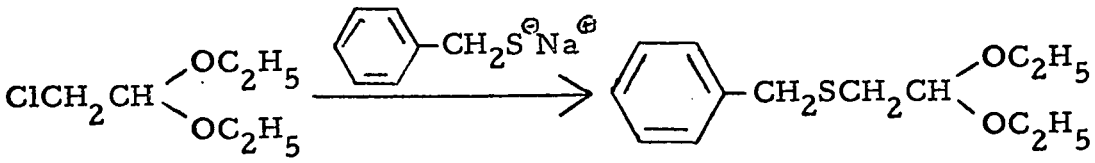
preparation of Grignard reagents from alkyl halides and magnesium metal (64a).

Further, Eliel and coworkers (65), and Legetter and Brown (66) have demonstrated the facile hydrogenolysis of cyclic acetals of tetrahydrofuran and tetrahydropyran on treatment with the mixed reagent $LiAlH_4/AlCl_3$. Ethers are inert under these conditions and again are often employed as solvents in this type of reduction process.



1. The preparation of acetals of benzylthioacetaldehyde

In 1914, Hutchison and Smiles (67) reported the synthesis of benzylthioacetaldehyde diethylacetal (XX) by treatment of chloroacetaldehyde diethylacetal with the sodium salt of ∝-toluenethiol.



XX

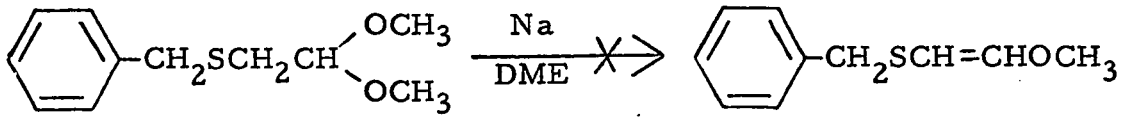
A modification of their procedure was used by Gawron and Glaid (68) who prepared benzylthioacetaldehyde dimethylacetal (XXI) in high yield by refluxing an ethanolic solution of sodium benzyl mercaptide with bromoacetaldehyde dimethylacetal for three hours.

In the current investigation XX, XXI and 2-(benzylthiomethyl)-1,3-dioxolane (XXII) were prepared by this method. The appropriate acetal of bromoacetaldehyde was allowed to react with sodium benzyl mercaptide in refluxing ethanol.

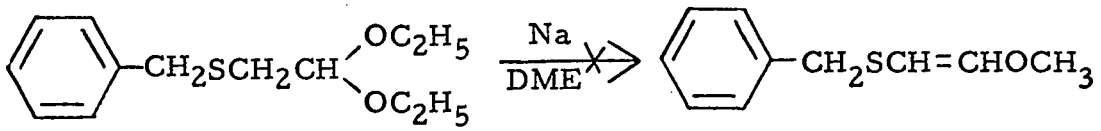
2. The treatment of XX, XXI and XXII with sodium in DME

Reaction of XX, XXI and XXII with powdered sodium in refluxing DME (2) afforded unchanged starting material only. No evidence could be found for the presence of the olefinic products XXIII, XXIV and XXV which would have been formed if the expected elimination process had occurred (Chart 3).

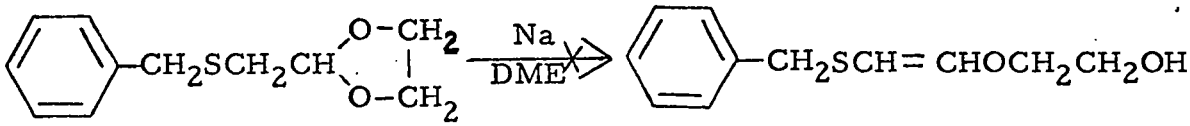
Again consumption of sodium took place, and a brown precipitate formed in each case, which proved to be strongly basic on solution in water.



XXI XXIV



XX XXIII



XXII XXV

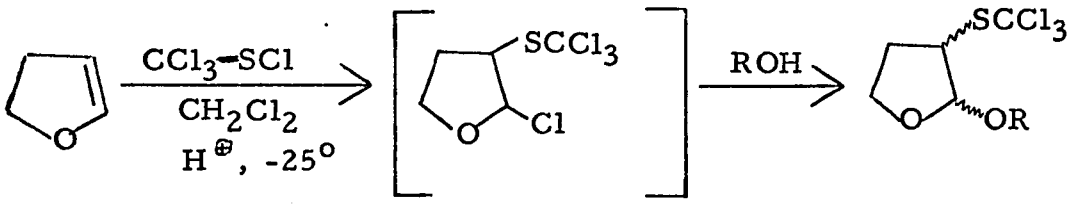
CHART 3

C. THE PREPARATION OF 3-ALKYLTHIO-2-METHOXYTETRAHYDROPYRANS AND THEIR REACTION ON TREATMENT WITH SODIUM METAL IN REFLUXING DME

The failure of XX, XXI and XXII to undergo any reaction above suggested the necessity of using compounds which even more closely model III, VIII and IX but are less complicated than the carbohydrates themselves. For this reason the syntheses of a number of 3-alkylthio-2-methoxytetrahydropyrans were undertaken in order to investigate their reaction with sodium in DME.

1. The preparation of 3-alkylthio-2-methoxytetrahydropyrans

Senning and Lawesson (69) have reported the synthesis of several 2-alkoxy-3-trichloromethylthiotetrahydrofurans by what was considered to be an acid catalyzed addition of trichloromethanesulfenyl chloride to 2,3-dihydrofuran, followed by displacement of the halogen by an alkoxy group.



R = alkyl

They were unable to isolate the intermediate α-chloroether since distillation at reduced pressure resulted only in decomposition. The final product, 2-alkoxy-3-trichloromethylthiotetrahydrofuran,

was much more stable and could be obtained in a pure form by vacuum distillation, except in the case where R (alkyl) was a bulky group such as t-butyl. The addition of the sulfenyl halide was observed to proceed exclusively in a Markovnikov manner and was considered to occur via an ionic mechanism (p. 48).

Preparation of several 3-alkylthio-2-methoxytetrahydropyrans was achieved by applying a modification of Senning and Lawesson's procedure (69) to 3,4-dihydro-2H-pyran (XXVI).

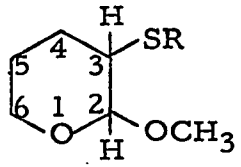
Reaction of the sodium salt of methyl alcohol with the products obtained from the addition of methane-, ethane- and α-toluenesulfenyl chlorides to 3,4-dihydro-2H-pyran (XXVI) at low temperatures, all in equimolar amounts, gave good yields of the products XXVII, XXVIII and XXIX (Table 3).

Proof for the assignment of structures to these compounds (Table 3) was afforded by their 60 MHz n.m.r. spectra ($CDCl_3$ solvent).

The 60 MHz n.m.r. spectrum of XXIX is shown in Figure III. The singlet at τ2.84 (5H) was assigned to the aromatic protons of the benzylthio group and the two doublets at τ5.62 (J = 3.0 Hz) and τ5.85 (J = 5.2 Hz), integrating together for 1H, to the C-2 anomeric proton in the cis and trans isomers respectively. The latter assignment is discussed subsequently in more detail (p. 42). The two singlets at τ6.64 and τ6.72 (integrating together for 3H) were assigned to the $-OCH_3$ group protons in the cis and trans isomeric mixture. The n.m.r. spectrum of a sample of pure trans

TABLE 3

ANALYTICAL AND PHYSICAL DATA FOR 3-ALKYLTHIO-2-METHOXYTETRAHYDROPYRANS



Compound		Boiling point °C	Refractive index	Yield %	% cis	% trans	Anomeric proton signal* (a) cis τ	cis $J_{2,3}$ (Hz)	trans τ	trans $J_{2,3}$ (Hz)
XXVII	R = CH_3	47-48 at 0.3 mm	n_D^{23} = 1.4854	79	50* 57[1] ≤5[2]	50* 43[1] ≥95[2]	5.49	3.0	5.80	5.2
XXVIII	R = CH_3-CH_2-	43 at 0.01 mm	n_D^{24} = 1.4829	82	48* 58[1] ≤5[2]	52* 42[1] ≥95[2]	5.53	3.0	5.85	5.2
XXIX	R = CH_2-C_6H_5	121-122 at 0.2 mm	n_D^{24} = 1.5487	84	45* 43[1] 5[2]	55* 57[1] 95[2]	5.62	3.0	5.85	5.2

(a) referred to tetramethylsilane
(*) acid catalyzed equilibrium mixture
(1) the result of thermal isomerization
(2) in the crude reaction mixture before purification by distillation

XXIX isolated from the crude reaction mixture (p. 48) showed the $-OCH_3$ group signal at τ6.64 only, thus the signal at τ6.72 can be assigned to the OCH_3 group protons in the cis isomer. The broad multiplet centered at τ7.54 (1H) was assigned to H-3.

Confirmation for the latter assignment was provided by the following spin decoupling experiment carried out on a Varian HA-100 MHz spectrometer. Irradiation of the signal due to the C-3 proton at 260 Hz downfield from tetramethylsilane caused a collapse of the two H-2 doublets, centered at τ 5.62 and τ5.85, to two singlets.

The signals at τ6.23 and τ6.29 were assigned to the benzylthio group methylene protons in the trans isomer, and the signal at τ6.37 to the same protons in the cis isomer. The latter signal was absent in the spectrum of the pure trans compound. The 100 MHz spectrum of XXIX showed an increase in the chemical shift difference between the signals assigned to the benzylthiogroup methylene protons for the trans isomer above (from 4.0 Hz to 6.0 Hz) indicating that the close spacing of these two signals did not in fact represent a coupling. Also, at 100 MHz, the signal at τ6.37 resolved into two closely spaced (1.0 Hz) singlets. These observations are explicable on the basis that the two benzylthio group methylene protons are non-equivalent in both the cis and trans isomers as might be expected from their close proximity to the asymmetric center C-3.

Although 2-methoxy-3-methylthiotetrahydropyran (XXVII) could be distilled intact at 1.1 mm, attempted distillations of this compound at pressures in the range 20-80 mm yielded mixtures of XXVII and its

thermal decomposition product 5-methylthio-3,4-dihydro-2H-pyran (XXX) (Table 4). Careful fractional distillation failed to separate these compounds. However, preparative g.l.c. on a column of diethyleneglycol succinate proved to be successful in effecting the separation and permitted the isolation of pure XXX. Compound XXVIII, 3-ethylthio-2-methoxytetrahydropyran, required a distillation pressure of 0.01 mm to avoid partial decomposition to 5-ethylthio-3,4-dihydro-2H-pyran (XXXI).

The crude material obtained from treatment of 3,4-dihydro-2H-pyran (XXVI) with α-toluenesulfenyl chloride and subsequent reaction of the product with sodium methoxide, contained the desired 3-benzylthio-2-methoxytetrahydropyran (XXIX) along with benzyl disulfide as a contaminant. The latter was doubtless formed during the preparation of α-toluenesulfenyl chloride via the free radical chlorination of α-toluenethiol by N-chlorosuccinimide (70) (Chart 4).

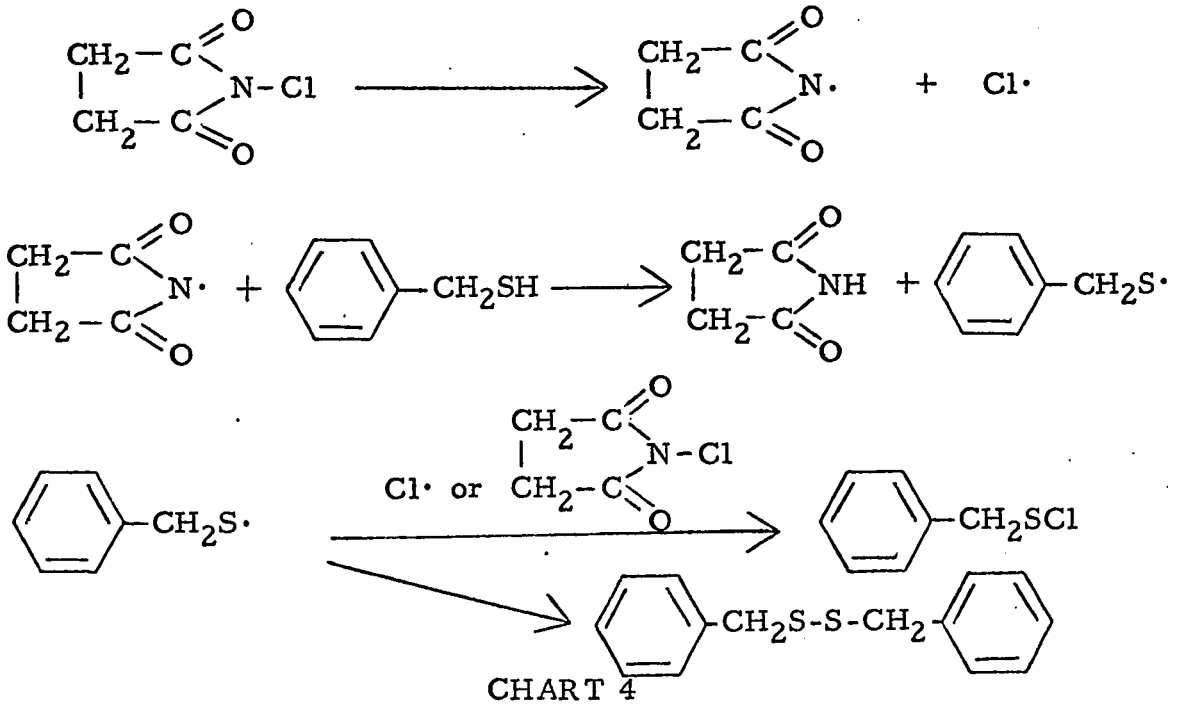
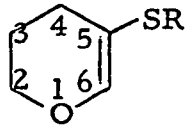


CHART 4

TABLE 4

ANALYTICAL AND PHYSICAL DATA FOR 5-ALKYLTHIO-3,4-DIHYDRO-2H-PYRANS



Compound	Boiling Point (°C)	Refractive Index	Yield (%)	C_1-proton Signal (τ)	Vinyl ether* Absorption (cm^{-1})
XXX R = CH_3	90° at 21 mm[a]	n_D^{23} = 1.5148	-	3.57	1,620 (s)
XXXI R = C_2H_5	57° at 8.0 mm	n_D^{28} = 1.5061	74	3.42	1,619 (s)
XXXII R = CH_2-C_6H_5	85° at 0.01 mm	n_D^{24} = 1.5776	84	3.60	1,620 (s)

(a) microdetermination
* s = strong

Attempted purification of the α-toluenesulfenyl chloride by distillation resulted in extensive decomposition and tar formation. All attempts to obtain pure XXIX by distillation of the crude reaction product above, even at 10^{-4} mm, failed to prevent almost complete decomposition to 5-benzylthio-3,4-dihydro-2H-pyran (XXXII). However, removal of the benzyl disulfide by reduction of the crude mixture with lithium aluminum hydride (71)* and subsequent distillation of the product mixture afforded pure XXIX (Table 3).

A sample of pure XXIX was also prepared by refluxing a solution of XXXII in methanol containing a catalytic amount of hydrochloric acid.

The fact that the addition of methanol occurred exclusively in the direction indicated provides evidence for the greater stability of the intermediate oxocarbonium ion (XXXIII) over the alternative thiocarbonium ion XXXIV (Chart 5).

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* Arnold, Lien and Alm (71) have reported the facile cleavage of a number of aliphatic and aromatic disulfides on treatment with lithium aluminum hydride. In the reduction process hydrogen was evolved and cleavage of the disulfide S-S bond occurred to yield the lithium-aluminum complex of the corresponding mercaptans. Hydrolysis of this complex with dilute acid afforded the free mercaptan. They indicated that the overall stoichiometry of the process is as shown.

$$2\,R\text{-}S\text{-}S\text{-}R + LiAlH_4 \longrightarrow (RS)_4LiAl + 2H_2$$

$$(RS)_4LiAl \xrightarrow{H^{\oplus}} RSH$$

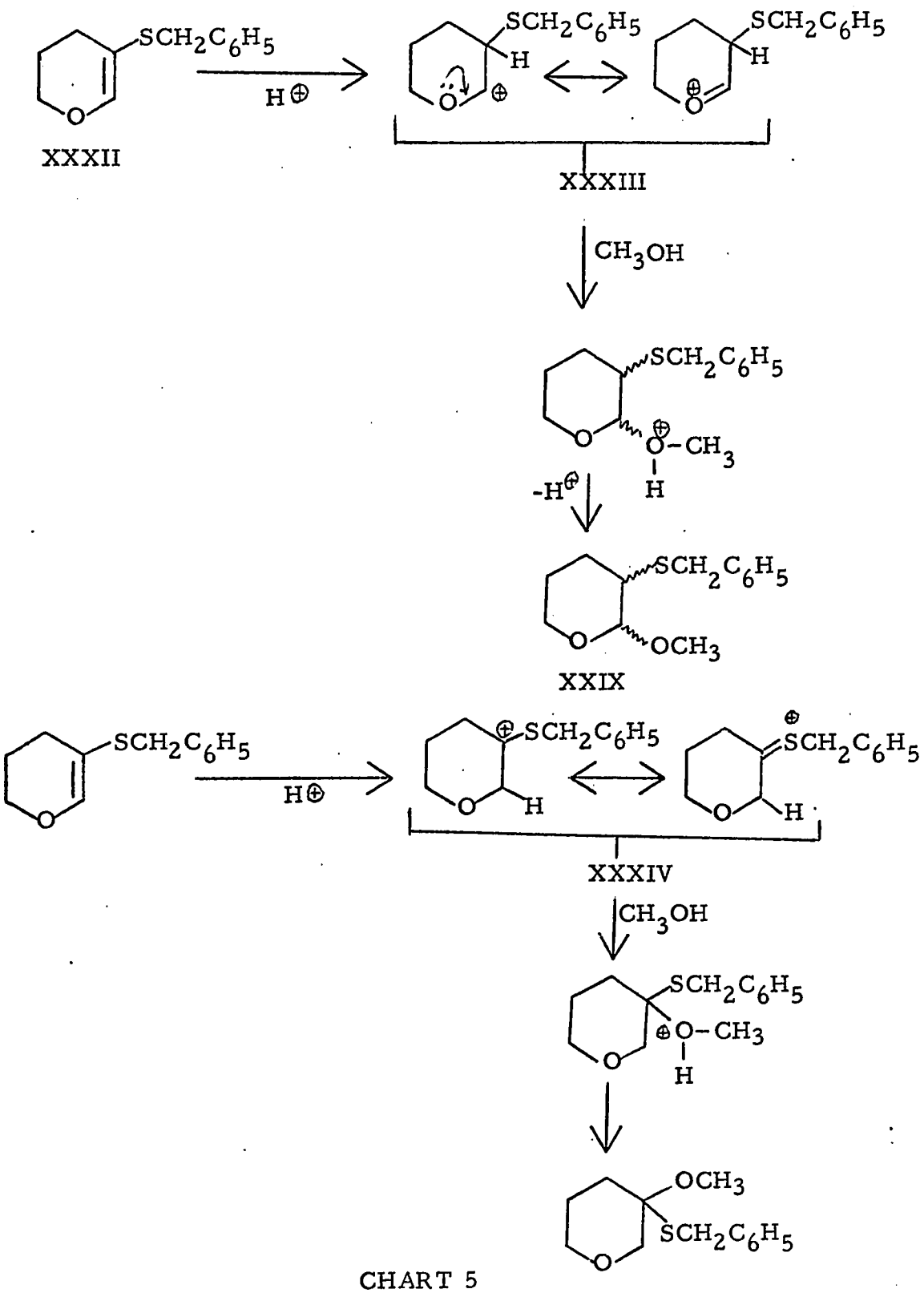
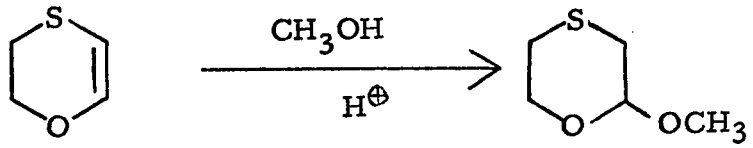


CHART 5

This observation is in agreement with the findings of Parham and coworkers (72) who showed that the acid catalyzed addition of methanol to p-oxathiene (XXXV) yielded exclusively 2-methoxy-1,4-oxathiane (XXXVI).



XXXV XXXVI

They interpreted this result as indicating that oxygen releases electrons more readily in the direction of its covalent bonds than does sulfur, a conclusion arrived at independantly by Baddeley (73) in his explanation of the course followed by reactions of other sulfur and oxygen compounds which had been reported in the literature. Baddeley (73) established a connection between the size of an atom and its mesomeric and electromeric effects. The ability of a covalently bonded atom to donate electrons was shown to be a function of atomic size and of the direction of electron displacement. Atoms with covalent bond radii which are small relative to their atomic radii were shown to be sterically most suitable for participation in double bond formation.

2. Conformational preferences of 3-alkylthio-2-methoxytetrahydropyrans

The distilled products XXVII, XXVIII and XXIX each consisted of a mixture of cis and trans isomers which proved to be inseparable

by fractional distillation, by column chromatography or by g.l.c.. From the n.m.r. spectra of these compounds it was possible to ascertain the relative proportion of the cis and trans isomers in each case. Table 3 shows the pertinent data for this analysis.

The anomeric proton in each of the compounds XXVII, XXVIII and XXIX gave rise to two distinct doublets corresponding to the cis and trans isomers. The doublet at higher field (τ 5.80-5.85) and with the larger coupling constant ($J_{2,3}$ = 5.2 Hz) was assigned to the trans isomer on the basis that, in a six membered pyranoside ring, the anomeric proton in an axial position shows a signal at higher field than does the equatorial anomeric proton (74), and that vicinal trans diaxial protons show larger spin-spin couplings than do vicinal trans diequatorial protons (74). The same arguments have been used by Sweet and Brown (75) to assign the configurations of the analogous 2,3-dialkoxytetrahydropyrans.

The two important conformers for each of the cis and trans isomers are shown in Chart 6.

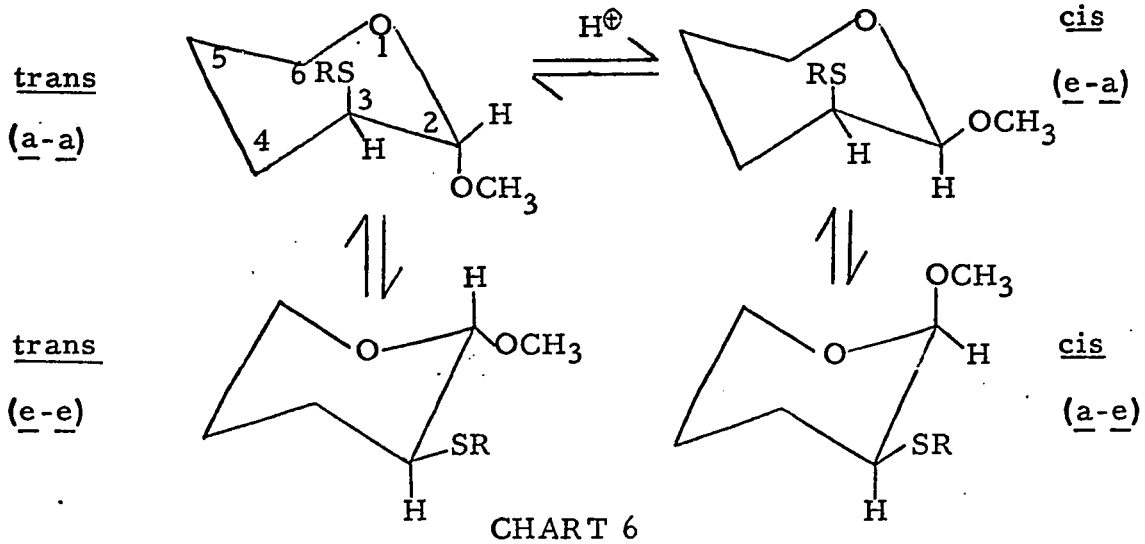
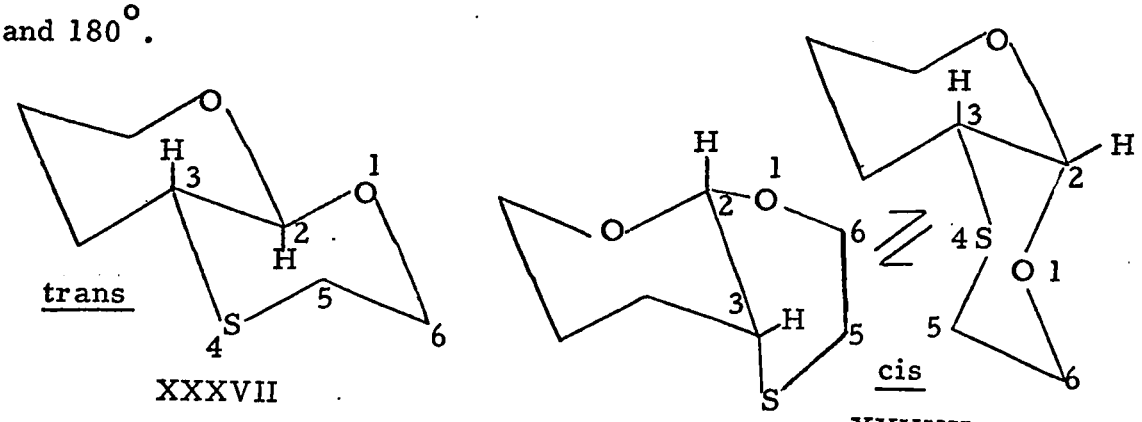


CHART 6

The relative proportions of the two trans conformers (a-a and e-e) could be obtained readily if the values of the coupling constants, J_{H_2,H_3}, for the pure trans-diaxial and trans-diequatorial forms were available. Accordingly it was felt necessary to obtain these values from a model compound in which the trans-diaxial or trans-diequatorial forms were rigidly fixed and which was structurally closely related to the 3-alkylthio-2-methoxytetrahydropyrans (XXVII, XXVIII and XXIX). Such a compound would be tetrahydropyrano-[2,3-b]-1,4-oxathiane (XXXVII)*.

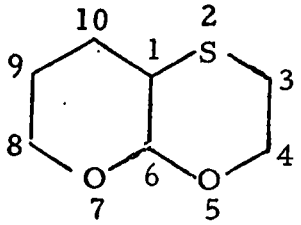
The trans isomer of XXXVII would no doubt exist primarily in the preferred chair-chair form (Chart 7), in which, from examination of models, the dihedral angle between H-2 and H-3 lies between 170° and 180°.



XXXVII XXXVII

CHART 7

* Compound XXXVII would more properly be named 5,7-dioxa-2-thiabicyclo [4.4.0] decane. For convenience however it will be considered as a derivative of 1,4-oxathiane and numbered accordingly (Chart 7).



In the preferred chair-chair conformations of the cis isomer (Chart 7), the H-2, H-3 dihedral angle is approximately 60°. With one ring in the twist boat form, this angle is still the same. If both rings are in the twist boat form, the dihedral angle between H-2 and H-3 is very nearly 60°.

A number of attempted syntheses of XXXVII, discussed later (p. 65), proved unsuccessful and hence such a model could not be used. However, in 1967 Sweet and Brown (76) achieved the synthesis of cis- and trans-tetrahydropyrano- [2,3-b] -1,4-dioxane (XXXVIII), the oxygen analog of XXXVII, which they used as a model for a study of the conformational preferences of a series of 2,3-dialkoxytetrahydropyrans. From the expanded 100 MHz spectra of the cis and trans isomers of XXXVIII, separated from each other by fractional distillation, the observed coupling constant $J_{2,3}$ and the chemical shift of H-2 were, respectively, 1.3 Hz and τ5.49, and 7.1 Hz and τ5.84.

Since it is known that the coupling constant for vicinal protons, on carbon atoms bearing substituents, decreases as the electronegativity of the substituents increases (77) then use of the model XXXVIII may be inaccurate for calculations to estimate the relative population of the different conformers in the series of 3-alkylthio-2-methoxytetrahydropyrans XXVII, XXVIII and XXIX.

Cohen and Schaefer (77) have shown that for substituted propanes ($^{3}CH_3$-$^{2}CH_2$-$^{1}CH_2$-X) where X is sulfur or oxygen, the couplings $J_{1,2}$ are 7.0 Hz and 6.3 Hz respectively. Since the

electronegativities of sulfur and oxygen are 2.64 and 3.31, this represents a difference of ~1 Hz per unit difference in electronegativity.

If such an electronegativity effect is additive, then for XXXVII, the sulfur analog of XXXVIII, the $J_{2,3}$ value might be 7.1 + 0.7 = 7.8 Hz in the trans isomer, and 1.3 + 0.7 = 2.0 Hz in the cis isomer. These figures were used to estimate the conformational equilibrium for the trans-3-alkylthio-2-methoxytetrahydropyrans XXVII, XXVIII and XXIX. The dihedral angle between H-2 and H-3 in the trans conformer having the alkylthio and methoxyl groups diaxial should be the same as that in either of the cis conformers (~60°). The relative population of each of the trans conformers (Chart 6) was calculated using the following formula (78):

$$J_{obs} = J_{\underline{a},\underline{a}} X_{\underline{a},\underline{a}} + (1 - X_{\underline{a},\underline{a}}) J_{\underline{e},\underline{e}}$$

where $X_{\underline{a},\underline{a}}$ = mole fraction of the conformer with H-2 and H-3 trans-diaxial

$X_{\underline{e},\underline{e}} = 1 - X_{\underline{a},\underline{a}}$ = mole fraction of the conformer with H-2 and H-3 trans-diequatorial

$J_{\underline{a},\underline{a}}$ = coupling constant corresponding to the conformer with H-2 and H-3 trans-diaxial (7.8 Hz)

$J_{\underline{e},\underline{e}}$ = coupling constant corresponding to the conformer with H-2 and H-3 trans-diequatorial (2.0 Hz)

J_{obs} = coupling constant observed experimentally (5.2 Hz, Table 3)

In this way $X_{\underline{a},\underline{a}}$ was calculated to be 0.55 and $X_{\underline{e},\underline{e}}$ to be 0.45. Thus, it would appear from this calculation that the favored conformer of trans-3-alkylthio-2-methoxytetrahydropyrans XXVII, XXVIII and XXIX would be the one in which the alkylthio and methoxyl groups are in a diequatorial arrangement.

The validity of the above calculation is dependent on the fact that the 0.7 Hz difference in coupling constant for vicinal protons in O and S substituted propanes (77) is applicable to all analogous systems whatever the observed value of the vicinal coupling constant in the O-substituted compound might be. Since the $J_{2,3}$ value observed by Sweet and Brown (76) in the trans isomer of XXXVIII (7.1 Hz) is close to that found by Cohen and Schaefer (77) for O-substituted propanes (6.3 Hz) then application of the 0.7 Hz factor may be reasonably accurate in this case. However, the $J_{2,3}$ value observed for the cis isomer of XXXVIII (1.3 Hz) (76) is considerably smaller than the coupling noted by Cohen and Schaeffer (77) and hence use of the 0.7 Hz factor may be inaccurate here. Perhaps a more reasonable value of $J_{\underline{e},\underline{e}}$, for use in the above calculation, might be 3.0 Hz. This is the coupling constant ($J_{2,3}$) observed for the cis isomer of the 3-alkylthio-2-methoxytetrahydropyrans XXVII, XXVIII and XXIX (Table 3). Examination of models shows that the H-2, H-3 dihedral angle in the trans-diequatorial-3-alkylthio-2-methoxytetrahydropyrans is approximately the same as that in either of the two cis conformers (60°).

Thus by the use of $J_{\underline{a},\underline{a}} = 7.8$ Hz and $J_{\underline{e},\underline{e}} = 3.0$ Hz in the above

formula, $X_{\underline{a},\underline{a}}$ was calculated to be 0.46 and $X_{\underline{e},\underline{e}}$ to be 0.56. These figures indicate that the preferred conformer of trans-3-alkylthio-2-methoxytetrahydropyran is that wherein the alkylthio and methoxyl groups are in a diaxial disposition.

The latter results are in agreement with those obtained by Sweet (79) for a series of 2,3-dialkoxytetrahydropyrans. Sweet (79) reports that the trans-diaxial arrangement of alkoxy groups in 2,3-dimethoxytetrahydropyran and 2-ethoxy-3-methoxytetrahydropyran is favored over the trans-diequatorial arrangement in the ratio $\underline{a}$-$\underline{a}$/$\underline{e}$-$\underline{e}$ = 60:40 and 61:39 respectively. This preference for the diaxial conformer is considered to be due to the anomeric effect (80).

The cis isomer of XXVII, XXVIII and XXIX should exist largely in the $\underline{a}$-$\underline{e}$ form (Chart 6) as a result of the anomeric effect (80), since the ΔG values for 1,3-interactions of R-O/H (0.7-0.9) and R-S/H (0.8) (81) are approximately equal in the two cis conformers.

Equilibration of the cis-trans isomeric mixtures of XXVII, XXVIII and XXIX, obtained by distillation (Table 3), was achieved by dissolving each compound in methanol containing a catalytic amount of HCl and refluxing the solution for 24 hours. The results of these experiments are shown in Table 3. Compounds XXVII, XXVIII and XXIX gave equilibrium mixtures in the ratio of cis to trans of 1:1, 1:1 and 5:6 respectively. These ratios must reflect the relative stabilities of the two isomers in each compound.

3. The mechanism for the addition of ethanesulfenyl chloride to 3,4-dihydro-2H-pyran

N.m.r. analysis of the crude reaction products obtained in the synthesis of the 3-alkylthio-2-methoxytetrahydropyrans XXVII, XXVIII and XXIX, before attempted distillation, indicated the presence of the trans isomer in at least 95% yield (Table 3). Heat or acids caused isomerization, so that under the influence of such conditions the proportion of the cis isomer increased (Table 3). These observations led to the proposal of a mechanism for the addition reaction as shown in Chart 8.

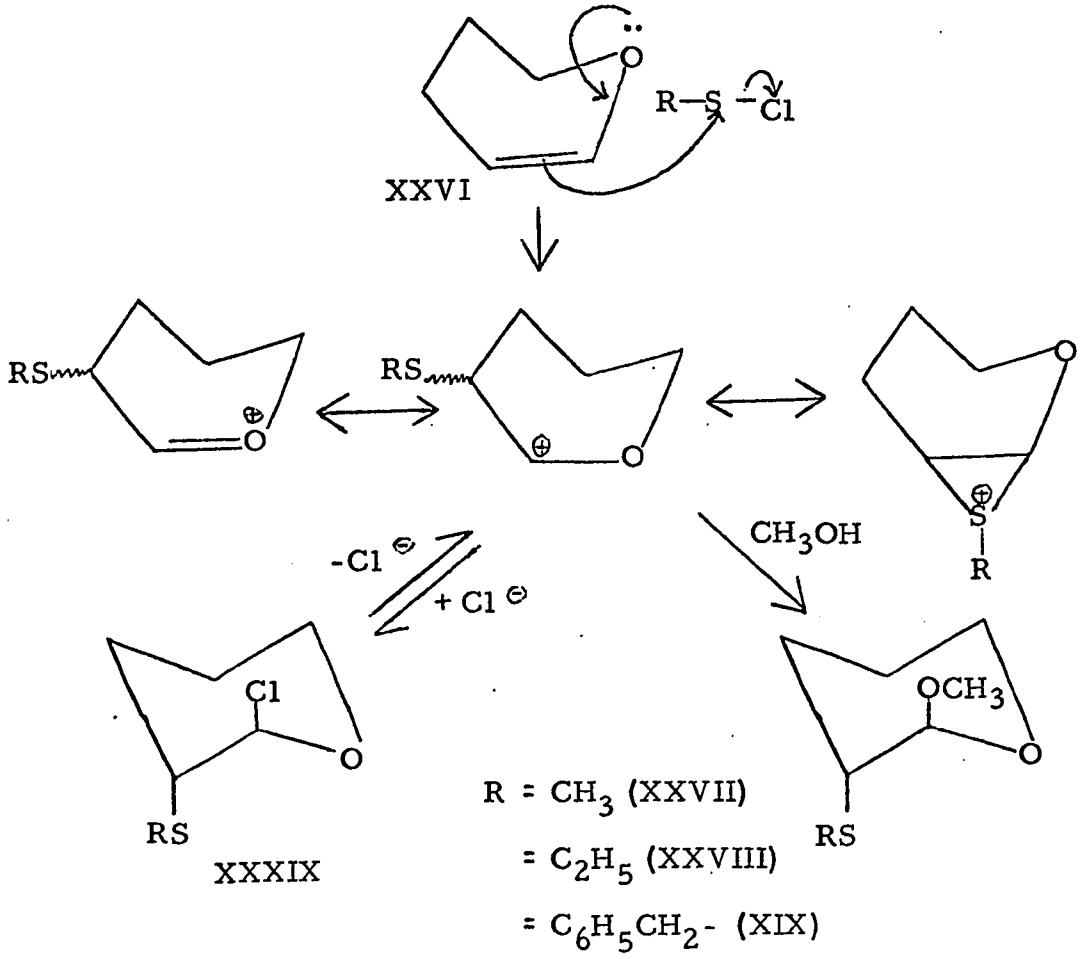


CHART 8

Nucleophilic attack of the α,β-unsaturated ether (XXVI) on the alkanesulfenyl chloride, would cause displacement of the halogen and would give an oxocarbonium-episulfonium ion in which the episulfonium contribution is considered to be paramount. Subsequent attack by chloride ion was believed to give, reversibly, 3-alkylthio-2-chlorotetrahydropyran (XXXIX). This α-chloroether (XXXIX) decomposed on attempts at its isolation and because of this instability was assigned the trans rather than the cis configuration, since the trans arrangment would permit anchimeric assistance by the sulfur atom in enhancing the reactivity of the C-Cl bond. Subsequently, in the presence of methanol the episulfonium ion obtained by loss of the chloride ion then would give, stereoselectively, the trans 3-alkylthio-2-methoxytetrahydropyran (XXVII, XXVIII or XXIX).

The proposal of the above mechanistic scheme (Chart 8) receives considerable support from the extensive literature studies on the addition of sulfenyl chlorides to olefinic systems. In 1949 Kharasch and Buess (82) postulated a mechanism involving a cyclic episulfonium ion intermediate to explain the trans addition of 2,4-dinitrobenzenesulfenyl chloride to olefins. Since then an increasing volume of work has appeared to support the view that, in the absence of radical initiators, the addition of sulfenyl halides to olefins proceeds via an ionic route to give products in which the halogen and alkyl-(or aryl)-thio group are trans.

Kharasch and Havlik (83, 84) showed that the addition of a variety of sulfenyl halides to cis and trans-2-butene gave products

that were diastereoisomeric racemates. These, upon solvolysis, led to racemic acetates. Enhancement of the rate of acetolysis by sulfur participation was also observed. Kwart and Miller (85) reported that the addition of 2,4-dinitrobenzenesulfenyl chloride to norbornene yields a trans addition product. Their work was confirmed by Cristol and coworkers (86) who showed that addition of p-toluenesulfenyl chloride to norbornene, norbornadiene and 9,10-ethenoanthracene yields trans products. They further noted the absence of products which might have arisen by Wagner-Meerwein rearrangement and attributed this fact to the stabilization of the intermediate carbonium ions by sulfur participation.

Recently, Mueller and Butler (87, 88) examined the addition of methane- and benzenesulfenyl chlorides to a number of olefins. The addition of both reagents to acenaphthylene gave stereoselectively the trans product. They also reported that addition of these two sulfenyl chlorides to propene, 2-methylpropene, 3-methyl-1-butene and 3,3-dimethyl-1-butene at -20° to -25° gave products which arose from anti-Markovnikov addition. It was assumed here that the chlorine and sulfur atoms in the sulfenyl halide possess a partial negative and partial positive charge respectively. Their view was that the pi bond of the olefin first reacted with the sulfur atom of the sulfenyl halide to give, directly, an episulfonium ion, which was then attacked by the chloride ion from the direction of the least steric hindrance. No evidence was obtained from their reactions to indicate discreet carbonium ion formation. The original anti-Markovnikov

products then rearranged to "normal" Markovnikov addition products when warmed to ambient temperatures. However, they did find that with an electronically biased* substrate, such as styrene, only Markovnikov addition was observed. The possibility that in this case also there had been, at first, an anti-Markovnikov addition followed by a fast rearrangement to the observed product, even at low reaction temperatures employed, was not examined by these authors (87, 88).

Although one might expect 3,4-dihydro-2H-pyran (XXVI) to react with sulfenyl halides in a manner similar to that observed for styrene, since this molecule (XXVI) can also be considered to be electronically biased*, in the light of Mueller and Butler's report (87, 88) a second route to the formation of the 3-alkylthio-2-methoxytetrahydropyrans (XXVII, XXVIII and XXIX) must now be considered (Chart 9). This involves initial formation of 2-alkylthio-3-chlorotetrahydropyran (XL) which then rearranges readily, no doubt anchimerically assisted by sulfur participation, either to 3-alkylthio-2-chlorotetrahydropyran (XXXIX) or to the episulfonium ion. The latter, or the former (XXXIX) by loss of chloride ion, reacts with methyl alcohol to form the isolable 3-alkylthio-2-methoxytetrahydropyran (XXVII, XXVIII or XXIX) (Chart 9).

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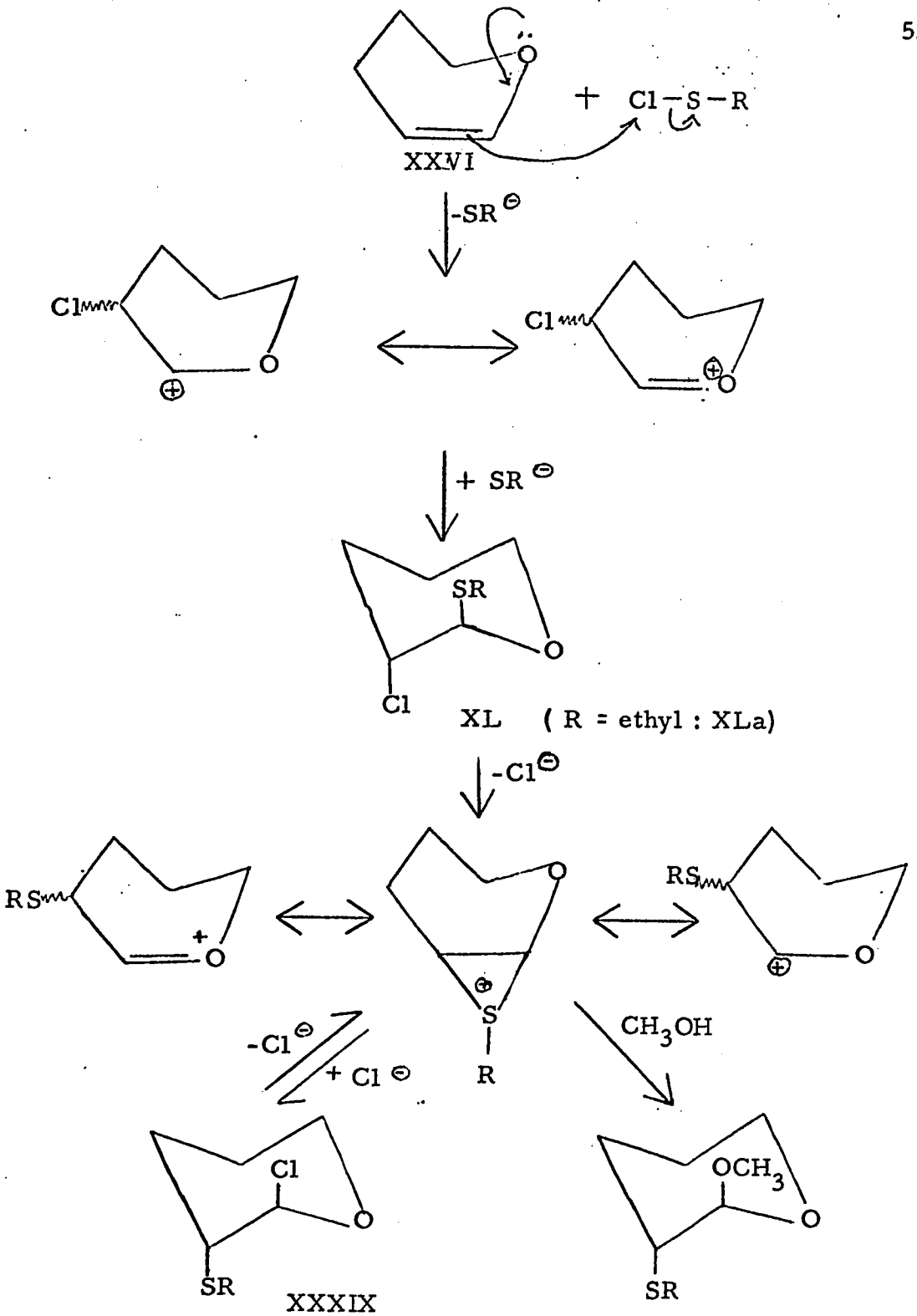
* Formation of a discreet carbonium ion at the benzylic carbon atom of styrene, or at the C_2- carbon atom of 3,4-dihydro-2H-pyran (XXVI) is somewhat favored over those possible in more simple alkenes, by the special stability of such ions. The former receives stabilization by resonance with the aromatic ring, and the latter by resonance with the adjacent electron pairs on oxygen.



