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THE REACTION PROPERTIES OF 3-SUBSTITUTED CYCLOHEXENE
OXIDES AND RELATED COMPOUNDS

by

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A thesis submitted in partial fulfillment
of the requirements for the degree of

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in the

Department of Chemistry

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PREFACE

To an organic chemist, it is always desirable to be in a position to predict the stereochemical pathways of a reaction which will produce various geometrical isomers. This, however, is not always an easy matter. With certain exceptions, notably those derived from the concept of conformational analysis and neighboring group participations, the route followed in the formation of geometrical isomers in cyclic systems cannot be predicted. The purpose of the present work was to investigate the stereochemical routes followed in the reactions of 3-substituted cyclohexene-1,2-bridged derivatives to bring about opening of the 1,2-bridge.

3-Methoxy- and 3-methylcyclohexene oxides were used as model compounds and their reactions with a variety of nucleophilic reagents were studied. The behavior of 3-methoxycyclohexene oxides towards some nucleophilic reagents was previously studied (70). Some of these reactions were reexamined whenever accurate analysis of the products was required.

This investigation involved also a study of the chemical properties of 3-methoxy- and 3-methylcyclohexene-1,2-bridged ionic species (iodonium, acetoxonium and ethyl-sulfonium ions) and a comparison of their chemical properties with those of the corresponding epoxides.

The author gratefully thanks his research supervisor, professor R.U. Lemieux, for his continuous guidance, invaluable advice and encouragement during the course of this research.

The technical assistance of the staff of the Department of Chemistry, University of Ottawa and fellow-students, is also gratefully acknowledged.

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ABSTRACT

The rate constants for the methanolysis of cyclohexene oxide, of the cis- and trans-3-methoxycyclohexene oxides and of the cis- and trans-3-methylcyclohexene oxides by sodium methoxide in methanol were determined using quantitative vapor phase chromatographic procedures. The relative rates of reaction indicated that the introduction of a methoxy or methyl group at the 3-position trans- to the oxide ring lowers the reactivities of both the 1- and 2-positions but to a greater degree of the 2-position. The effects at the 1-position were essentially the same. However, the deactivating effect at the 2-position was about five times greater for the methoxy than for the methyl group. The introduction of either the methoxy or methyl group at the 3-position of cyclohexene oxide in cis-relationship to the oxide ring had a slight activating effect at the 1-position but a strongly deactivating effect at the 2-position. A conformational analysis of these results is presented based on the probable structures for the transition states.

In accordance with the above results, trans-3-methoxycyclohexene oxide reacted preferentially (over 90%) at the 1-position with lithium aluminum hydride in ether or sodium thioethoxide in methanol. The extent of reaction

at the 1-position of trans-3-methylcyclohexene oxide with sodium methoxide in methanol and sodium thioethoxide in methanol were 77.5 and 63% respectively. Both the cis-3-methoxy and cis-3-methylcyclohexene oxides reacted largely (90-98%) at the 1-position with lithium aluminum hydride in ether, sodium thioethoxide in methanol, sodium methoxide in methanol or sodium hydroxide in aqueous dioxane.

The only exceptions to the routes of reaction observed in the methanolysis experiments were in the reaction of trans-3-methylcyclohexene oxide with lithium aluminum hydride in ether and sodium hydroxide in aqueous dioxane where the 2-position was attacked preferentially (65.5 and 55%, respectively). Rationalizations are offered for these exceptions.

The direction of the ring openings of 1,2-bridged cationic derivatives of 3-substituted cyclohexanes (iodonium, acetoxonium and sulfonium ions) was found to be similar to that of the corresponding epoxides. Thus, the cis-3-methoxy- and cis-3-methylcyclohexene-1,2-iodonium, cis-3-methoxycyclohexene-1,2-acetoxonium and cis-3-methoxy- and cis-3-methylcyclohexene-1,2-ethylsulfonium ions opened almost exclusively at the 1-positions. The trans-3-methoxycyclohexene-1,2-iodonium, and trans-3-methoxycyclohexene-1,2-acetoxonium ions opened mainly at the 1-positions. The trans-3-methylcyclohexene-1,2-iodonium and trans-3-methylcyclohexene-1,2-

ethylsulfonium ions were attacked to about equal extents at the 1- and 2-positions.

The rate constants for the acetolysis of trans-1-acetoxy-2-iodocyclohexane and its cis- and trans-3-methoxy-derivatives were determined.

In the course of this research, fifteen new 1,2,3-trisubstituted cyclohexanes were synthesized and their structures and configurations were established.