R = CH_3 (XXVII)

= C_2H_5 (XXVIII)

= $C_6H_5CH_2$ (XXIX)

CHART 9

In addition, following Mueller and Butler's view (87, 88), there exists the possibility that the episulfonium ion is formed directly and since XXVI is a strongly electronically biased* molecule, chloride ion attack would give only trans-3-alkylthio-2-chlorotetrahydropyran (XXXIX).

Since the alkylthiochlorotetrahydropyran proposed as one possible product, or an intermediate, (Chart 8) had not been isolated during the syntheses of XXVII, XXVIII and XXIX its structure was uncertain. The assumption that it was the trans-3-alkylthio-2-chlorotetrahydropyran (XXXIX) arose from its apparent instability. The further possibility then exists that this intermediate is in fact the cis isomer, arising from cis addition probably via a four-center reaction (Chart 10) as had been found for the addition of nitrosyl chloride to glycals (89).

In order to obtain evidence which would permit a decision concerning the routes of reaction suggested above (Charts 8-10) the isolation of the proposed alkylthiochlorotetrahydropyran intermediate was undertaken.

The possibility of a free radical addition process was excluded on the basis of Mueller and Butler's (87, 88) observation that the presence of radical inhibitors caused no change in their results or the ease with which the reaction proceeded. However, as confirmatory evidence, XXVI was allowed to react with methanesulfenyl chloride in the solvent cumene, followed by treatment of the reaction

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* See footnote on p. 51.

mixture with sodium methoxide. Only 2-methoxy-3-methylthio-tetrahydropyran (XXVII) was obtained in good yield. No products such as dicumyl, indicative of the intervention of free radicals, were found (90).

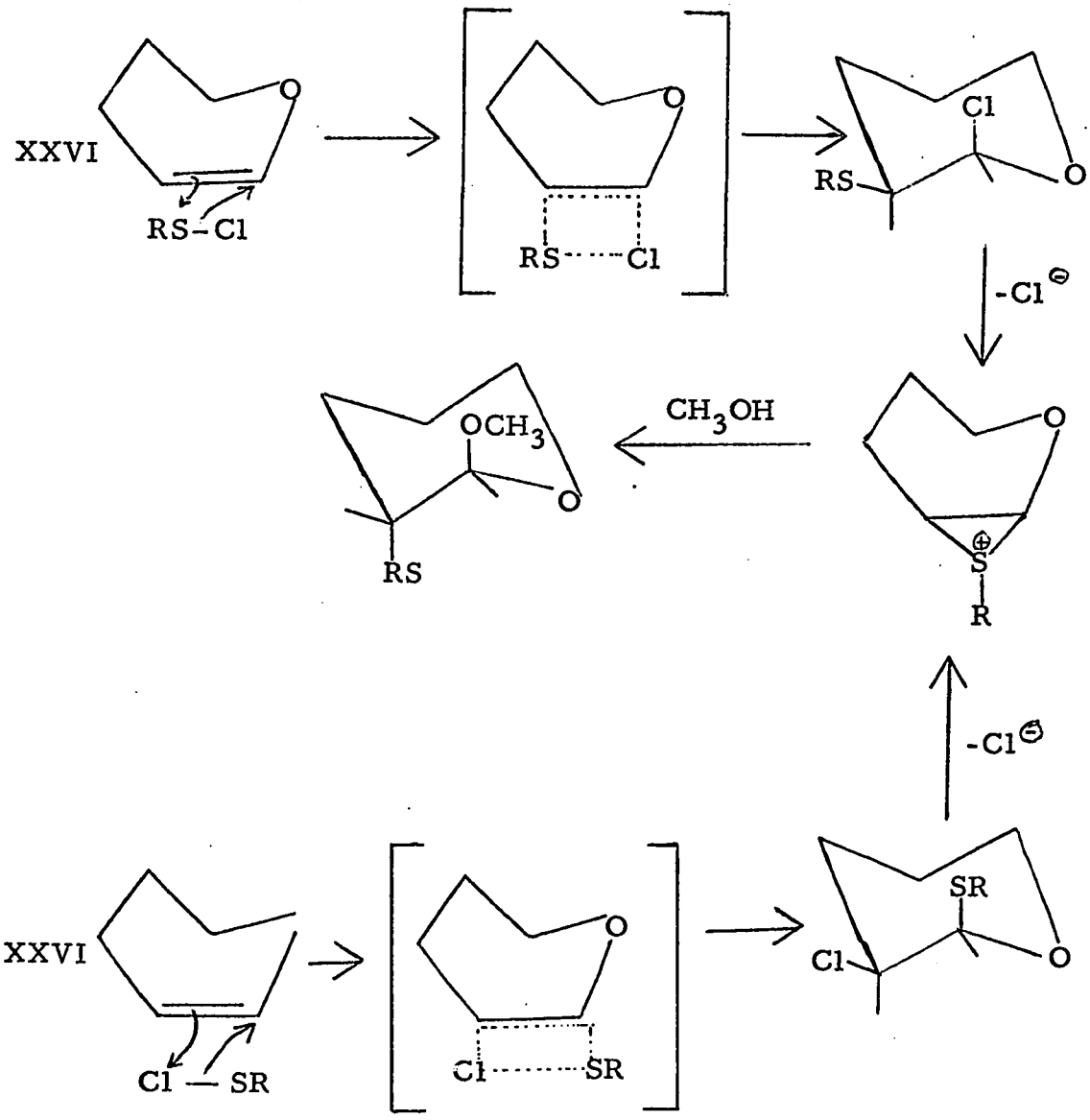


CHART 10

The reaction mixture, obtained from the addition of a slight excess of ethanesulfenyl chloride to 3,4-dihydro-2H-pyran (XXVI) at -40° in $CDCl_3$ solvent, was subjected directly to n.m.r. analysis, also at -40°. The 100 MHz n.m.r. spectrum is shown in Figure IV and agrees well with the assignment of the structure of the reaction product as trans-2-chloro-3-ethylthiotetrahydropyran (XXXIXa) in the preferred conformation having the chlorine and ethylthio substituents trans-diaxial (Chart 11).

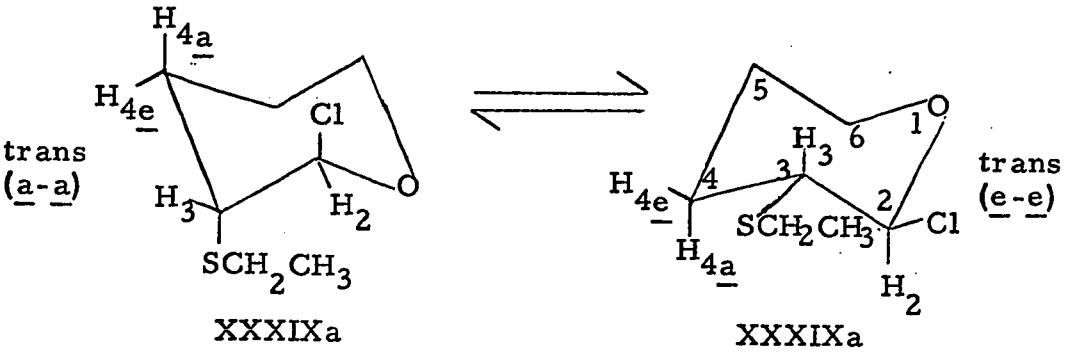


CHART 11

The singlet at τ 3.72 (referred to tetramethylsilane) with W/2 = 4 Hz was assigned to the anomeric proton (H-2) on the basis of the reported signal for the anomeric proton at τ3.79 (broad singlet, CCl_4) for 2-chlorotetrahydropyran (91), and at τ3.97 (broad singlet, $CDCl_3$) for trans-2,3-dichlorotetrahydropyran (92). The broad singlet at τ6.89 (W/2 = 8 Hz) in Figure V can be assigned only to H-3. The integration also agrees with these assignments. Further, irradiation of the signal at τ3.72 (H-2) caused a sharpening of the H-3 signal at τ6.89.

The appearance of the signal for H-3 as a broad singlet shows

that the couplings with the vicinal protons H-2, H-4a and H-4e are all small. This can only occur if H-3 is equatorial since if it were axial its coupling with H-4a would be expected to be $\geqslant$7 Hz (74), thus resulting in at least a quartet for H-3. The small coupling between H-2 and H-3 is expected whether the anomeric proton H-2 is equatorial or axial. Thus, from this information, no decision can be made concerning the axial or equatorial disposition of the anomeric proton and the chlorine atom attached to the anomeric carbon.

However, Anderson and Sepp (91) have found a value of 2.7 kcal/mole for the anomeric effect (80) in 2-chlorotetrahydropyran, a figure which indicates that this compound is practically completely in that conformation wherein the chlorine atom is axial.

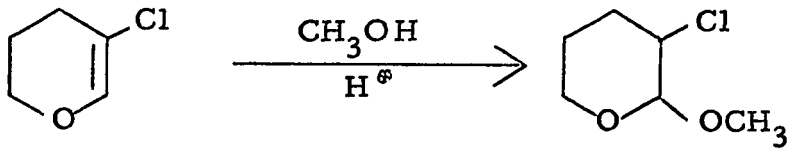
On this basis one might expect that in either cis- or trans-2-chloro-3-ethylthiotetrahydropyran (XXXIXa) the chlorine atom on the anomeric carbon would be in the axial position. Assuming a value of $\sim$0.4 kcal/mole for the interaction of the ethylthio group with one axial proton in XXXIXa (81) and accepting the figure of 2.7 kcal/mole for the anomeric effect, then XXXIXa at -40° is biased to the extent of $\sim$2.3 kcal/mole (> 99%, using the relationship $\Delta G = -RT \ln K$) in the conformation in which the chlorine atom on C-2 is axial.

Thus, the evidence above clearly demonstrates that the product obtained from the reaction of ethanesulfenyl chloride with XXVI is in fact trans-diaxial-2-chloro-3-ethylthiotetrahydropyran (XXXIXa).

To test the possible intermediacy of 3-chloro-2-ethylthiotetra-

hydropyran (XLa) which may have been formed initially and then undergone rapid rearrangement as postulated in Chart 9, the synthesis of this compound was undertaken.

In 1951 Riobe (93) had reported the preparation of 3-chloro-2-methoxytetrahydropyran by treatment of 5-chloro-3,4-dihydro-2H-pyran (XLII) with methanol containing a catalytic amount of dry HCl.



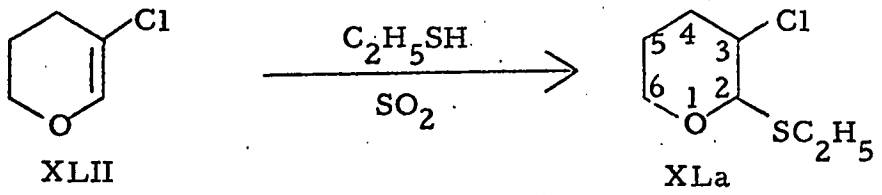
XLII

This method, then, of acid catalyzed addition of ethanethiol to XLII appeared to be an attractive route to the synthesis of XLa.

Addition of one molar equivalent of 3,4-dihydro-2H-pyran (XXVI) to a cooled (-30°) solution of chlorine in anhydrous carbon tetrachloride, according to the method of Jacobson (94), afforded 2,3-dichlorotetrahydropyran (XLI) in high yield. Subsequent distillation of XLI at atmospheric pressure caused its almost complete decomposition to 5-chloro-3,4-dihydro-2H-pyran (XLII) (93).

Reaction of XLII with an excess of ethanethiol, containing a catalytic amount of HCl, for 48 hours at room temperature gave, after work up, a crude product which by n.m.r. analysis was shown to contain mainly starting material along with a very small quantity of XLI. Distillation afforded starting material (XLII) only.

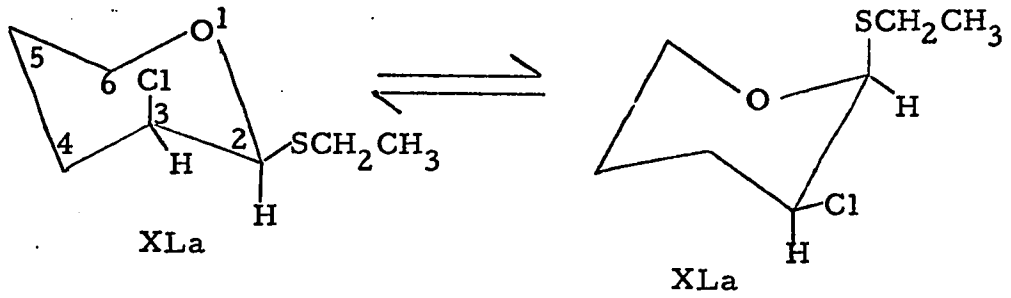
However, addition of ethanethiol to XLII in the presence of sulfur dioxide as catalyst gave the desired product (XLa) in 77% yield.



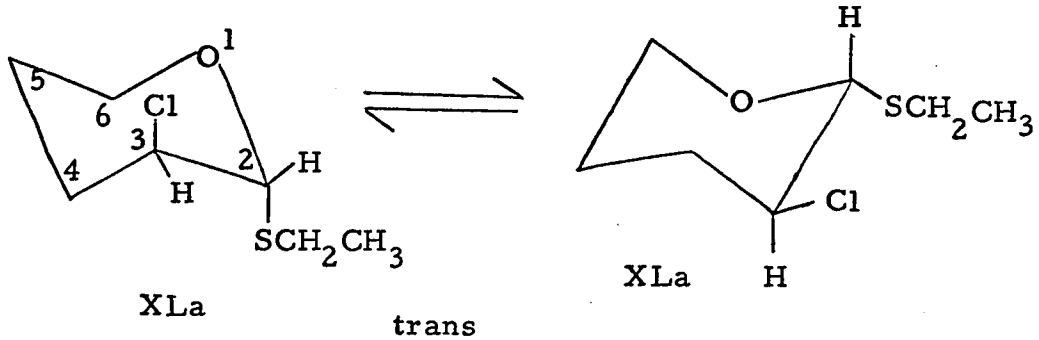
XLII XLa

A similar procedure had been used by Shostakovskii and coworkers (95) in the preparation of several oxathioacetals, via the addition of mercaptans to vinyl ethers.

The different conformers of cis and trans-3-chloro-2-ethylthiotetrahydropyran (XLa) are represented below.



cis



trans

The 60 MHz n.m.r. spectrum of XLa is shown in Figure V. The two doublets at τ4.84 (J = 4.5 Hz) and τ4.93 (J = 3.0 Hz) (integrating together for 1H) were assigned to the C-2 anomeric proton in the trans and cis isomers; the multiplet lying between τ5.57 and τ6.14 (2H) to the C-6 protons; the multiplet between

τ6.19 and τ6.7 (1H) to the C_3-proton; the two quartets centered at τ7.33 and τ7.38 (total integration - 2H: J = 7.5 Hz) to the $S-CH_2-CH_3$ group methylene protons in the two isomers; the multiplet lying between τ7.6 and τ8.48 (4H) to the C-4 and C-5 protons and the triplet at τ8.7 (3H: J = 7.5 Hz) to the ethylthio group methyl protons.

The signals assigned to the anomeric C-2 proton in Figure V are of interest. The larger coupling (J = 4.5 Hz) observed in the low field doublet (τ4.84) suggests that this signal must result from the C_2-H in the trans isomer of XLa, since it is known that vicinal trans diaxial protons show larger spin-spin couplings than do vicinal trans diequatorial protons (74). However, one would normally expect to see this signal at higher field than that for the corresponding proton in the cis isomer (74). It therefore appears that in the n.m.r. spectrum of XLa the chemical shifts of the anomeric proton signals are reversed.

Attempts to clarify this apparent anomaly by separation of the cis and trans isomers of XLa were unsuccessful. G.l.c. analysis of XLa on columns of butanediol succinate on Gas-Chrom P and Carbowax 20M on Gas-Chrom P showed only one symmetrical peak. Ordinary column chromatography was not attempted since experience with other 2,3-disubstituted tetrahydropyrans had always resulted in failure to achieve separation of such isomers.

A second possible route to the synthesis of XLa was based on the observations of Paul (96), Quehennen and Normant (97), and

Woods and Sanders (98) who showed that the preparation of 2-alkoxy-3-chloro-(or bromo)-tetrahydropyrans could be achieved by treatment of 2,3-dichloro- (or dibromo)-tetrahydropyran (XLI) with either sodium alkoxide (96, 97) or with an ammoniacal solution of an alcohol (98).

Accordingly treatment of XLI with an excess of sodium ethyl mercaptide in DME at room temperature for 24 hours gave a product, the n.m.r. spectrum of which indicated the presence of the desired compound (XLa) (C-2 anomeric hydrogen, two doublets at τ4.84 (J = 4.5 Hz) and τ4.93 (J = 3.0 Hz)), along with the starting material XLI (anomeric proton as a singlet at τ3.96) and 5-chloro-3,4-dihydro-2H-pyran (XLII) (C_2-H as triplet at τ3.5, J = 1.5 Hz) in the molar ratio 12:1:2. Thus, in addition to the expected product, which would result from nucleophilic attack of ethylmercaptide ion on C-2, some dehydrochlorination must have occurred, probably via abstraction of the C_3-H by mercaptide, with concommitant loss of chloride ion from C_2. Attempted distillation of this product mixture resulted only in extensive decomposition.

The fact that XLa, prepared according to the method of Shostakovskii (95) above, could be purified by distillation under reduced pressure is good evidence that it does not rearrange at -40° to XXXIXa, certainly as rapidly as is obviously necessary to accommodate the route outlined in Chart 9.

Treatment of XLa with ethanesulfenyl chloride, under similar conditions to those used for the reaction of XXVI with the latter reagent, gave only diethyldisulfide and 2,3-dichlorotetrahydropyran

(XLI), both in high yield. There was no evidence for the formation of XXXIXa, either from the n.m.r. spectrum of the reaction mixture or by isolation by fractional distillation.

This information, coupled with that obtained from the identification of the intermediate XXXIXa above, clearly supports the view that the reaction of ethanesulfenyl chloride with XXVI follows the course shown in Chart 8.

The conversion of XLa by ethanesulfenyl chloride to XLI and diethyldisulfide might occur by a route such as that shown in Chart 12.

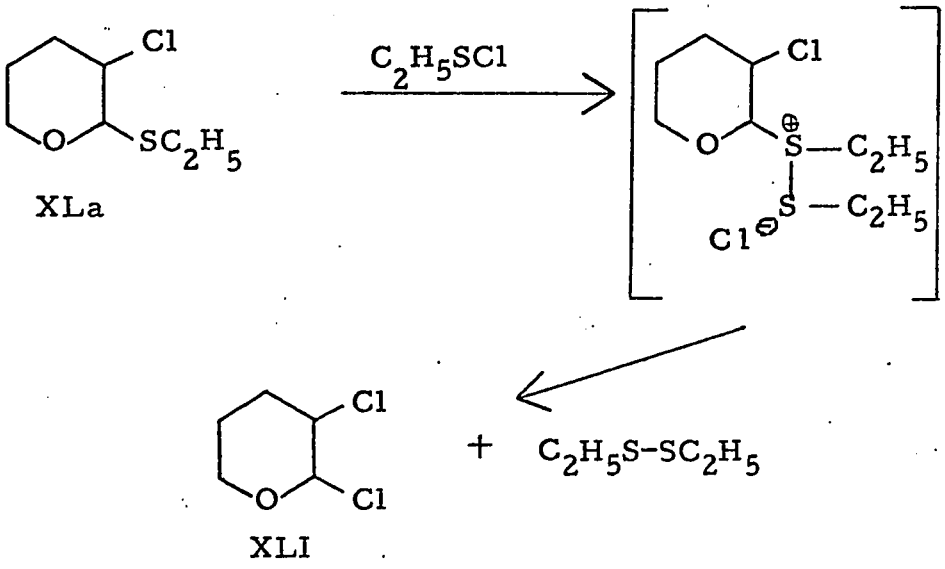


CHART 12

Similar reactions of sulfenylhalides with sulfides have been reported by Moore and Porter (99). If this mechanistic pathway (Chart 12) is correct then it offers support for the assumption that the S-Cl bond of ethanesulfenyl chloride tends to cleave in such a way that the chlorine atom emerges negatively charged.

4. The addition of trichloromethanesulfenyl chloride to 2,3-dihydrofuran and 3,4-dihydro-2H-pyran (XXVI)

As has been noted earlier (p. 33), Senning and Lawesson (69) have reported the preparation of several 2-alkoxy-3-trichlormethylthiotetrahydrofurans by the addition of trichloromethanesulfenyl chloride to 2,3-dihydrofuran in the presence of an acid catalyst, followed by displacement of the C-2 halogen from the proposed 2-chloro-3-trichloromethylthiotetrahydrofuran intermediate by an alcohol. They further commented (69) that their work represented the first example of an acid catalyzed addition of a sulfenyl halide to an olefin and compared it to the acid catalyzed pyranylation of alcohols with 3,4-dihydro-2H-pyran (XXVI).

The observation, in the current investigation, that methane-, ethane- and α-toluenesulfenyl chlorides added readily to 3,4-dihydro-2H-pyran (XXVI) in the absence of an acid catalyst, even at low temperatures (p. 34) prompted a reinvestigation of their results.

Although Senning and Lawesson (69) proposed no mechanism for the acid catalyzed addition of trichloromethanesulfenyl chloride to 2,3-dihydrofuran, a possible pathway is outlined in Chart 13.

The first step of the addition process would be protonation of the vinyl ether to yield the oxocarbonium ion XLIII. Subsequent reaction of this species with trichloromethanesulfenyl chloride could afford 2-chlorotetrahydrofuran and the trichloromethyl sulfonium ion. Attack of the latter moiety on a second molecule of the 2,3-dihydrofuran would yield the intermediate XLIV which, on

reaction with the sulfenyl halide, would produce the proposed intermediate 2-chloro-3-trichloromethylthiotetrahydrofuran and a second trichloromethyl sulfonium ion. Thus the acid would have simply served to initiate the overall addition process.

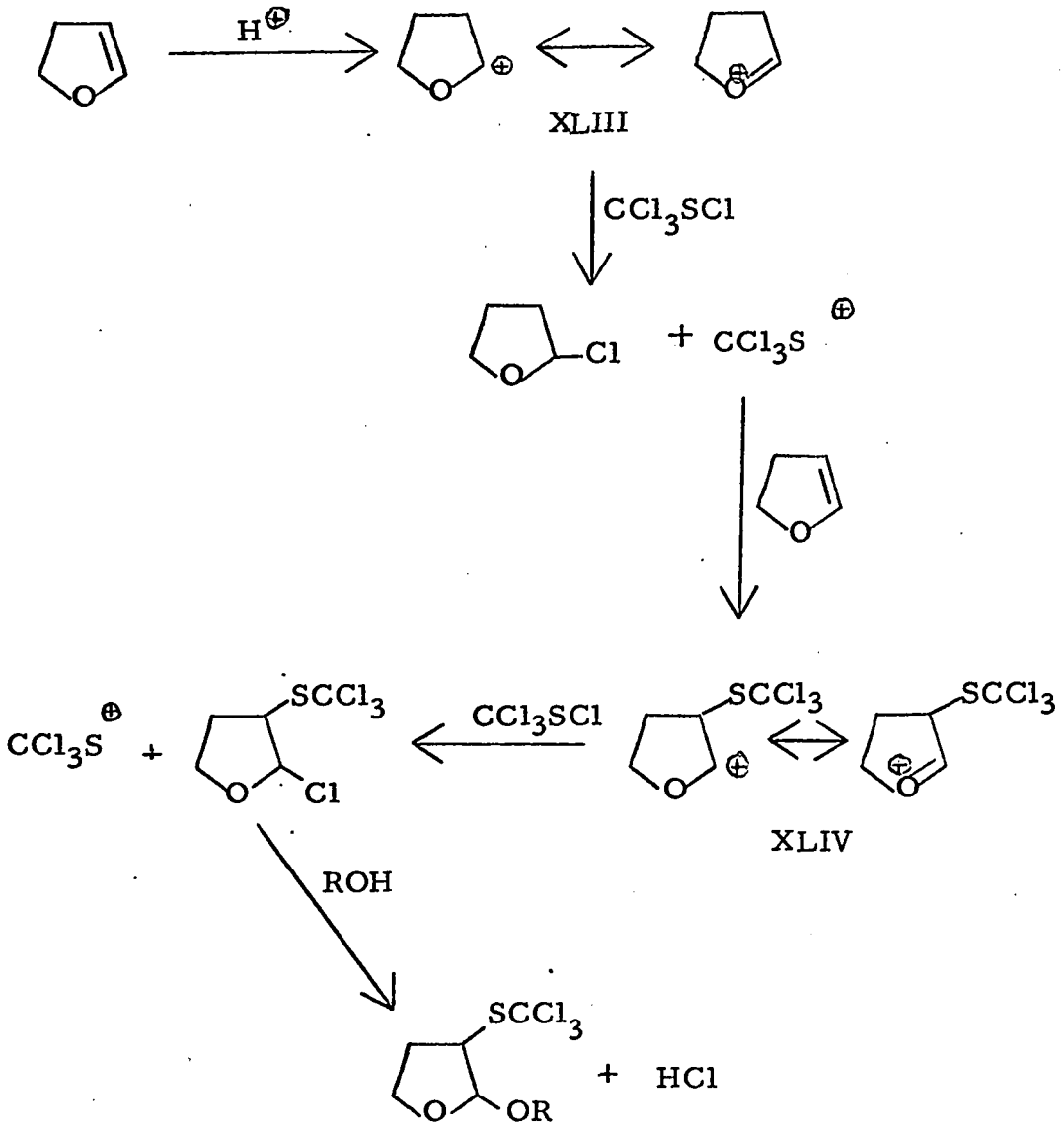


CHART 13

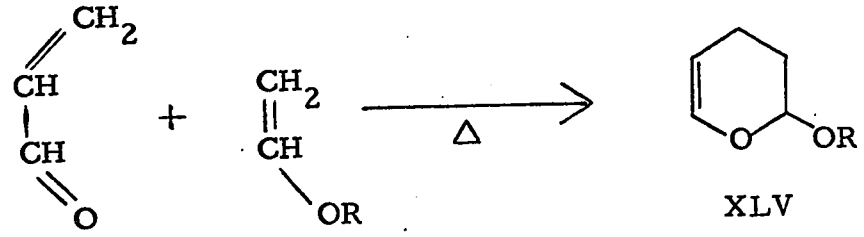
Dropwise addition of trichloromethanesulfenyl chloride, obtained commercially and purified by distillation under vacuum, to 2,3-dihydrofuran, prepared by the base catalyzed isomerization of 2,5-dihydrofuran according to the method of Eliel (65), at 0°, in both the presence and absence of a few drops of hydrochloric acid, resulted in an extremely exothermic reaction accompanied by extensive decomposition. Even with careful attention to their experimental directions, duplication of Senning and Lawesson's results (69) proved impossible. The decomposition experienced above, in both the presence and absence of acid catalysts, sheds some doubt on the acid catalyzed nature of the reaction which they observed (69).

No evidence for an addition reaction could be found when 3,4-dihydro-2H-pyran (XXVI) was treated with trichloromethanesulfenyl chloride, either in the presence or absence of an acid catalyst, even after stirring solutions of the reagents at room temperature for several hours. N.m.r. analysis of the product obtained from the reaction performed in the absence of acid catalyst indicated the presence of unchanged XXVI only. Similar analysis of the product obtained from stirring the reagents together at room temperature for 3 hours in the presence of 3 drops of concentrated HCl again indicated unchanged XXVI along with a small amount of unidentified polymeric material. No evidence could be found for the presence of 2-chloro-3-trichloromethylthiotetrahydropyran which would have resulted from addition of the sulfenyl halide to the vinyl ether (XXVI).

5. The attempted preparation of tetrahydropyrano-[2,3-b]-1,4-oxathiane (XXXVII)

(a) Via a Diels-Alder condensation between p-oxathiene and acrolein

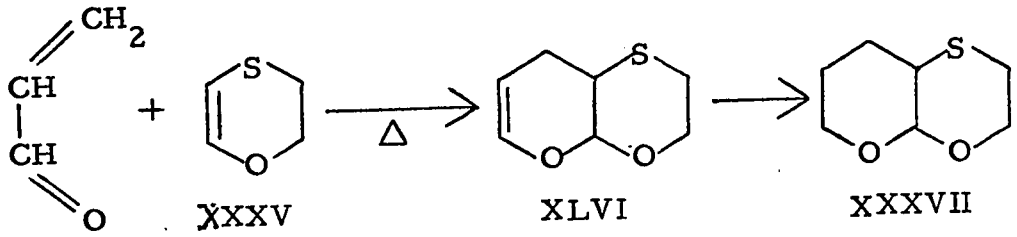
In 1950 Longley and Emerson (100) reported the synthesis of a number of 2-alkoxy-3,4-dihydro-2H-pyrans (XLV) by the condensation of acrolein with a variety of alkyl vinyl ethers under conditions of heat and pressure.



XLV

R = alkyl

It was hoped, therefore, that if the simple alkyl vinyl ethers were replaced by p-oxathiene (XXXV) condensation with acrolein would occur to give XLVI which on subsequent reduction of the double bond would yield the desired product XXXVII.



XXXV XLVI XXXVII

Preparation of XXXV was achieved by the route indicated in Chart 14. Reaction of the monosodium salt of 2-mercaptoethanol with bromoacetaldehyde dimethylacetal afforded a 72% yield of

2-hydroxyethylthioacetaldehyde dimethylacetal (XLVII) (101). Treatment of XLVII with a methanolic solution of HCl at room temperature for 12 hours caused a trans-acetalation, with the resultant formation of 2-methoxy-1,4-oxathiane (XXXVI). Distillation of XXXVI from phosphorus pentoxide gave pure XXXV via loss of the elements of methanol (72).

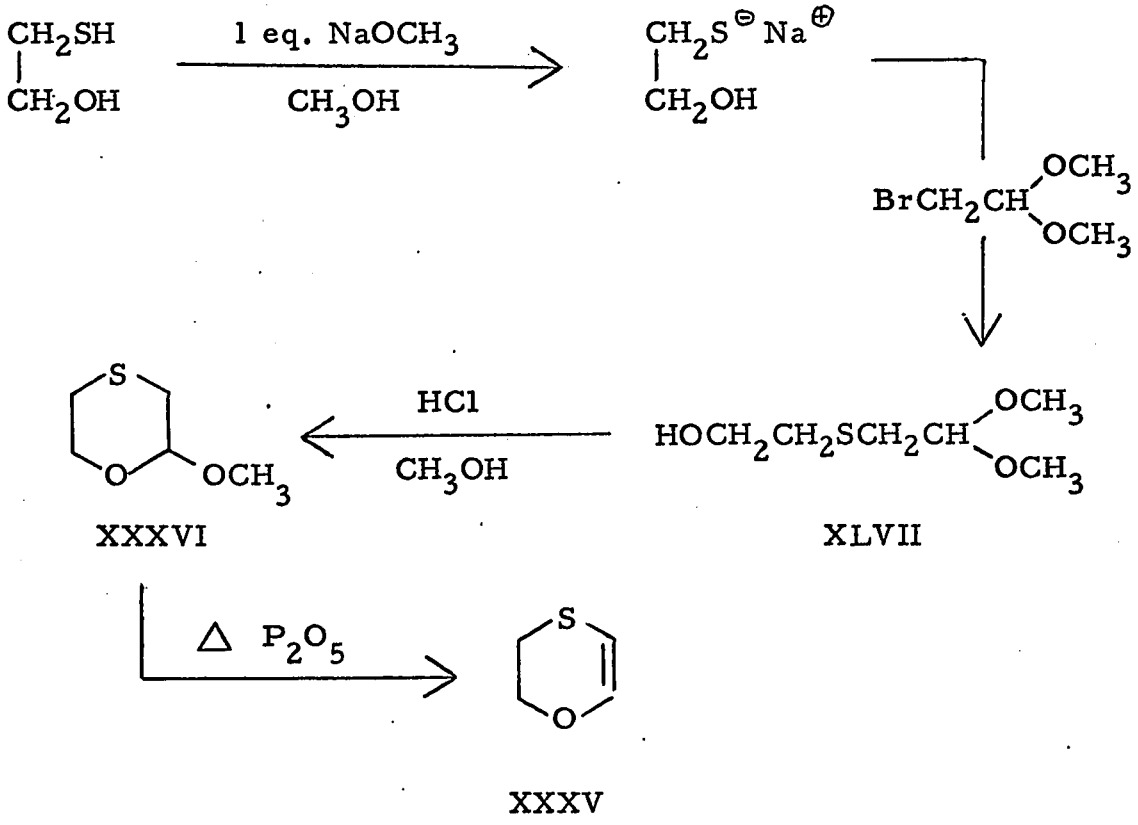


CHART 14

Samples of XXXV were then treated with 1.5 molar equivalents of acrolein (benzene solution), in a stainless steel autoclave, under a variety of different temperatures and reaction times.

In no case was evidence found for the formation of the expected product XLVI. Allowing p-oxathiene (XXXV) and acrolein to react together at 80° for a period of 5 hours resulted in a nearly quantitative

recovery of unchanged XXXV along with a small amount of an intractable residue. As reaction temperatures and times were increased the quantity of tar formed rose at the expense of XXXV. Thus, reaction of XXXV and acrolein at 210° for 12 hours resulted in only a 53% recovery of starting material (XXXV) and considerable tar formation.

The fact that the condensation process was not effective at high temperatures is perhaps not surprising in view of the thermal instability of the compounds XXVII, XXVIII and XXIX (p. 36).

(b) Via 3-chloro-2-(β-mercaptoethoxy)tetrahydropyran

A second route leading to the possible synthesis of XXXVII was formulated as shown in Chart 15. It was hoped that acid catalyzed addition of 2-mercaptoethanol to 5-chloro-3,4-dihydro-2H-pyran (XLII) would afford 3-chloro-2-(β-mercaptoethoxy)tetrahydropyran (XLVIII). Subsequent treatment of XLVIII with sodium hydride would lead to its mercaptide salt which could displace intramolecularly, the chlorine atom from C-3 and thus yield the desired product (XXXVII).

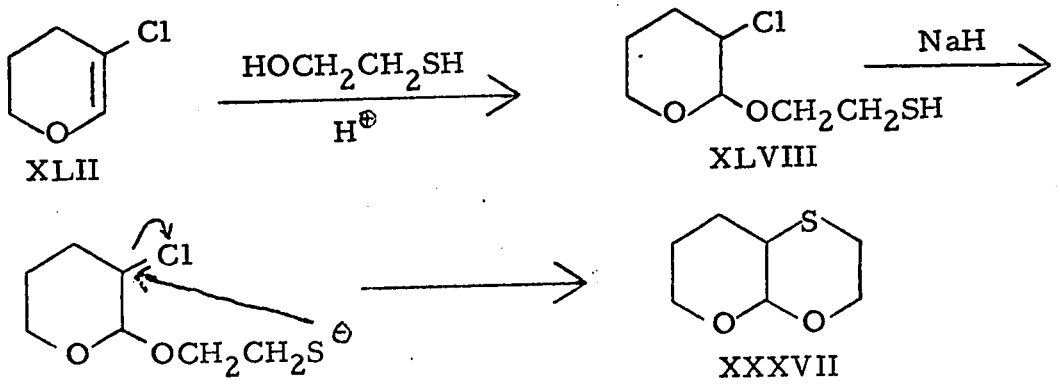


CHART 15

Accordingly, equivalent quantities of XLII and 2-mercaptoethanol were allowed to react for 48 hours at room temperature in diethyl ether containing a catalytic amount of concentrated HCl. Work-up of the reaction mixture afforded the expected product XLVIII. The 60 MHz n.m.r. spectrum (CCl_4 solvent) of XLVIII (Figure VI) showed two doublets at τ5.38 (J = 2.9 Hz) and τ5.58 (J = 4.0 Hz) which were assigned to the anomeric C-2 proton in the cis and trans isomers respectively (74). N.m.r. analysis ($CDCl_3$ solvent) of 3-chloro-2-ethoxytetrahydropyran, prepared by the acid catalyzed addition of ethanol to XLII (93), showed analogous doublets at τ5.44 (J = 2.9 Hz) and τ5.60 (J = 3.5 Hz) which were also assigned to H-2 in the cis and trans isomers respectively. The infrared (I.R.) spectrum of XLVIII showed a weak absorption at 2580 cm^{-1} which was assigned to the S-H stretching frequency of the mercapto group (Figure VII) (102).

Addition of 2-mercaptoethanol to XLII might have been expected to occur in one of two possible ways (Chart 16). Initial protonation of XLII would yield the oxocarbonium ion L. Subsequent attack of the 2-mercaptoethanol on L could then occur via sulfur or oxygen to yield either 3-chloro-2-(β-hydroxyethylthio)tetrahydropyran (LI) or the observed product XLVIII. The exclusive production of XLVIII deserves further comment.

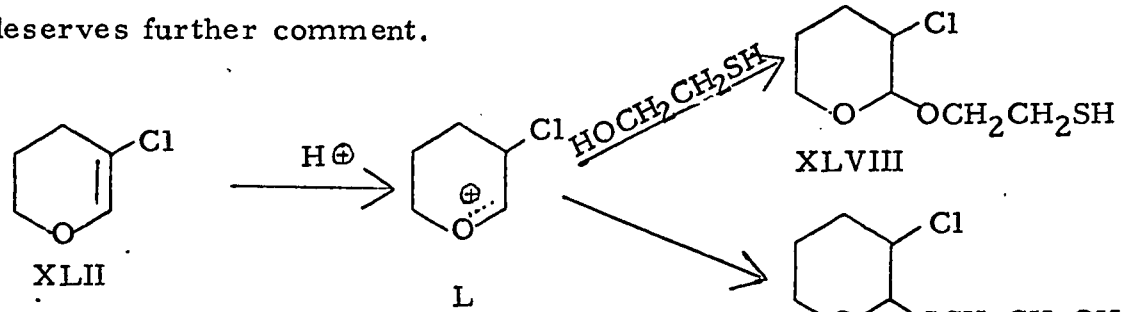


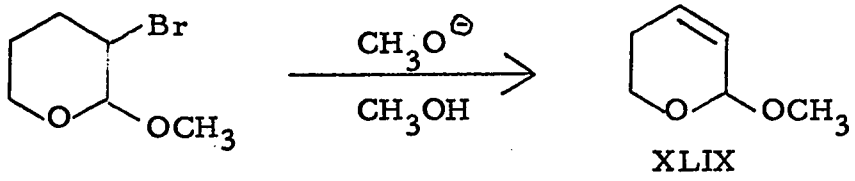
CHART 16

Although, to the author's knowledge, no systematic study has been made on the relative rates of acid catalyzed hydrolysis of acetals and oxathioacetals, Whistler and Van Es (103) have shown that methyl β-D-xylopyranoside is hydrolyzed about twice as fast as is the analogous methyl 1-thio-β-D-xylopyranoside. This suggests that, in fact, oxathioacetals are hydrolyzed more slowly than the corresponding oxygen acetals. On this basis one would have expected LI to be the preferred product above (Chart 16).

However, Tarbell and Harnish (104, 105) have reported the facile cleavage of ethers, compared to thioethers, on treatment with acidic reagents. Suter and Hanson (106) confirmed these observations by treatment of alkyl p-methoxyphenyl sulfides with a solution of HBr in acetic acid. Exclusive formation of alkyl p-hydroxyphenyl sulfides occurred. Leggetter and Brown (107) have noted that the hydrogenolysis of a number of 1,3-oxathiolanes by the mixed reagent $LiAlH_4/AlCl_3$ yielded the corresponding hydroxy-thioethers. They accounted for the selective cleavage of the oxathiolane C-O bond, rather than the C-S bond, as being due to the greater ease of coordination of oxygen, compared to sulfur, with the Lewis acid. An analogously greater affinity of oxygen for the postively charged intermediate L (Chart 16) would account for the observed course followed in the addition of 2-mercaptoethanol to 5-chloro-3,4-dihydro-2H-pyran (XLII).

Treatment of XLVIII with an equivalent quantity of sodium hydride resulted only in the recovery of unchanged starting material.

The failure of XLVIII to undergo ring closure to XXXVII under these conditions can only be accounted for by an apparent difficulty in effecting a nucleophilic displacement reaction at position C-3 of 3-substituted 2-alkoxytetrahydropyrans. This is in agreement with the observation of exclusive formation of 2-methoxy-5,6-dihydro-2H-pyran (XLIX) when 3-bromo-2-methoxytetrahydropyran was treated with sodium methoxide in refluxing methanol (Chart 17) (98).



XLIX

CHART 17

Sweet (108) has noted this same phenomenom in his attempts to effect displacement of the C-3 halogen from a number of 3-halo-2-alkoxytetrahydropyrans with a variety of nucleophiles. The stability of such a halogen to nucleophilic displacement may well be a result of the inductive effect of the two oxygen atoms on the neighbouring C-2 carbon atom. Electron withdrawing groups are known to decrease the S_N2 reactivity of compounds which possess such groups located on the carbon atom adjacent to the reactive center (111).

6. The treatment of XXVII, XXVIII and XXIX with sodium in DME

Samples of XXVII, XXVIII and XXIX were separately allowed to react with one equivalent of sodium metal in refluxing DME for 24 hours (2). In all cases, near quantitative recovery of unchanged

starting material was observed. The implications of these results along with those obtained from the similar treatment of compounds XVIII-XXII are discussed later in this dissertation (p. 109).

D. THE ATTEMPTED PREPARATION OF 3-ALKYLTHIO-2,4-DIMETHOXYTETRAHYDROPYRANS

To the authors knowledge, no report exists in the literature of the synthesis of 3-alkylthio-2,4-dimethoxytetrahydropyrans, which may be regarded as methyl S-alkyl-3-O-methyl-4,6-dideoxy-2-thio-hexopyranosides, starting from simple pyran structures. For this reason the preparation of such compounds was undertaken. These compounds should also possess chemical properties which are more closely related to those of the carbohydrates III, VIII and IX than are those of any of the simple model structures whose syntheses have been reported thus far in this dissertation (XVIII-XXII and XXVII-XXIX). Two synthetic routes were considered.

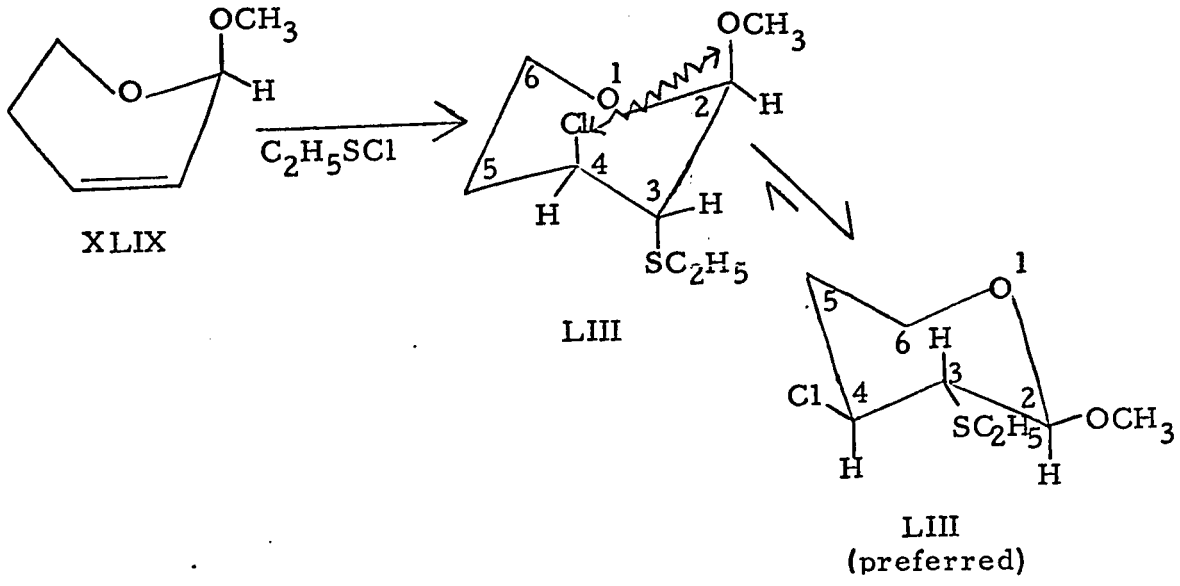
1. The attempted preparation of 3-ethylthio-2,4-dimethoxytetrahydropyran (LII) via the addition of ethanesulfenyl chloride to 2-methoxy-5,6-dihydro-2H-pyran

In 1946 Woods and Sanders (98) reported the synthesis in 51% yield of 2-methoxy-5,6-dihydro-2H-pyran (XLIX) by treatment of 3-bromo-2-methoxytetrahydropyran with an excess of sodium methoxide in refluxing methanol (Chart 17). A repetition of their procedure with subsequent analysis of the crude reaction product by

g.l.c. indicated the quantitative formation of XLIX. However on work-up of this solution the highest yields of pure XLIX obtainable were in the order of 55-60%. This was attributed to losses during solvent removal, due no doubt to the volatility of XLIX, and to losses during subsequent work-up due to the high solubility of XLIX in water.

A more productive route to the preparation of XLIX was achieved by dropwise addition of 3-bromo-2-methoxytetrahydropyran to a solution of a slight excess of sodium methoxide in anhydrous dimethyl sulfoxide at room temperature. A strongly exothermic reaction ensued and isolation of XLIX in yields of up to 80% proved possible by its direct distillation from the reaction mixture under reduced pressure.

Addition of an equivalent amount of ethanesulfenyl chloride to XLIX at -25° to -30° afforded a high yield of a product to which was assigned the structure trans, trans-4-chloro-3-ethylthio-2-methoxy-tetrahydropyran (LIII).



Such an assignment was based on (a) the fact that all ionic additions of sulfenyl halides to olefins which have been reported to date (p. 49) have led to products in which the alkylthio group and the halogen are trans to each other, and on (b) the 60 MHz n.m.r. spectrum of LIII which is shown in Figure VIII. The doublet at τ5.80 (J = 6.5 Hz) was assigned to the C-2 anomeric proton. The observed chemical shift for this signal is very close to that (τ 5.85) found for the C-2 proton in the trans isomer of 3-ethylthio-2-methoxytetrahydropyran (XXVIII) (Table 3), and is identical to that observed for the C-2 proton in the trans isomer of 2-methoxy-3-methylthiotetrahydropyran (XXVII) (Table 3). It is somewhat higher than the value found (τ5.57) for the analogous proton in the trans isomer of 3-chloro-2-methoxytetrahydropyran. The relatively large coupling constant (J = 6.5 Hz) also supports the view that this signal results from H-2 in the isomer of LIII having the methoxyl and ethylthio groups in a trans-diequatorial disposition.

Corroboration for these assignments was provided by the following spin-decoupling experiments performed on a Varian HA-100 MHz n.m.r. spectrometer. Irradiation of the proton giving the signal at 427 Hz downfield from tetramethylsilane (anomeric proton doublet) caused the collapse of the H-3 quartet at 268 Hz to a doublet having J = 7.5 Hz. This doublet must result from the coupling between H-3 and H-4. The magnitude of this coupling constant agrees well with the assigned trans-diequatorial arrangement for the C-3 ethylthio group and C-4 chlorine atom (74).

Irradiation of the proton giving the quartet at 268 Hz downfield from tetramethylsilane caused the collapse of the anomeric proton doublet at 427 Hz to a singlet and simplification of signals in the region τ6.10-τ6.40 - the expected region for appearance of signals due to the C-4 proton (109a). Analysis of the latter signals proved impossible because of their overlap with the signals due to the equatorial proton at C-6.

The preferred conformation for LIII would be that in which the halogen, ethylthio group and methoxyl group are all equatorially disposed since this would remove the serious 1,3-diaxial non-bonded interactions present in the alternate conformer having all three groups axial.

The exclusive production of LIII, above, requires further comment. If the first step in the addition of the sulfenyl halide to the olefin is considered to be episulfonium ion formation, as has been suggested by Mueller and Butler (87, 88), then electrophilic attack of the ethanesulfenyl chloride on XLIX would occur preferentially from the least hindered side of the molecule, (i.e. opposite from the side occupied by the C-2 methoxyl group which would sterically obstruct approach of the sulfenyl halide) to yield the episulfonium intermediate LIV (Chart 18).

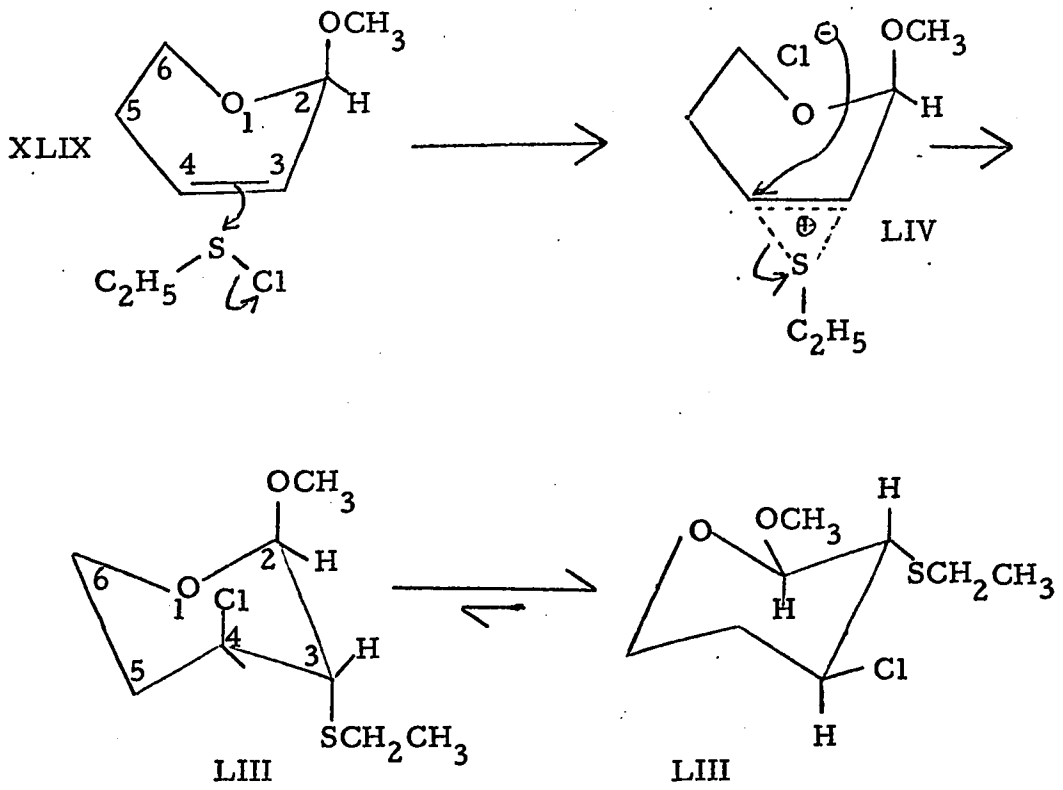


CHART 18

Subsequent attack of chloride ion could now occur at either C-3 or C-4 with simultaneous opening of the episulfonium three membered ring. Attack at C-4 appears to be favored. This course of reaction can be rationalized in terms of steric effects. Attack by chloride ion at C-4 in the trans episulfonium ion intermediate LIV would lead to the transition state represented by LV in Chart 19.

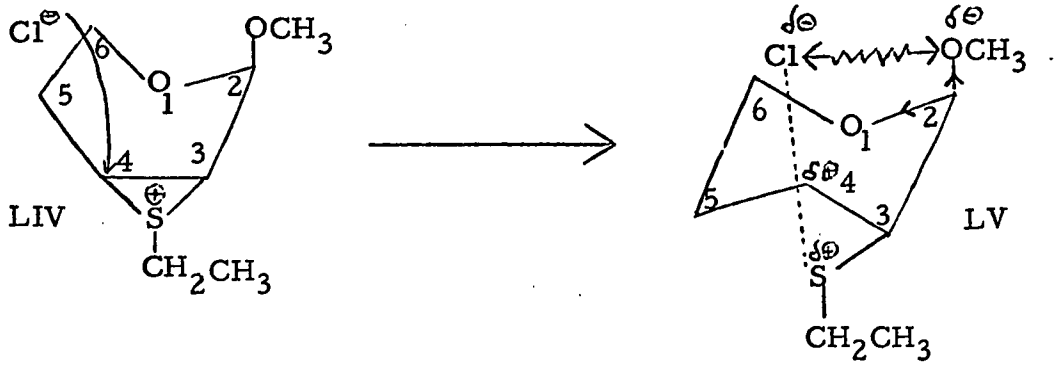


CHART 19

The geometry of this transition state (LV) places the 2-methoxy substituent in a quasi-axial position. This results in a 1,3-diaxial interaction between the incoming nucleophile and the 2-methoxyl group. On the other hand the transition state LVI (Chart 20), resulting from the chloride ion attack on C-3, appears to be far less favorable than LV. In LVI the chloride ion and the methoxyl group are strongly eclipsed. Such steric interaction would no doubt be greater than a 1,3-diaxial interaction (110). In addition, there may be an electrostatic repulsion ($Cl^{\delta\ominus} \leftrightsquigarrow O^{\delta\ominus}$) between the incoming nucleophile and the 2-methoxy oxygen atom.

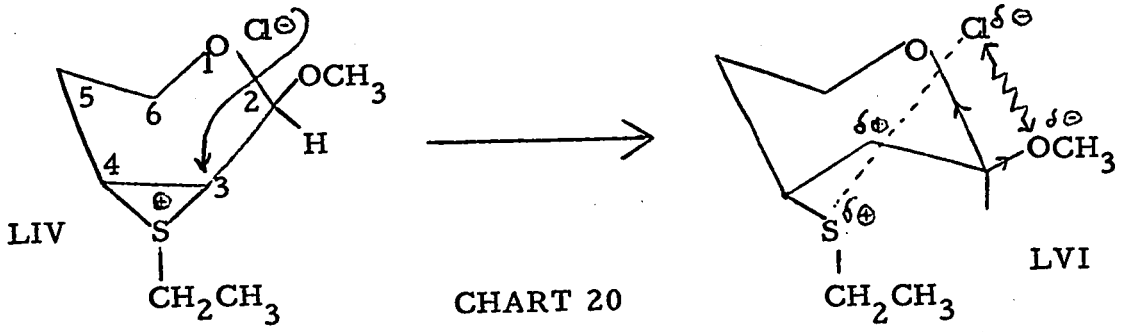
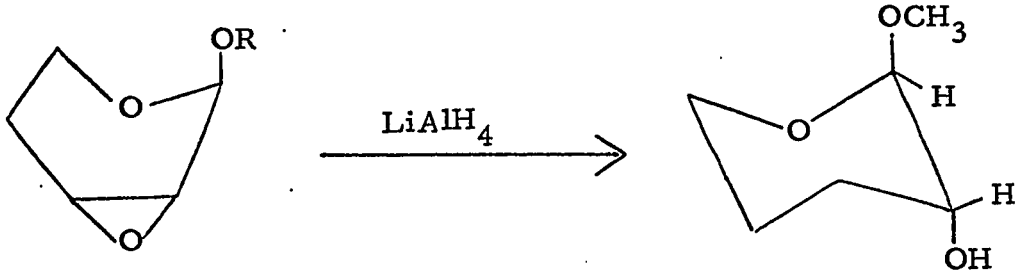


CHART 20

Inductive effects also may be responsible for preferential attack by chloride ion at C-4 in LIV. It is known (111) that electron withdrawing groups and electron releasing groups have a definite effect on the reactivity of compounds undergoing S_N2 reactions. Generally, electron withdrawing groups decrease the S_N2 reactivity when such groups are located on the carbon atom adjacent to the reactive center. As the electron attracting group is located further from the site of reaction its effect on S_N2 reactivity greatly declines (111).

Thus in the case of LIV, if we consider attack of chloride ion to proceed via a process which would probably possess substantial S_N2 character, then the reactivity at C-3 (Chart 20) would be expected to be considerably less than that at C-4 (Chart 19), resulting from the strongly electron withdrawing oxygen atoms on C-2. Even if we consider attack by chloride ion on LIV to proceed by an exclusively S_N1 process the formation of a discreet positive charge on C-3 would also be destabilized relative to the formation of a similar charge at C-4 by the inductive effects of the C-2 oxygen atoms. It would appear reasonable that a combination of both steric and electronic factors determines the direction of episulfonium ring-opening in LV.

Sweet and Brown (112) have observed the same direction of epoxide ring opening in the lithium aluminum hydride reduction of



trans-2-alkoxy-3-hydroxytetrahydropyrans. Lemieux, Kullnig and Moir (113) have reported the analogous reaction of trans-2,3-epoxy-1-methoxycyclohexane with $LiAlH_4$ which produced preferentially trans-2-methoxycyclohexanol, while with aqueous sodium hydroxide the same epoxide gave selectively 3α-methoxy-1α,2β-cyclohexanediol (Chart 21). This selective attack on the epoxide carbon remote

from the methoxy substituent was attributed to both steric and electronic factors (113).

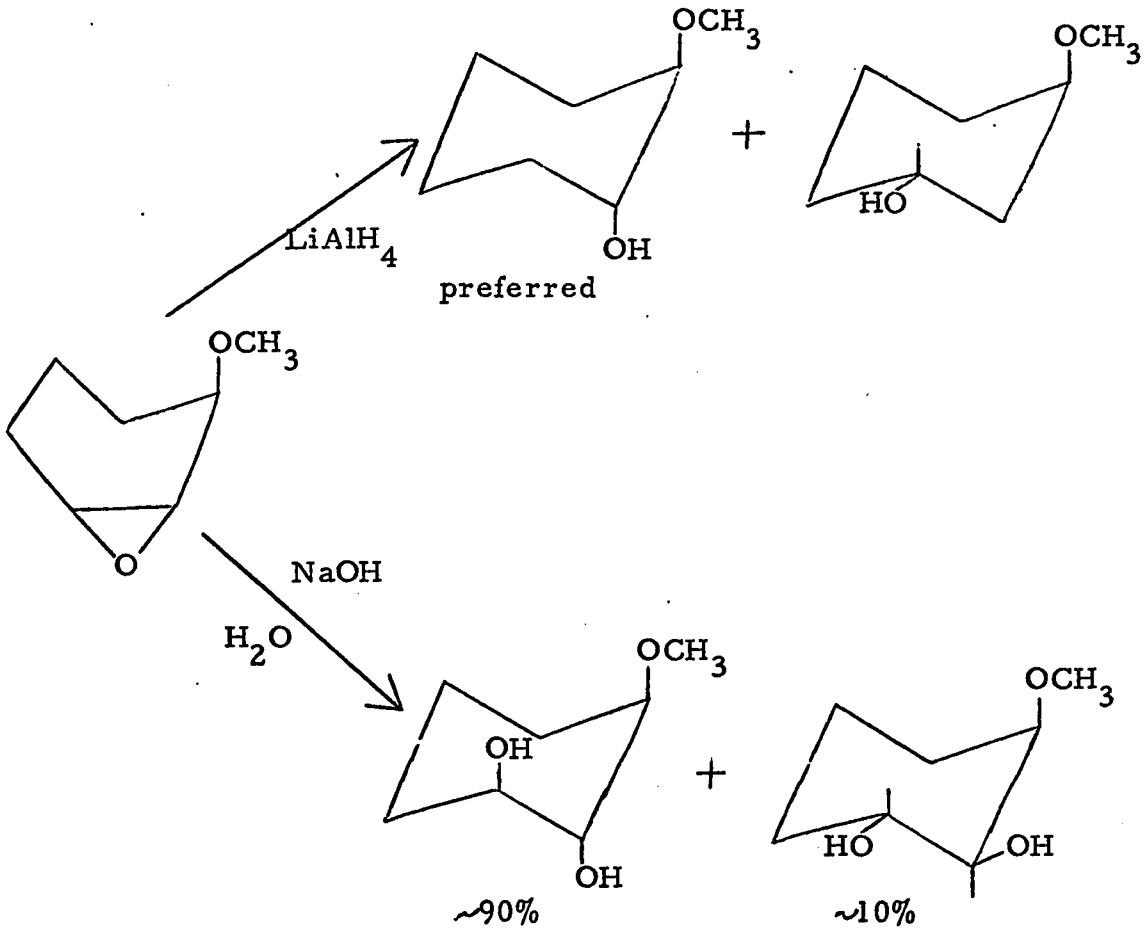


CHART 21

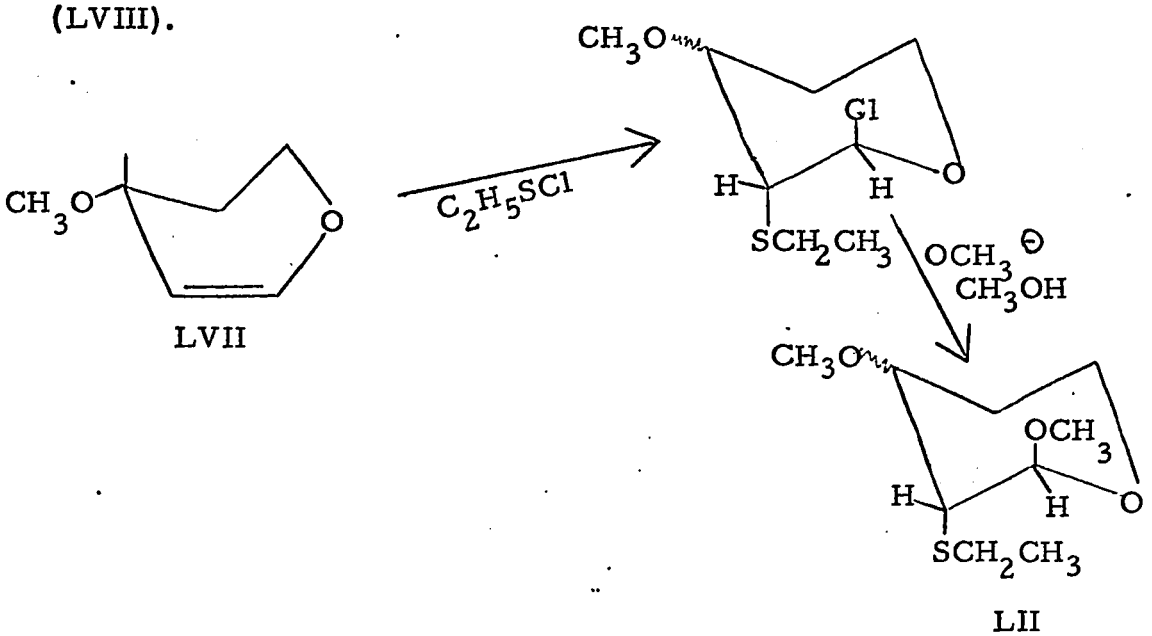
Treatment of LIII with a two-fold excess of sodium methoxide in refluxing methanol afforded a product which on n.m.r. analysis showed the presence of starting material along with an unidentified olefinic material (signals in the region τ4.0-4.5) which probably arose via base catalyzed dehydrohalogenation of LIII. No evidence could be found for the presence of the desired product 3-ethylthio-2,4-dimethoxytetrahydropyran (LII) which would have resulted from nucleophilic displacement of the C-4 chlorine atom by methoxide.

Attempts to effect a similar displacement by treatment of LIII with methanol containing an excess of silver carbonate, a method analogous to the Koenigs-Knorr procedure for the conversion of glycopyranosyl halides to methyl glycopyranosides (114), resulted in recovery of unchanged LIII only.

The C-4 halogen of LIII thus proved quite unreactive to attempted nucleophilic displacements by methoxide or methanol under the conditions employed in this laboratory.

2. The attempted preparation of 3-ethylthio-2,4-dimethoxytetrahydropyran (LII) via the addition of ethanesulfenyl chloride to 4-methoxy-3,4-dihydro-2H-pyran

A second route for the preparation of LII, somewhat analogous to that reported above, was formulated as shown in Chart 22. Its success depended on the availability of 4-methoxy-3,4-dihydro-2H-pyran (LVII). Addition of ethanesulfenyl chloride to LVII might be expected to yield 2-chloro-3-ethylthio-4-methoxytetrahydropyran (LVIII).



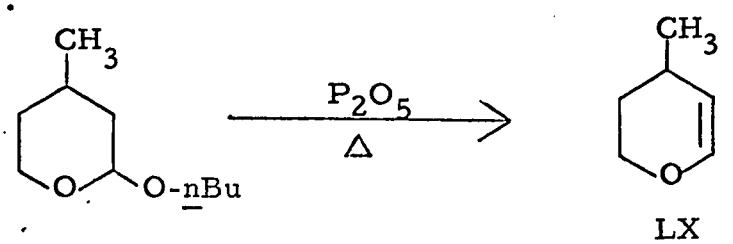
LVII

LII

This direction of reaction has already been observed for the addition of ethanesulfenyl chloride to 3,4-dihydro-2H-pyran (XXVI) (p. 49). However, the formation of the intermediate episulfonium ion in this addition process would most likely not be subject to the same steric control as was observed for the addition of ethanesulfenyl chloride to 2-methoxy-5,6-dihydro-2H-pyran (XLIX). In the former case the C-4 methoxy group would most likely be disposed in a quasi-equatorial position. The anomeric C-2 methoxyl group of XLIX would doubtless prefer a quasi-axial disposition due to the anomeric effect (80). The facile displacement of chloride ion from the α-chloroether LVIII could then be achieved by reaction with sodium methoxide in methanol, a technique already applied successfully in the preparation of the 3-alkylthio-2-methoxytetrahydropyrans XXVII, XXVIII and XXIX (p. 49).

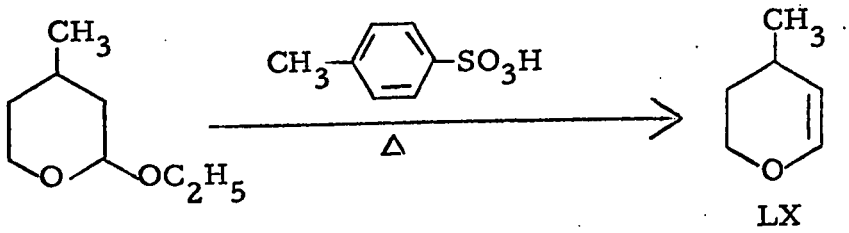
(a) The attempted preparation of 4-methoxy-3,4-dihydro-2H-pyran by the dehydromethoxylation of 2,4-dimethoxytetrahydropyran in the presence of acids.

In 1951 Parham and Holmquist (115) were able to prepare 4-methyl-3,4-dihydro-2H-pyran (LX) in 72% yield by distillation of 2-n-butoxy-4-methyltetrahydropyran from phosphorus pentoxide at 180°-190°.



LX

Twelve years later, Julia and Jacquet (116) reported the synthesis of LX by the dehydroethoxylation of 2-ethoxy-4-methyltetrahydropyran in the presence of p-toluenesulfonic acid. Accordingly



LX

2,4-dimethoxytetrahydropyran (LIX), prepared by the method of Sweet and Brown (117) involving acid catalyzed addition of methanol to 2-methoxy-5,6-dihydro-2H-pyran (XLIX), was treated, first, at 180° with a catalytic amount of phosphorus pentoxide (115). Exhaustive decomposition occurred. A repetition of this procedure, but with heating to only 130°, afforded a near quantitative yield of unchanged starting material.

Treatment of LIX with a catalytic amount of p-toluenesulfonic acid at 150° (116) resulted in the exclusive production of 2-methoxy-5,6-dihydro-2H-pyran (XLIX). This result was somewhat surprising since, of the two methoxyl groups present in LIX, the one situated at C-2 would appear to be the more acid labile. Protonation of the C-2 methoxyl group in LIX and subsequent loss of methanol would afford the oxocarbonium ion LXI (Chart 23a). This species would be expected to form somewhat more readily than that produced (LXII) by analogous reaction at the C-4 methoxyl function (Chart 23b).

Of the two possible olefins (XLIX and LXIII) which could be formed by loss of a proton either from C-3 or C-5 of LXII respect-

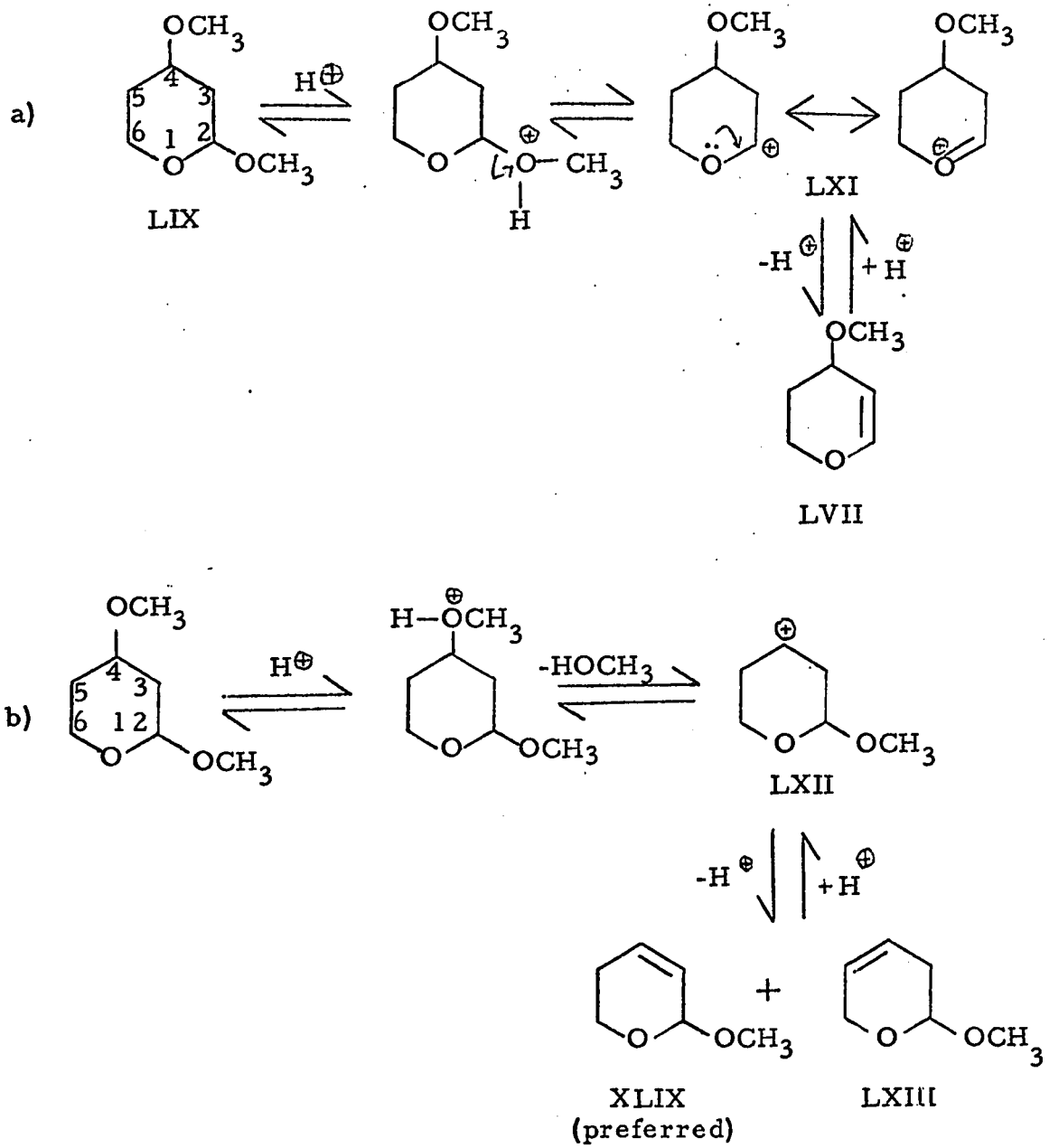


CHART 23

ively (Chart 23b), the former would be expected to predominate. The hydrogens on C-3 should be somewhat more acidic than those on C-5 due to the inductive effect of the neighbouring C-2 dioxy

function.

It therefore appears likely that XLIX must have arisen via acid catalyzed rearrangement of LVII, which would be formed first in the reaction mixture. A possible route for such a rearrangement is outlined in Chart 24.

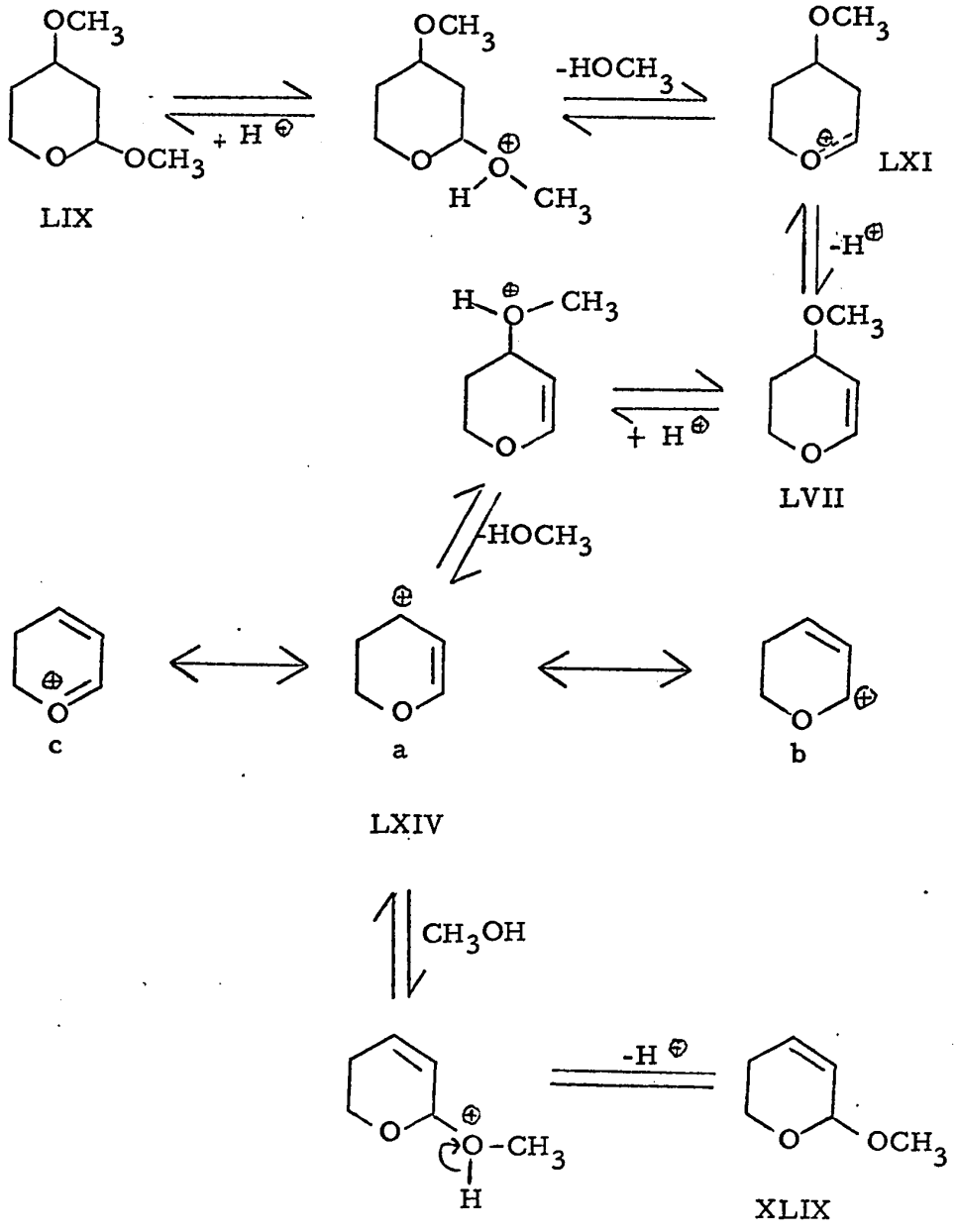
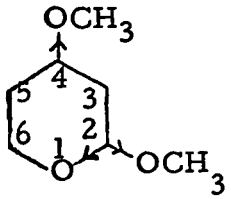


CHART 24

Of the different canonical structures (a, b, and c) which can be drawn for the ion LXIV, LXIVb might be expected to offer the greatest contribution to the overall structure of the resonance hybrid. In LXIVb the positive charge is both allylic and adjacent to an oxygen atom. Thus subsequent attack of methanol on LXIV would lead to the observed product XLIX.

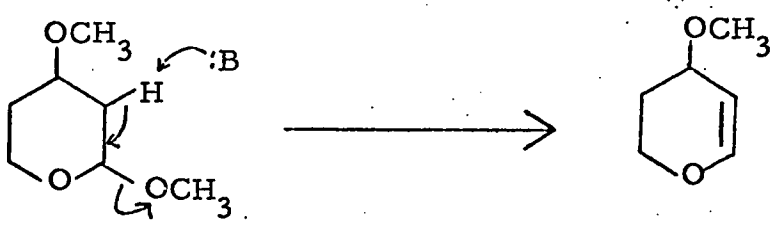
(b) The attempted preparation of 4-methoxy-3,4-dihydro-2H-pyran by the base catalyzed dehydromethoxylation of 2,4-dimethoxytetrahydropyran.

A consideration of the relative acidities of the different protons in LIX led to the conclusion that those situated on C-3 would probably be the most acidic. This was rationalized as being due to the combined inductive effects of the two oxygen atoms on the adjacent C-2 carbon atom and of the oxygen atom in the neighbouring C-4 methoxyl group. These would tend to favor carbanion formation at C-3.



LIX

It was therefore hoped that treatment of LIX with a powerful base would in fact effect proton abstraction at C-3, with elimination of the C-2 methoxyl group and formation of the desired product LVII.



LIX LVII

Accordingly LIX was allowed to react with an equivalent amount of n-butyl lithium. The choice of this reagent resulted from its high basicity but low nucleophilicity. Powerful nucleophiles (e.g. Grignard reagents) are known to displace alkoxyl groups from acetals and ketals (64). However, this procedure yielded unchanged starting material only.

(c) The attempted preparation of 4-methoxy-3,4-dihydro-2H-pyran by treatment of 3-bromo-2,4-dimethoxytetrahydropyran with zinc in ethanol or sodium in benzene.

A method commonly used for the preparation of olefins is that first realized by Boord (118) in 1930, involving the reductive displacement of a halogen and an alkoxyl group from a β-haloethyl ether on treatment with zinc metal in refluxing alcohol.

$$R-\underset{\underset{X}{|}}{CH}-CH_2OCH_3 \xrightarrow[C_2H_5OH]{Zn} RCH=CH_2 + Zn(OCH_3)X$$

X = halogen

The method has been adapted to the synthesis of olefinic haloethers by the action of zinc and alcohol on dibromoacetals (119). A similar elimination from α-halo-orthoesters occurs by means of

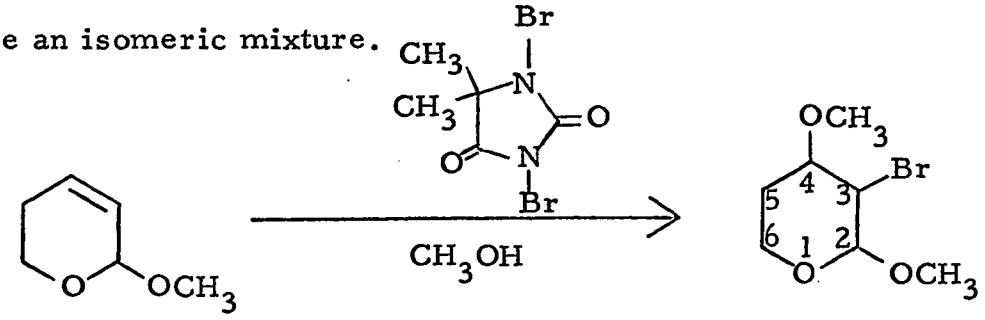
$$CHBr_2-CH(OR)_2 \xrightarrow[C_2H_5OH]{Zn} BrCH=CH-OR$$

sodium sand in refluxing benzene and has led to the formation of ketene acetals (120).

$$R-\underset{\underset{Br}{|}}{CH}-C(OC_2H_5)_3 \xrightarrow[C_6H_6]{Na} RCH=C\begin{matrix}OC_2H_5\\OC_2H_5\end{matrix}$$

It was therefore hoped that treatment of 3-bromo-2,4-dimethoxy-tetrahydropyran (LXV) under the above reaction conditions would result in the formation of LVII via elimination of the C-3 bromine atom and the C-2 methoxyl group.

Preparation of LXV was achieved by application of the bromo-methoxylation technique of van de Sande and Kopecky (121) to 2-methoxy-5,6-dihydro-2H-pyran (XLIX). Treatment of XLIX with an ether/methanol solution of 1,3-dibromo-5,5-dimethylhydantoin (LXVI) afforded a high yield of LXV which proved on n.m.r. analysis to be an isomeric mixture.



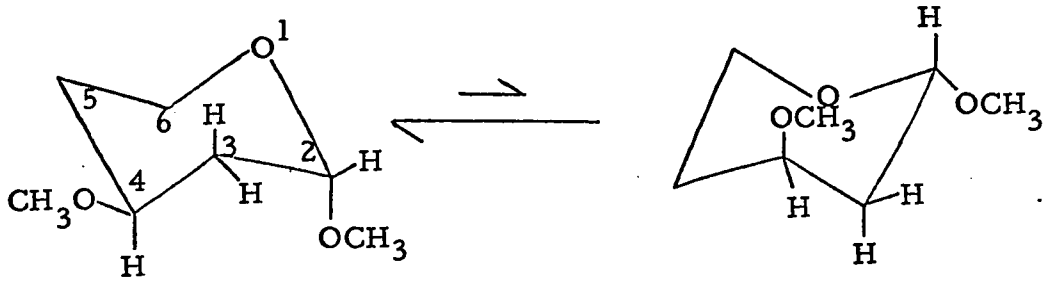
XLIX LXV

The 100 MHz n.m.r. spectrum of LXV is shown in Figure IX. The doublets at τ5.21 (J = 2.6 Hz) and τ5.62 (J = 7.5 Hz) were assigned to the H-2 anomeric proton in the isomers of LXV having the C-3

bromine atom and C-2 methoxyl group cis and trans respecively (74). The relatively large coupling constant (7.5 Hz) observed for the higher field doublet suggests that in the trans isomer both the C-3 halogen and C-2 methoxyl group are equatorially disposed (74). Integration of these two signals indicated the presence of the cis and trans isomers in the ratio 1:2.

Further evidence for the validity of the structure assigned to LXV was provided by the following experiment. Catalytic hydrogenation of the mixture of isomers obtained above, in the presence of sodium methoxide to prevent anomerization during reduction, afforded an isomeric mixture of 2,4-dimethoxytetrahydropyran (LIX) in the ratio cis : trans = 2:1, thereby proving that the halogen of LXV had in fact been located at C-3.

The structures of cis- and trans-2,4-dimethoxytetrahydropyran (LIX) can be written in alternate chair conformations, as represented in Chart 25.

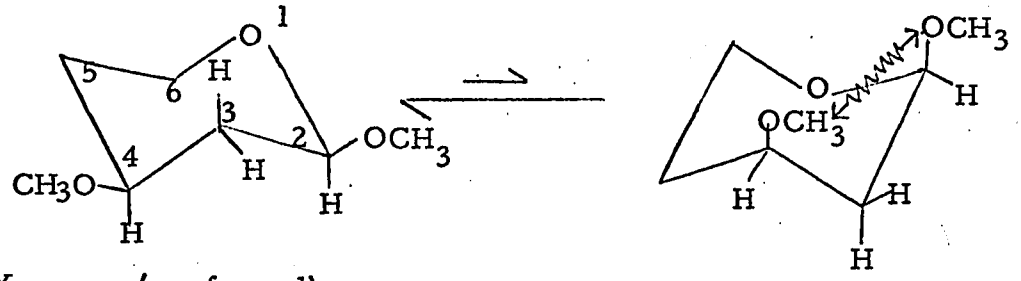


LIX (preferred)

trans-isomer H-2 τ5.28

$J_{2,3e} = J_{2,3a} = 2.9$ Hz

CHART 25



LIX (preferred)

cis-isomer H-2 τ5.68

$J_{2,3_a}$ = 8.3 Hz

$J_{2,3_e}$ = 2.8 Hz

CHART 25

The cis-isomer (Chart 25) undoubtedly exists primarily in the conformation in which both methoxyl groups are in equatorial positions. In this conformation an unfavorable 1,3-diaxial interaction between the two methoxyl groups is avoided (112). Such a conformation is consistent with the n.m.r. spectrum of LIX in which the signal at τ5.68 (quartet: $J_{2,3_a}$ = 8.3 Hz, $J_{2,3_e}$ = 2.8 Hz) had been assigned to the H-2 proton in the cis isomer (117).

The remaining H-2 signal, a triplet at τ5.28 (J = 2.9 Hz) was assigned to the trans isomer (117). As shown in Chart 25 the trans isomer can exist in what appears to be two equivalent forms. The fact that the signal for H-2 in this isomer appears at lower field than that for the corresponding cis-isomer, and that it is a triplet, suggests that in fact the preferred conformation in this case is that wherein the C-2 methoxyl group is axial. Such a conformation

would be favored by the anomeric effect (80).

Since the bromomethoxylation of XLIX should lead to products in which the halogen and methoxyl group are trans to each other (123) then the preferred conformations of the cis and trans isomers of LXV will be as shown in Chart 26.

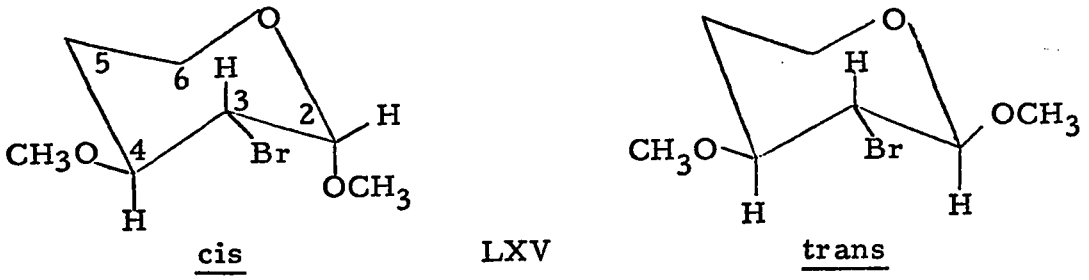


CHART 26

The above data also confirms that the isomeric ratio for LXV must then be cis : trans = 1 : 2 (Chart 26). The predominance of the trans isomer can be rationalized in terms of a preferred trans attack of the 1,3-dibromo-5,5-dimethylhandantoin (LXVI) on XLIX. Such an attack would avoid interaction of LXVI with the quasi-axial C-2 methoxyl group (Chart 27).