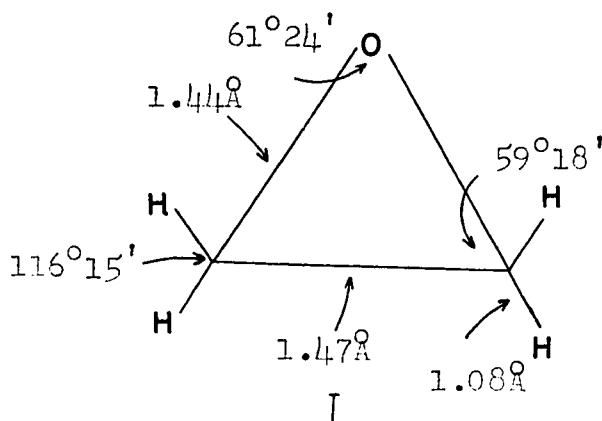
INTRODUCTION

A. Reaction of the α -Epoxides with Nucleophilic Reagents

(1) Structure of the α -epoxides

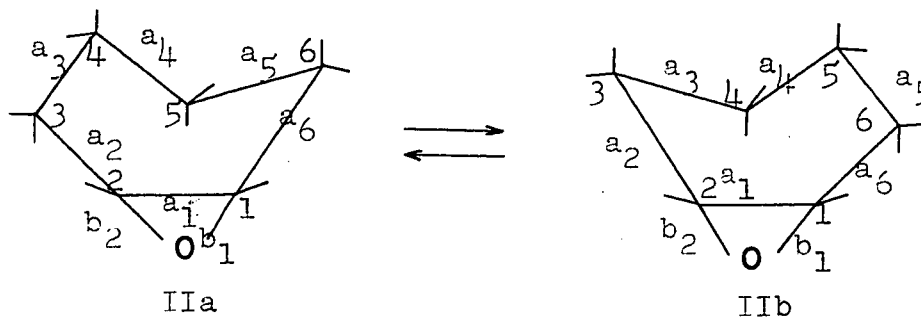
The α -, or 1,2-epoxides are a large class of organic compounds which contain two carbon atoms and one oxygen atom in a 3-membered ring. The simplest member of this class of compounds is the ethylene oxide (I). All the other α -epoxides can be regarded as derived from ethylene oxide by substitution of the methylene-hydrogens with other groups.

The structure of ethylene oxide (I) was determined by electron diffraction (1) and by microwave spectroscopic studies (2). The bond lengths and angles in the ethylene oxide molecule as determined in the above way are shown in the formula I. Both methylene groups are in planes at right angles to the plane of the oxide ring. The angle between the



plane of each methylene group and the carbon-carbon bond is $159^{\circ} 25'$.

The structure of cyclohexene oxide (IIa and IIb) was determined by Ottar (3) by electron diffraction studies. The formulas IIa and IIb represent the two half-chair conformations



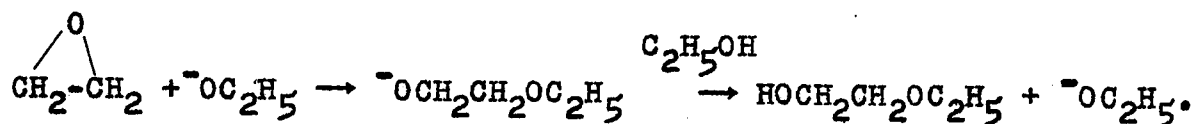
in which the cyclohexene oxide molecule exists. In both conformations, the carbon atoms 1, 2, 3 and 6 are on the same plane. Carbon atoms 4 and 5 are above and below this plane depending on the conformation. The interatomic distances and the valence angles for the atoms in cyclohexene oxide were determined by Ottar (3) and are as follows. The carbon-carbon bonds represented by a's in IIa and IIb are $1.54\text{\AA}$, the carbon-oxygen bonds represented by b's are $1.42\text{\AA}$, and the angles are,

$$\begin{aligned} \angle a_1 a_2 &= \angle a_6 a_1 = 118.5^{\circ} \\ \angle a_2 a_3 &= \angle a_5 a_6 = 116.0^{\circ} \\ \angle a_3 a_4 &= \angle a_4 a_5 = 109.5^{\circ} \\ \angle b_1 a_6 &= \angle b_2 a_2 = 115.0^{\circ} \end{aligned}$$

Substituents at the 3- and 6-positions are said to occupy quasi-axial and quasi-equatorial orientations (4).