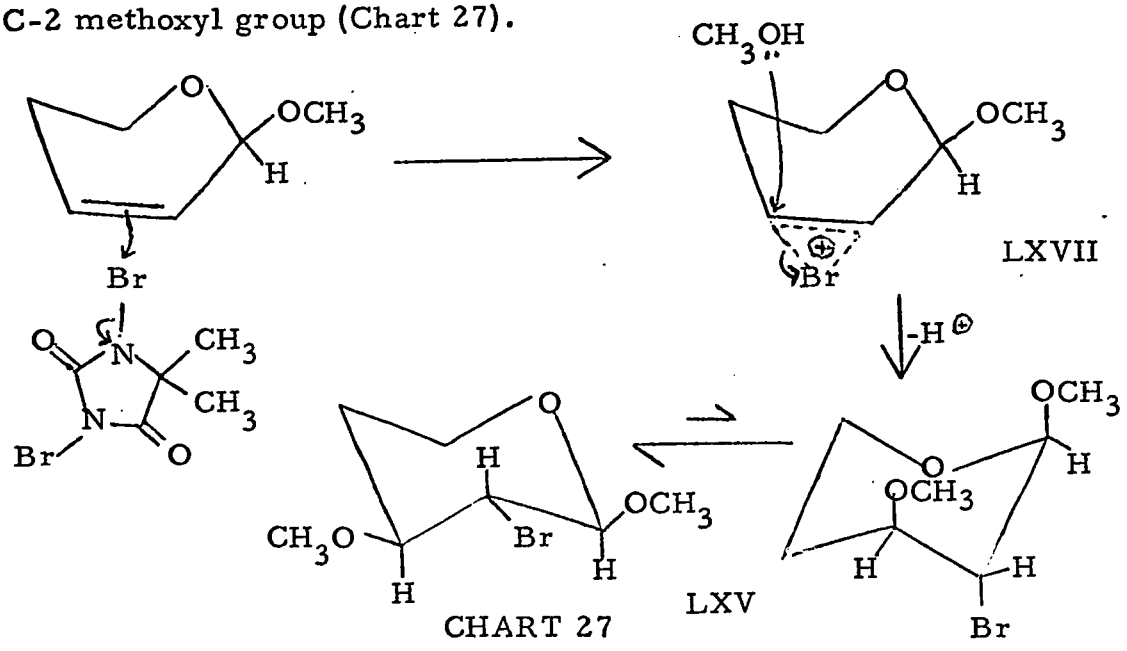


CHART 27

Consideration of the two possible transition states that can play a part in attack by methanol on the intermediate bromonium ion (LXVII) (Chart 28) leads to the conclusion that the most stable form would be the one involving attack at C-4.

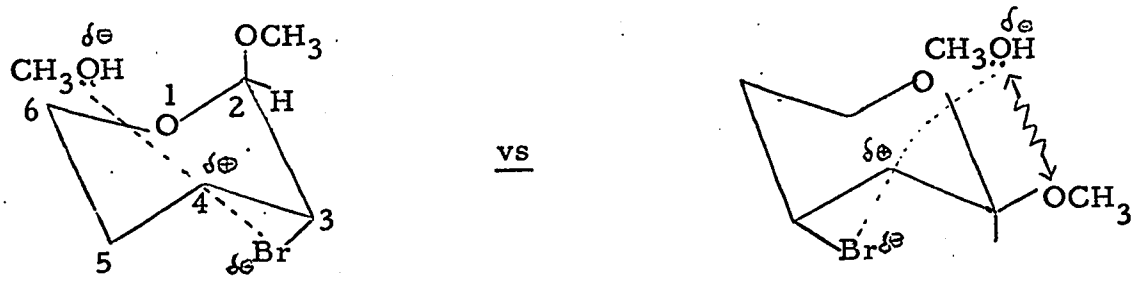


CHART 28

Opening of LXVII by methanol can be regarded as analogous to opening of the episulfonium ion LIV by chloride ion in the addition of ethanesulfenyl chloride to 2-methoxy-5,6-dihydro-2H-pyran (XLIX) (Charts 19 and 20). The factors influencing the latter ring opening process have been discussed earlier in detail (p. 74).

Treatment of LXV with a two molar excess of zinc in refluxing ethanol according to the method of Boord and coworkers (118) afforded mainly unchanged starting material along with a small amount of 2-methoxy-5,6-dihydro-2H-pyran (XLIX). No evidence could be found for the presence of the desired product LVII.

Reaction of LXV with two equivalents of powdered sodium in refluxing benzene (120) resulted in the isolation of unchanged starting material only. Since again no evidence was found for the formation of LVII work on this type of reaction was not pursued further.

(d) The attempted preparation of 4-methoxy-3,4-dihydro-2H-pyran by pyrolysis of the carbonate and acetate esters of 2-hydroxy-4-methoxytetrahydropyran.

A valuable synthetic route for the preparation of olefins is the pyrolysis of the acetate esters of alcohols (124). In the case of primary and secondary alcohols yields of the olefinic product are generally good.

$$RCH_2CH_2OH \xrightarrow[C_5H_5N]{(CH_3CO)_2O} RCH_2CH_2OCOCH_3 \xrightarrow{\Delta} RCH{=}CH_2$$

A significant aspect of such a pyrolysis reaction is that the product usually contains no isomeric olefins (124).

More recently Bailey and Baylouny (125) have reported the preparation of olefins by pyrolysis of the carbonate esters of alcohols. This technique has an advantage over acetate pyrolysis in that somewhat lower temperatures can be employed than those used for the latter process, and in the formation of carbon dioxide and an alcohol as by-products, rather than acetic acid.

Thus the preparation of the acetate and carbonate esters of 2-hydroxy-4-methoxytetrahydropyran (LXVIII) was undertaken.

The conversion of 2,4-dimethoxytetrahydropyran (LIX) to LXVIII was effected by solution of LIX in a mixture of water/DME (3:1 v/v) containing Amberlite I.R. 120 ion exchange resin. After the reaction mixture was stirred for 48 hours at room temperature,

a 65% yield of LXVIII was obtained. N.m.r. analysis of LXVIII showed it to be a mixture of cis and trans isomers. The 60 MHz n.m.r. spectrum of LXVIII (CCl_4 solvent) showed two broad poorly resolved signals at τ4.86 and τ5.40 which were assigned to the C-2 anomeric proton in the trans and cis isomers respectively. However, the 100 MHz n.m.r. spectrum (D_2O solvent) of LXVIII gave rise to two clearly resolvable signals for H-2 which are discussed below.

The structures of cis- and trans-2-hydroxy-4-methoxytetrahydropyran can be written in alternate chair conformations as represented in Chart 29.

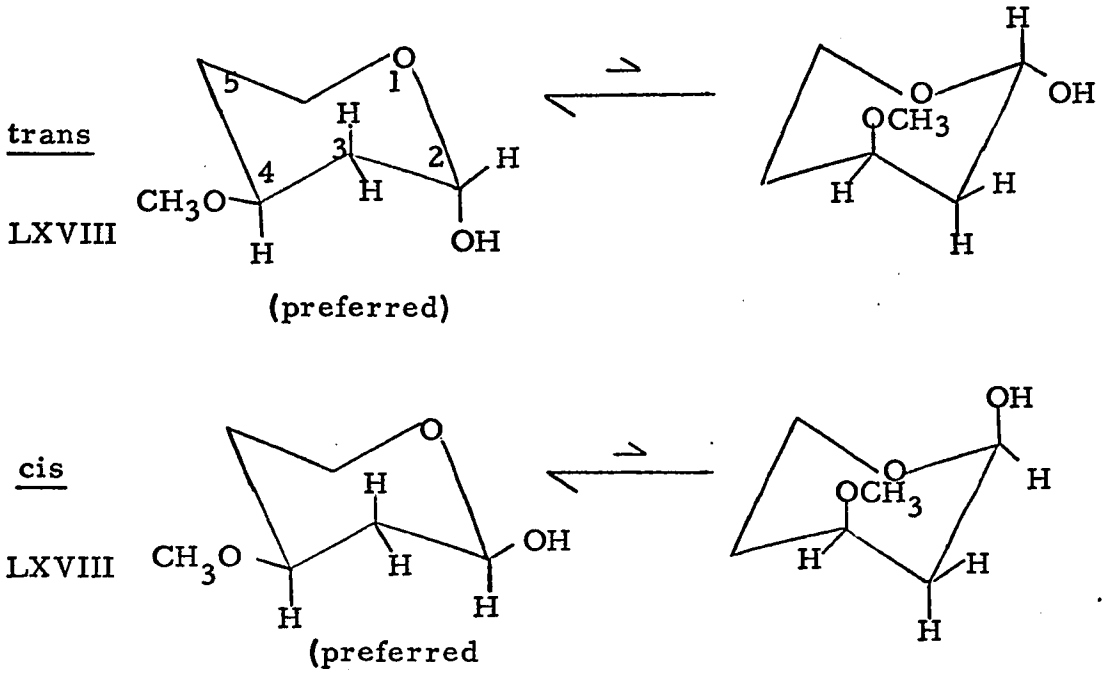


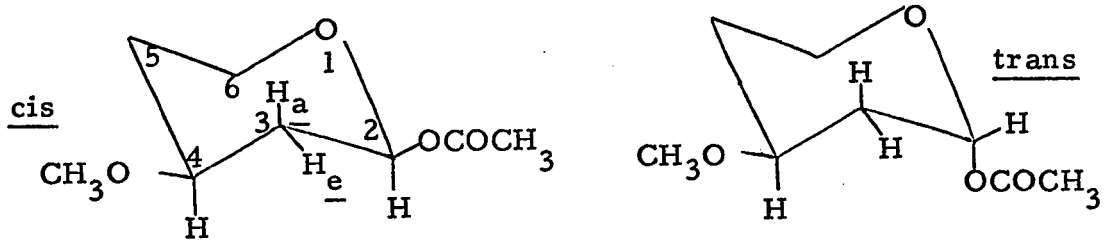
CHART 29

The appearance of the anomeric C-2 proton signals in the 100 MHz n.m.r. spectrum (D_2O solvent) of LXVIII, as a triplet at τ4.80 (J = 3.7 Hz) and a quartet at τ5.28 ($J_{H_2,H_{3_a}}$ = 7.5 Hz; $J_{H_2,H_{3_e}}$ =

2.0 Hz) suggested, by analogy with the n.m.r. spectrum of 2,4-dimethoxytetrahydropyran (LIX) discussed earlier (p. 88), that the cis and trans isomers of LXVIII exist in the preferred conformations shown (Chart 29). Integration of the C-2 anomeric proton signals indicated the presence of the cis and trans isomers of LXVIII in the ratio 1 : 1. Thus the free energy difference between the two isomers is 0 kcal/mole. Inspection of the preferred conformers of cis and trans-2-hydroxy-4-methoxytetrahydropyran (LXVIII) (Chart 29), suggests that the conformer possessing an equatorial hydroxyl group at C-2 should be preferred over that having an axial hydroxyl group at C-2 by 0.9 kcal/mole, as a result of the interaction of the axial hydroxyl group in the latter with two syn-axial hydrogens (at C-4 and C-6) (126). The equilibrium composition observed above (1 : 1) indicates that the value of the anomeric effect for LXVIII must then also be 0.9 kcal/mole. Sweet and Brown (117) have calculated the anomeric effect for 2,4-dimethoxytetrahydropyran to be 1.42 kcal/mole. The somewhat smaller value observed for LXVIII in aqueous solution is not surprising since it is known that the anomeric effect on free hydroxyl groups in aqueous solution is generally less than that for methoxyl or acetoxyl groups because of the high dielectric constant of water (127). Thus, in the equilibrium mixture of glucose in aqueous solution, the β-pyranose form (with equatorial OH) predominates to the extent of 64% (127).

Treatment of the cis, trans mixture of LXVIII with acetic anhydride in pyridine (128) yielded 2-acetoxy-4-methoxytetrahydro-

pyran (LXIX). The 60 MHz n.m.r. spectrum ($CDCl_3$ solvent) of LXIX is shown in Figure X. The signals at τ3.88 (triplet: J = 3.0 Hz) and at τ4.34 (quartet $J_{2,3_a}$ = 7.5 Hz, $J_{2,3_e}$ = 3.0 Hz) were assigned to the H-2 anomeric protons in the trans and cis isomers respectively. The preferred conformers of cis- and trans-2-acetoxy-4-methoxytetrahydropyran (LXIX) are represented in Chart 30 (cf. p. 87).



LXIX

Preferred conformations of cis- and trans-2-acetoxy-4-methoxytetrahydropyran.

CHART 30

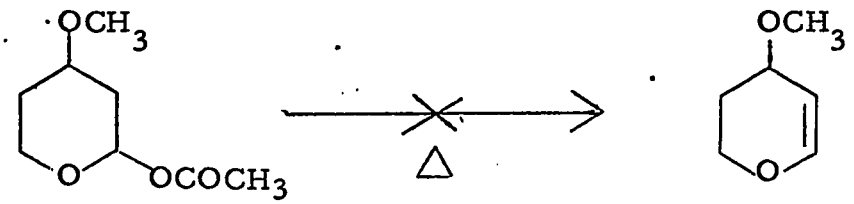
The ratio of cis to trans LXIX obtained above was identical (1 : 1) to that obtained for the starting material (LXVIII) used. This is not surprising since in the basic (pyridine) esterification medium no anomerization would be expected to occur.

In an experiment designed to permit calculation of the value of the anomeric effect for 2-acetoxy-4-methoxytetrahydropyran (LXIX) the cis-trans mixture of this compound, obtained above, was dissolved in glacial acetic acid containing a catalytic amount of p-toluenesulfonic acid, and the solution stirred at room temperature for 24 hours.

Anderson and Sepp (129) have used the same procedure in their calculation of the anomeric effect for 2-acetoxy-4-methyltetrahydropyran.

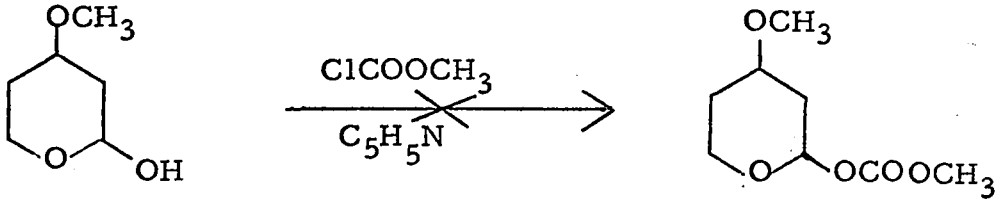
However, in the present case, darkening of the solution occurred within one hour, and n.m.r. analysis of the crude reaction product indicated the complete absence of the signals (τ3.88 and τ4.34) assigned to the anomeric C-2 proton in LXIX. A comparison of the basicities of the oxygen atoms in LXIX suggests that protonation would probably occur at either the ring oxygen atom or the C-4 methoxyl group oxygen atom rather than at the C-2 acetoxy group oxygen atom. Hence, simple anomerization would not be preferred.

Pyrolysis of LXIX at temperatures of 180° and 290° resulted only in extensive decomposition. No evidence could be found for the presence of the desired product 4-methoxy-3,4-dihydro-2H-pyran (LVII).



LXIX LVII

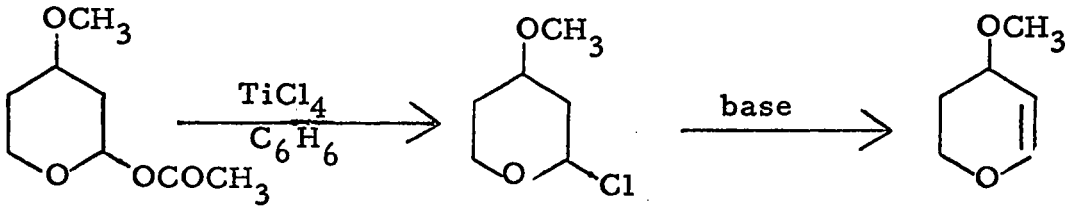
Attempted preparation of the carbonate ester (LXX) of LXVIII by reaction of LXVIII with methyl chloroformate in pyridine (125) resulted only in recovery of unchanged starting material in high yield.



LXVIII LXX

(e) The attempted preparation of 4-methoxy-3,4-dihydro-2H-pyran by dehydrohalogenation of 2-chloro-4-methoxytetrahydropyran.

Lemieux and Brice (130) have reported the synthesis of tetra-O-acetyl-β-D-glucopyranosyl chloride by treatment of β-D-glucose pentaacetate with titanium tetrachloride in benzene. It was therefore hoped that analogous treatment of 2-acetoxy-4-methoxytetrahydropyran (LXIX) would afford 2-chloro-4-methoxytetrahydropyran (LXXI). LXXI, on subsequent reaction with base, should undergo facile dehydrohalogenation and yield the desired vinyl ether (LVII) (Chart 31). Accordingly LXIX was allowed to react with $TiCl_4$ as



LXIX LXXI LVII

CHART 31

described (130). Within five minutes the reaction mixture became black and attempted work-up yielded only an intractable tar.

At this point in the work, further attempts to synthesize 3-alkylthio-2,4-dimethoxytetrahydropyrans were abandoned.

E. THE PREPARATION OF METHYL S-BENZYL-4,6-O-ETHYLIDENE-3-O-METHYL-2-THIO-β-D-ALTROPYRANOSIDE AND ITS REACTION ON TREATMENT WITH SODIUM METAL IN DME.

In the view of the failure of model compounds XVIII-XXII and XXVII-XXIX to undergo any elimination reaction on treatment with sodium metal in refluxing DME it was decided to investigate the possibility of further examples of this type of elimination process in the field of carbohydrates. Examination of the structures of the three compounds III, VIII and IX, which had been observed to yield olefinic products on treatment with sodium, or with a variety of bases, in DME (2, 3), indicated that the following features were common to all of them:

i) They were conformationally rigid.

ii) They possessed an alkylthio group at C-2*.

iii) They had methoxyl groups at both C-1 and C-3 which were axially disposed and which therefore would give rise to a significant 1,3-diaxial interaction.

In order to establish the possible importance of the latter feature in relation to the elimination process observed (2, 3) the synthesis was undertaken of a compound in which such a 1,3-diaxial interaction would be absent, but which would nevertheless fulfill the conditions of conformational rigidly and possession of a C-2 alkyl-

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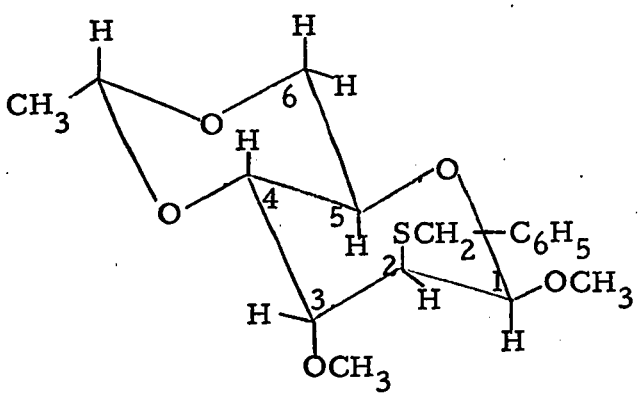
* The numbering system of the carbohydrates assigns the anomeric carbon atom as C-1.

thio group. Such a compound would be methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-β-D-altropyranoside (LXXII).



LXXII

1. The preparation of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-β-D-altropyranoside (LXXII).

Nayak, Sharma and Brown (3) have reported the synthesis of methyl 4,6-O-ethylidene-3-O,S-dimethyl-2-thio-β-D-altropyranoside (LXXIII) by the sequence of reactions shown in Chart 32. Reaction of methyl β-D-glucopyranoside with 1,1-dimethoxyethane in the presence of a catalytic amount of sulfuric acid afforded methyl 4,6-O-ethylidene-β-D-glucopyranoside (LXXIV) (131).

Subsequent treatment of LXXIV with an excess of p-toluenesulfonyl chloride in pyridine gave a high yield of methyl 4,6-O-ethylidene-2,3-di-O-p-toluenesulfonyl-β-D-glucopyranoside (LXXV) (132). A refluxing solution of LXXV in methanol, containing two equivalents of sodium methoxide, gave methyl 2,3-anhydro-4,6-O-ethylidene-β-D-allopyranoside (LXXVI) (132), which on reaction with sodium methyl mercaptide in methanol afforded methyl 4,6-O-ethylidene-S-methyl-2-thio-β-D-altropyranoside (LXXVII). Methylation of

LXXVII by the method of Diner, Sweet and Brown (113) gave a quantitative yield of the product LXXIII.

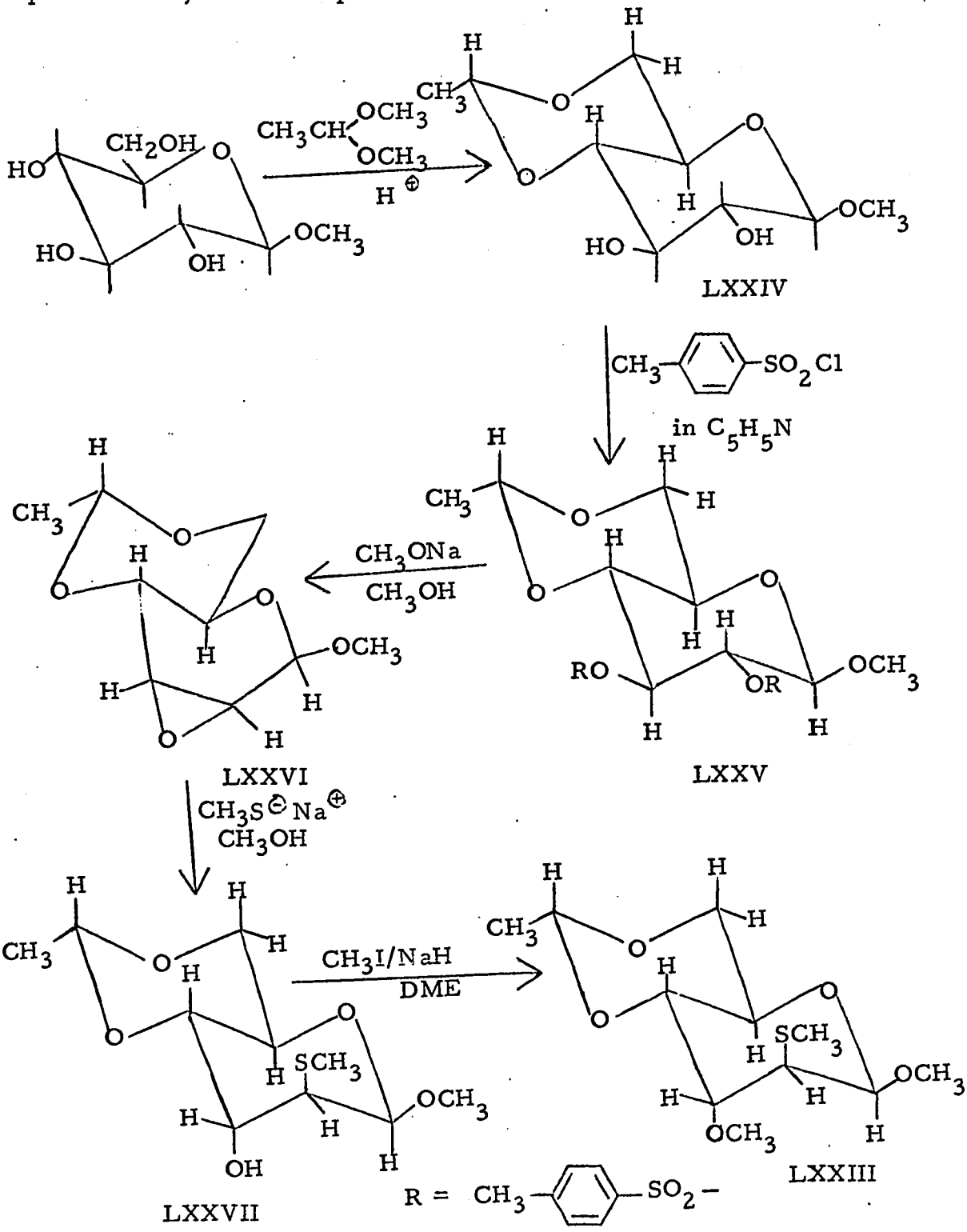


CHART 32

In the present case, LXXVI was prepared according to published directions (131, 132) and then subjected to reaction with sodium benzyl mercaptide in methanol to yield methyl S-benzyl-4,6-O-ethylidene-2-thio-β-D-altropyranoside (LXXVIII) (Chart 33). Methylation of LXXVII with CH_3I/NaH in DME (113) afforded a high yield of the desired product methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-β-D-altropyranoside (LXXII) (Chart 33).

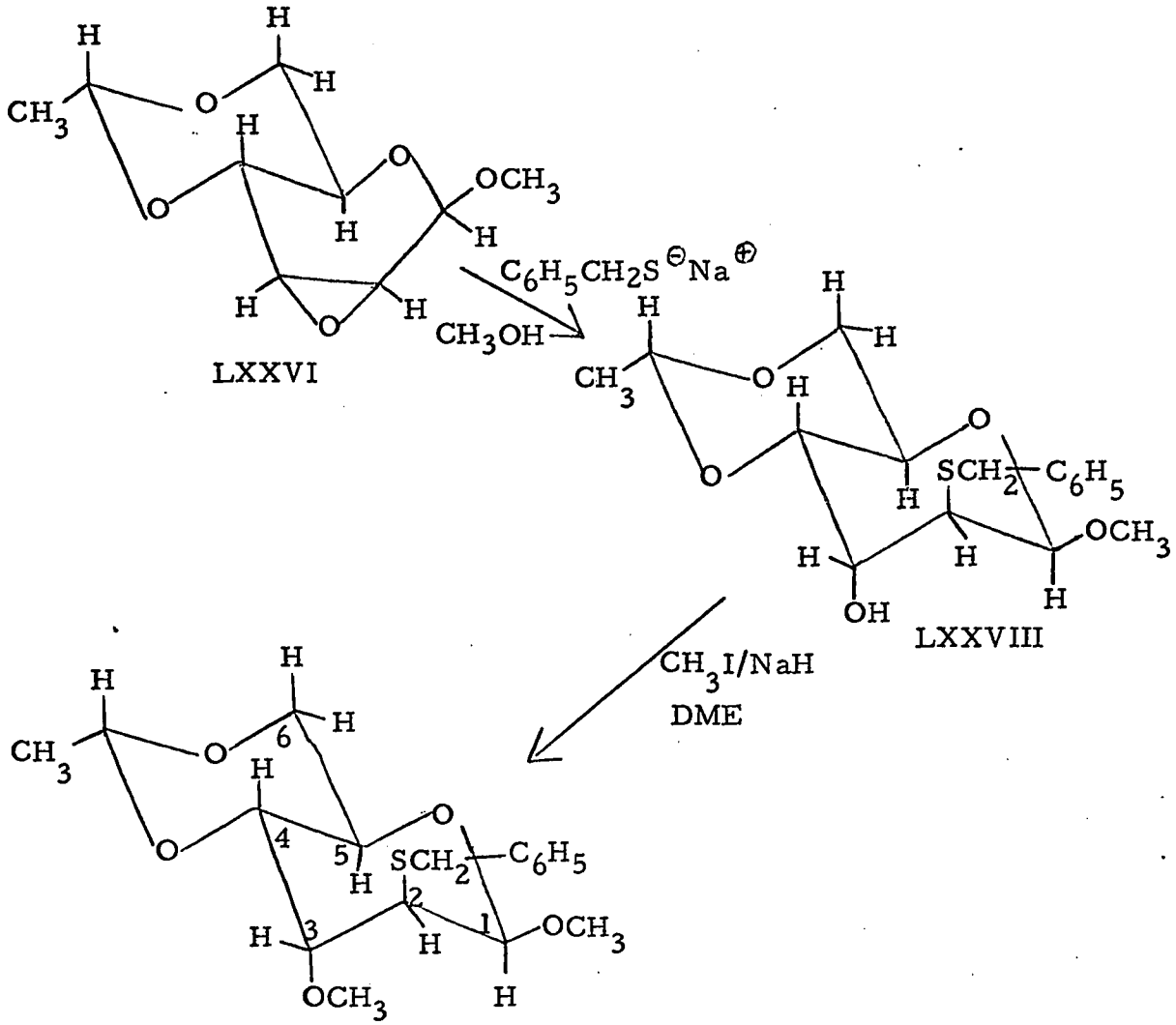


CHART 33

The 60 MHz n.m.r. spectrum of LXXII ($CDCl_3$ solvent) is shown in Figure XI. The doublet at τ 5.15 (J = 2.0 Hz) was assigned to the C-1 anomeric proton and the triplet at τ 6.94 to the C-2 proton. The 100 MHz n.m.r. spectrum of LXXII resolved the latter signal into a quartet having $J_{1,2}$ = 2.0 Hz and $J_{2,3}$ = 3.3 Hz. These couplings are compatible with the trans-diaxial relationship of the C-2 benzylthio group and the C-3 methoxyl group, and the cis relationship between the groups at C-1 and C-2.

Confirmation for these assignments was afforded by the following experiment performed on a Varian HA 100 MHz n.m.r. spectrometer. Irradiation at 480 Hz downfield from tetramethylsilane (anomeric C-1 proton doublet) caused collapse of the quartet at 302 Hz (C-2 proton) to a doublet having a spacing of 3.3 Hz. This figure must then represent the coupling constant $J_{2,3}$. Irradiation at 302 Hz downfield from tetramethylsilane (H-2) caused the collapse of the doublet at 480 Hz to the singlet. Unfortunately the position of the H-3 signals could not be located with certainty because of the interference of beat frequencies.

A comparison of Figure XI with the 60 MHz n.m.r. spectrum* of methyl 4,6-O-ethylidene-3-O,S-dimethyl-2-thio-β-D-altropyranoside (LXXIII) showed striking similarities. Thus, in the n.m.r. spectrum of LXXIII, Sharma (134) assigned the doublet at τ5.15 (J = 2.0 Hz) to the anomeric C-1 proton, and the poorly resolved quartet at τ6.92 ($J_{1,2}$ = 2.0 Hz: $J_{2,3}$ = 3.3 Hz) to the proton at C-2.

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* Kindly furnished by Dr. M. Sharma

A second route leading to the synthesis of LXXII was also investigated. Nayak, Sharma and Brown (3) have reported the isolation of a 35% yield of methyl 4,6-O-ethylidene-3-O,S-dimethyl-β-D-altropyranoside (LXXIII) by the trans-acetalation of methyl 4,6-O-benzylidene-3-O,S-dimethyl-2-thio-α-D-altropyranoside (VIII) in 1,1-dimethoxyethane containing a catalytic amount of concentrated sulfuric acid (Chart 34). Not only had trans-acetalation occurred,

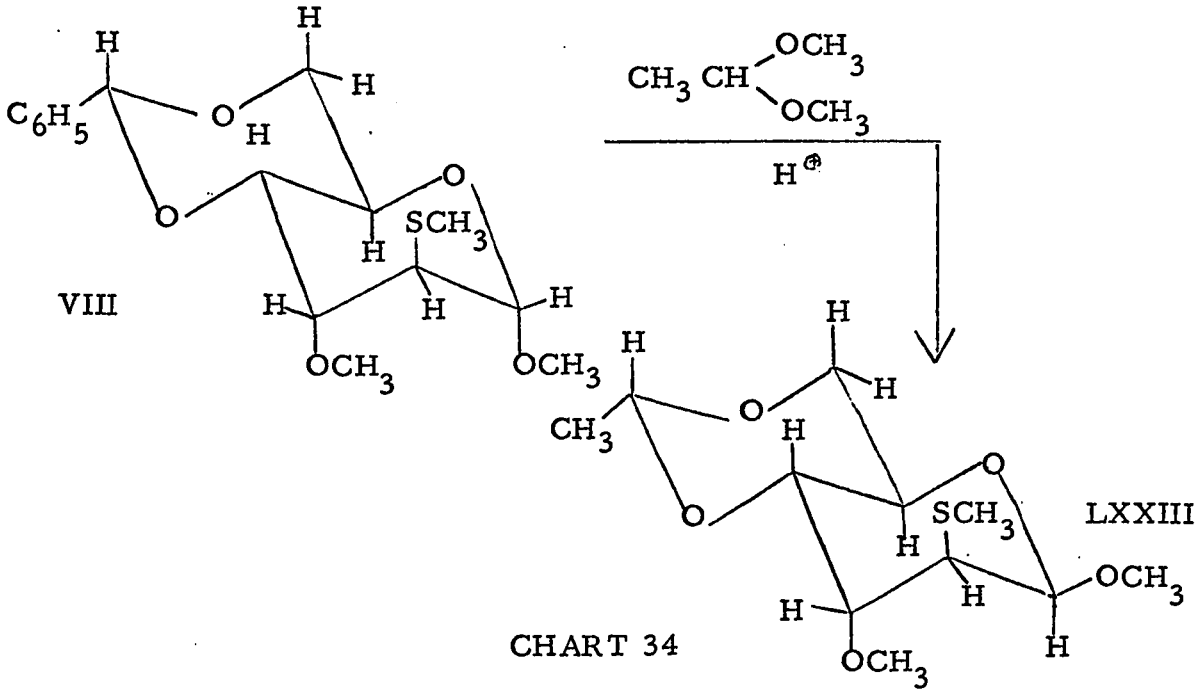


CHART 34

but also anomerization at C-1. This is understandable in view of the 1,3-diaxial interaction present in VIII, which would tend to favor production of the β-anomer (C-1 methoxyl group equatorial). Anomerization would no doubt be assisted by anchimeric participation of the C-2 methylthio group in stabilizing a positive charge at C-1 through formation of an episulfonium ion and thus facilitate removal of the C-1 methoxy group in the α isomer. No such assistance would occur in the β isomer, hence the β isomer would accumulate.

It was therefore anticipated that similar treatment of methyl S-benzyl-4,6-O-benzylidene-3-O-methyl-2-thio-α-D-altropyranoside (III) would lead to the production of LXXII.

Reaction of III, prepared according to the method of Nayak, Sharma and Brown (2) with 1,1-dimethoxyethane in the presence of an acid catalyst afforded a product which, on the basis of its 100 MHz n.m.r. spectrum (Figure XII) and other physical data (see experimental), was assigned the structure methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-α-D-altropyranoside (LXXIX). In Figure XII the singlet at τ5.48 was assigned to the C-1 anomeric proton and the quartet at τ6.98 ($J_{1,2}$ = 0.7 Hz; $J_{2,3}$ = 2.5 Hz) to the proton at C-2. Confirmation for these assignments was provided by the following spin decoupling experiment performed on a Varian HA 100 MHz n.m.r. spectrometer.

Irradiation at 452 Hz downfield from tetramethylsilane (H-1, singlet) caused a collapse of the signal at 302 Hz (H-2) to a doublet having a spacing of 2.5 Hz. This must therefore represent the coupling between H-2 and H-3 and is consistent with the trans-diaxial disposition of the benzylthio and methoxyl groups at C-2 and C-3 respectively. The small coupling (0.7 Hz) between H-1 and H-2 is in agreement with those observed for the analogous protons in methyl S-benzyl-4,6-O-benzylidene-3-O-methyl-2-thio-α-D-altropyranoside (III) and methyl 4,6-O-benzylidene-3-O,S-dimethyl-2-thio-α-D-altropyranoside (VIII) (134).

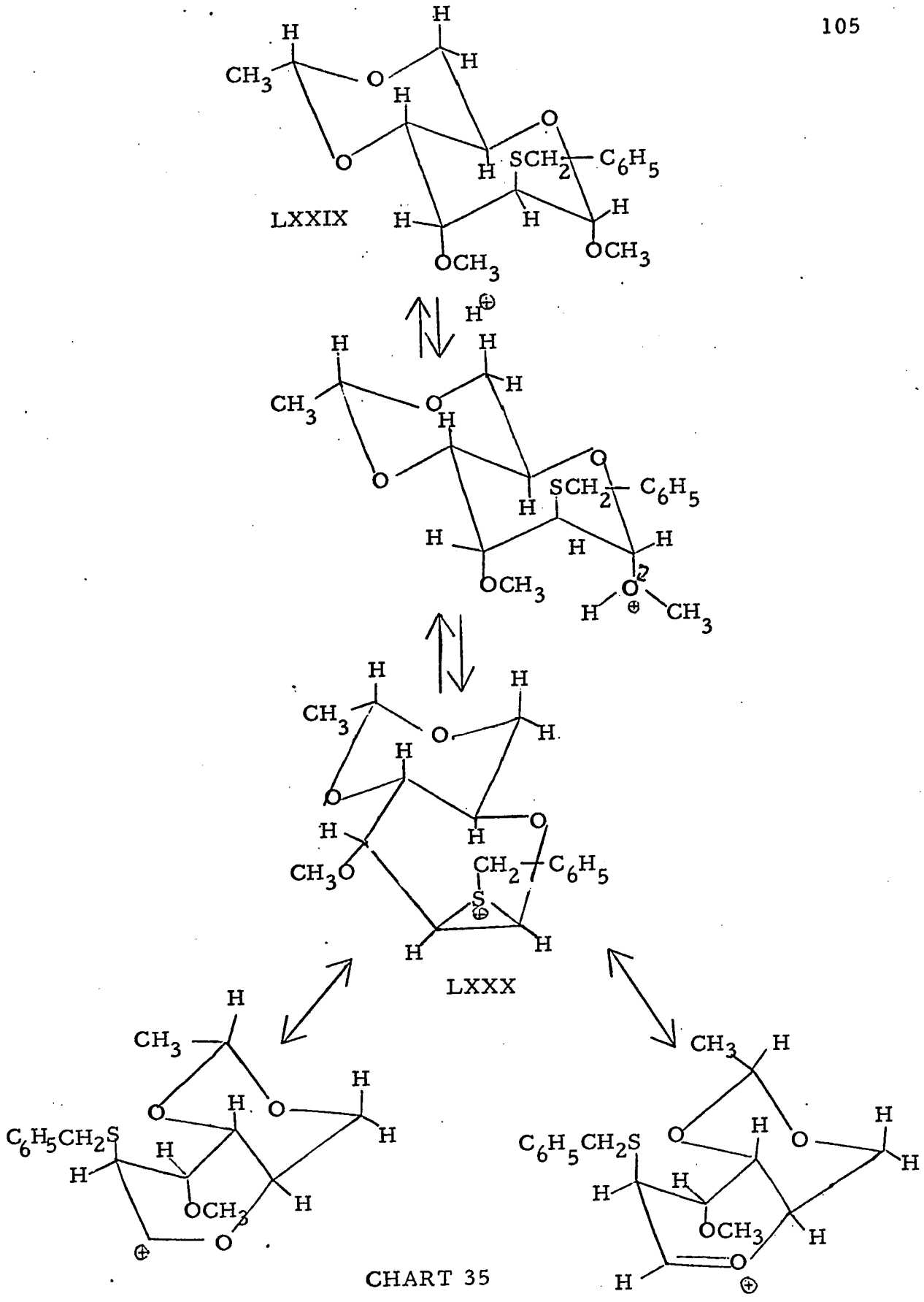
In view of the observed anomerization (3) which occurred during

trans-acetalation of VIII to LXXIII, but which was absent in the analogous formation of LXXIX from III, some further comment is required.

Lemieux (135) has proposed that the acid catalyzed anomerization of glycosides proceeds via coordination of the acid catalyst with the oxygen of the aglycon group. Thus the first step in the anomerization of LXXIX, in the presence of sulfuric acid, would be protonation at the C-1 methoxyl group (Chart 35). Subsequent loss of methanol from C-1 would no doubt be assisted by participation of the benzylthio group at C-2 in stabilizing the resultant positive charge on the intermediate LXXX (Chart 35).

Examination of models of the episulfonium ion LXXX showed that the anomeric C-1 center in this structure would be substantially shielded from above by the aromatic ring of the benzylthio group, in such a way that subsequent attack of methanol from an equatorial directions would be sterically hindered. This factor could account for the observed lack of anomerization in this reaction.

An attempt was also made to synthesize methyl S-benzyl-4,6-O-benzylidene-3-O-methyl-2-thio-β-D-altropyranoside, the β-isomer of III, starting from methyl β-D-glucopyranoside (Chart 36). Reaction of methyl β-D-glucopyranoside with benzaldehyde containing a suspension of anhydrous zinc chloride afforded methyl 4,6-O-benzylidene-β-D-glucopyranoside (LXXXI) (136, 137) (Chart 36).



LXXIX

LXXX

CHART 35

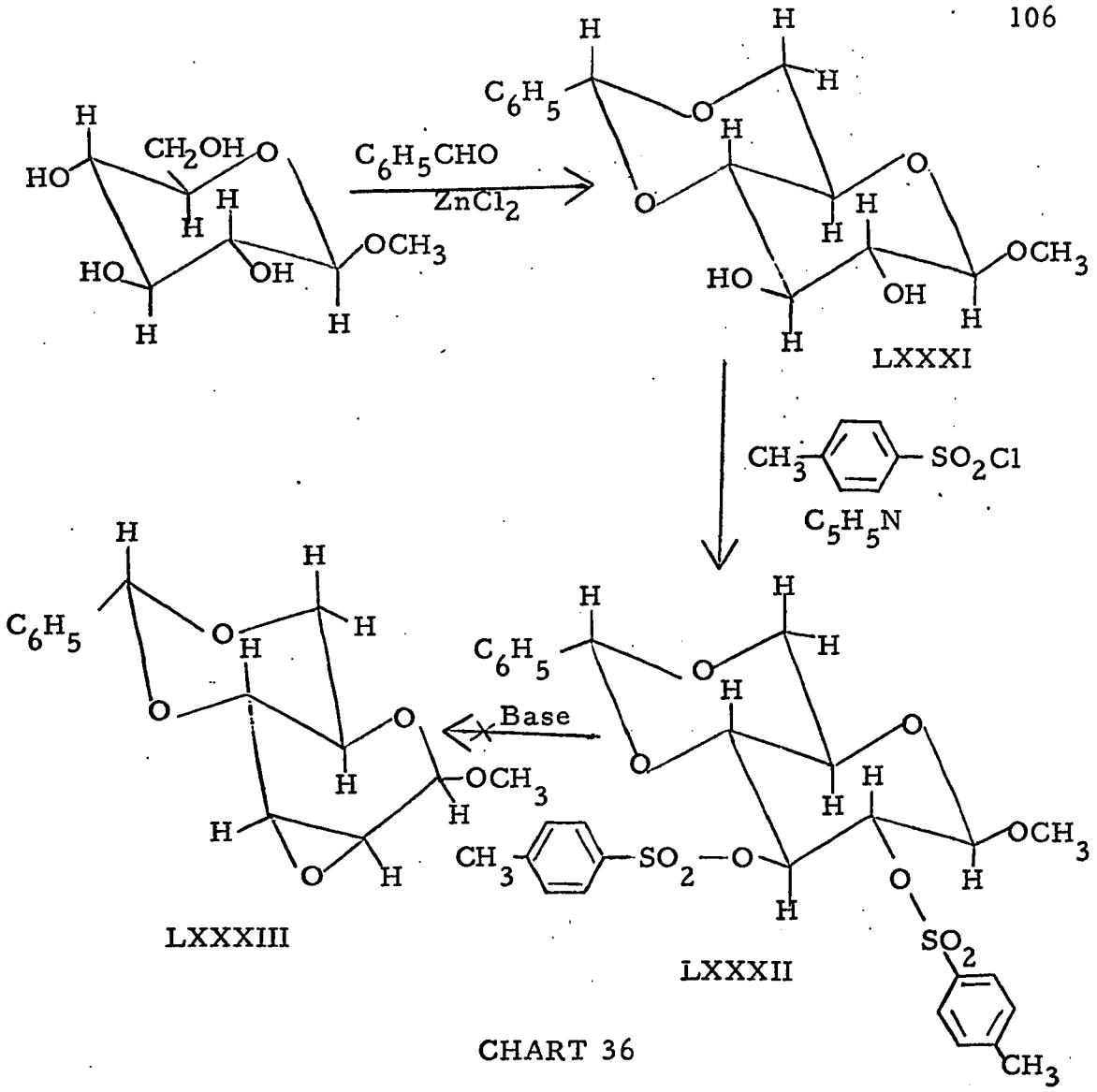
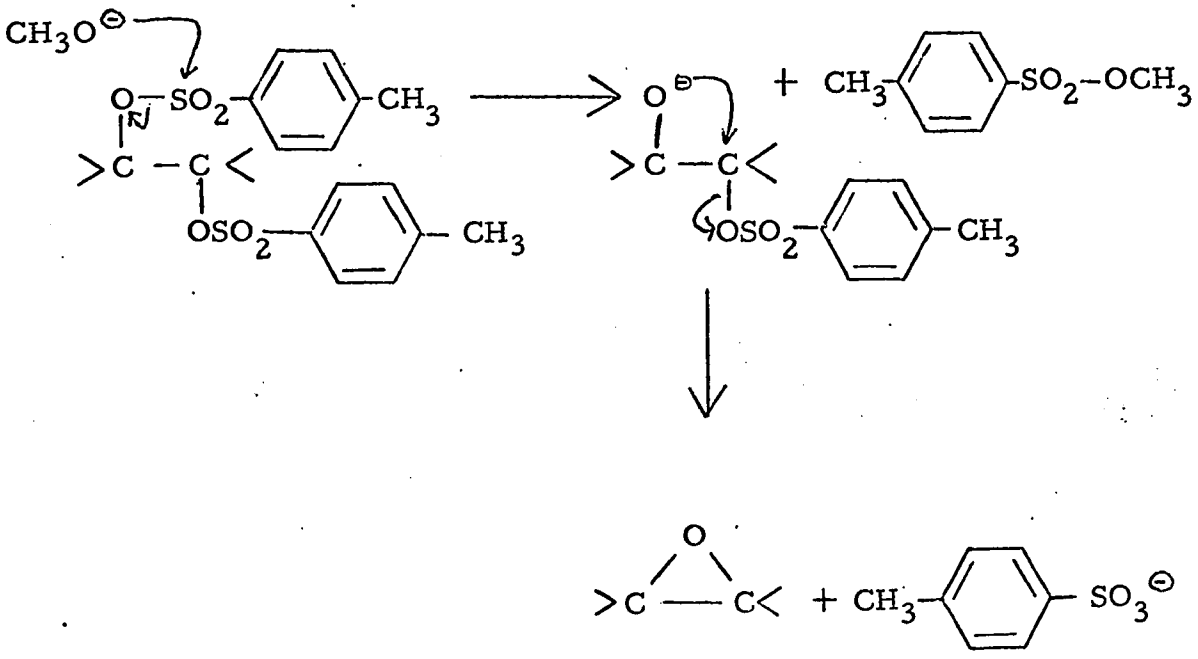


CHART 36

Treatment of LXXXI with an excess of p-toluenesulfonyl chloride in pyridine yielded methyl 4,6-O-benzylidene-2,3-di-O-p-toluenesulfonyl-β-D-glucopyranoside (LXXXII) (Chart 36) (138). However, all attempts to effect conversion of LXXXII to methyl 2,3-anhydro-4,6-O-benzylidene-β-D-allopyranoside (LXXXIII) met with failure. Hedgley, Overend and Rennie (139) have reported a similar observation on treatment of LXXXII with sodium methoxide in methanol at room temperature, conditions under which the corresponding α-di-p-toluenesulfonate undergoes quantitative conversion to methyl 2,3-

anhydro-4,6-O-benzylidene-α-D-allopyranoside.

In the current investigation, even treatment of LXXXII with sodium methoxide in refluxing methanol failed to achieve the desired reaction. This was somewhat suprising in view of the conversion of methyl 4,6-O-ethylidene-2,3-di-O-p-toluenesulfonyl-β-D-glucopyranoside (LXXV) to methyl 2,3-anhydro-4,6-O-ethylidene-β-D-allopyranoside (LXXVI) achieved under similar conditions (p. 100). It therefore appears that the 4,6-O-alkylidene group exerts some influence on epoxide ring formation, although the nature of this effect is obscure. Indeed, the whole mechanistic picture of anhydro sugar formation from vicinal di-p-toluenesulfonates is at present little understood (140). Newth (140) proposed that the based induced saponification of the "more accessible" of the p-toluenesulfonate ester functions occurs first with subsequent displacement of the second p-toluenesulfonoxy group by the oxygen anion thus formed.



However the factors determining the accessibility of one or other of the p-toluenesulfonoxy groups for the initial attack by base are not clearly defined.

2. The treatment of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-β-D-altropyranoside (LXXII) with sodium in DME.

Subjection of LXXII to treatment with one equivalent of powdered sodium in refluxing DME for 24 hours (2, 3) afforded a nearly quantitative recovery of unchanged starting material. Similar reaction of a sample of methyl 4,6-O-ethylidene-3-O,S-dimethyl-2-thio-β-D-altropyranoside (LXXIII)*, also resulted in the recovery of unchanged starting material only, in high yield.

Thus, both LXXII and LXXIII failed to undergo any elimination reactions analogous to those observed by Nayak, Sharma and Brown (2,3) for the compounds III, VIII and IX. The significance of these results is discussed later (p. 109).

3. The treatment of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-α-D-altropyranoside (LXXIX) with sodium in DME.

LXXIX was allowed to react with one equivalent of sodium metal in refluxing DME for 24 hours. On work up of the reaction mixture a nearly quantitative yield of unchanged starting material was recovered along with an insoluble brown precipitate. No evidence could be found for the presence of olefinic products such as

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* Kindly made available by Dr. M. Sharma

those obtained (2, 3) on similar treatment of the analogous ∝-sugars III, VIII and IX. This unexpected result is discussed in the following section.

Solution of the brown precipitate obtained above in water afforded a solution which gave a strongly basic reaction with Hydrion pH paper. However electrometric titration of a standard solution of the solid showed that it contained only a small amount of alkaline material. Gravimetric analysis indicated the complete absence of sulfur but the presence of about 10% carbon and 1% hydrogen. N.m.r. analysis of a sample of the solid dissolved in D_2O showed the complete absence of absorptions other than that for DOH at τ 5.2. Successful analysis by infrared spectroscopy proved impossible in view of the insolubility of the solid in organic solvents and its failure to mull with nujol or halo-oil. Thus the nature of the precipitate formed remains obscure.

4. Concerning the mechanisms of olefin production from the treatment of III, VIII and IX with sodium in DME.

In their discussion on the production of olefinic products achieved by treatment of III and VIII with sodium metal, or bases, in DME, Nayak, Sharma and Brown (2) proposed the reaction mechanism outlined in Chart 37.

They considered that olefin formation resulted from a base catalyzed elimination process. Support for this concept was afforded by the fact that the formation of olefinic products occurred not only

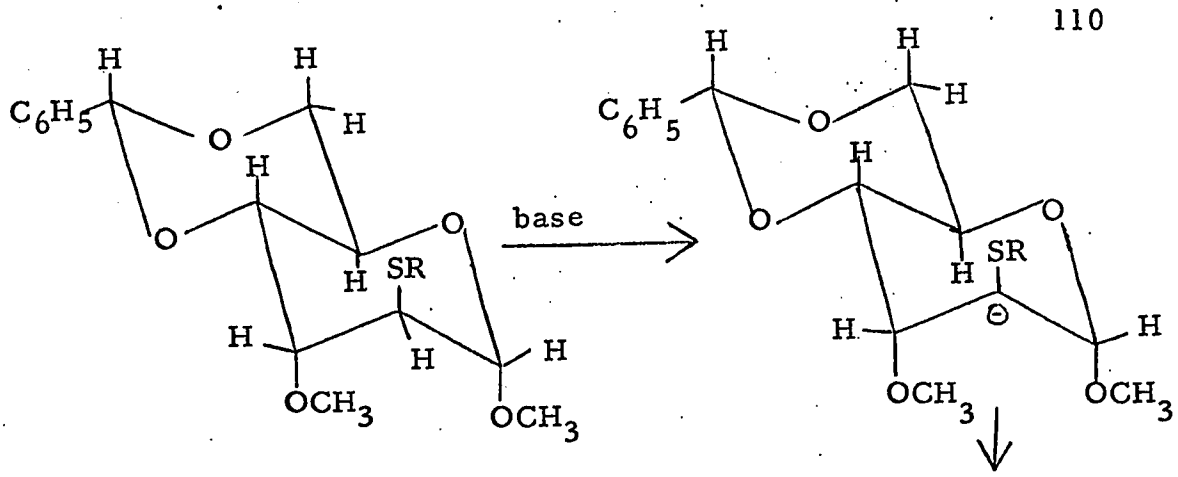


CHART 37

in the presence of sodium and DME, but also on treatment of III and VIII with a variety of bases (sodium hydride, sodium methoxide and potassium hydroxide) in DME. The possibility that elimination of the methoxyl group from C-1 or C-3 was due to anchimeric assistance by the sulfur atom on the neighbouring carbon, by the formation of an intermediate episulfonium ion, was discounted. Such an episulfonium ion intermediate had been found to react readily with the highly nucleophilic sodium azide (141). No evidence for such a reaction could be detected. They further proposed (2) that the 1,3-interaction of the methoxyl groups at C-1 and C-3 may have a bearing on the elimination process.

It would seem that, in view of the results obtained in the current investigation, the presence of such a 1,3-interaction is, in fact, of paramount importance for elimination to proceed. Thus none of the model compounds, XVIII-XXII and XXVII-XXIX, nor the two β-sugars LXXII or LXXIII were observed to yield olefinic products on treatment with sodium in DME.

In order to investigate the significance of having sodium, or bases, present in the reaction medium a sample of III was dissolved in DME alone and the solution refluxed for a 24 hour period. Only unchanged starting material was recovered.

In a series of experiments designed to establish whether or not a reversible proton abstraction, actually represented the first and rate-determining step of the elimination process, compounds III, IX, LXXII, LXXIII and LXXIX were separately dissolved in d_1-methanol containing a three molar excess of sodium methoxide, and the resultant solutions refluxed for a 24 hour period. In all cases isolation of the reaction products indicated nearly quantitative recovery of unchanged starting material, and their subsequent analysis by n.m.r. spectroscopy showed no evidence for deuterium incorporation. The latter would have resulted in a reduction of the integrated areas for the various absorptions in the n.m.r. spectra due to protons undergoing exchange.

What was perhaps of greater significance than the failure of compounds III, IX, LXXII, LXXIII and LXXIX to undergo base catalyzed deuterium exchange was the observation that methyl S-benzyl-4,6-O-benzylidene-3-O-methyl-2-thio-α-D-altropyranoside (III) and methyl 4,6-O-ethylidene-3-O,S-dimethyl-2-thio-α-D-altropyranoside (IX) failed to yield olefinic products when treated with sodium methoxide in d_1-methanol. Nayak, Sharma and Brown (2, 3) had reported that both sugars (III and IX) underwent olefin formation on treatment with sodium methoxide in DME. Thus it is apparent that the nature

of the solvent is also of importance.

A review of the foregoing data has led to the re-appraisal of the proposed pathway for the elimination process (Chart 37), since such a mechanism would no longer account for the observed experimental results. The formulation of an alternate mechanistic route was based on the following considerations:

i) that the production of olefinic products has, as yet, been observed only in compounds possessing 1,3-diaxial methoxyl groups. Calculations show that conformations possessing such an interaction are destabilized to the extent of about 0.7 kcal/mole (110).

ii) that the presence of an alkylthio group on the carbon atom adjacent to the C-1 and C-3 methoxyl groups is a necessary factor for elimination to proceed.

iii) that the presence of sodium, or bases, is necessary for olefin production to occur.

iv) that compounds which undergo elimination on treatment with sodium methoxide in DME, undergo neither deuterium exchange nor elimination on treatment with sodium methoxide in d_1-methanol.

The mechanistic pathway shown in Chart 37 is an essentially ElcB process (142) with formation of a discreet carbanion prior to the elimination of methoxide ion and resultant olefin formation.

It is now proposed that elimination occurs via a process possessing partial El character. Since oxygen is somewhat more electronegative than carbon, the C-OCH_3 bonds would tend to be polarized in the direction $C^{\delta\oplus} \!\!-\!\!- {}^{\delta\ominus}OCH_3$. As a result of the 1,3-

diaxial interaction between the C-1 and C-3 methoxyl groups of compounds III, VIII and IX, mutual repulsion of such groups might be expected to cause stretching of the C_1-O and C_3-O bonds and thus result in an increased partial positive character associated with either or both C-1 and C-3. This effect would no doubt be enhanced further by participation of the alkylthio group at C-2 which would not only stabilize a partial positive charge at either C-1 or C-3 by anchimeric assistance, but would, in so doing, facilitate the departure of the methoxyl group, as a negatively charged species, from either site. A transition state can thus be imagined in which C-OCH_3 bond rupture is beginning to occur (LXXXIV) (Chart 38). As soon as such a transition state is attained rapid proton removal from C-2 would take place in the presence of base, with concommitant olefin formation and elimination of methoxide ion (Chart 38).

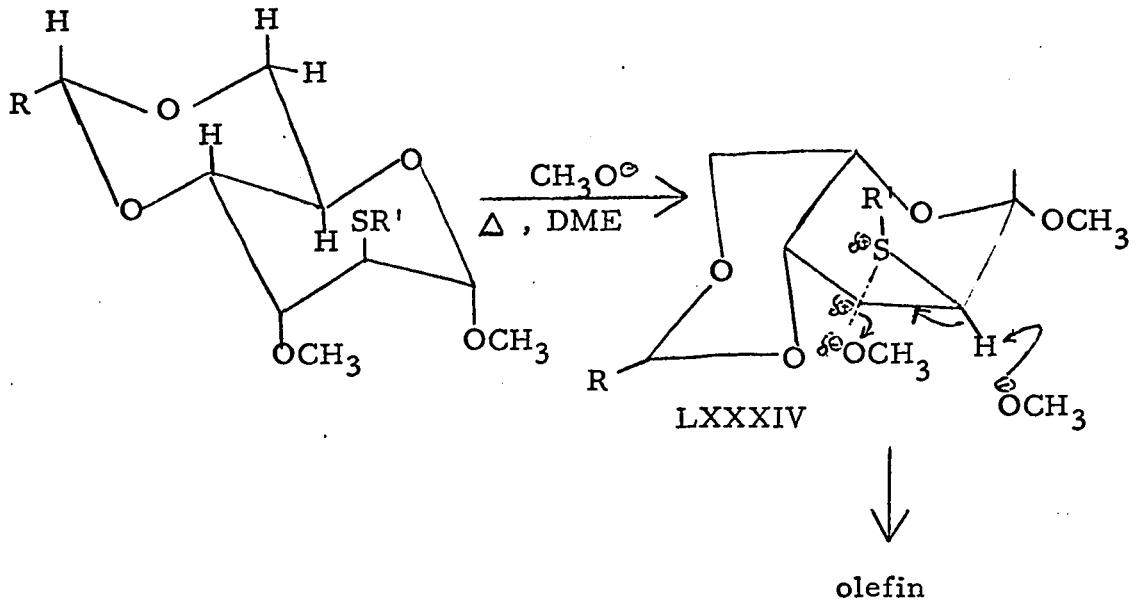
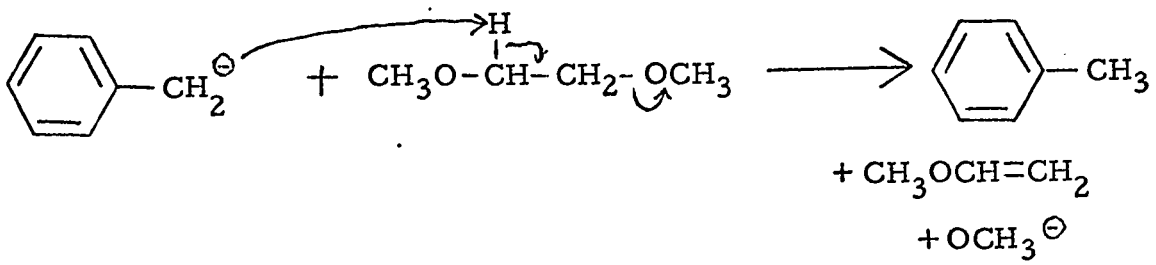


CHART 38

Since discreet episulfonium-carbonium ion formation is not proposed above, then such a mechanism would account for the failure of Brown and coworkers (2) to observe reaction with the highly nucleophilic sodium azide. Further, since no discreet carbanion is formed in the above pathway (Chart 38), then this mechanism would also account for the failure of III and IX to undergo base-catalyzed deuterium exchange. The failure of III and IX to undergo elimination in the solvent methanol might be accounted for by preferential solvation of the sulfur atom of the C-2 alkylthio group in this solvent thus preventing what is considered to be a necessary participation of the alkylthio group in attainment of the transition state LXXXIV (Chart 38).

Thus such a mechanism could account for the observed experimental data.

The presence of an alkaline species in those elimination reactions employing sodium metal in DME could have arisen via a side reaction involving cleavage of the carbohydrate alkylthio group C-S bond. Thus cleavage of the benzylthio group C-S bond by sodium metal in III and VIII would yield a mercaptide ion and a benyl carbanion (42-44). The latter species could react directly in the transition state LXXXIV as a proton abstractor, or with the solvent to yield toluene, methyl vinyl ether and methoxide ion.



This latter course of reaction has already been noted by Gerdil and Lucken (42-44) when benzyl sulfides were allowed to react with potassium metal in anhydrous DME.

The failure of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-α-D-altropyranoside (LXXIX) to undergo elimination on treatment with sodium in DME is somewhat of an anomaly. As yet, the apparent stability of LXXIX under these reaction conditions is not understood. LXXIX differs in structure from III only in the presence of a 4,6-O-ethylidene group rather than a 4,6-O-benzylidene group. That this should be of significance is surprising in view of the fact that both methyl 4,6-O-benzylidene-3-O,S-dimethyl-2-thio-α-D-altropyranoside (VIII) and methyl 4,6-O-ethylidene-3-O,S-dimethyl-2-thio-α-D-altropyranoside (IX) were found to react under analogous conditions to yield olefinic products (2, 3). It appears that the nature of the S-alkyl and 4,6-O-alkylidene groups must together exert some subtle influence on the overall reactivity of the molecule, but the nature of this effect is, as yet, obscure. Mention has already been made of a somewhat analogous case in which reaction of methyl 4,6-O-ethylidene-2,3-di-O-p-toluenesulfonyl-β-D-glucopyranoside (LXXV) with sodium methoxide in methanol afforded methyl 2,3-anhydro-4,6-O-ethylidene-β-D-allopyranoside (LXXVI), whereas under similar conditions the 4,6-O-benzylidene analog of LXXV proved completely inert (p. 107).

SPECTRA

Unless otherwise stated all n.m.r. spectra were obtained in deuteriochloroform and the reference was tetramethylsilane.

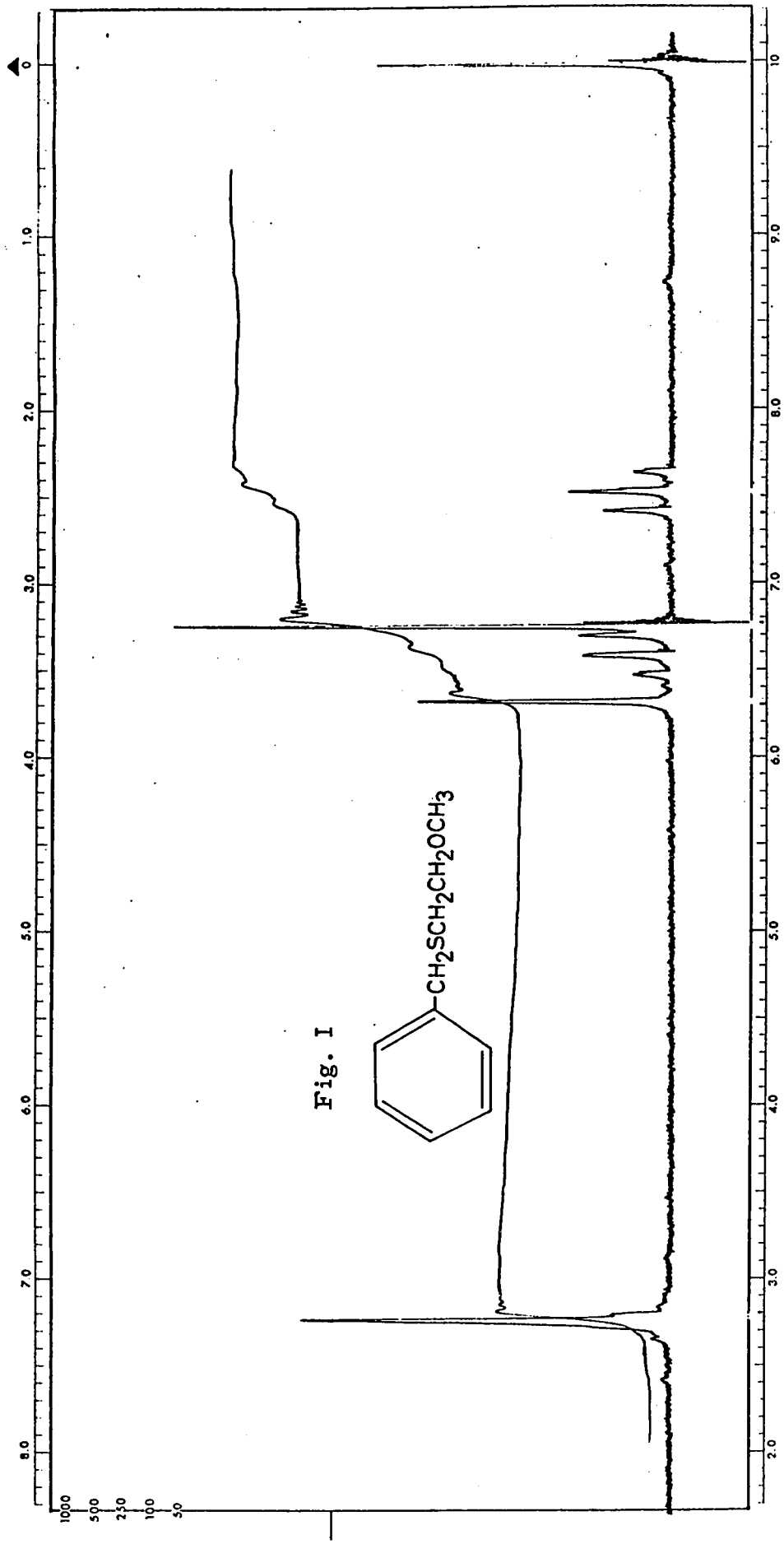
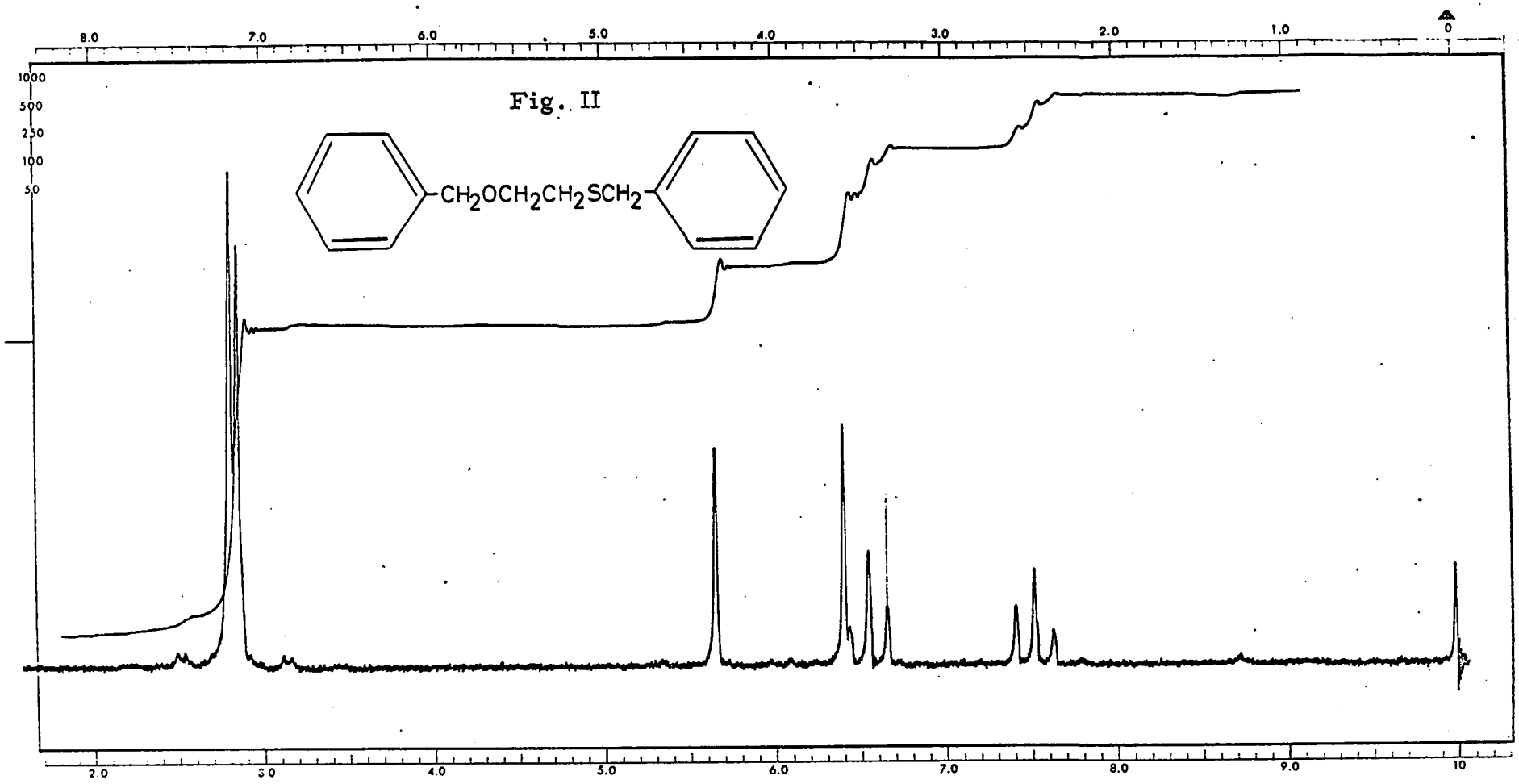


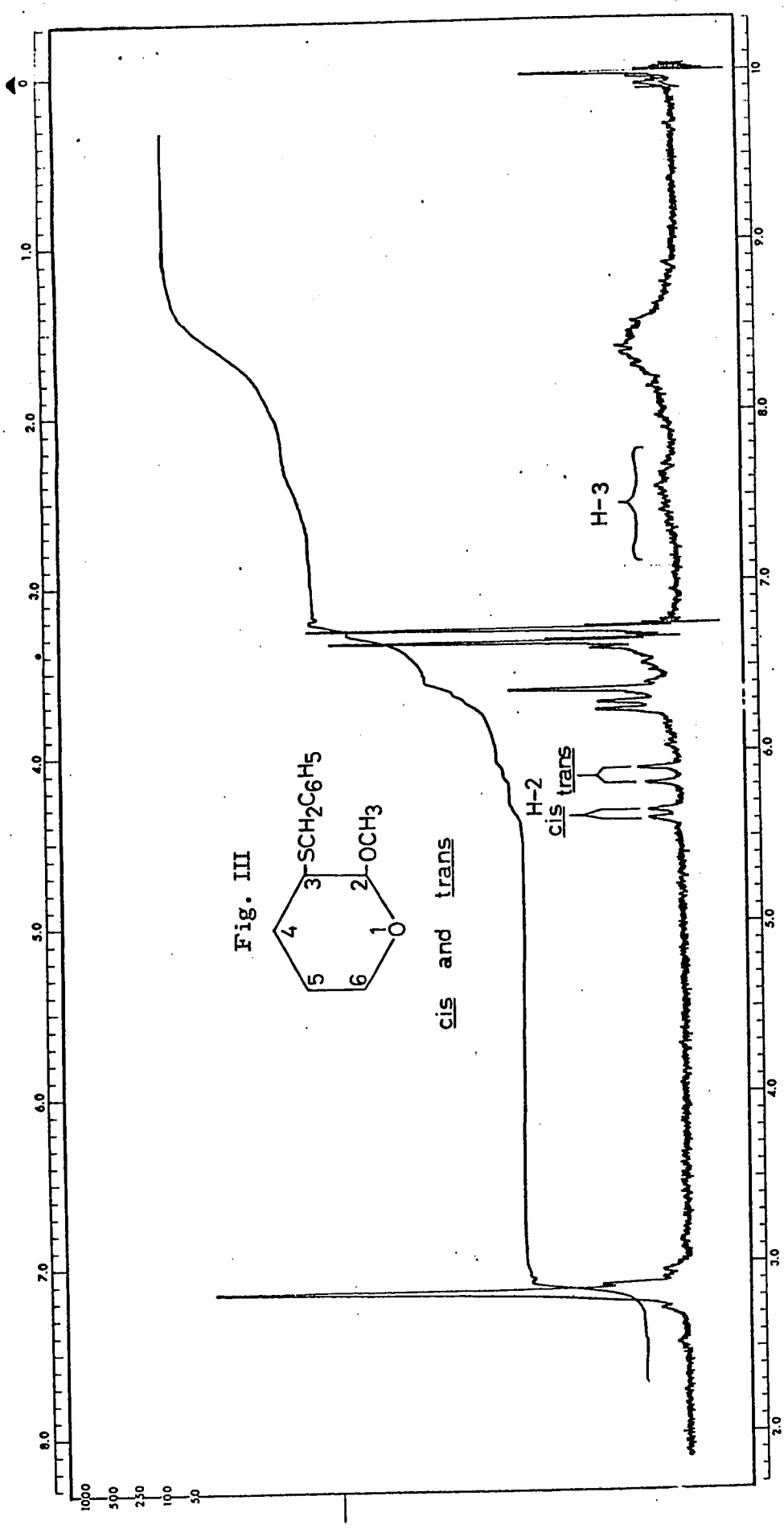
Fig. I

N.m.r. spectrum (60 MHz) of methyl β-benzylthioethyl ether (CCl_4 solvent).

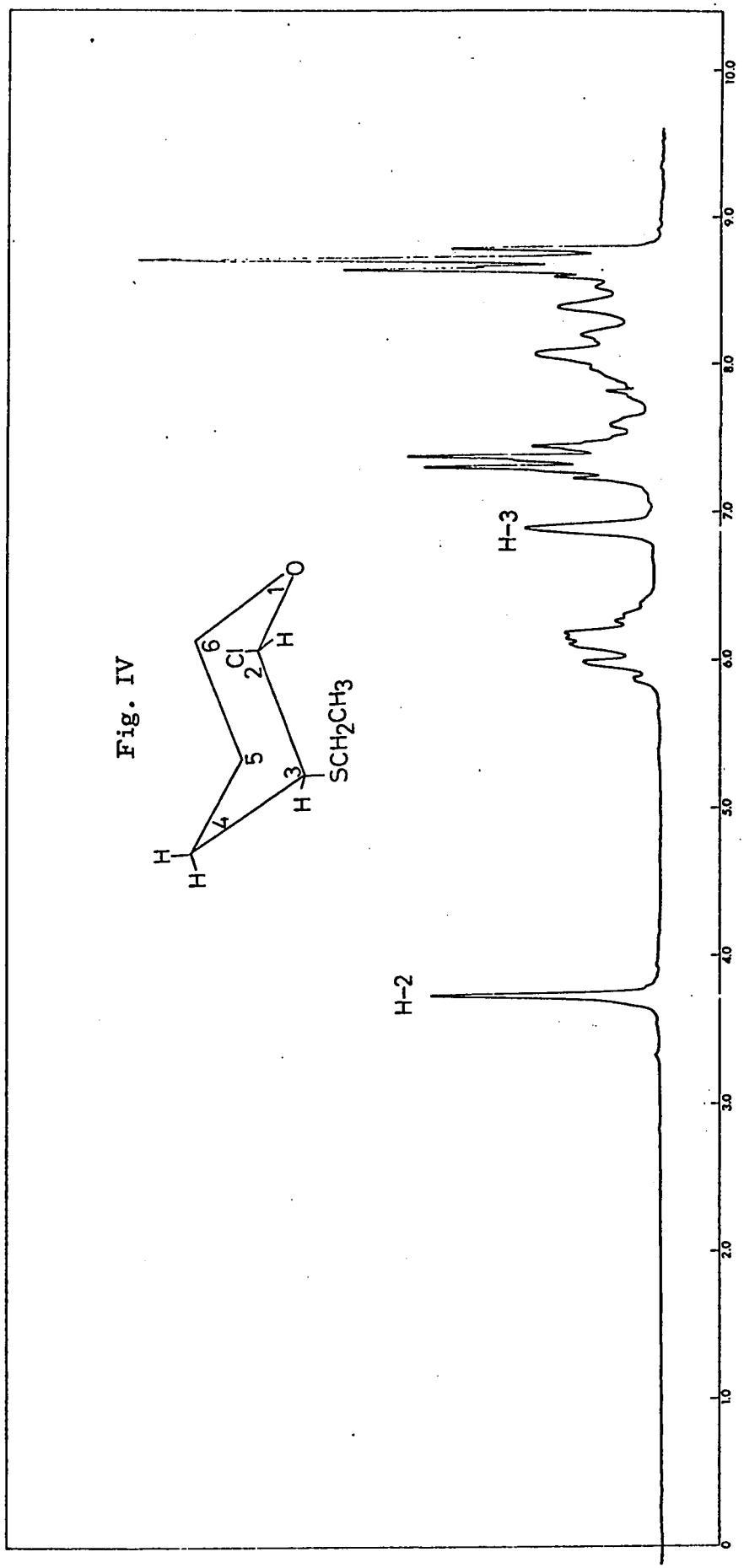
Fig. II



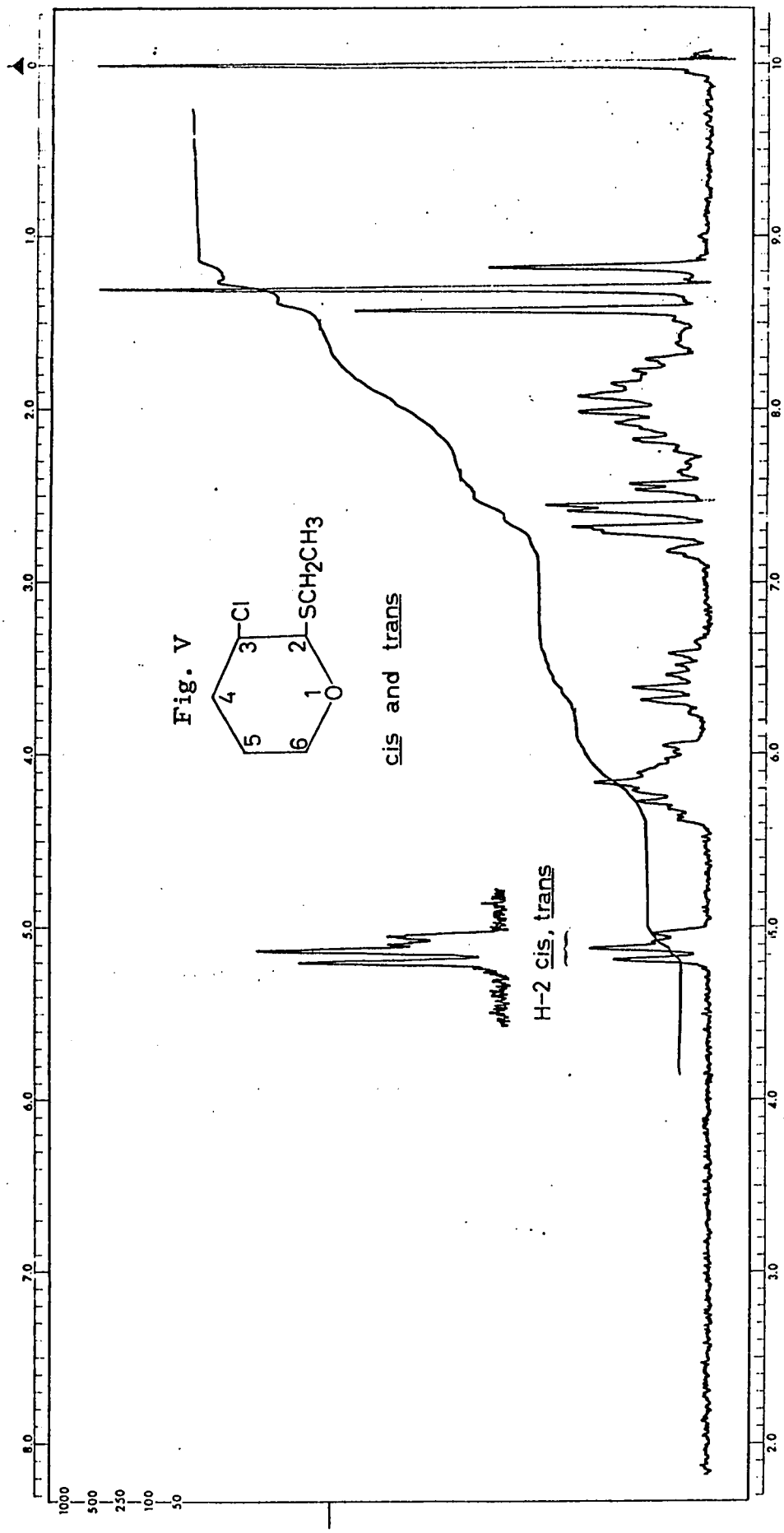
N.m.r. spectrum (60 MHz) of benzyl β-benzylthioethyl ether.
(CCl_4 solvent)



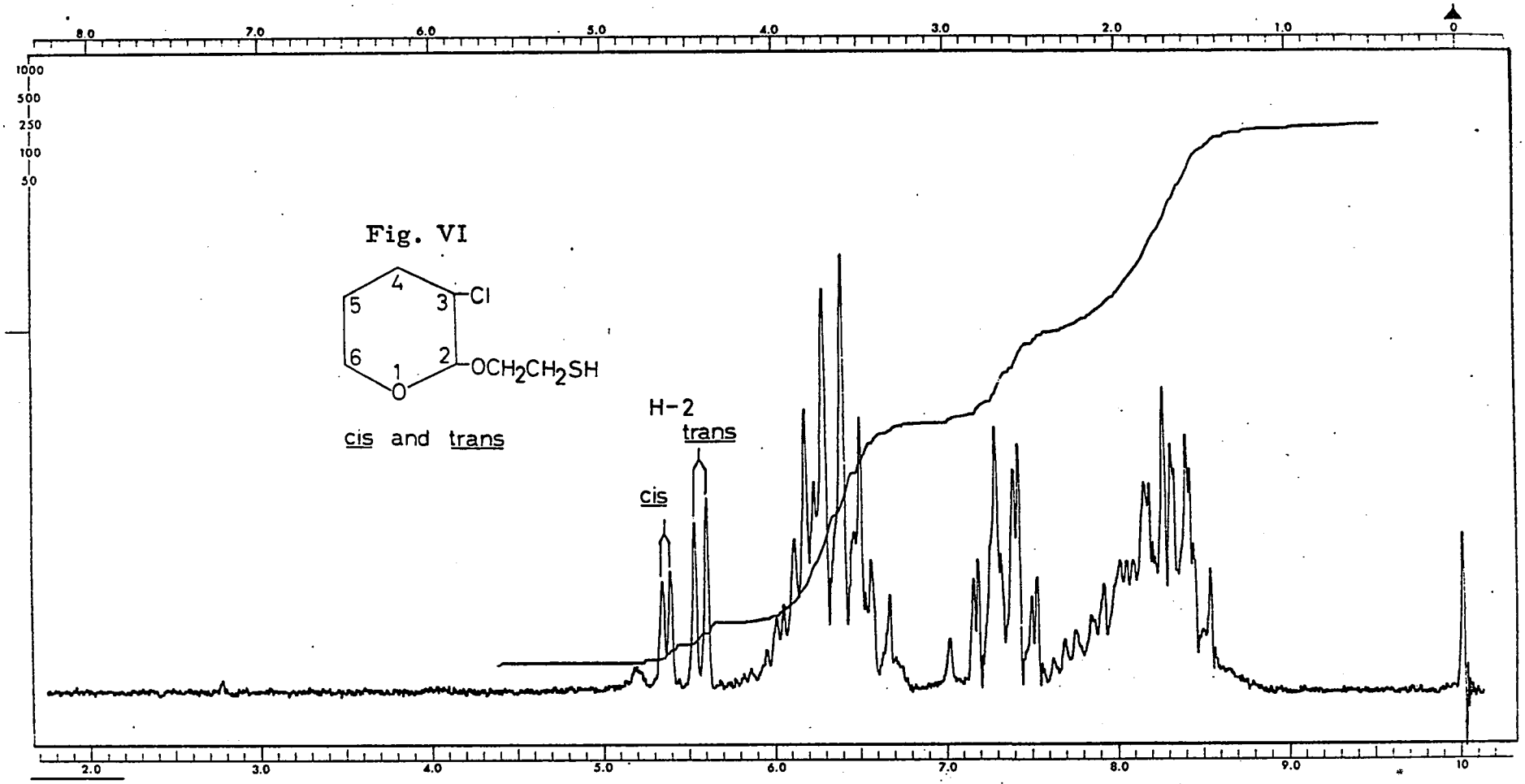
N.m.r. spectrum (60 MHz) of cis- and trans-3-benzylthio-2-methoxytetrahydropyran.



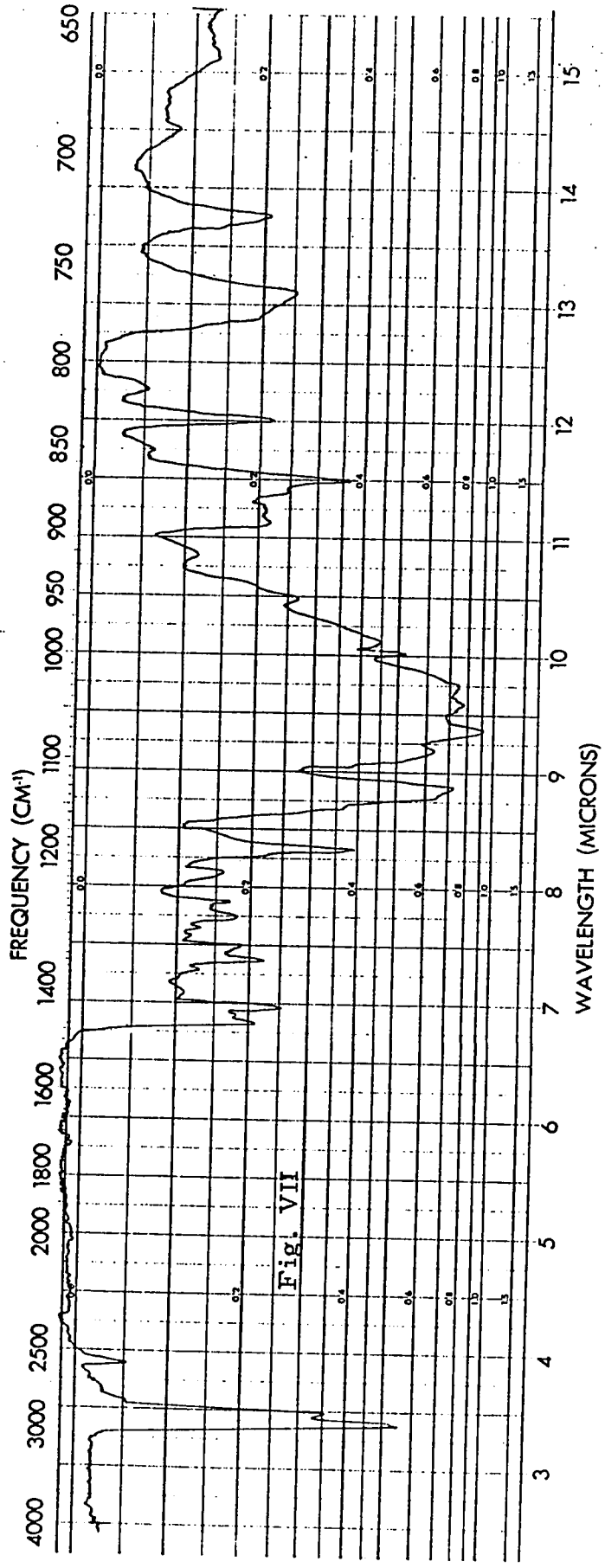
N.m.r. spectrum (100 MHz) of trans-2-chloro-3-ethylthiotetrahydropyran.