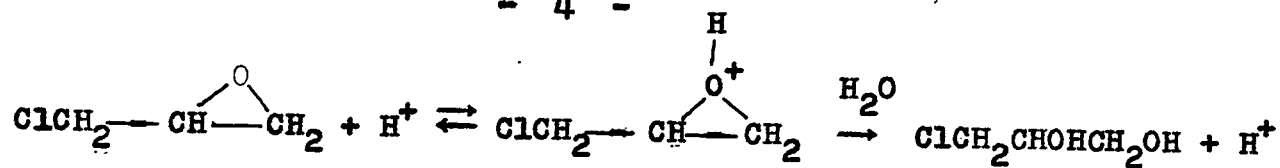
(2) Acid- and base-catalysis in the opening of the ring of α -epoxides

The reactions of α -epoxides with nucleophilic reagents involve the opening of the oxide ring and the addition of one molecule of a reagent, for example,



In this case, since the ethoxide ion is not consumed, the reaction is referred to as base-catalysed reaction. The opening of the ring by the anion of a nucleophilic reagent is much faster than that by the nucleophilic reagent itself. This was shown by Boyd and Marle (5) through kinetic investigations of the reactions of several oxides with phenols under neutral and alkaline conditions.

The reactions of the α -epoxides with most nucleophilic reagents is considerably accelerated by acids and this is due to the reversible formation of the more reactive conjugate acid of the epoxide. Thus, the reaction of epichlorohydrin with water in 1 N acid solution and at 20° is 400 times faster than the reaction with water under neutral conditions (6).



(3) Mechanism of the opening of the epoxide ring

It is well established that the opening of an α -epoxide ring under neutral or basic conditions takes place by an SN^2 mechanism (see Winstein and Henderson (7) and also Parker and Isaacs (8) for review of the reactions of epoxides).

The following facts support this mechanism. Kinetic studies of a considerable number of α -epoxides with nucleophilic reagents such as ammonia and a number of amines, thiocyanate ion, halogen ions, nitrate ion, hydroxide ion, and a series of phenols and phenoxide ions (p. 766 of ref. 8) have shown that these reactions are first order in both the epoxide and the nucleophilic reagent. These results indicate that both the oxide and the nucleophilic reagent are involved in the formation of the activated complex. In the case of reaction with substituted phenoxide ion it was shown (5) that the rate of the reaction increases with increase basicity for the phenoxide ion, the result expected for an SN^2 mechanism. Furthermore, the stereochemistry of the reaction of the opening of the oxide ring also supports an SN^2 mechanism. Inversion of the configuration of the carbon atom undergoing reaction is the rule. As an example, the reaction of trans-2,3-epoxy-

butane with ammonia (9) can be cited. The only product of this reaction is the erythro-3-amino-2-butanol. The direction of the opening of the ring of unsymmetrical epoxides, having alkyl groups as substituents, is that which is sterically less hindered rather than the direction which would be expected to yield the more stable carbonium ion intermediates (10,11,12, 13,14). Thus, these results also favor the S_N2 mechanism.

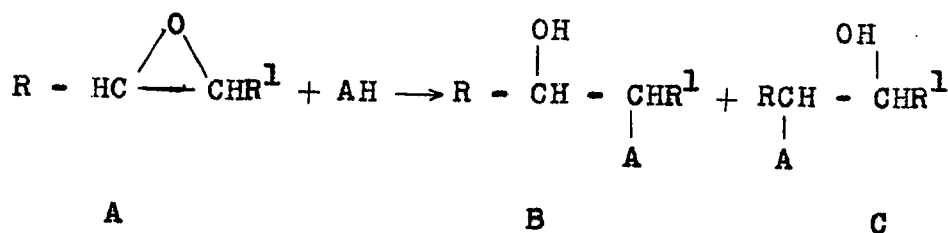
The mechanism of the opening of the ring of the α -epoxides under acidic conditions is known with less certainty. The inversion of the configuration of the carbon atom of the oxide ring undergoing reaction would appear to favor an S_N2 mechanism for this reaction. The direction of the opening of the oxide ring in unsymmetrical epoxides is that which would be expected for S_N1 type of mechanism. For example, alkyl substituted α -epoxides show a tendency to open at the more highly substituted carbon atom of the oxide ring. For this reason, Winstein and Henderson (7) suggested that the rate controlling step in these reactions is the unimolecular opening of oxide-conjugate acid to give an open carbonium ion. The same mechanism was supported by Pritchard and Long (15) who arrived at this conclusion through a kinetic investigation of the acid hydrolysis of a number of α -epoxides. Parker and Isaacs (8) have suggested the so-called modified S_N2 mechanism for the opening of the oxide ring of α -epoxides

under acid conditions, in order to account for the inversion of the configuration which is always observed in these reactions.