N.m.r. spectrum (60 MHz) of cis- and trans-3-chloro-2-ethylthiotetrahydropyran.



N.m.r. spectrum (60 MHz) of cis- and trans-3-chloro-2-(β-mercaptoethoxy)-tetrahydropyran.



I.R. spectrum (neat) of 3-chloro-2-(β-mercaptoethoxy)-tetrahydropyran.

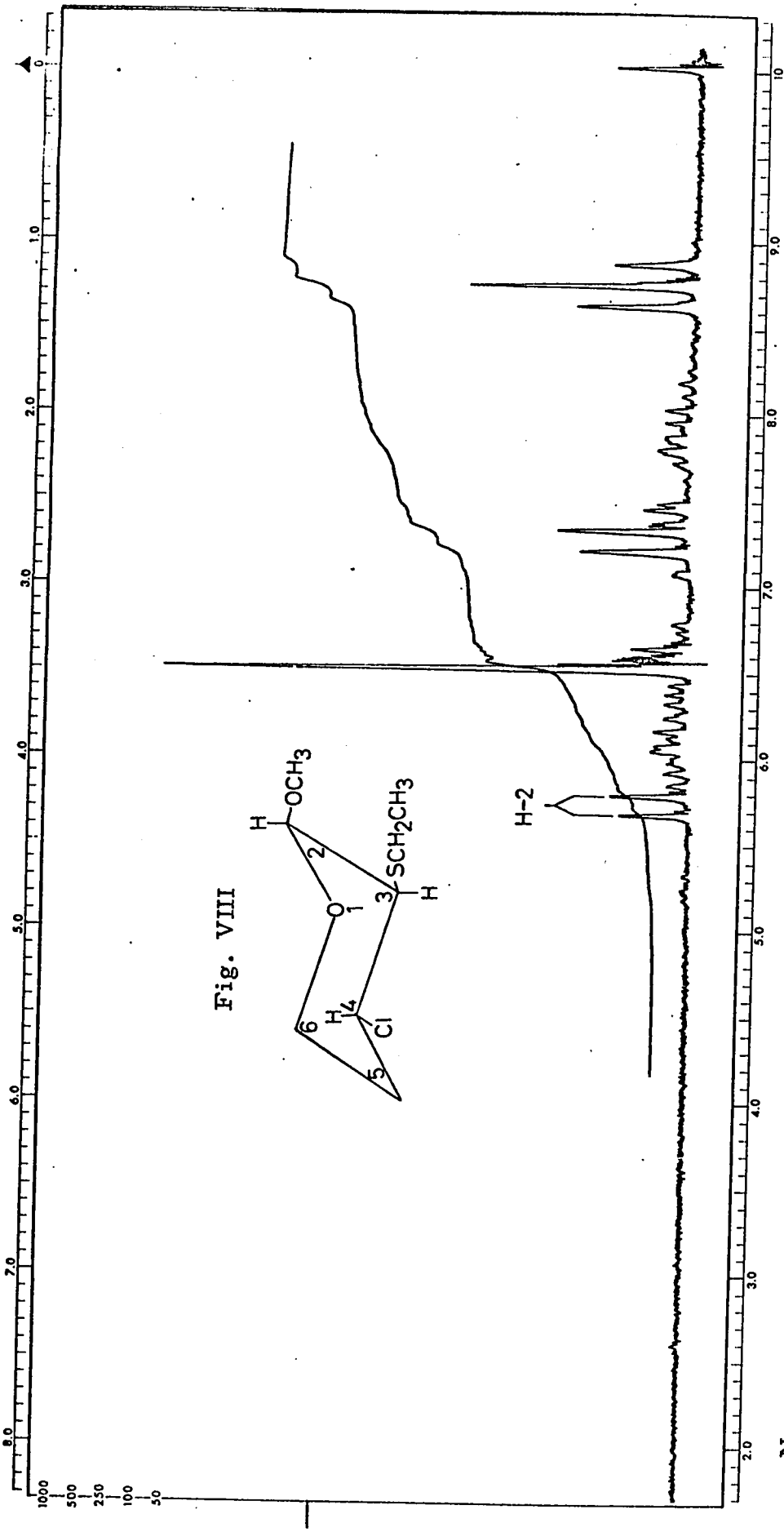
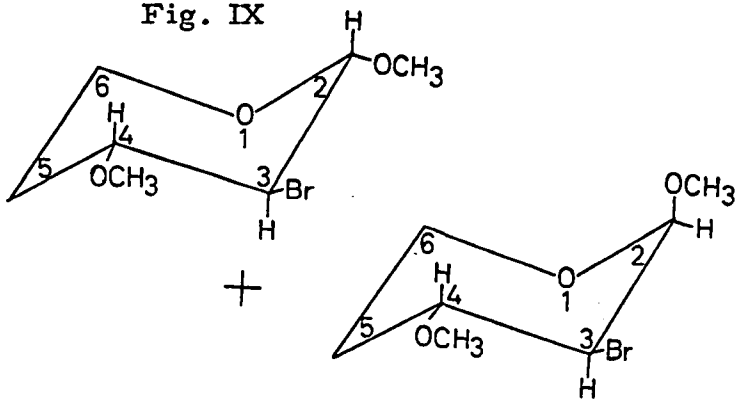


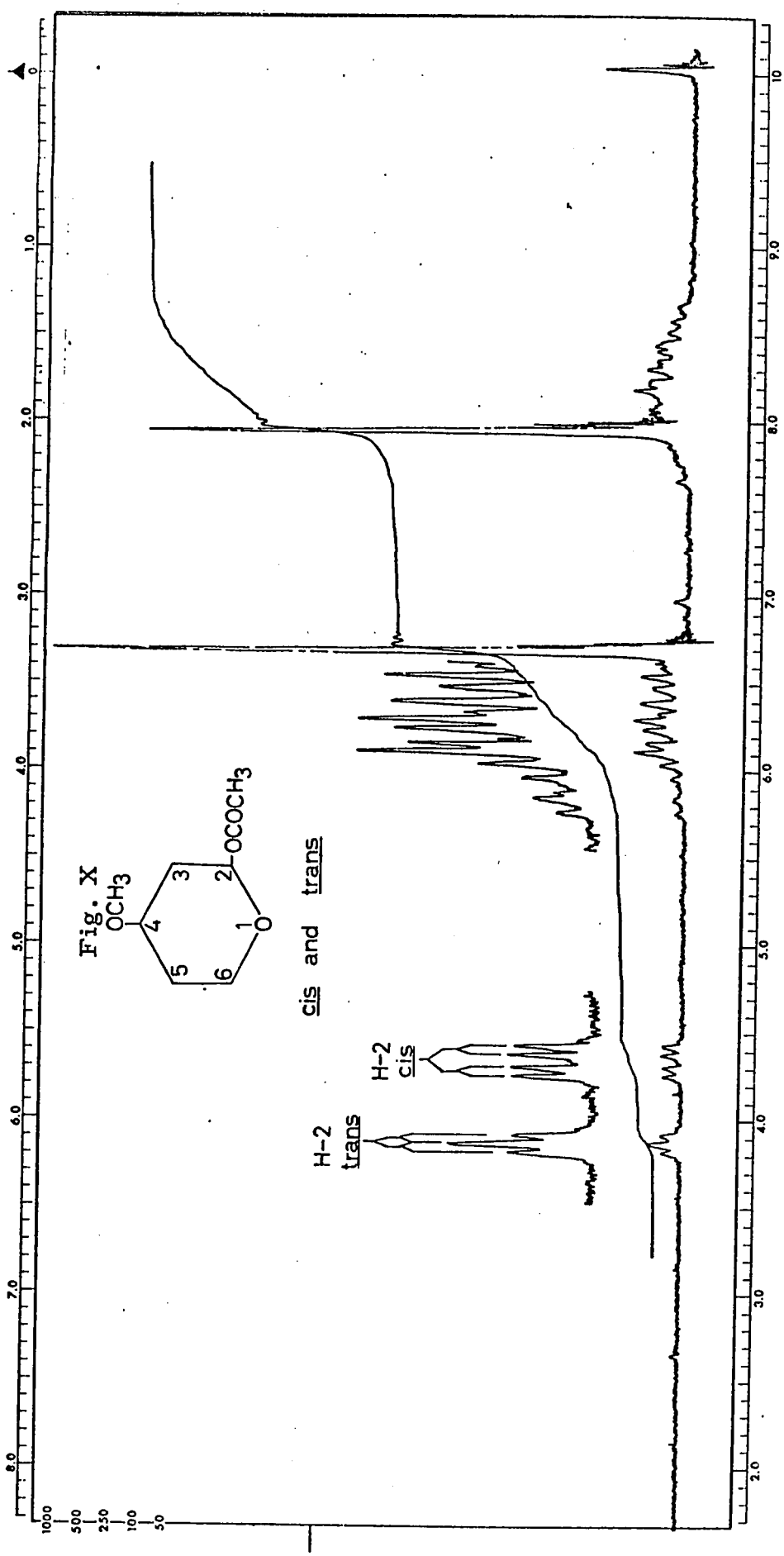
Fig. VIII

N.m.r. spectrum (60 MHz) of trans, trans-4-chloro-3-ethylthio-2-methoxytetrahydropyran.

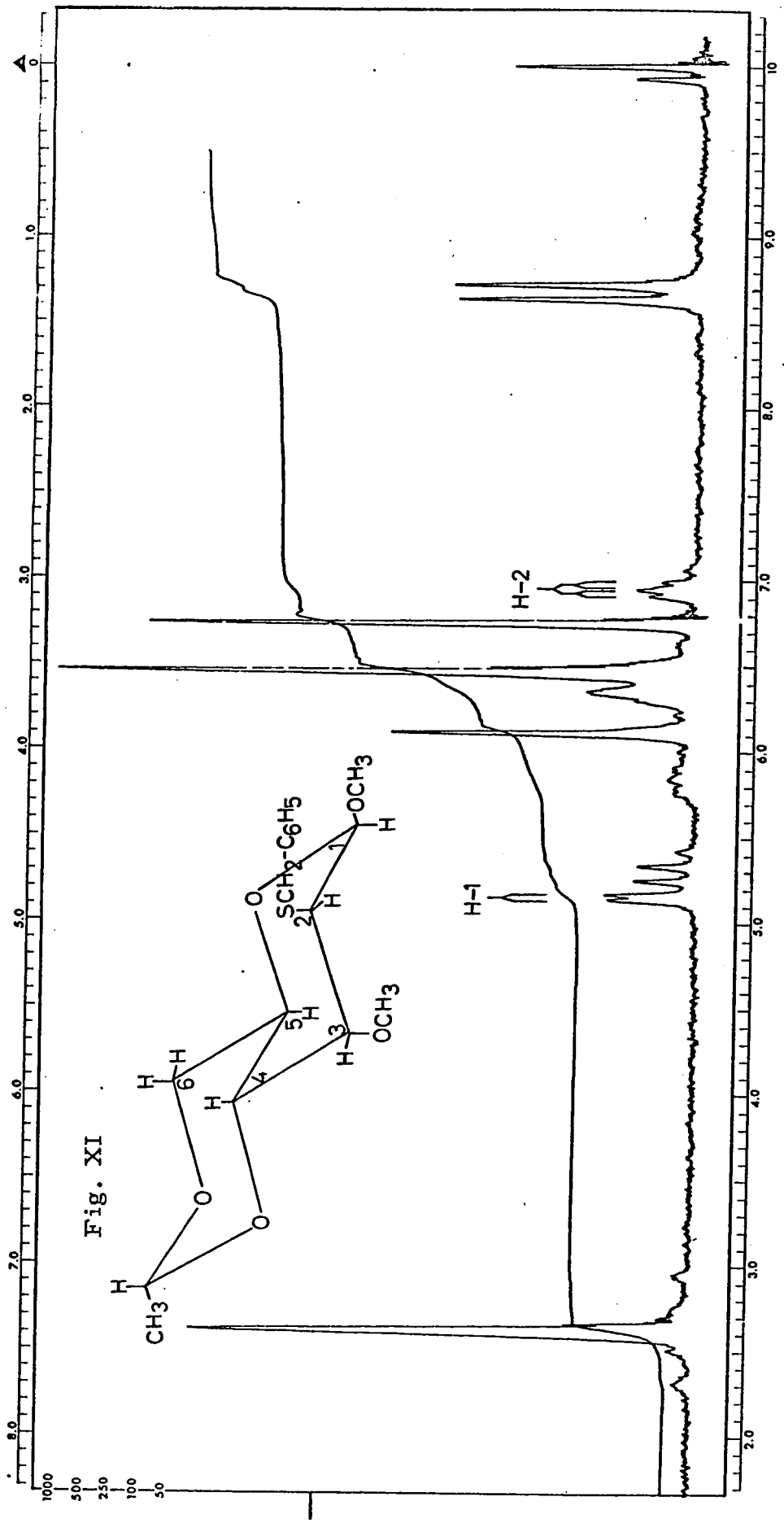
Fig. IX



N.m.r. spectrum (100 MHz) of cis- and trans-3-bromo-2,4-dimethoxytetrahydropyran.

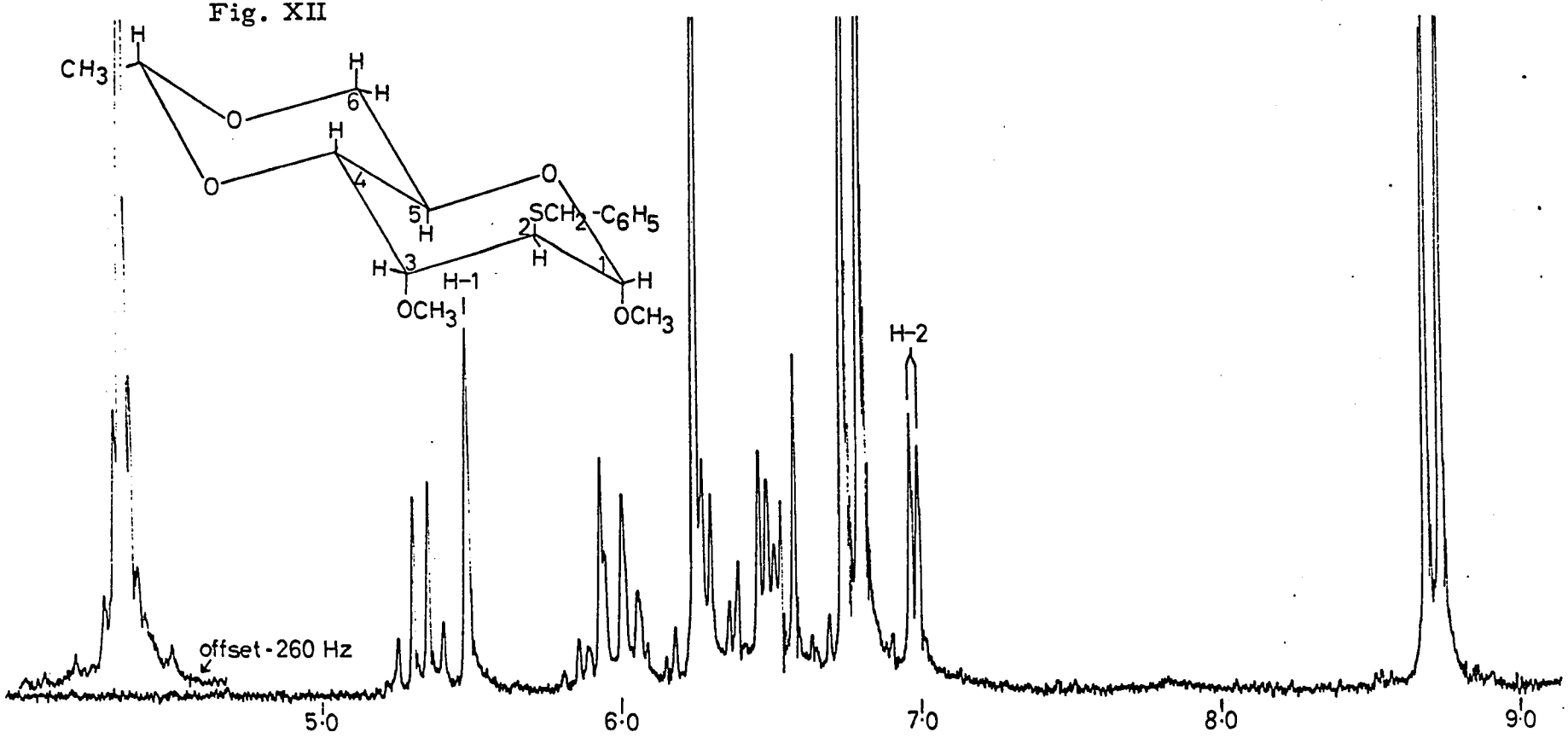


N.m.r. spectrum (60 MHz) of cis- and trans-2-acetoxy-4-methoxytetrahydropyran.



N.m.r. spectrum (60 MHz) of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-β-D-altropyranoside.

Fig. XII



N.m.r. spectrum (100 MHz) of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-α-D-altropyranoside.

EXPERIMENTAL

EXPERIMENTAL

All boiling points and melting points are uncorrected.

Gas liquid chromatography (g.l.c.) was performed with an F and M Model 700 gas liquid chromatograph equipped with 1/8" x 12' stainless steel columns. Two column packings were generally used which Sweet (79) had found to give good separation of isomeric acetals, alcohols and substituted tetrahydropyrans: (i) 20% butanediol succinate on Gas Chrom-P (60-80 mesh), and (ii) 25% carbowax 20M on Gas Chrom-P (60 mesh). Helium was the carrier gas used at a flow rate of 40 ml per minute. The column temperatures employed for analytical work depended on the boiling points of the compounds under analysis.

The above mentioned chromatograph was equipped with a linear temperature programmer, and an integrator attached to the strip chart recorder. Quantitative analyses were made by measuring the integrated peak areas corresponding to the various components in a mixture. These areas were compared to those obtained from carefully prepared mixtures of authentic samples analyzed under identical conditions.

Infrared Spectra were recorded on Perkin-Elmer Instruments, Models 21 and 421.

N.m.r. spectra were obtained with a Varian Associates Model A-60 (60 MHz) spectrometer, a Varian Associates Model A-56/60 (60 MHz) spectrometer or a Varian Associates Model HA-100 (100 MHz) Spectrometer. Unless otherwise stated n.m.r. spectra were

obtained of samples dissolved in $CDCl_3$. Tetramethylsilane was used as an internal reference.

The above spectroscopic equipment was operated by Mr. Bob Swindlehurst, Mr. Glen Bigam or by the author.

Optical Rotations were obtained using a Perkin-Elmer Model 141 Polarimeter equipped with a sodium light source.

All the above mentioned equipment comprises a part of the facilities of the Department of Chemistry, University of Alberta.

In the work-up procedures reported for the various syntheses described herein, solvents were removed with a rotatory evaporator under reduced pressure unless otherwise stated.

Elemental analyses for carbon, hydrogen, halogens and sulfur, and molecular weight determinations were carried out by Mrs. Darlene Mahlow in the Chemistry Department of the University of Alberta.

A. REACTIONS INVOLVING β-BENZYLTHIOETHYL ETHERS

1. The synthesis of starting materials

2-Methoxyethyl p-toluenesulfonate was prepared according to the method of Tipson (60). To a cooled (0°) solution of 2-methoxyethanol (Eastman Kodak Co.) (22 g, 0.3 mole) in 300 ml of anhydrous pyridine (distilled from KOH pellets) was added 63 g (0.33 mole) of p-toluenesulfonyl chloride. The resultant solution was stirred at 0° for 2 hours and then left standing in the refrigerator overnight. The mixture was poured into 2 liters of ice-cold dilute HCl and extracted three times with ether. The ether extracts were combined

and washed several times with cold (0°) dilute HCl, then with saturated sodium bicarbonate solution followed by water. The solvent was removed from the dried ($MgSO_4$) ether solution and the residual oil distilled under reduced pressure to yield 52 g (88%) of 2-methoxyethyl p-toluenesulfonate. B.p., 137° at 0.1 mm; η_D^{22}, 1.5090. Lit. b.p., 144° at 0.2 mm; η_D^{25}, 1.5085 (60).

β-Benzylthioethyl methyl ether was prepared by a modification of the method of Drahowzal and Klamann (59). To a mechanically stirred solution of α-toluenethiol (12.4 g, 0.1 mole) in 500 ml of anhydrous DME (distilled from potassium metal) was added 2.4 g (0.1 mole) of sodium hydride (obtained as a 56.7% suspension in mineral oil and freed from the latter by washing with anhydrous ether) in small portions. During the course of the addition the reaction mixture was kept under a dry nitrogen atmosphere and stirred vigorously to avoid undue frothing of the solution. To the resulting mixture was added, dropwise, a solution of 23 g (0.1 mole) of 2-methoxyethyl p-toluenesulfonate in 50 ml of anhydrous DME. On completion of the addition, the reaction mixture was heated under reflux for 30 minutes after which time the solvent was removed. The residual sludge was taken up in water and extracted several times with ether. The combined extracts were washed with water, dried over anhydrous $MgSO_4$ and the solvent removed. Distillation of the residual oil under reduced pressure afforded 9.8 g (57%) of β-benzylthioethyl methyl ether. B.p., 80° at 0.8 mm; η_D^{25}, 1.5408. Anal. Calcd. for $C_{10}H_{14}OS$: C, 65.89; H, 7.75; S, 17.59.

Found: C, 65.66; H, 7.69; S, 17.51. The 60 MHz n.m.r. spectrum of the product is shown in Figure I. Assignments of the various absorptions have been discussed earlier (p.27).

2-Benzyloxyethanol was prepared by a modification of the method of Butler et al (62). To 150 ml of anhydrous ethylene glycol was added, with stirring, 12 g (0.5 mole) of sodium hydride in small portions. On completion of the addition, benzyl chloride (63 g, 0.5 mole) was added dropwise to the resultant solution and the whole heated at 60° for 12 hours. Direct distillation of the reaction mixture, under reduced pressure, afforded 88 g (58%) of 2-benzyloxyethanol. B.p., 88° at 1 mm. Lit. b.p., 131° at 13 mm (62).

2-Benzyloxyethyl p-toluenesulfonate was prepared in 77% yield by the same method as has been reported for 2-methoxyethyl p-toluenesulfonate above, starting from 2-benzyloxyethanol and p-toluenesulfonyl chloride in pyridine. M.p., 44-45°. Lit. m.p., 45° (61).

Benzyl β-benzylthioethyl ether was prepared in 52% yield by treatment of 2-benzyloxyethyl p-toluenesulfonate with sodium benzyl mercaptide using the same procedure as has been described above for the preparation of β-benzylthioethyl methyl ether. B.p., 140° at 1.0 mm, η_D^{23}, 1.5706. Anal. Calcd. for $C_{16}H_{18}OS$: C, 74.37; H, 7.03; S, 12.41 Found: C, 74.50; H, 6.98; S, 12.22.

The 60 MHz n.m.r. spectrum of the product is shown in Figure II. Assignment of the various signals has been discussed earlier (p. 27).

2. Reactions of β-benzylthioethyl methyl ether and benzyl β-benzylthioethyl ether with sodium metal in DME.

1,2-Dimethoxyethane (DME) was obtained from the Ansul Chemical Co. Marinette, Wisconsin and was purified by its double distillation from potassium metal. In the later stages of the work $LiAlH_4$ replaced potassium metal as a drying agent for DME and gave equally satisfactory results.

Sodium sand was prepared by heating pieces of the metal in xylene until just molten and then stirring the mixture vigorously, by means of a high-speed stirrer, for a few minutes during which time the heat source was removed and the solution allowed to cool. The metal sodidified into fine particles. The xylene was decanted and replaced by anhydrous DME. The sodium sand was stored under this solvent in a sealed flask until needed.

Treatment of β-benzylthioethyl methyl ether with sodium in DME. To a suspension of 460 mg (0.02 mole) of pulverized sodium metal in 500 ml of anhydrous DME, was added 3.6 g (0.02 mole) of β-benzylthioethyl methyl ether. The resulting solution was heated under reflux in a N_2 atmosphere for 24 hours. The solution became brown within the first hour of reflux, and the formation of a precipitate was observed. On completion of the reaction, the solid residue (0.9 g) was separated by filtration on a Büchner funnel and the solvent removed from the filtrate by fractional distillation at atmospheric pressure. The resultant oil was taken up in ether, and the whole washed with water, dried over anhydrous $MgSO_4$ and the solvent

removed by distillation at atmospheric pressure to yield 3.2 g (89%) of a product which proved by n.m.r. and I.R. analysis to be identical with the starting material.

A portion of the solid material formed above was added to 1 ml of 95% ethanol. No effervescence was observed which would have occurred if any unchanged sodium metal remained. Solution of the solid in water yielded a dark brown liquid which gave an alkaline reaction with Hydrion pH paper. Acidification of this solution with dilute hydrochloric acid caused the evolution of hydrogen sulfide (positive test with lead acetate paper). Extraction of the acidified solution with ether and subsequent removal of the solvent from the dried ($MgSO_4$) extract by fractional distillation at atmospheric pressure afforded 70 mg of an oil, which on g.l.c. analysis proved to be identical with α-toluenethiol. No further attempts were made to discover the nature of the solid residue.

In a subsequent experiment the stream of nitrogen flowing through the reaction vessel during the reflux period was passed into a trap cooled in a dry ice–acetone bath. Examination of the liquid present in the trap on completion of the reaction by I.R., n.m.r. and g.l.c. analysis showed it to be pure DME.

Treatment of benzyl β-benzylthioethyl ether with sodium in DME. Reaction of benzyl β-benzylthioethyl ether with one equivalent of pulverized sodium in DME as described above, resulted in the recovery of unchanged starting material only (87%).

B. REACTIONS INVOLVING ACETALS OF BENZYLTHIOACETALDEHYDE.

1. Preparation of starting materials.

Benzylthioacetaldehyde dimethylacetal was prepared by a modification of the method of Hutchison and Smiles (67). Sodium metal (4.6 g, 0.2 mole) was added in small pieces to 500 ml of 95% ethanol contained in a 1 liter 3-neck flask fitted with a condenser, mechanical stirrer and dropping funnel. When all the metal had dissolved, α-toluenethiol (25 g, 0.2 mole) was added dropwise and on completion of the addition the resulting solution was heated under reflux for 2 hours. The solution was allowed to cool whereupon chloroacetaldehyde dimethylacetal (25 g, 0.2 mole) was added dropwise and the solution heated under reflux for a further 2 hour period. After the reaction mixture had cooled, the bulk of the solvent was removed and the residual oil taken up in ether. The ether solution was washed twice with water, then dried over anhydrous $MgSO_4$ and the solvent removed. Distillation of the product afforded 36 g (84%) of benzylthioacetaldehyde dimethylacetal B.p., 96° at 0.7 mm; η_D^{23}, 1.5303. Lit. b.p., 140 - 141° at 6 mm; η_D^{22}, 1.5303 (68).

Benzylthioacetaldehyde diethylacetal was prepared in 72% yield from chloroacetaldehyde diethylacetal as above. B.p., 111° at 1.3 mm; η_D^{20}, 1.5197. Lit. b.p., 192-195° at 30 mm (67).

2-Chloromethyl-1,3-dioxolane was prepared according to a modification of the method of McElvain and Curry (143). A solution

of chloroacetaldehyde dimethylacetal (25 g, 0.2 mole) and ethylene glycol (15.5 g, 0.25 mole) in 300 ml of anhydrous toluene containing 2 drops of conc. HCl was heated at 90° for 3 hours in an apparatus designed for normal downward distillation. During the period of heating 6 g of methanol distilled from the reaction vessel. To the residual solution was added 1 g of anhydrous sodium carbonate. Subjection of this mixture to distillation under atmospheric pressure yielded 20.7 g (84%) of 2-chloromethyl-1,3-dioxolane. B.p., 154-156° at 690 mm; η_D^{20}, 1.4480. Lit. b.p., 155-159° at 740 mm; η_D^{25}, 1.4465 (143).

2-Benzylthiomethyl-1,3-dioxolane was prepared in 64% yield from 2-chloromethyl-1,3-dioxolane by the method described above for the analogous preparation of benzylthioacetaldehyde dimethylacetal. B.p., 91° at 1.2 mm; η_D^{20}, 1.5551. Anal. Calcd. for $C_{11}H_{14}O_2S$: C, 62.82; H, 6.71; S, 15.25. Found: C, 63.05; H, 6.80; S, 15.31.

The 60 MHz n.m.r. spectrum of 2-benzylthiomethyl-1,3-dioxolane showed: a singlet at τ2.70 (5H) - aromatic hydrogens; a triplet at τ4.96 (1H, J = 4.5 Hz) - H-2 on the dioxolane ring; an AB quartet, the outer limbs of which were not clearly resolved, centered at τ6.07 (4H) - the two C-4 and two C-5 protons; a singlet at τ6.20 (2H) - methylene protons of benzylthio group; and a doublet at τ7.40 (2H, J = 4.5 Hz) - remaining S-CH_2 protons.

Treatment of benzylthioacetaldehyde dimethylacetal with sodium in DME by the procedure earlier afforded an 86% yield of unchanged

starting material. Benzylthioacetaldehyde diethylacetal and 2-benzylthiomethyl-1,3-dioxolane on similar treatment gave 85% and 92% recovered starting material respectively.

Analysis of the reaction products above by n.m.r. and I.R. spectroscopy indicated the absence of olefinic compounds which would have been found if any elimination reaction had occurred.

C. REACTIONS INVOLVING 3-ALKYLTHIO-2-METHOXYTETRAHYDROPYRANS.

1. Preparation of starting materials

3,4-dihydro-2H-pyran, obtained from Eastman Organic Chemicals, Rochester, N.Y., was purified by distillation.

Ethanesulfenyl chloride was prepared by a modification of the method of Brintzinger et al (144). Ethyl disulfide (60 g, 0.4 mole), in a 1-liter flask protected with a $CaCl_2$ drying tube, was cooled to -70° by means of a dry ice-acetone bath. To this was added, dropwise, ethanesulfenyl chloride (55 g, 0.4 mole). The solution became orange immediately upon addition of the first portions of sulfenyl chloride. During the addition the solution was allowed to warm slowly to room temperature, thus preventing precipitation of the reactants. Upon completion of the addition, the reaction mixture was heated on a water bath at 45° for 20 minutes to aid in the removal of dissolved SO_2. The mixture was then distilled under reduced pressure to yield 51 g (66%) of an orange liquid of b.p., 40° at 60 mm. Lit. b.p., 51° at 74 mm (144). Ethanesulfenyl chloride was generally used

immediately after its preparation, since on standing at room temperature it turned a dark red color within a few hours. Even storage in the freezing compartment of a refrigerator failed to prevent its extensive decomposition.

Methanesulfenyl chloride was prepared in a 62% yield by an analogous route starting from methyl disulfide. The product distilled as an orange liquid of b.p., 25° at 45 mm. Lit b.p., 27-28° at 53-60 mm (145).

α-Toluenesulfenyl chloride was prepared by the method of Emde (70). To a stirred, cooled (10°) suspension of N-chlorosuccinimide (32.5 g, 0.24 mole) in 900 ml of sodium dried benzene was added dropwise α-toluenethiol (29.8 g, 0.24 mole) dissolved in 50 ml of anhydrous benzene. During the addition period the reaction temperature was maintained at 10° by means of an ice-water bath. The solution became pale yellow. On completion of the addition, the succinimide which had formed during the reaction, was removed by filtration in a Büchner funnel. The filtrate was stripped of solvent and the residual yellow oil taken up in pentane to effect precipitation of any further succinimide which had remained in solution.

Filtration of the pentane solution in a Büchner funnel and subsequent removal of the solvent gave 36.5 g (96%) of crude α-toluenesulfenyl chloride. Attempted purification by distillation under reduced pressure resulted only in extensive decomposition. The crude product was therefore used directly in subsequent reactions.

General procedure for the preparation of 3-alkylthio-2-methoxy-tetrahydropyrans.

To a stirred solution of the alkanesulfenyl chloride (0.5 mole) in 300 ml of dried ($CaCl_2$) methylene chloride, cooled to -20° by means of a dry ice-acetone bath, was added dropwise 3,4-dihydro-2H-pyran (42 g, 0.5 mole). The temperature was maintained at -20° throughout the addition. During this period the color of the sulfenyl halide slowly disappeared. When all of the halide had been added, a solution of sodium methoxide (30 g, 0.55 mole) in 250 ml of methanol was added at such a rate that the temperature rose only to 0°. The mixture was then stirred and allowed to come to room temperature (1 hour). The solid which formed was removed by filtration under suction. The solvents were removed from the filtrate at a temperature not exceeding 40°. The residual oil, dissolved in 200 ml of ether, was washed with water and dried ($MgSO_4$). Removal of the ether under reduced pressure gave an oil which was distilled under reduced pressure. The physical data for the 3-alkylthio-2-methoxytetrahydropyrans prepared are given below.

2-Methoxy-3-methylthiotetrahydropyran was prepared by the above procedure starting from methane sulfenyl chloride. Distillation of the crude product afforded 64 g (79%) of pure 2-methoxy-3-methylthiotetrahydropyran as a mixture of cis and trans isomers having b.p., 47-48° at 0.3 mm, η_D^{23}, 1.4854. Anal. Calcd. for $C_7H_{14}O_2S$: C, 51.81; H, 8.69; S, 19.77. Found: C, 51.64; H, 8.68; S, 19.76.

The n.m.r. and I.R. spectra were consistent with the structure assigned. Relevant data are shown in Table 3. Attempted distillation of the product at pressures in the range 20-80 mm yielded mixtures of 2-methoxy-3-methylthiotetrahydropyran and 5-methylthio-3,4-dihydro-2H-pyran which proved inseparable even on fractional distillation using a Nestor-Faust spinning band column.

Distillation of the crude product, above, at 21 mm resulted in the isolation of a liquid having b.p., 97.5° which on n.m.r. analysis was shown to contain 2-methoxy-3-methylthiotetrahydropyran and its thermal decomposition product 5-methylthio-3,4-dihydro-2H-pyran in the molar ratio 5:1.

The distilled product was subjected to preparative g.l.c. using an Aerograph Autoprep Model A-700 fitted with a 20' x 1/4" stainless steel column. On a column packing of 20% diethyleneglycol succinate on Gas Chrom-P, at a temperature of 185° and with a helium gas flow rate of 250 ml/min, injection of 50 µl samples afforded two peaks having integrated areas in the ratio 1:3. Collection of the material comprising the first peak and its subsequent analysis indicated it to be pure 5-methylthio-3,4-dihydro-2H-pyran. B.p. 90° at 21 mm*; η_D^{23}, 1.5148. Anal. Calcd. for $C_6H_{10}OS$: C, 55.35; H, 7.74; S, 24.63. Found: C, 55.70; H, 7.44; S, 24.29.

The 60 MHz n.m.r. spectrum (CCl_4 solvent) showed a narrow triplet at τ3.57 (1H, J = 1.4 Hz) assigned to H-2, a triplet at τ6.22 (2H, J = 5.0 Hz) assigned to the two C-6 protons, a singlet at τ7.99

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* micro determination

(3H) assigned to the protons of the methyl thio group, and a multiplet lying between τ7.70 and τ8.40 (4H) assigned to the remaining protons at C-4 and C-5. The I.R. spectrum (neat) indicated a strong absorption at 1620 cm^{-1}, the region expected for the double bond stretching frequency of a vinyl ether.

3-Ethylthio-2-methoxytetrahydropyran was prepared by the general method reported above starting from ethanesulfenyl chloride. N.m.r. analysis of the crude reaction product prior to distillation indicated the presence of 3-ethylthio-2-methoxytetrahydropyran as being $\geq$95% the trans isomer (Table 3).

Distillation of this crude material at low pressures afforded 72 g (82%) of pure 3-ethylthio-2-methoxytetrahydropyran as a mixture of cis and trans isomers (Table 3). B.p., 43° at 0.01 mm; η_D^{24}, 1.4829. Anal. Calcd. for $C_8H_{16}O_2S$: C, 54.51; H, 9.15; S, 18.19. Found: C, 54.76; H, 9.06; S, 17.81.

N.m.r. and I.R. analysis of the product afforded spectra which were consistent with the assigned structure. Relevant data are given in Table 3.

A repetition of the above preparative procedure but with distillation at a pressure of 8.0 mm resulted in the isolation of 53 g (74%) of 5-ethylthio-3,4-dihydro-2H-pyran. B.p., 57° at 8.0mm, η_D^{28}, 1.5061. Anal. Calcd. for $C_7H_{12}OS$: C, 58.29; H, 8.32; S, 22.23. Found: C, 58.54; H, 8.38; S, 22.03.

3-Benzylthio-2-methoxytetrahydropyran was prepared by the general method reported above starting from α-toluenesulfenyl

chloride. N.m.r. analysis of the crude reaction product prior to distillation indicated the presence of 3-benzylthio-2-methoxytetrahydropyran as being 95% the trans isomer (Table 3), along with a small quantity (~7%) of benzyl disulfide.

Distillation of this material under reduced pressure resulted in extensive thermal decomposition and the isolation of 86 g (82%) of pure 5-benzylthio-3,4-dihydro-2H-pyran. B.p., 85° at 0.01 mm; η_D^{24}, 1.5776. Anal. Calcd. for $C_{12}H_{14}OS$: C, 69.85; H, 6.84; S, 15.54. Found: C, 69.58; H, 6.77; S, 15.92.

N.m.r. and I.R. analysis supported the assigned structure. Relevant data are given in Table 4.

In a subsequent experiment (0.3 molar quantities) preparation of 65 g of crude 3-benzylthio-2-methoxytetrahydropyran was achieved by the general procedure described above. Analysis of this material by n.m.r. spectroscopy indicated the presence of 18.2% of benzyl disulfide impurity. Removal of the latter substance was achieved by the method of Arnold et al (71) and is described below.

The crude reaction product was dissolved in 50 ml of anhydrous ether and added dropwise to a vigorously stirred suspension of 1.7 g (0.045 mole) of $LiAlH_4$ in 250 ml of anhydrous ether at room temperature. When addition to the $LiAlH_4$ was completed, the reaction mixture was stirred for a further 2 hour period, after which time 25 ml of a 10% aqueous potassium hydroxide solution was added to effect decomposition of any residual $LiAlH_4$. The resultant white suspension was filtered under vacuum and the filtrate poured into a

1-liter separatory funnel. The ether solution was washed five times with water, dried ($MgSO_4$) and the solvent removed. The residual pale yellow oil was subjected to distillation under reduced pressure to yield 42 g (82%) of a cis, trans mixture of 3-benzylthio-2-methoxytetrahydropyran (Table 3). B.p., 133° at 0.05 mm; η_D^{24}, 1.5487. Anal. Calcd. for $C_{13}H_{18}O_2S$: C, 65.49; H, 7.61; S, 13.45. Found: C, 65.58; H, 7.32; S, 13.60.

The n.m.r. spectrum of the product is shown in Figure III and the various assignments have been discussed earlier (p. 34).

A further sample of pure 3-benzylthio-2-methoxytetrahydropyran was prepared by dissolving 20.6 g (0.1 mole) of 5-benzylthio-3,4-dihydro-2H-pyran in 100 ml of methanol containing 3 drops of concentrated HCl. The solution was heated under reflux for 12 hours, and upon cooling was stirred while 1.0 g of solid sodium bicarbonate was added to neutralize the acid. The excess sodium bicarbonate was removed by filtration and the filtrate freed from solvent. The residual pale yellow oil was dissolved in 150 ml of ether, washed several times with water, and then dried ($MgSO_4$). Removal of the ether gave 22.5 g (95%) of a pale yellow oil (η_D^{23}, 1.5493) which proved upon I.R. and n.m.r. analysis to be pure 3-benzylthio-2-methoxytetrahydropyran.

Isomeric equilibration of 3-alkylthio-2-methoxytetrahydropyrans.

Equilibration of the cis, trans isomeric mixtures obtained above was achieved by dissolving 2.0 g of each of the compounds 2-methoxy-3-methylthiotetrahydropyran, 3-ethylthio-2-methoxytetrahydropyran

and 3-benzylthio-2-methoxytetrahydropyran separately in 45 ml quantities of methanol, each containing 3 drops of concentrated HCl and heating the solutions under reflux (N_2 atmosphere) for 12 hours. The solutions were cooled and 1.0 g of anhydrous sodium bicarbonate was added to neutralize the acid. The excess sodium bicarbonate was removed by filtration and the filtrate freed from solvent. The residual oil was taken up in ether, washed with water, dried ($MgSO_4$) and the solvent removed yielding products which on n.m.r. analysis contained the cis and trans isomers in the proportions shown:

	cis	:	trans
2-methoxy-3-methylthiotetrahydropyran	50	:	50
3-ethylthio-2-methoxytetrahydropyran	48	:	52
3-benzylthio-2-methoxytetrahydropyran	45	:	54

Separation of the cis and trans isomers in each case above by g.l.c., by column chromatography on neutral alumina (Grade 1) and Silica Gel, and by fractional distillation, proved impossible.

Treatment of 3-alkylthio-2-methoxytetrahydropyrans with sodium in DME.

3-Benzylthio-2-methoxytetrahydropyran (2.4 g, 0.01 mole) was dissolved in 50 ml of anhydrous DME. Sodium sand (230 mg, 0.01 mole) was added and the resulting mixture was heated under reflux in a nitrogen atmosphere for 24 hours. On cooling, the reaction mixture was filtered in a Büchner funnel and the filtrate stripped of solvent. The residual pale yellow oil was taken up in ether, washed with water, dried over anhydrous $MgSO_4$ and the solvent removed to

give 2.15 g (90%) of a product which proved to be unchanged starting material by comparison of its refractive index, n.m.r. and I.R. spectra to those of an authentic sample.

3-Ethylthio-2-methoxytetrahydropyran and 2-methoxy-3-methylthiotetrahydropyran afforded a 90% and 92% recovery of unchanged starting material, respectively, upon similar reaction.

D. REACTIONS INVOLVED IN THE ELUCIDATION OF MECHANISM FOR THE ADDITION OF ETHANESULFENYL CHLORIDE TO 3,4-DIHYDRO-2H-PYRAN.

Addition of 3,4-dihydro-2H-pyran to ethanesulfenyl chloride.

A quantity (2.1 g, 0.025 mole) of 3,4-dihydro-2H-pyran was added dropwise to a cold (-40°) stirred solution of 2.45 g (0.254 mole) of ethanesulfenyl chloride in 5 ml of dry $CDCl_3$. The temperature of the reaction mixture was maintained at -40° throughout the addition. The disappearance of the yellow color of the sulfenyl halide provided an indication of the progress of the reaction. When the addition was completed a sample was removed, kept at -40° and immediately subjected to n.m.r. analysis at -40° using the HA-100 spectrometer. The spectrum is shown in Figure IV and has been discussed earlier (p. 55). The reaction mixture was allowed to warm to room temperature when extensive decomposition occurred.

The preparation of 3-chloro-2-ethylthiotetrahydropyran.

2,3-Dichlorotetrahydropyran was prepared by a modification of the method of Jacobson (94). A solution of anhydrous chlorine (32 g,

0.45 mole), dissolved in 200 ml of dry ($CaCl_2$) carbon tetrachloride, was cooled to -30°. To this was added dropwise with stirring 37.8 g (0.45 mole) of 3,4-dihydro-2H-pyran so that the temperature of the reaction mixture remained at -30°. When the addition was completed the solvent was removed under reduced pressure and the colorless oil then fractionally distilled. B.p., 85° at 21 mm; yield 64 g (91%). Lit. b.p., 79-83° at 18 mm (94).

5-Chloro-3,4-dihydro-2H-pyran was prepared by the method of Riobe (93). Distillation of 2,3-dichlorotetrahydropyran at atmospheric pressure afforded an 87% yield of 5-chloro-3,4-dihydro-2H-pyran. B.p., 62° at 48 mm; η_D^{25}, 1.4784. Lit. b.p., 139-140° at atmospheric pressure; η_D^{20}, 1.4814 (93).

3-Chloro-2-ethylthiotetrahydropyran was obtained by a modification of a published procedure (95). A mixture of 3.9 g (0.063 mole) of ethanethiol and 11.8 g (0.1 mole) of 5-chloro-3,4-dihydro-2H-pyran was cooled to -20° by means of a dry ice-acetone bath. A slow stream of sulfur dioxide was passed into the solution for two minutes. The mixture was then stirred while it slowly attained room temperature. After standing overnight it was fractionally distilled under reduced pressure and gave 8.7 g (77%) of a colorless oil boiling at 63° at 0.15 mm; η_D^{28}, 1.5081. Anal. Calcd. for $C_7H_{13}ClOS$: C, 46.54; H, 7.24; Cl, 19.63. Found: C, 46.70; H, 6.97; Cl, 19.68.

The n.m.r. spectrum of the product was consistent with the structure 3-chloro-2-ethylthiotetrahydropyran and is shown in

Figure V. The various assignments have been discussed earlier (p. 58).

Two previous attempts had been made to synthesize 3-chloro-2-ethylthiotetrahydropyran by alternate routes. In the first, 2,3-dichlorotetrahydropyran (4.65 g, 0.03 mole) was added dropwise to a solution of sodium hydride (0.96 g, 0.04 mole) in 50 ml of ethanethiol at room temperature. On completion of the addition, the reaction mixture was stirred at room temperature for 24 hours. Ether (50 ml) was added and the solid material which precipitated was removed by filtration. The filtrate was freed from solvents and the residual oil taken up in ether, dried over anhydrous $MgSO_4$ and the solvent removed. This gave 4.4 g of a colorless oil which on n.m.r. analysis proved to be a mixture of the desired product and of 2,3-dichlorotetrahydropyran and 5-chloro-3,4-dihydro-2H-pyran in the molar ratio 12:1:2. Attempted distillation of this mixture under reduced pressure resulted only in decomposition.

In a further experiment, 5-chloro-3,4-dihydro-2H-pyran (3.5 g, 0.03 mole) was stirred in 50 ml of ethanethiol containing 3 drops of concentrated HCl at room temperature for 48 hours, under an atmosphere of nitrogen. Sodium bicarbonate (500 mg) was then added to neutralize the acid catalyst and the resulting mixture filtered on a Büchner funnel. The filtrate was freed from solvent to give 2.9 g of a colorless oil which on n.m.r. analysis was shown to contain mainly unchanged starting material along with a small quantity ($<5\%$) of 2,3-diclorotetrahydropyran. Distillation of this material under

reduced pressure afforded 2.5 g of 5-chloro-3,4-dihydro-2H-pyran which had boiling point, I.R. and n.m.r. spectra identical to those of an authentic sample (93).

The reaction of 3-chloro-2-ethylthiotetrahydropyran with ethanesulfenyl chloride.

A solution of 1 g (0.01 mole) of ethanesulfenyl chloride in 2 ml of dry $CDCl_3$ was cooled to -40° by means of a dry ice-acetone bath. To the stirred solution was added dropwise 1.8 g (0.01 mole) of 3-chloro-2-ethylthiotetrahydropyran. On completion of the addition the solution was stirred for 15 minutes and then freed from solvent by distillation under reduced pressure. The residual oil was fractionally distilled. The following fractions were collected. Fraction I, b.p., 78° at 46 mm (1 g). Fraction II, b.p., 104° at 46 mm (1.3 g). Fractions I and II were found to be diethyl disulfide and 2,3-dichlorotetrahydropyran respectively, as shown by comparison of their boiling points, n.m.r., and I.R. spectra with those of authentic samples.

Addition of 3,4-dihydro-2H-pyran to methanesulfenyl chloride in the solvent cumene. Test for free radical intervention.

To a cold (-5°) solution of 1.64 g (0.02 mole) of methansulfenyl chloride in 5 ml of cumene was added dropwise, with cooling, 1.68 g (0.02 mole) of 3,4-dihydro-2H-pyran. To the resulting colorless solution was added 1.62 g (0.03 mole) of sodium methoxide in 15 ml of methanol. The mixture was stirred at room temperature for 1 hour, then the precipitated solid was removed by filtration. The

filtrate was freed from methanol. The residue was taken up in ether, washed with water and dried ($MgSO_4$). The ether was removed by distillation and the oil fractionated under reduced pressure. Cumene (4.2 ml) was collected in a dry ice-acetone trap. G.l.c. analysis showed no evidence of any other substance in the cumene. Further distillation of the above oil gave 2.6 g (86%) of 2-methoxy-3-methylthiotetrahydropyran, b.p., 46° at 0.2 mm, identical with authentic material. A negligible amount of residue remained in the distillation flask.

E. REACTIONS INVOLVING THE ADDITION OF TRICHLOROMETHANESULFENYL CHLORIDE TO 3,4-DIHYDRO-2H-PYRAN AND TO 2,3-DIHYDROFURAN.

Trichloromethanesulfenyl chloride was obtained commercially from Eastman Organic Chemicals, Rochester, N.Y. and was purified by distillation under reduced pressure.

2,5-Dihydrofuran was obtained commercially from the Aldrich Chemical Co., Milwaukee, Wisconsin.

Potassium t-butoxide was obtained commercially from the M.S.A. Research Corp., Evans City, Pa.

2,3-Dihydrofuran was prepared by a modification of the method of Eliel et al (65). A mixture of 2,5-dihydrofuran (50 g) and potassium t-butoxide (12 g) in 50 ml of t-butyl alcohol was heated to 180° for 6 hours in a stainless-steel autoclave. The cooled solution was poured into a round-bottom flask and submitted to fractional distil-

lation using a Nestor-Faust Teflon spinning band column. The fraction of b.p., 54-55° at 700 mm was collected. Yield, 35 g (70%); η_D^{28}, 1.4190. Lit. b.p., 53-55° at 745 mm, η_D^{20}; 1.4200 (65).

The I.R. spectrum of the product showed the characteristic vinyl ether absorption at 1615 cm^{-1}.

The addition of trichloromethanesulfenyl chloride to 2,3-dihydrofuran.

(a) in the presence of an acid catalyst (69).

To 2.8 g (0.04 mole) of 2,3-dihydrofuran, cooled to 0° by means of an ice bath, was added one drop of concentrated HCl. To the resulting solution was added dropwise trichloromethanesulfenyl chloride (3.7 g, 0.02 mole). When two or three drops of the sulfenyl halide had been added a vigorous reaction ensued. The mixture in the reaction vessel became hot and formed a dark brown intractable tar.

(b) in the absence of an acid catalyst.

A repetition of the above procedure but in the absence of the hydrochloric acid catalyst produced the same results. No attempt was made to work up the tarry residue produced.

The addition of trichloromethanesulfenyl chloride to 3,4-dihydro-2H-pyran.

(a) in the presence of an acid catalyst.

To a cooled (0°) sample of 3,4-dihydro-2H-pyran (6.8 g, 0.08 mole) containing 3 drops of concentrated HCl was added dropwise

7.4 g (0.04 mole) of trichloromethanesulfenyl chloride. No loss of color took place, which would have been evidence for the expected addition reaction. The reaction mixture was stirred at room temperature for 3 hours and a sample removed for n.m.r. analysis. The n.m.r. spectrum of the reaction mixture showed the presence of unchanged 3,4-dihydro-2H-pyran along with broad signals in the region τ6.2- τ7.0 and τ8.3- τ9.0 which were thought to be due to the polymeric product arising from acid-catalyzed self-condensation of the vinyl ether.

(b) in the absence of an acid catalyst.

A repetition of the above procedure, but in the absence of the hydrochloric acid catalyst, afforded unchanged 3,4-dihydro-2H-pyran only, even after the reaction mixture, had been stirred at room temperature for 3 hours.

F. THE ATTEMPTED PREPARATION OF TETRAHYDROPYRANO-[2,3-b]-1,4-OXATHIANE.

1. Via p-oxathiene

2-Hydroxyethylthioacetaldehyde dimethylacetal was prepared according to the method of Parham (101). 2-Mercaptoethanol (156 g, 2 moles) was added slowly to a stirred solution of sodium methoxide (108 g, 2 moles) in 750 ml of methanol. On completion of the addition 10 g of powdered potassium iodide were added followed by bromoacetaldehyde dimethylacetal (338 g, 2 moles) dropwise. The resultant mixture was heated under reflux overnight. On cooling, the

precipitated solids were removed by filtration, and the filtrate freed from the bulk of the solvent. Chloroform (300 ml) was added to the residual oil to effect precipitation of dissolved salts, which were then removed by filtration. The filtrate was stripped of solvent and the product distilled under reduced pressure to afford 2-hydroxyethylthioacetaldehyde dimethyl acetal (239 g, 72%). B.p., 87° at 0.5 mm; η_D^{23}, 1.4792. Lit. b.p., 90° at 0.63 mm; η_D^{20}, 1.4810 (101).

2-Methoxy-1,4-oxathiane was prepared by the method of Parham, Gordon and Swalen (72). Anhydrous methanol (25 ml) was cooled to 0° and through this was bubbled HCl gas for 30 minutes. The resulting solution was added, with stirring, to 2-hydroxyethylthioacetaldehyde dimethylacetal (154 g, 0.81 mole) and the whole stirred at room temperature overnight. Anhydrous sodium carbonate was added to neutralize the acid catalyst until evolution of CO_2 ceased and the resulting mixture subjected directly to distillation under reduced pressure to yield 81 g (75%) of 2-methoxy-1,4-oxathiane. B.p., 74° at 15 mm; η_D^{22}, 1.4912. Lit. b.p., 57° at 5 mm; η_D^{23}, 1.4911 (72).

p-Oxathiene was prepared by the method of Parham et al (72). To 2-methoxy-1,4-oxathiane (81 g, 0.6 mole) was added 0.7 g of phosphorus pentoxide in an apparatus designed for downward distillation and the whole heated under N_2 to 155°. The mixture was maintained at this temperature for $3\frac{1}{2}$ hours during which time 22.5 ml of methanol distilled off. The reaction mixture was allowed to

cool and then subjected to distillation under reduced pressure to yield 58 g (96%) of p-oxathiene. B.p., 44° at 17 mm; η_D^{24}, 1.5340. Lit. b.p., 54° at 20 mm; $\eta_D^{20.7}$, 1.5357.

The reaction of p-oxathiene with acrolein was achieved according to the method of Longley and Emmerson (100). p-Oxathiene (5.1 g, 0.05 mole) and acrolein (4.2 g, 0.075 mole) were dissolved in 50 ml of anhydrous benzene containing 100 mg of hydroquinone. The resulting solution was heated, with stirring, to 130° for 12 hours in a sealed stainless-steel autoclave. The cooled reaction mixture was filtered and the solvent removed from the filtrate by fractional distillation. The residual yellow oil was distilled under reduced pressure to yield unchanged p-oxathiene (3.0 g, 59%) - b.p., 47° at 18 mm, and an orange syrupy residue. The latter proved insoluble in a variety of organic solvents. No evidence could be found for the presence of the desired product.

The above experiment was repeated under a variety of different reaction temperatures and times starting in all cases with 5.1 g of p-oxathiene. The quantities of recovered p-oxathiene are shown below.

Temperature	Time (hours)	Recovered p-oxathiene (g)
80°	5	4.8
150°	18	3.3
165°	21	3.5
180°	28	3.1
210°	12	2.7

2. Via 3-chloro-2-(β-mercaptoethoxy)-tetrahydropyran.

3-Chloro-2-(β-mercaptoethoxy)-tetrahydropyran. To a solution of 2-mercaptoethanol (4.6 g, 0.06 mole) and 5-chloro-3,4-dihydro-2H-pyran (7.2 g, 0.06 mole) in 20 ml of anhydrous ether was added 2 drops of concentrated HCl. The mixture was stirred at room temperature under N_2 for 48 hours. Anhydrous sodium carbonate (500 mg) was added to neutralize the acid catalyst and the solvent removed. Distillation of the residue under reduced pressure afforded 4.5 g (38%) of 3-chloro-2-(β-mercaptoethoxy)-tetrahydropyran. B.p., 92° at 0.06 mm. Anal. Calcd. for $C_7H_{13}O_2SCl$: C, 42.74; H, 6.67; Cl, 18.02; S, 16.29. Found: C, 42.95; H, 6.96; Cl, 17.81; S, 16.04.

The n.m.r. and I.R. spectra of the product are shown in Figures VI and VII respectively and have been discussed earlier (p. 68).

Attempted distillation of the pot residue at a pressure of 0.05 mm and with a bath temperature of 160° failed to yield any distillate. However, analysis of the pot residue by n.m.r. suggested the presence of more 3-chloro-2-(β-mercaptoethoxy)-tetrahydropyran (Doublets at τ5.44 (J = 2.9 Hz) and τ5.60 (J = 3.5 Hz)).

3-Chloro-2-ethoxytetrahydropyran was prepared by a modification of the method of Riobe (93). A solution of 5-chloro-3,4-dihydro-2H-pyran (9.5 g, 0.08 mole) in 50 ml of 98% ethanol containing 50 mg of p-toluenesulfonic acid was stirred at room temperature for 12 hours. Sodium bicarbonate (500 mg) was added to neutralize the

acid catalyst and the filtered solution was freed from solvent. Distillation of the residual oil under reduced pressure afforded 3-chloro-2-ethoxytetrahydropyran (9.2 g, 71%), b.p., 87° at 20 mm; η_D^{23}, 1.4553. Lit. b.p. 83° at 17 mm; η_D^{10}, 1.4601 (93).

Treatment of 3-chloro-2-(β-mercaptoethoxy)-tetrahydropyran with NaH.

A quantity (420 mg, 0.02 mole) of NaH was added in small portions to a stirred, cooled (0°) solution of 3-chloro-2-(β-mercaptoethoxy)-tetrahydropyran (4.0 g, 0.02 mole) in 30 ml of anhydrous DME. On completion of the addition the solution was heated at 60° for 12 hours under a nitrogen atmosphere. A few drops of water were added cautiously to the cooled solution to effect decomposition of any unreacted sodium hydride, and then the solvent was removed. The residue was dissolved in water and the aqueous solution extracted with ether. The ether extract was dried ($MgSO_4$) and freed from solvent under vacuum to yield a few mg of an unidentified oil. The aqueous solution, above, was carefully neutralized by the addition of dilute hydrochloric acid and then rendered slightly basic by the further addition of 1 g of sodium carbonate. An oil separated from the solution. Extraction of the above solution with ether and, after drying ($MgSO_4$), subsequent removal of the solvent from the ether extract afforded 3.7 g (92%) of an oil which proved to be identical with an authentic sample of 3-chloro-2-(β-mercaptoethoxy)-tetrahydropyran on subjection to I.R. and n.m.r. analysis.

G. THE ATTEMPTED SYNTHESIS OF 3-ALKYLTHIO-2,4-DIMETHOXYTETRAHYDROPYRANS.

1. The addition of ethanesulfenyl chloride to 2-methoxy-5,6-dihydro-2H-pyran.

3-Bromo-2-methoxytetrahydropyran was prepared by a modification (146) of the method of Woods and Sanders (98). A solution of 3,4-dihydro-2H-pyran (84 g, 1 mole) in a mixture of 100 ml of anhydrous liquid ammonia and 1 liter of methanol was cooled to -60° by means of a dry ice-acetone bath. To the stirred solution, kept between -55° and -60°, was added dropwise a solution of 160 g (1 mole) bromine in 200 ml of carbon tetrachloride. A precipitate of ammonium bromide appeared when about half of the bromine had been added. When the bromine addition was completed the cooling bath was removed and the reaction mixture was stirred overnight and thus came to room temperature. The residual ammonia and methanol were removed. To the remaining material was added 500 ml of dry ether. The precipitated ammonium bromide was removed by filtration in a Buchner funnel and the filtrate dried ($MgSO_4$) and freed from solvent under reduced pressure. Distillation of the residual oil under reduced pressure afforded 180 g (92%) of 3-bromo-2-methoxytetrahydropyran. B.p., 92° at 22 mm; η_D^{24}, 1.4840. Lit. b.p. 88-89° at 18 mm; η_D^{25}, 1.4838 (98).

Dimethylsulfoxide was obtained commercially from the Fisher Scientific Company, Fair Lawn, N.J. and was dried by its passage

through a 1 meter x 2 cm chromatography column packed with molecular sieves (Type 4A: 1/16" pellets). It was stored over molecular sieves, and passed a second time through the above column immediately prior to use.

2-Methoxy-5,6-dihydro-2H-pyran was prepared by a modification of the method of Woods and Sanders (98). To a stirred solution of sodium methoxide (29.7 g, 0.55 mole) in 300 ml of anhydrous dimethylsulfoxide was added dropwise 3-bromo-2-methoxytetrahydropyran (97 g, 0.5 mole). An exothermic reaction ensued and the rate of addition was controlled such that the reaction temperature did not exceed 60°. On completion of the addition the reaction mixture was stirred for a further 15 minutes and then subjected directly to distillation under reduced pressure. All the material in the boiling range 62° at 700 mm to 90° at 23 mm was collected in a dry ice-acetone cooled receiver. The resulting mixture was redistilled under reduced pressure using a Nestor-Faust spinning band column and afforded 44 g (77%) of 2-methoxy-5,6-dihydro-2H-pyran. B.p. 66° at 67 mm; η_D^{23}, 1.4430. Lit. b.p., 136-138° at 760 mm; η_D^{25}, 1.4425 (98).

4-Chloro-3-ethylthio-2-methoxytetrahydropyran. To a cold (-30°), stirred solution of ethanesulfenyl chloride (9.6 g, 0.1 mole) in 25 ml of anhydrous methylene chloride was added dropwise 2-methoxy-5,6-dihydro-2H-pyran (11.4 g, 0.1 mole). During the course of the addition the yellow color of the sulfenyl halide slowly disappeared. On completion of the addition a solution of sodium methoxide (5.4 g, 0.1 mole) in 25 ml of methanol was added and the

reaction mixture allowed to warm to room temperature. Removal of the solvents under reduced pressure left a sludge which was taken up in ether upon which precipitation of dissolved solids occurred. The ethereal solution was filtered, washed with water, dried ($MgSO_4$) and the solvent removed. Distillation of the residual pale yellow oil afforded 14 g (67%) of trans, trans-4-chloro-3-ethylthio-2-methoxytetrahydropyran. B.p., 77-79° at 0.05 mm; η_D^{26}, 1.5001. Anal. Calcd. for $C_8H_{15}ClO_2S$: C, 45.61; H, 7.18; Cl, 16.83. Found: C, 45.70; H, 7.31; Cl, 16.83. Molecular weight: Calcd. 210; Found 208. The n.m.r. spectrum is shown in Figure VIII and has been discussed earlier (p. 73).

The attempted preparation of 2,4-dimethoxy-3-ethylthiotetrahydropyran.

(a) 4-Chloro-3-ethylthio-2-methoxytetrahydropyran (6.3 g, 0.03 mole) was dissolved in 50 ml of methanol containing sodium methoxide (3.2 g, 0.06 mole) and the resulting solution was heated under reflux in a N_2 atmosphere for 6 hours. The solvent was removed from the cooled mixture under reduced pressure and the residue dissolved in ether. Precipitated solids were removed by filtration. The filtrate was washed with water, dried ($MgSO_4$) and freed from solvent to yield 6.0 g of a colorless oil. N.m.r. analysis indicated the presence of starting material along with a small amount of an olefinic material (signals in the region τ4.0- τ4.5). No evidence could be seen for the presence of the desired product and, in view of this fact, no further work-up was attempted.

(b) 4-Chloro-3-ethylthio-2-methoxytetrahydropyran (6.3 g, 0.03 mole) was dissolved in 50 ml of anhydrous methanol containing a suspension of silver carbonate (9.7 g, 0.035 mole). The resulting solution was stirred under nitrogen for 3 hours. Anhydrous ether (50 ml) was added and the solid removed by filtration on a Büchner funnel. Removal of the solvents from the filtrate under vacuum afforded 6.1 g of a pale yellow oil which proved to be identical to starting material on comparison of its refractive index, n.m.r. and I.R. spectra to those of an authentic sample.

2. The attempted preparation of 4-methoxy-3,4-dihydro-2H-pyran.

(a) Via 2,4-dimethoxytetrahydropyran

2,4-Dimethoxytetrahydropyran was prepared according to the method of Sweet and Brown (117). To a stirred solution of 100 mg of p-toluenesulfonic acid in 100 ml of anhydrous methanol was added 14.0 g (0.123 mole) of 2-methoxy-5,6-dihydro-2H-pyran. The resulting mixture was heated under reflux for 4 hours. The cooled solution was neutralized with powdered sodium methoxide and the bulk of the solvent then removed by fractional distillation. The residue, dissolved in 100 ml of ether, was washed with 20 ml of water, dried ($MgSO_4$) and freed from solvent by fractional distillation. The residual oil, distilled under reduced pressure on a Nestor-Faust spinning band column, gave 15 g (83%) of 2,4-dimethoxytetrahydropyran. B.p., 45° at 4.5 mm; η_D^{23}, 1.4336. Lit. b.p., 109° at 100 mm; η_D^{25}, 1.4330 (117). N.m.r. analysis of the product

showed it to be a mixture of cis and trans isomers in the ratio 1 : 4. The triplet at τ 5.28 (J = 2.9 Hz) and the quartet centered at τ 5.68 ($J_{2,3a}$ = 8.3 Hz; $J_{2,3e}$ = 2.8 Hz) were assigned to the H-2 anomeric proton in the trans and cis isomers respectively (117).

Treatment of 2,4-dimethoxytetrahydropyran with phosphorus pentoxide was carried out according to the procedure of Parham and Holmquist (115). To 6.0 g (0.04 mole) of 2,4-dimethoxytetrahydropyran was added 200 mg of phosphorus pentoxide. The whole was heated slowly to 180° by means of a silicone oil bath. The reaction mixture began to darken when the temperature reached 170°, and at 180° extensive decomposition occurred.

The above procedure was therefore repeated but with heating to only 130°. After maintaining the reactants at this temperature for a period of $1\frac{1}{2}$ hours the mixture was distilled under reduced pressure to afford 5.3 g (88%) of unchanged starting material. B.p., 70° at 14 mm. N.m.r. and I.R. spectra were identical to those of an authentic sample.

Treatment of 2,4-dimethoxytetrahydropyran with p-toluenesulfonic acid was achieved by a analogous method to that of Julia and Jacquet (116). A solution of 100 mg of p-toluenesulfonic acid in 20 g (0.137 mole) of 2,4-dimethoxytetrahydropyran was heated to 150° for a period of 2 hours. Distillation of the reaction product under reduced pressure afforded 13.5 g (86%) of 2-methoxy-5,6-dihydro-2H-pyran, b.p., 69° at 70 mm. Comparison of the boiling point, I.R.and n.m.r. spectra of the product with those of an authentic sample of

2-methoxy-5,6-dihydro-2H-pyran confirmed the assigned structure of the product.

Treatment of 2,4-dimethoxytetrahydropyran with n-butyl lithium. A quantity (32 ml, 0.05 mole) of a standardized 10% solution of n-butyl lithium in pentane was carefully transferred by means of a hypodermic syringe to a 100 ml three-neck round bottom flask fitted with a rubber seal, condenser and dropping funnel and maintained under an atmosphere of dry nitrogen. The flask and contents were cooled to 0^{o} by means of an ice-water bath and 2,4-dimethoxytetrahydropyran (7.3 g, 0.05 mole), dissolved in 10 ml of anhydrous ether, was added dropwise over a period of 1 hour. On completion of the addition the reaction mixture was heated on a water-bath at 40^{o} for 3 hours. The flask and contents were again cooled to 0^{o} and ice-cold water was added dropwise to decompose any unreacted base. The reaction mixture was washed several times with water and the combined water washes extracted twice with ether. The ether extracts were combined with the reaction product, and the whole was dried ($MgSO_4$) and then the solvents removed by fractional distillation. Distillation of the residual oil under reduced pressure afforded 6.5 g (89%) of a material which on comparison of its boiling point, n.m.r. and I.R. spectra with those of an authentic sample proved to be identical with the starting material.

(b) Via 3-bromo-2,4-dimethoxytetrahydropyran.

3-Bromo-2,4-dimethoxytetrahydropyran was prepared by the

general bromomethoxylation technique of van de Sande and Kopecky (121). 1,3-Dibromo-5,5-dimethylhydantoin (7.0 g, 0.025 mole) was added in small portions to a cold (-50°) stirred solution of 2-methoxy-5,6-dihydro-2H-pyran (5.7 g, 0.05 mole) in a mixture of 10 ml of anhydrous ether and 10 ml of anhydrous methanol. On completion of the addition the reaction mixture was allowed to warm to room temperature and then poured into ice-cold saturated sodium bicarbonate solution. The resulting mixture was extracted with ether, washed with saturated sodium bisulfite solution and with saturated sodium bicarbonate solution. The ethereal solution was then dried ($MgSO_4$) and freed from solvent. Distillation of the residual oil under reduced pressure afforded 8.0 g (72%) of 3-bromo-2,4-dimethoxy-tetrahydropyran. B.p., 63° at 0.05 mm; η_D^{22}, 1.4832. Anal. Calcd. for $C_7H_{13}BrO_3$: C, 37.36; H, 5.82; Br, 35.50. Found: C, 37.35; H, 5.77; Br, 35.78. Molecular weight Calcd., 225; Found, 225. The n.m.r. spectrum of the product is shown in Figure IX and indicates it to be an isomeric mixture. The details of this analysis have been discussed earlier (p. 86).

Reductive debromination of 3-bromo-2,4-dimethoxytetrahydropyran. To 3-bromo-2,4-dimethoxytetrahydropyran (5.2 g, 0.023 mole) in 50 ml of anhydrous methanol containing 1.7 g (0.03 mole) of sodium methoxide was added 500 mg of 5% palladium on charcoal. The resulting mixture was poured into a pressure bottle and shaken for 24 hours on a Parr catalytic hydrogenator under a pressure of 55 lbs p.s.i. of hydrogen. On completion of the reaction, solids were filtered off in a Buchner funnel and the solvent removed from the filtrate. The residual paste was dissolved in ether, washed with

water, dried ($MgSO_4$) and the solvent removed by fractional distillation to yield 2.2 g (67%) of 2,4-dimethoxytetrahydropyran whose refractive index, n.m.r. and I.R. spectra were identical to those of an authentic sample. N.m.r. analysis showed the product to be a mixture of cis and trans isomers in the ratio 2:1.

Treatment of 3-bromo-2,4-dimethoxytetrahydropyran with zinc in ethanol was achieved by the method of Boord et al (118). A solution of 3-bromo-2,4-dimethoxytetrahydropyran (2.25 g, 0.01 mole) in 15 ml of 98% ethanol containing 1.2 g (0.02 mole) of powdered zinc metal was heated under reflux for 12 hours. The cooled solution was filtered and the solvent removed from the filtrate by fractional distillation. Analysis of the crude product by n.m.r. spectroscopy indicated the presence of unchanged starting material along with 2-methoxy-5,6-dihydro-2H-pyran. Distillation of the crude product under reduced pressure afforded 0.5 g (44%) of 2-methoxy-5,6-dihydro-2H-pyran, b.p., 70° at 71 mm, and 1.1 g of unchanged starting material, b.p., 55° at 0.03 mm. The n.m.r. and I.R. spectra of both compounds were identical to those of authentic samples.

Treatment of 3-bromo-2,4-dimethoxytetrahydropyran with sodium metal in benzene was achieved by the method of McElvain, Kent and Stevens (120). A suspension of 1.6 g (0.07 mole) of powdered sodium metal in 75 ml of anhydrous benzene was placed in a 250 ml three-neck indented flask fitted with a high-speed stirrer, dropping funnel and a condenser protected from moisture by a calcium

chloride tube filled with Drierite. The solution was heated to reflux and then 7.5 g (0.033 mole) of 3-bromo-2,4-dimethoxytetrahydropyran was added dropwise. On completion of the addition (30 minutes) the solution was heated under reflux for a further 16 hours. The cooled solution was filtered on a Büchner funnel, the solids washed with benzene and the combined filtrate and washings freed from solvent by fractional distillation at atmospheric pressure to yield 3.3 g (44%) of a colorless oil which on distillation under reduced pressure proved to be identical with unchanged starting material. B.p., 58° at 0.04 mm. The refractive index, n.m.r. and I.R. spectra of the product were identical to those of an authentic sample of 3-bromo-2,4-dimethoxytetrahydropyran.

(c) Via the acetate and carbonate esters of 2-hydroxy-4-methoxytetrahydropyran.

2-Hydroxy-4-methoxytetrahydropyran was prepared by stirring a solution of 2,4-dimethoxytetrahyropyran (7 g, 0.454 mole) in 75 ml of water and 25 ml of DME containing 1.5 g of Amberlite I.R. 120 ion exchange resin at room temperature for 24 hours. On completion of the reaction the solution was filtered and the filtrate freed from solvents. Toluene (10 ml) was added towards the end of the latter process to effect complete removal of water by azeotropic distillation. Distillation of the residual oil under reduced pressure afforded 4.7 g (78%) of 2-hydroxy-4-methoxytetrahydropyran as a mixture of cis and trans isomers. B.p., 65° at 0.1 mm; η_D^{23}, 1.4573. Anal. Calcd.

for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.61; H, 9.37. The I.R. spectrum of the product showed a broad absorption at 3400 cm^{-1} (O-H stretching frequency). The n.m.r. spectrum of the product was consistent with the assigned structure and has been discussed earlier (p. 92).

2-Acetoxy-4-methoxytetrahydropyran was prepared by the general procedure outlined in Wagner and Zook (128). A solution of 2-hydroxy-4-methoxytetrahydropyran (8 g, 0.06 mole) and acetic anhydride (10.2 g, 0.1 mole) in 50 ml of anhydrous (KOH) pyridine was heated under reflux for 15 minutes. Water (125 ml) was added to the cooled reaction mixture followed by solid sodium bicarbonate until evolution of carbon dioxide ceased. The resultant mixture was extracted three times with ether and the combined extracts washed with ice-cold 10% hydrochloric acid, saturated sodium bicarbonate solution and water. Removal of the solvent from the dried ($MgSO_4$) ether solution gave a colorless oil which on distillation under reduced pressure afforded 6.4 g (61 %) of 2-acetoxy-4-methoxytetrahydropyran as a mixture of cis and trans isomers. B.p., 67° at 0.05 mm, η_D^{22}; 1.4447. Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.07; H, 7.91. The n.m.r. spectrum of the product is shown in Figure X, and has been discussed earlier (p. 94).

The attempted anomerization of 2-acetoxy-4-methoxytetrahydropyran was performed according to the method of Anderson and Sepp (129). 2-Acetoxy-4-methoxytetrahydropyran (0.7 g) was dissolved in 5 ml of glacial acetic acid containing a catalytic amount (one small

crystal) of p-toluenesulfonic acid. The resulting solution was stirred at room temperature for 12 hours. Within the first hour a brown coloration developed. Analysis of the solution by n.m.r. spectroscopy indicated the total absence of the signals attributed to the H-2 anomeric proton of 2-acetoxy-4-methoxytetrahydropyran (p. 94).

The pyrolysis of 2-acetoxy-4-methoxytetrahydropyran. A solution of 2-acetoxy-4-methoxytetrahydropyran (2.7 g, 0.016 mole) in 5 ml of pentane was passed via a stream of dry nitrogen through a one-meter quartz glass pyrolysis tube packed with glass helices, at a temperature of 290°. The column effluent was passed into a trap cooled by means of a dry ice-acetone bath. The contents of the trap were poured into 50 ml of saturated sodium bicarbonate solution and the resulting mixture subjected to continuous extraction with ether for a 24 hour period. Inspection of the pyrolysis tube packing when cool indicated the presence of a brown intractable residue. Removal of the solvent from the dried ($MgSO_4$) ether extract above by fractional distillation at atmospheric pressure afforded 200 mg of an unidentified pale yellow oil which darkened on standing. A repetition of the above procedure at a pyrolysis temperature of 180° resulted in the isolation of 250 mg of an unidentified oil which also decomposed extensively on standing.

The attempted preparation of the carbonate ester of 2-hydroxy-4-methoxytetrahydropyran was performed according to the method of Bailey and Baylouny (125). To a cooled (0°) solution of 2-hydroxy-

4-methoxytetrahydropyran (3.9 g, 0.03 mole) in 10 ml of anhydrous pyridine was added dropwise methyl chloroformate (4.7 g, 0.05 mole). The resulting mixture was heated on an oil bath at 90° for 2 hours. The cooled solution was poured into a 100 ml of ice-cold dilute HCl, saturated with sodium chloride and extracted three times with ether. The combined ether extracts were dried ($MgSO_4$) and freed from solvent. Distillation of the residue under reduced pressure afforded 3.6 g (91%) of unchanged 2-hydroxy-4-methoxytetrahydropyran having a boiling point, and I.R. and n.m.r. spectra identical to those of an authentic sample.

(d) Via 2-chloro-4-methoxytetrahydropyran.

The attempted preparation of 2-chloro-4-methoxytetrahydropyran was performed by a modification of the method of Lemieux and Brice (130). To a stirred, cooled (0°) solution of titanium tetrachloride (5.7 g, 0.03 mole) in 30 ml of anhydrous benzene was added dropwise a solution of 5.1 g (0.03 mole) of 2-acetoxy-4-methoxytetrahydropyran in 30 ml of anhydrous benzene. The reaction mixture became dark brown during the addition of the first portions of the acetate. After being stirred at 0° for 10 minutes the mixture was poured into 100 ml of ice-cold saturated sodium bicarbonate solution. A solid black residue remained in the reaction flask, which proved to be insoluble in benzene, ether or water. The yellow benzene layer was separated, washed with saturated sodium bicarbonate solution, then with water, and finally dried over

anhydrous $MgSO_4$. Removal of the solvent under reduced pressure afforded 50 mg of an unidentified yellow oil which darkened on standing.

H. REACTIONS INVOLVING METHYL S-BENZYL-4,6-O-ETHYLIDENE-3-O-METHYL-2-THIO-β-D-ALTROPYRANOSIDE.

1. The preparation of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-β-D-altropyranoside.

Methyl 4,6-O-ethylidene-β-D-glucopyranoside was prepared by the method of O'Meara and Shepherd (131). Methyl β-D-glucopyranoside (34 g, 0.175 mole) (obtained commercially from Pfanstiehl Laboratories, Waukegan, Illinois) was dissolved in 150 ml of 1,1-dimethoxyethane containing 0.5 ml of concentrated sulfuric acid. The resulting solution was shaken vigorously for 48 hours at room temperature. On completion of the reaction, the precipitated solid was isolated by filtration on a Büchner funnel, washed several times with pentane and recrystallized from 95% ethanol to afford 24 g (63%) of methyl 4,6-O-ethylidene-β-D-glucopyranoside. M.p., 188°; $[\alpha]_D^{23}$, -78.7 (c, 2.0 in H_2O). Lit. m.p., 188-189°; $[\alpha]_D^{20}$, -79.4 (c, 1.9 in H_2O) (131).

Methyl 4,6-O-ethylidene-2,3-di-O-p-toluenesulfonyl-β-D-glucopyranoside was prepared according to the method of Ansell and Honeyman (132). p-Toluenesulfonyl chloride (88 g, 0.463 mole) was added in portions to a cooled (0°) solution of methyl 4,6-O-ethylidene-β-D-glucopyranoside (44 g, 0.2 mole) in 150 ml of anhydrous pyridine.

The resulting mixture was stirred at room temperature for 96 hours and then poured into ice-water (2000 ml). A pasty solid separated. The solution was extracted with chloroform (3 x 300 ml) and the combined extracts washed several times with ice-cold dilute hydrochloric acid followed by saturated sodium bicarbonate solution and then with water. Removal of the solvent from the dried ($MgSO_4$) chloroform solution yielded a white crystalline solid which on recrystallization from methanol afforded 78 g (73%) of methyl 4,6-O-ethylidene-2,3-di-O-p-toluenesulfonyl-β-D-glucopyranoside, m.p., 163-165°; $[\alpha]_D^{23}$, -33.1 (c, 1 in $CHCl_3$). Lit. m.p., 164°; $[\alpha]_D^{20}$, -33.6 (c, 0.64 in $CHCl_3$) (132).

Methyl 2,3-anhydro-4,6-O-ethylidene-β-D-allopyranoside was prepared by a modification of the procedure of Ansell and Honeymann (132). To a solution of sodium metal (2.5 g, 0.109 mole) in 250 ml of anhydrous methanol was added methyl 4,6-O-ethylidene-2,3-di-O-p-toluenesulfonyl-β-D-glucopyranoside (28.5 g, 0.054 mole). The reaction mixture was heated under reflux for 24 hours during which time it became a dark brown color. The cooled solution was stripped of solvent until the volume of liquid remaining was about one tenth of the original. Water (200 ml) was added and the solution extracted with chloroform (6 x 100 ml). The combined extracts were washed with water, dried ($MgSO_4$) and freed from solvent. The residual brown oil was taken up in 100 ml of anhydrous ether whereupon precipitation of a solid occurred. The solid (5 g) was isolated by filtration and proved on analysis to be unchanged starting material.

The filtrate was freed from solvent under vacuum and the residual oil subjected to chromatography on 100 g of neutral alumina (Grade I). Elution with ether : pentane (1 : 6) afforded 3.1 g (33%) of methyl 2,3-anhydro-4,6-O-ethylidene-β-D-allopyranoside. M.p., 78°; $[\alpha]_D^{23}$, -44.0 (c, 0.8 in $CHCl_3$). Lit. m.p. 79°; $[\alpha]_D^{18}$, -43.6 (c, 0.8 in $CHCl_3$) (132).

Methyl S-benzyl-4,6-O-ethylidene-2-thio-β-D-altropyranoside was prepared employing the method of Nayak and Brown (1). Sodium methoxide (485 mg, 0.009 mole) was dissolved in 20 ml of anhydrous methanol. A continuous stream of nitrogen was passed through the the apparatus and α-toluenethiol (6.2 g, 0.05 mole) was then added. When the solution had been stirred for 15 minutes, 1.7 g (0.0084 mole) of methyl 2,3-anhydro-4,6-O-ethylidene-β-D-allopyranoside was added and the solution heated under reflux for 24 hours. When cooled, the solution was poured into 100 ml of ice-water and extracted with chloroform (2 x 50 ml). The combined extracts were washed with 10% sodium hydroxide solution (3 x 50 ml) followed by water, and the solvent removed from the dried ($MgSO_4$) chloroform solution under reduced pressure. The resulting solid was recrystallized from ethanol to give 2.3 g (85%) of methyl S-benzyl-4,6-O-ethylidene-2-thio-β-D-altropyranoside. M.p., 122-123°; $[\alpha]_D^{25}$, -168° (c, 0.7 in $CHCl_3$). Anal. Calcd. for $C_{16}H_{22}O_5S$: C, 58.88; H, 6.77; S, 9.83. Found: C, 58.58; H, 6.67; S, 10.13.

The 60 MHz n.m.r. spectrum of the product showed a doublet at τ5.14 (1H, J = 2.0 Hz) assigned to the C-1 anomeric proton, a quartet at τ7.02 (1H, $J_{1,2}$ = 2.0 Hz; $J_{2,3}$ = 3.5 Hz) assigned to the

proton at C-2 and a broad singlet at τ 7.58 (1H, W/2 = 3.0 Hz) assigned to the C-3 hydroxyl group proton. Addition of one drop of D_2O to the sample under analysis caused a loss of the latter signal. The I. R. spectrum of the product ($CHCl_3$ solvent) showed a narrow absorption at 3580 cm^{-1} assigned to the stretching frquency of the C-3 hydroxyl group.

Methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-β-D-altropyranoside was prepared using the methylation procedure of Diner, Sweet and Brown (133). A solution of 660 mg (0.002 mole) of methyl S-benzyl-4,6-O-ethylidene-2-thio-β-D-altropyranoside and 1 g (0.007 mole) of methyl iodide in 10 ml of anhydrous DME was cooled to 0°. Sodium hydride (100 mg) was added in small portions, followed by a further 1 g of methyl iodide. The resulting solution was stirred at 0° for 30 minutes and then at room temperature for a further $1\frac{1}{2}$ hours. The cloudy solution was freed from solvent under reduced pressure, water was carefully added to the residue, the mixture extracted with ether, and the ether solution was washed with water, dried ($MgSO_4$) and freed from solvent. Analysis of the clear residual syrup (660 mg, 96%) proved it to be pure methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-β-D-altropyranoside. All attempts to effect crystallization of the syrup met with failure. For the syrup, $[\alpha]_D^{23}$, - 157.1° (c, 0.7 in $CHCl_3$). Anal. Calcd. for $C_{17}H_{24}O_5S$: C, 58.52; H, 7.37; S, 9.76. Found: C, 58.61; H, 7.33; S, 9.97.

The 60 MHz n.m.r. spectrum of the product is shown in Figure

XI and has been discussed earlier (p. 101). The I.R. spectrum ($CHCl_3$ solvent) of the product showed the absence of signals between 3400 cm^{-1} and 3600 cm^{-1}, the region expected for the stretching frequencies of hydroxyl groups.

2. The treatment of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-β-D-altropyranoside with sodium in DME by the method described earlier (2, 3) (p. 134) afforded unchanged starting material in 94% yield. The n.m.r. and I.R. spectra of the product were identical to those of the starting material.

A sample of methyl 4,6-O-ethylidene-3-O,S-dimethyl-2-thio-β-D-altropyranoside (kindly made available by Dr. M. Sharma) similarly afforded a 92% yield of unchanged starting material on treatment with sodium in DME.

I. REACTIONS INVOLVING METHYL S-BENZYL-4,6-O-ETHYLIDENE-3-O-METHYL-2-THIO-α-D-ALTROPYRANOSIDE.

1. The preparation of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-α-D-altropyranoside by the trans acetalation of methyl S-benzyl-4,6-O-benzylidene-3-O-methyl-2-thio-α-D-altropyranoside.

Methyl 4,6-O-benzylidene-α-D-glucopyranoside was prepared by a modification of the method of Freudenberg et al (136). Methyl α-D-glucopyranoside (obtained commercially from the Fisher Scientific Co., Fair Lawn, N.J.) (28 g, 0.144 mole) was dissolved

in a suspension of powdered anhydrous zinc chloride (21 g) in 130 ml of benzaldehyde. The reaction mixture was shaken vigorously for 12 hours. The resulting viscous solution was poured, with vigorous stirring, into water whereupon a white precipitate formed. The latter was isolated by filtration on a Büchner funnel, washed several times with pentane and dissolved in 300 ml of chloroform. Removal of the solvent from the dried ($MgSO_4$) solution and subsequent recrystallization of the product from chloroform/ether afforded 29 g (71%) of methyl 4,6-O-benzylidene-α-D-glucopyranoside m.p., 163°; $[\alpha]_D^{23}$, 109.7° (c, 1.7 in $CHCl_3$). Lit. m.p., 163-164°; $[\alpha]_D$, 110.4° (c, 2.0 in $CHCl_3$) (148).

Methyl 4,6-O-benzylidene-2,3-di-O-p-toluenesulfonyl-α-D-glucopyranoside was prepared from methyl 4,6-O-benzylidene-α-D-glucopyranoside by the method described above for the analogous preparation of methyl 4,6-O-ethylidene-2,3-di-O-p-toluenesulfonyl-β-D-glucopyranoside. Yield, 72%. M.p., 147-148°; $[\alpha]_D^{23}$, 13.9° (c, 1 in $CHCl_3$). Lit. m.p., 148-149°, $[\alpha]_D$, 13.0° (c, 1.505 in $CHCl_3$) (137).

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside was prepared according to literature directions (147). To a cooled (0°) solution of methyl 4,6-O-benzylidene-2,3-di-O-p-toluenesulfonyl-α-D-glucopyranoside (100 g, 0.17 mole) in 1000 ml of $CHCl_3$ was added a cooled (0°) solution of sodium methoxide (45.4 g, 0.84 mole) in 350 ml of methanol. The mixture was allowed to stand in the refrigerator for 3 days with occasional shaking and then at room temperature for an additional day. The bulk of the solvent was

removed under reduced pressure and the residue poured into 500 ml of water, extracted with chloroform (3 x 300 ml) and the combined extracts washed, dried ($MgSO_4$) and freed from solvent under reduced pressure. Crystallization of the residue from chloroform/ether afforded 38 g (85%) of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside. M.p., 199°; $[\alpha]_D^{25}$, 141.2° (c, 1.8 in $CHCl_3$). Lit. m.p. 200°; $[\alpha]_D$; 140° (c, 2.2 in $CHCl_3$) (147).