As a first stage in a study of the effect of 3-substituents on the relative reactivities of the two reactive positions of cyclohexene oxide, it was decided to study reactions with strongly nucleophilic reagents. Thus, the uncertainties of the acid catalyzed reactions were avoided and the transition state could be envisaged with confidence.

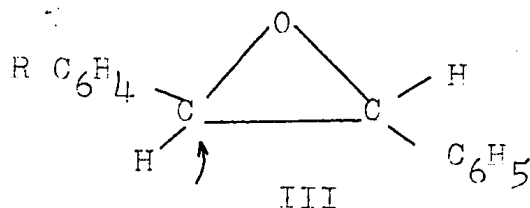
(4) Direction of the opening of the oxide ring in unsymmetrical α -epoxides

The unsymmetrical α -epoxides of the general structure A possess two different centers for reaction. Therefore, nucleophilic attack by a reagent AH, can lead to the formation



of two different products, B and C. When the substituents R and R' are alkyl group the predominant route for reaction is the one which involves the less hindered attack by the nucleophilic reagent. For example, the opening of trimethylethylene oxide with methoxide ion (13) and with amines (16,17)

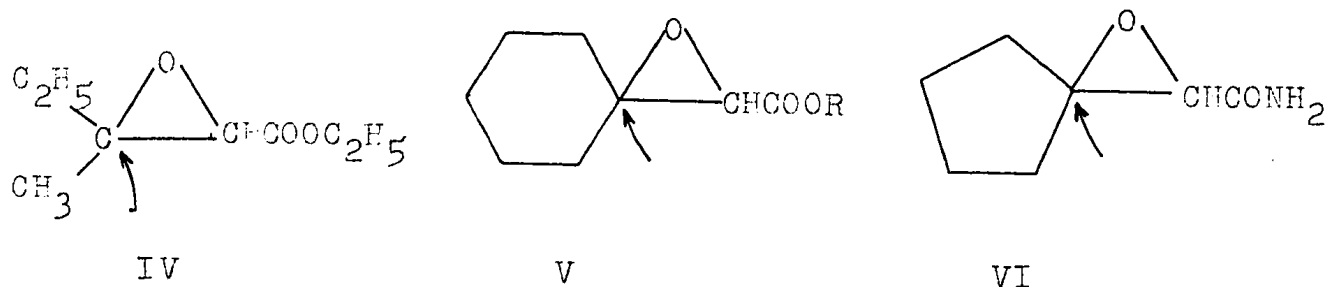
proceeds almost exclusively by attack at the secondary carbon atom. However, it was early recognized that electronic factors play an important role in the direction of the opening of the ring of an α -epoxide. Thus, VanderWerf and coworkers (18) have shown that the reaction of mono-substituted trans-stilbene oxides with lithium aluminum hydride proceeds in the way shown in formula III to the extent of 60% when the R-substituent is the methyl group but to the extent of 40% when the R-substituent



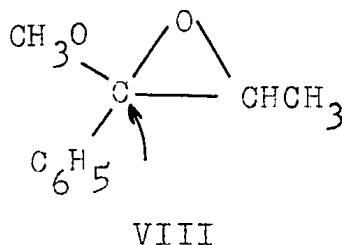
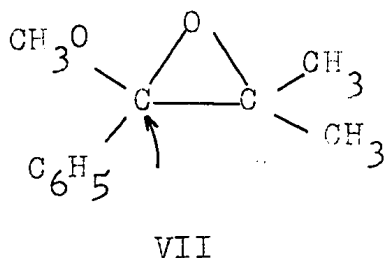
is the chlorine atom. The results were rationalized (18,19) as meaning that the reacting center in the oxide ring develops a positive charge in going to the transition state which is greater than that in the ground state. Therefore, an electron-releasing substituent will facilitate reaction at the carbon-atom of the oxide ring to which it is attached whereas an electron-withdrawing substituent will inhibit^{reaction}/at this carbon.