Methyl S-benzyl-4,6-O-benzylidene-2-thio-α-D-altropyranoside was prepared from methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside by the method described earlier for the analogous preparation of methyl S-benzyl-4,6-O-ethylidene-2-thio-β-D-altropyranoside. Yield, 84%. M.p., 136-137°; $[\alpha]_D^{23}$, 93.8 (c, 1.1 in $CHCl_3$). Lit. m.p., 136-137°, $[\alpha]_D^{25}$, 94.7° (c, 1.0 in $CHCl_3$) (1).

Methyl S-benzyl-4,6-O-benzylidene-3-O-methyl-2-thio-α-D-altropyranoside was prepared from methyl S-benzyl-4,6-O-benzylidene-2-thio-α-D-altropyranoside by the method described earlier for the analogous preparation of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-β-D-altropyranoside. Yield 92%. M.p., 67-68°; $[\alpha]_D^{23}$, 90.5° (c, 1 in $CHCl_3$). Lit. m.p. 68-69°, $[\alpha]_D^{25}$, 91° (c, 1 in $CHCl_3$) (2).

Methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-α-D-altropyranoside. A solution of methyl S-benzyl-4,6-O-benzylidene-3-O-methyl-2-thio-α-D-altropyranoside (3.5 g, 0.0087 mole) in 100 ml of 1,1-dimethoxyethane containing 0.2 ml of concentrated sulfuric acid was stirred at room temperature for 24 hours.

Dichloromethane (250 ml) was added, and the solution was washed with saturated sodium bicarbonate solution and water, and then dried ($MgSO_4$). Removal of the volatile solvents gave 2.9 g of a syrup which was subjected to chromatography on 50 g on neutral alumina (Grade I). Elution with ether-hexane (1 : 1) afforded 2.4 g (81%) of a syrup which was proved on analysis to be pure methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-α-D-altropyranoside. A sample of the syrup crystallized on standing at room temperature for 3 weeks. M.p., 73-75°; $[\alpha]_D^{23}$, 60.54° (c, 1.37 in $CHCl_3$). Anal. Calcd. for $C_{17}H_{24}O_5S$: C, 58.52; H, 7.37; S, 9.76. Found: C, 58.36; H, 7.08; S, 10.05.

The 100 MHz n.m.r. spectrum of the product is shown in Figure XII. Assignments of the various signals have been discussed earlier (p. 103).

The treatment of methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-α-D-altropyranoside with sodium in DME was achieved by the method described earlier (p. 134). Reaction of 660 mg (0.002 mole) of the carbohydrate with 46 mg (0.002 mole) of sodium metal in DME (10 ml) gave starting material (620 mg, 94%) along with an insoluble precipitate (85 mg) which was removed from the reaction mixture by filtration on a Hirsch funnel. Solution of a few mg of this material in 3 drops of water gave a solution which proved to be alkaline with Hydrion pH paper. Titration of an aqueous solution of 51 mg of the solid against N/10 hydrochloric acid needed 0.32 ml of the acid for neutralization. Gravimetric analysis of the solid showed it to contain

C, 10.03%; H, 1.34% and indicated the absence of sulfur. An n.m.r. spectrum of the solid dissolved in D_2O showed only the characteristic DOH absorption at τ 5.2. Analysis of the solid by I.R. spectroscopy proved impossible due to its insolubility in organic solvents and its inability to form a mull with either nujol or halo-oil.

J. THE ATTEMPTED SYNTHESIS OF METHYL S-BENZYL-4,6-O-BENZYLIDENE-3-O-METHYL-2-THIO-β-D-ALTROPYRANOSIDE.

Methyl 4,6-O-benzylidene-β-D-glucopyranoside was prepared from methyl β-D-glucopyranoside by the method described earlier in the analogous preparation of methyl 4,6-O-benzylidene-α-D-glucopyranoside. Yield, 61%. M.p., 205°; $[\alpha]_D^{25}$, -60.7° (c, 0.8 in $CHCl_3$). Lit. m.p., 205°; $[\alpha]_D$, -62.3° (c, 1.012 in $CHCl_3$) (136, 137).

Methyl 4,6-O-benzylidene-2,3-di-O-p-toluenesulfonyl-β-D-glucopyranoside was prepared by the method described earlier in the preparation of the analogous α-compound. Yield, 69%. M.p., 157-158°; $[\alpha]_D^{22}$, -54.95 (c, 0.9 in $CHCl_3$). Lit. m.p. 158°, $[\alpha]_D^{19}$, -54.70 (c, 2.796 in $CHCl_3$) (138).

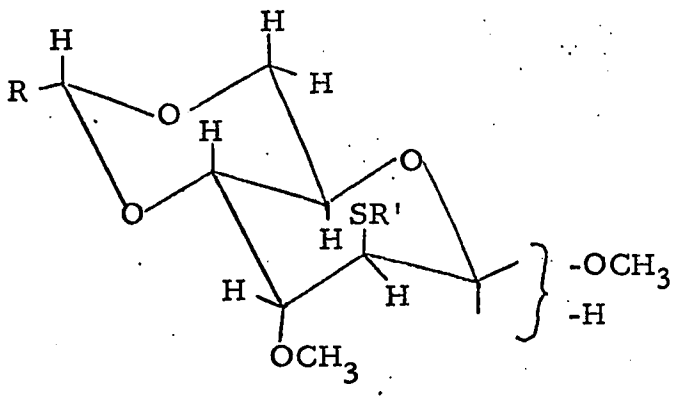
The attempted preparation of methyl 2,3-anhydro-4,6-O-benzylidene-β-D-allopyranoside was carried out by treatment of methyl 4,6-O-benzylidene-2,3-di-O-p-toluenesulfonyl-β-D-glucopyranoside with sodium methoxide in refluxing methanol. This

procedure has already been described for the analogous preparation of methyl 2,3-anhydro-4,6-O-ethylidene-β-D-allopyranoside. Work-up of the reaction mixture, in the manner indicated, afforded an 80% recovery of unchanged starting material having melting point, I.R. and n.m.r. spectra identical to those of an authentic sample.

K. DEUTERIUM EXCHANGE EXPERIMENTS.

General procedure for the treatment of methyl S-alkyl-4,6-O-alkylidene-3-O-methyl-2-thio-α(-β)-D-altropyranoside with sodium methoxide in d_1-methanol.

To a solution of 500 mg of the sugar in 15 ml of d_1-methanol (>99% isotopic purity: obtained commercially from Carl Roth OHG, Karlsruhe, West Germany) was added 3 molar equivalents of sodium methoxide. The resulting mixture was stirred and heated under reflux for 24 hours in an atmosphere of dry nitrogen. The cooled solution was freed from solvents and the residue taken up in chloroform (10 ml), washed with deuterium oxide (2 x 5 ml), dried ($MgSO_4$) and freed from solvent under reduced pressure. In all cases a high yield of unchanged starting material was recovered. N.m.r. analysis of the products with careful integration of the various peak areas indicated the absence of deuterium incorporation in all cases. The relevant data are shown below.



C_1-OCH_3	R	R'	Recovery
α	CH_3	$C_6H_5CH_2$	95%
β	CH_3	$C_6H_5CH_2$	95%
α	C_6H_5	$C_6H_5CH_2$	92%
β *	CH_3	CH_3	95%
α *	CH_3	CH_3	94%

* samples made available by Dr. M. Sharma.

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REFERENCES

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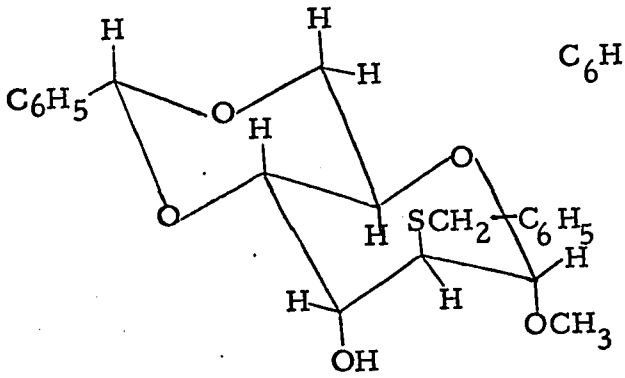
APPENDIX

APPENDIX A

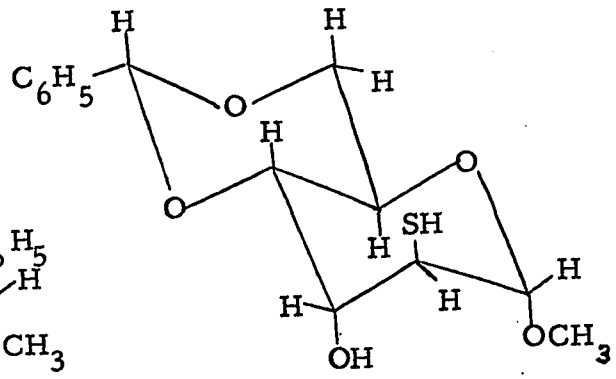
NUMERICAL TABLE OF COMPOUNDS

I



methyl S-benzyl-4,6-O-benzylidene-2-thio-α-D-altropyranoside

II



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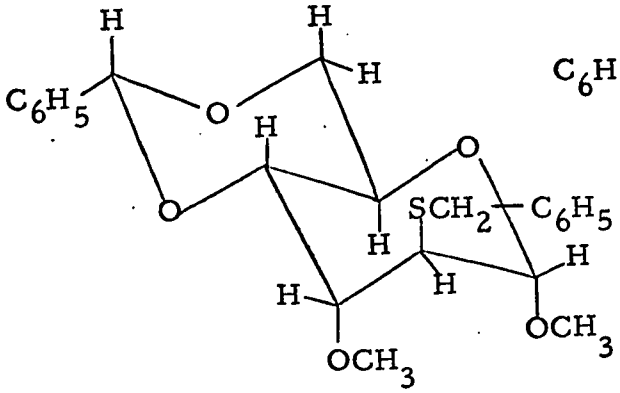

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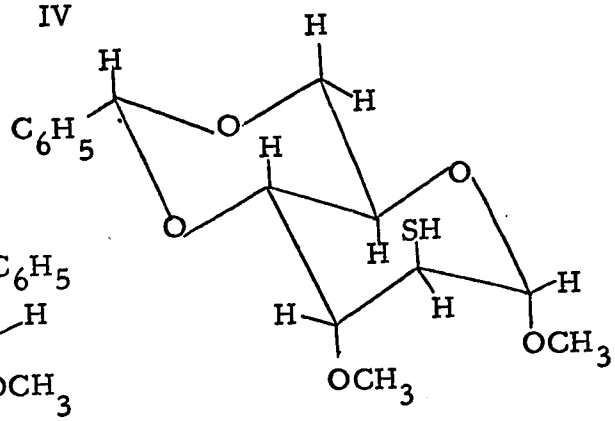
IV



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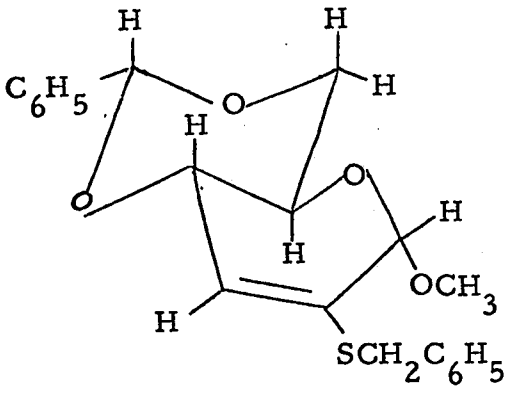

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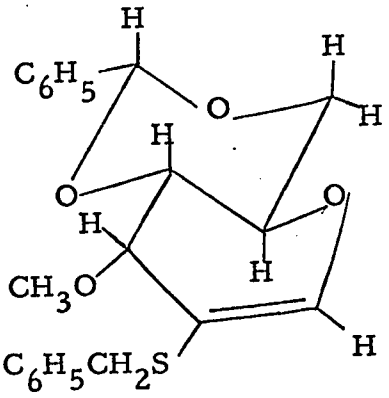
VI



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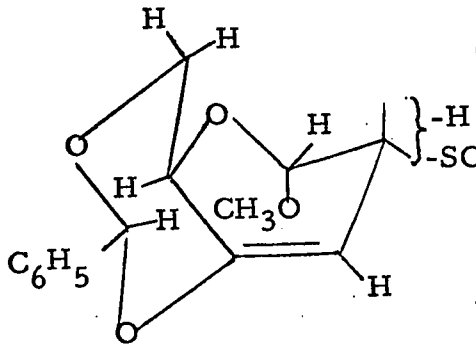
VII



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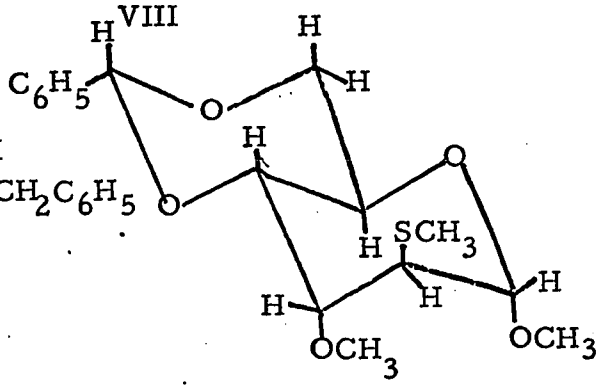
VIII



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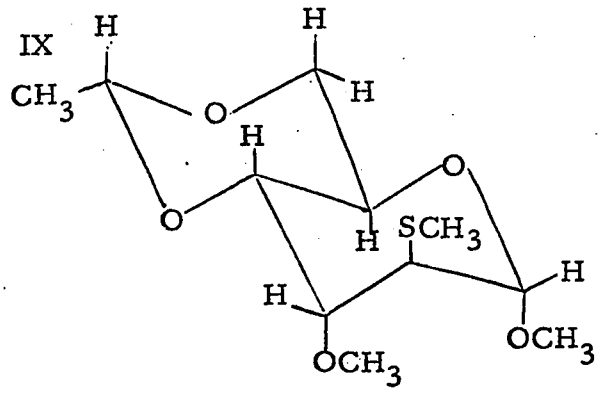

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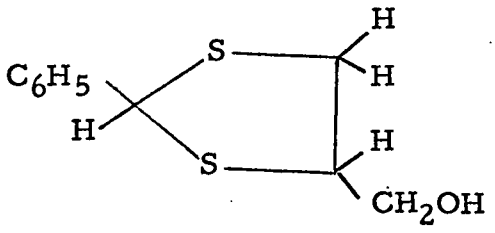

2-phenyl-4-hydroxymethyl-1,3-dithiolane

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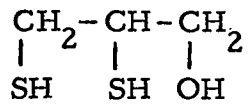

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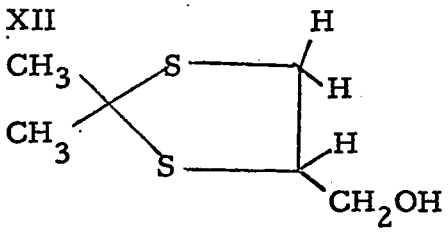

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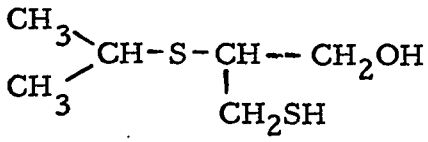
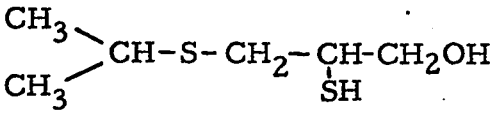


3-mercapto-2-isopropylthiopropanol-1

XIV



2-mercapto-3-isopropylthiopropanol-1

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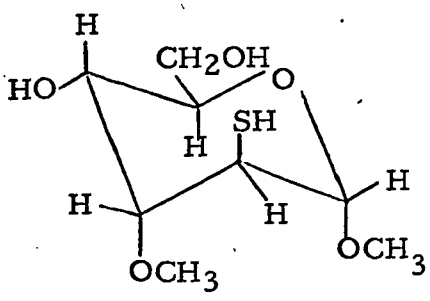
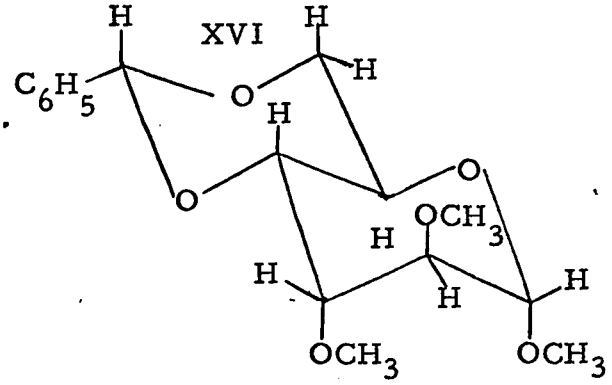


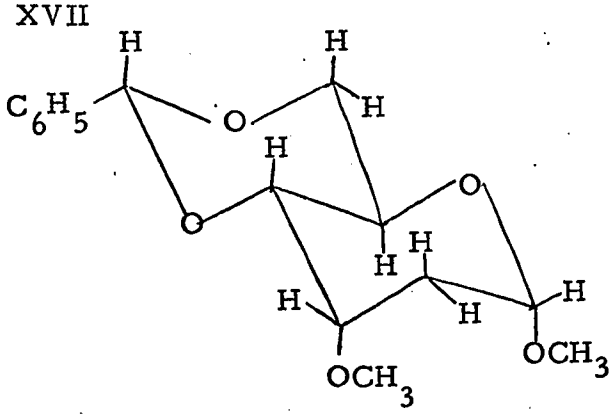
methyl 3-O-methyl-2-thio-α-D-altropyranoside

XVI



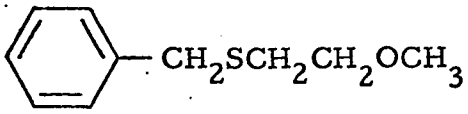
methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-altropyranoside

XVII



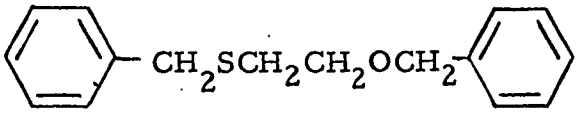
methyl 4,6-O-benzylidene-2-deoxy-3-O-methyl-α-D-altropyranoside

XVIII



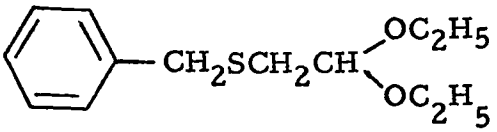
methyl β-benzylthioethyl ether

XIX



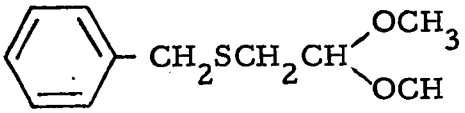
benzyl β-benzylthioethyl ether

XX



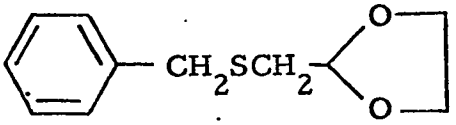
benzylthioacetaldehyde diethylacetal

XXI



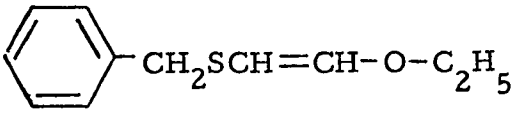
benzylthioacetaldehyde dimethyl acetal

XXII



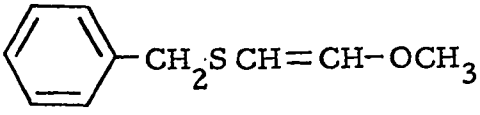
2-(benzylthiomethyl)-1,3-dioxolane

XXIII



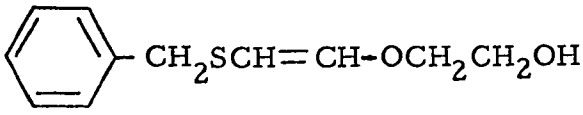
benzyl 2-ethoxyvinyl sulfide

XXIV



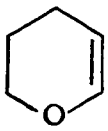
benzyl 2-methoxyvinyl sulfide

XXV



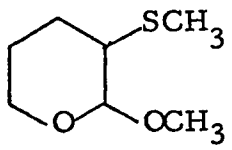
benzyl 2-(β-hydroxyethoxy)vinyl sulfide

XXVI



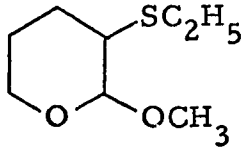
3,4-dihydro-2H-pyran

XXVII



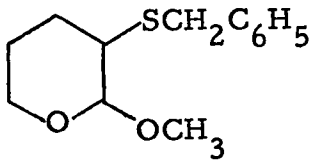
2-methoxy-3-methylthiotetra-hydropyran

XXVIII



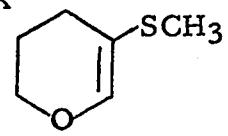
3-ethylthio-2-methoxytetra-hydropyran

XXIX



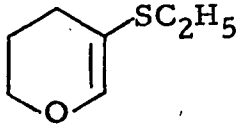
3-benzylthio-2-methoxytetra hydropyran

XXX



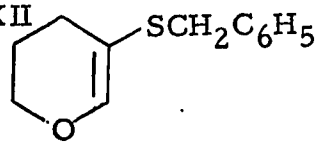
5-methylthio-3,4-dihydro-2H-pyran

XXXI



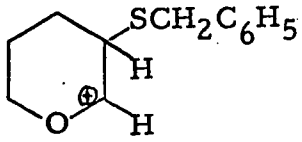
5-ethylthio-3,4-dihydro-2H-pyran

XXXII

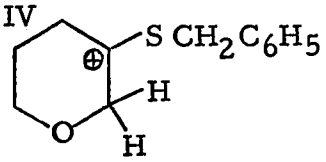


5-benzylthio-3,4-dihydro-2H-pyran

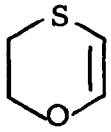
XXXIII



XXXIV

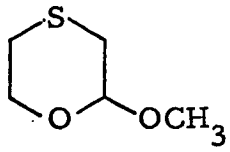


XXXV



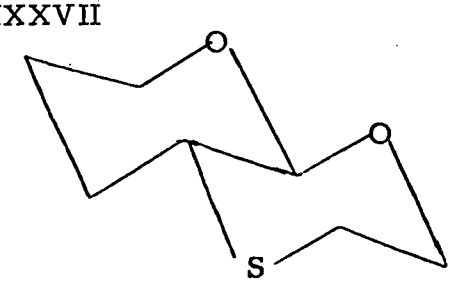
p-oxathiene

XXXVI



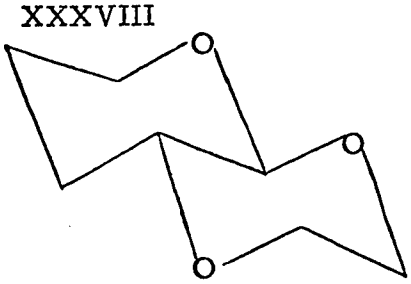
2-methoxy-1,4-oxathiane

XXXVII



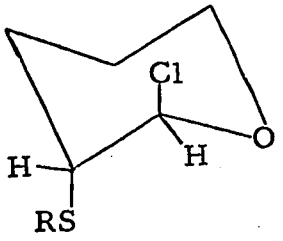
tetrahydropyrano[2,3-b]-1,4-oxathiane

XXXVIII



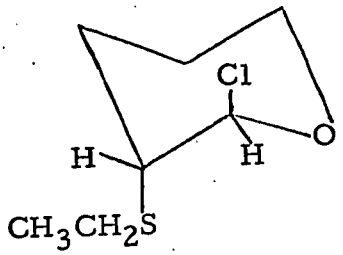
tetrahydropyrano[2,3-b]-1,4-dioxane

XXXIX



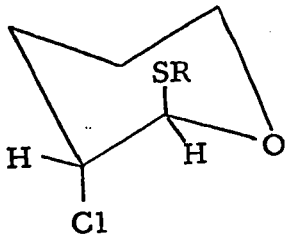
trans-3-alkylthio-2-chloro-tetrahydropyran

XXXIXa



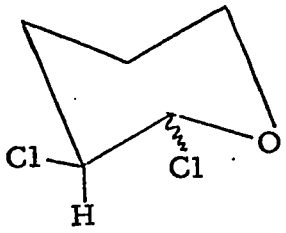
trans-2-chloro-3-ethylthio-tetrahydropyran

XL



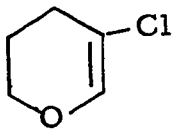
trans-2-alkylthio-3-chlorotetra-hydropyran (XLa: R = C_2H_5)

XLI



2,3-dichlorotetrahydropyran

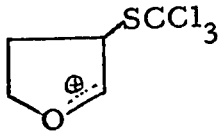
XLII



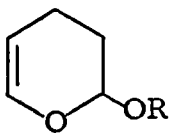
5-chloro-3,4-dihydro-2H-pyran

XLIII

XLIV

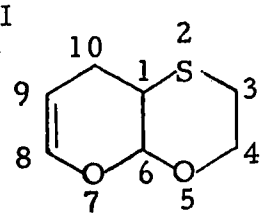


XLV



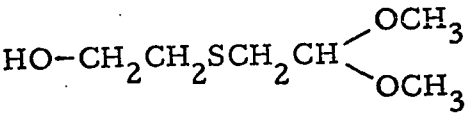
2-alkoxy-3,4-dihydro-2H-pyran

XLVI



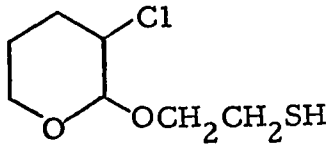
5,7-dioxa-2-thiabicyclo[4·4·0]dec-8-ene

XLVII



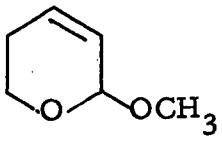
2-hydroxyethylthioacetaldehyde dimethylacetal

XLVIII



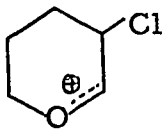
3-chloro-2-(β-mercaptoethoxy)-tetrahydropyran

XLIX

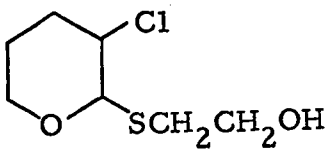


2-methoxy-5,6-dihydro-2H-pyran

L

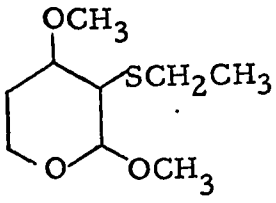


LI



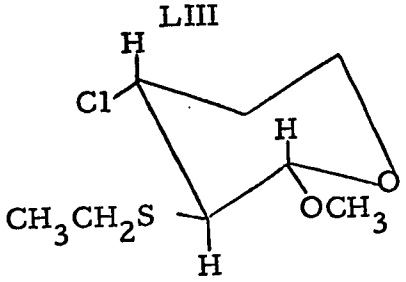
3-chloro-2-(β-hydroxyethylthio)-tetrahydropyran

LII



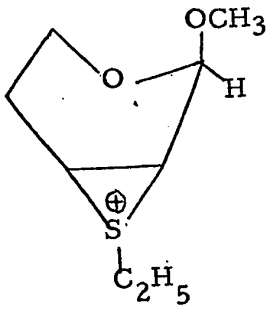
3-ethylthio-2,4-dimethoxy-tetrahydropyran

LIII

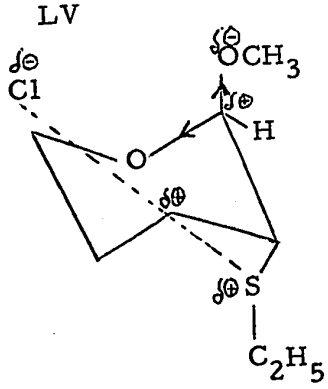


trans-4-chloro-trans-3-ethylthio-2-methoxytetrahydropyran

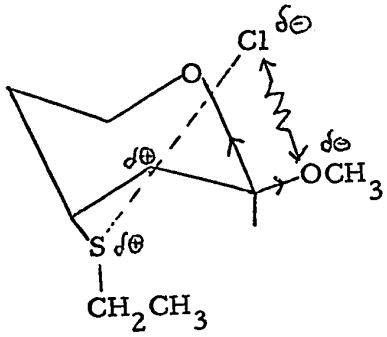
LIV



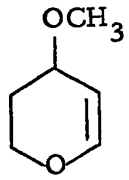
LV



LVI

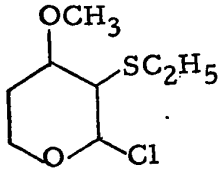


LVII



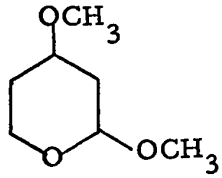
4-methoxy-3,4-dihydro-2H-pyran

LVIII



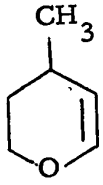
2-chloro-3-ethylthio-4-methoxy-tetrahydropyran

LIX



2,4-dimethoxytetrahydropyran

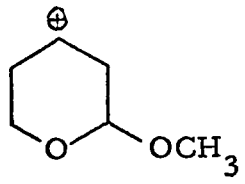
LX



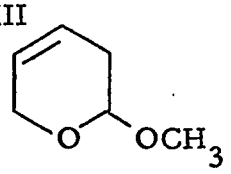
4-methyl-3,4-dihydro-2H-pyran

LXI

LXII

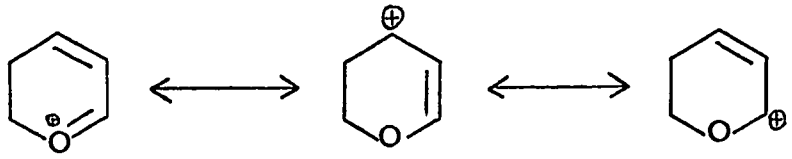


LXIII



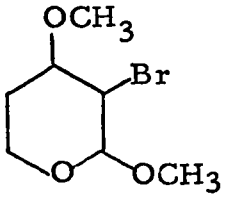
6-methoxy-5,6-dihydro-2H-pyran

LXIV



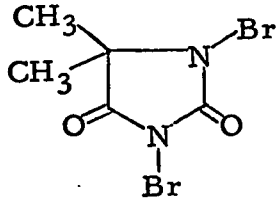
(c) (a) (b)

LXV



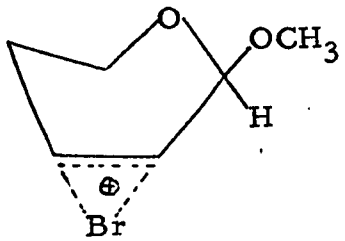
3-bromo-2,4-dimethoxytetrahydropyran

LXVI

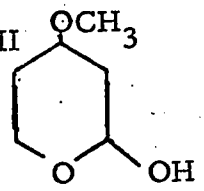


1,3-dibromo-5,5-dimethylhydantoin

LXVII

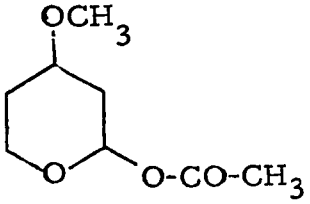


LXVIII



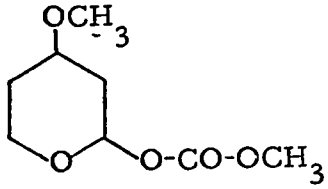
2-hydroxy-4-methoxytetrahydropyran

LXIX



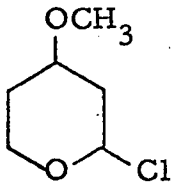
2-acetoxy-4-methoxytetrahydropyran

LXX



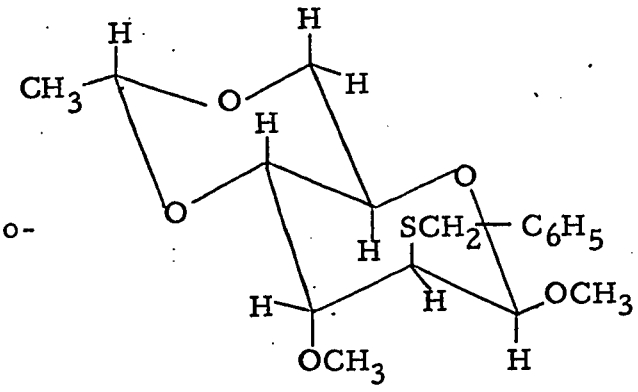
methyl 4-methoxytetrahydropyranyl-2 carbonate

LXXI



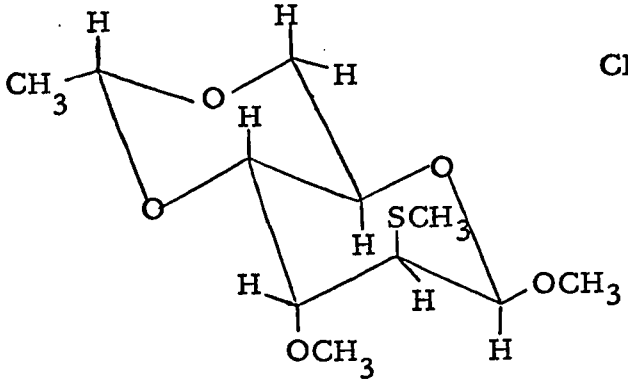
2-chloro-4-methoxytetrahydropyran

LXXII



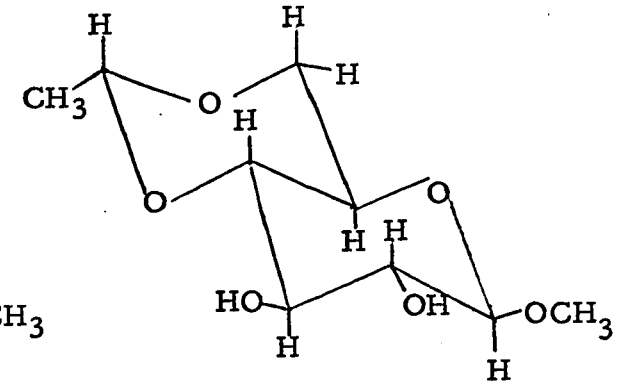
methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-β-D-altropyranoside

LXXIII



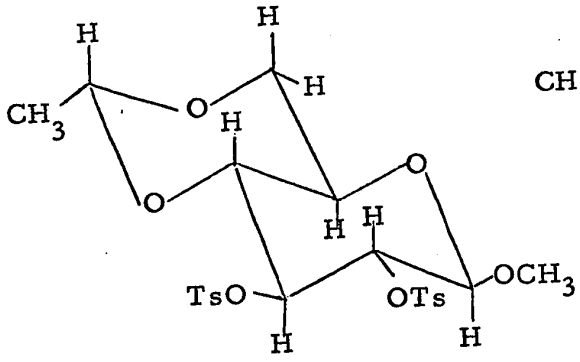
methyl 4,6-O-ethylidene-3-O,S-dimethyl-2-thio-β-D-altropyranoside

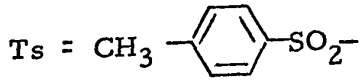
LXXIV



methyl 4,6-O-ethylidene-β-D-glucopyranoside

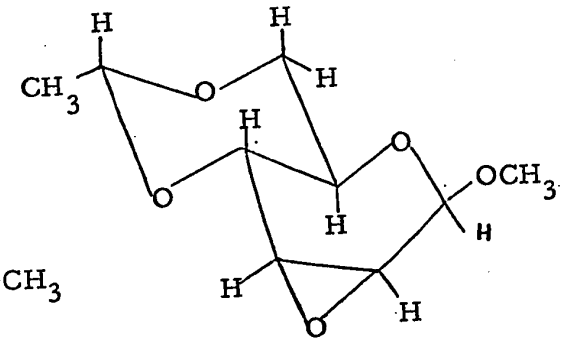
LXXV



Ts = 

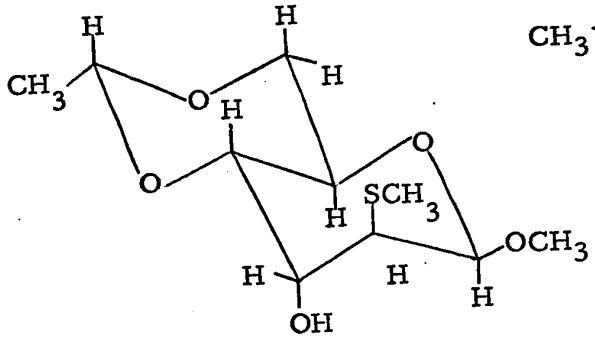
methyl 4,6-O-ethylidene-2,3-di-O-p-toluenesulfonyl-β-D-gluco-pyranoside

LXXVI



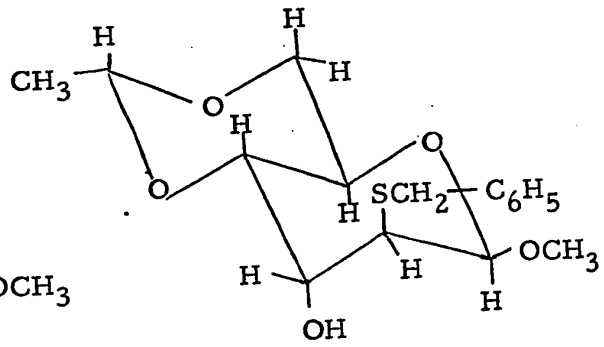
methyl 2,3-anhydro-4,6-O-ethylidene-β-D-allopyranoside

LXXVII



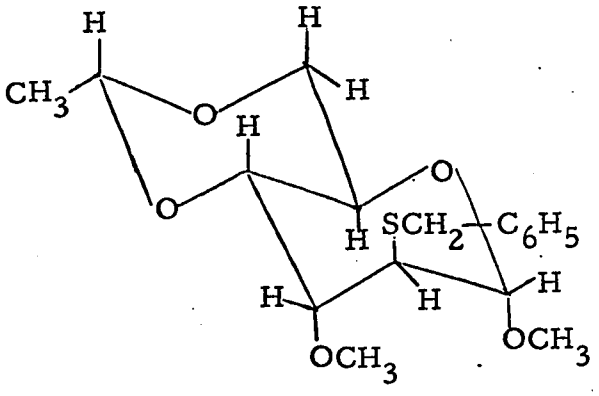
methyl 4,6-O-ethylidene-S-methyl-2-thio-β-D-altropyranoside

LXXVIII



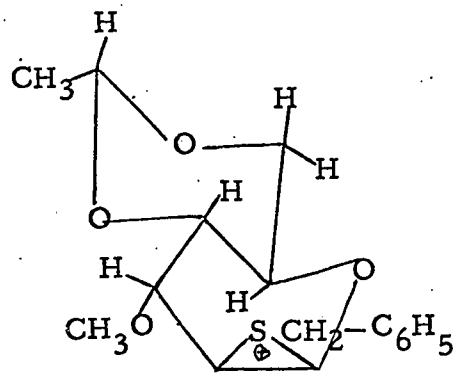
methyl S-benzyl-4,6-O-ethylidene-2-thio-β-D-altropyranoside

LXXIX

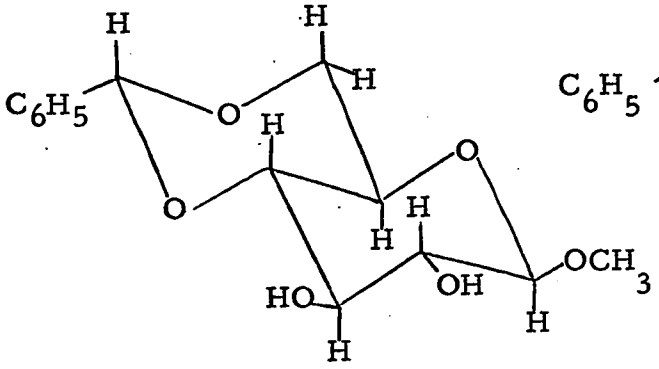


methyl S-benzyl-4,6-O-ethylidene-3-O-methyl-2-thio-α-D-altropyranoside

LXXX

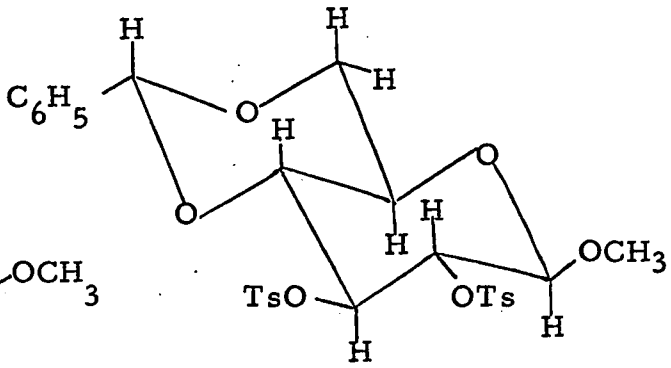


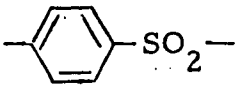
LXXXI



methyl 4,6-O-benzylidene-β-D-glucopyranoside

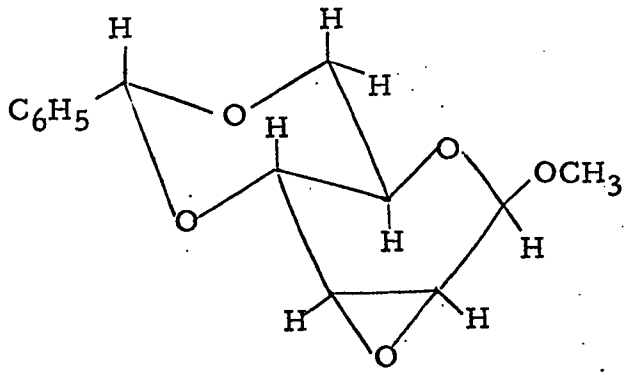
LXXXII



Ts = 

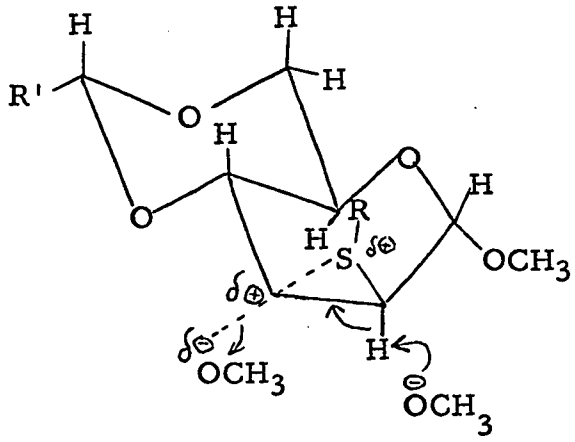
methyl 4,6-O-benzylidene-2,3-di-O-p-toluenesulfonyl-β-D-glucopyranoside

LXXXIII



methyl 2,3-anhydro-4,6-O-benzylidene-β-D-allopyranoside

LXXXIV



APPENDIX B

The following is a list of publications taken from this thesis and from other investigations by the author while work for this thesis was in progress.

1. Concerning the preparation of p-allylphenol from safrole by sodium-liquid ammonia reduction.
   M. J. Baldwin and R. K. Brown. Can. J. Chem. 43, 2621 (1965).

2. Rearrangment of allyl 2,6-dichlorophenyl ether on column packings during gas-liquid chromatographic analysis.
   M. J. Baldwin and R. K. Brown. Can. J. Chem. 44, 1743 (1966).

3. The preparation of 3-alkylthio-2-methoxytetrahydropyrans.
   M. J. Baldwin and R. K. Brown. Can. J. Chem. 45, 1195 (1967).

4. Concerning the mechanism of the addition of ethanesulfenyl chloride to 3,4-dihydro-2H-pyran.
   M. J. Baldwin and R. K. Brown. Can. J. Chem. 46, 1093 (1968).