Recently, Parker and Isaacs (8) have reviewed the opening of α -epoxides and came to the same conclusion as VanderWerf. That is, these S_N2 -type of reactions involve a transition state with an increased positive charge on the

reacting carbon-atom. It is seen from Parker and Isaacs' tables that electron-withdrawing groups such as $C - NR_2$, $C - OH$, $C - OR$, $C - Cl$, $C - Br$, $COOR$, $CONH_2$ when attached to a carbon-atom of the oxide ring inhibit the reaction on this carbon. In some cases the reagent avoids attack at the carbon-atom carrying one of the above groups even though the alternate route of reaction is subject to very considerable steric hindrance. For example, the epoxides IV - VI open exclusively at the most substituted carbon-atom when reacted with amines (20,21,22,23,24).



Electron-releasing groups attached to a carbon-atom of the oxide ring tend to facilitate the reaction at this center. Parker and Isaacs (8) have reported a study of the reactions of a number of compounds which contain electron-releasing substituents. When the substituent was an alkoxy group the opening took place preferentially at the carbon atom bonded to the alkoxy group. For example, the oxides VII and VIII reacted with lithium aluminum hydride and with sodium



methoxide in the manner indicated (25,26). These results are of course related (as in the case of reactions of α -halogenoethers) to the strong electron-releasing ability of the oxygen of the alkoxy group. This type of oxide has never been observed to react in the other direction. When the substituent is less electron releasing, for example, a benzene ring, then the composition of the product is the result of a compromise between the steric and electronic effects.

(5) The Furst-Plattner rule

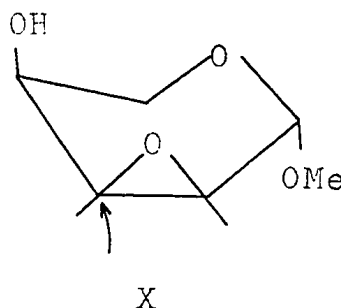
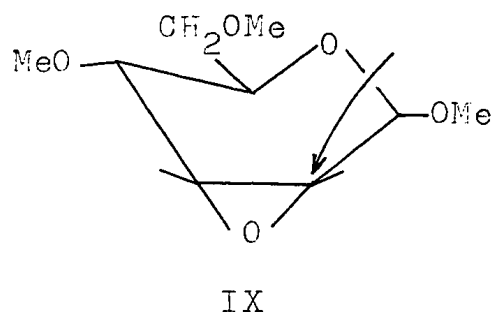
The opening of the ring of an α -epoxide in a steroid under neutral, basic or acidic conditions always results in inversion of the configuration of the reacting center. Since the cyclohexene oxide ring in these compounds has a fixed conformation, two isomeric products are theoretically possible; one which has both groups in axial orientation and one in which both are in equatorial orientation. The diaxial

product is formed in major yield. Fürst and Plattner (28) have formulated this stereochemical result into a rule which can be expressed as follows. An α -epoxide situated on a six-membered ring can be expected to undergo opening of the oxide ring in the direction which will place the entering group in axial orientation.

The rule, although first established in the field of steroids, is of general applicability for the opening of the oxide ring of α -epoxides situated on six-membered rings. The opening of oxide rings has been of great value to carbohydrate chemistry for the interconversion of sugars and for the preparation of a variety of sugar derivatives such as aminosugars, deoxysugars, etc. This work has been the subject of a number of recent reviews (29,30,31,32,39). The main general purpose of these reviews was to test the Fürst-Plattner rule in the field of carbohydrate chemistry.

Mills (33) pointed out that the rule can be applied unambiguously when the six-membered ring is conformationally rigid. For many reactions, this is the case (31) and the opening of the epoxide ring takes place in accordance with the Fürst-Plattner rule (28). For many of the derivatives of sugars in the pyranose ring form and which contain an α -epoxide ring, the two half-chair conformations are readily accessible for reaction (32). The course of the reactions of these

compounds is not easily predicted. Newth (29) has suggested that the opening of the epoxide ring of these anhydro sugars is also the diaxial opening and the predominant product of the reaction will have its origin in the more stable conformation of the anhydro sugar. That is, the proportion of each isomeric product will reflect the energy difference between the two conformations of the anhydro sugar. On this basis, it would be expected that methyl 4,6-di-O-methyl-2,3-anhydro- β -D-allopyranoside should react with sodium methoxide preferentially at the 2-position as shown in formula IX. This is actually



the case; the product from reaction at the 2-position was 66% (34). However, methyl 2,3-anhydro- β -L-ribofuranoside reacts preferentially (63%) with ammonia at the 3-position (35). For diaxial opening to take place, the compound must react in the conformation shown in formula X. Newth (29) has suggested that this conformation is the more stable due to the hydrogen-bonding between the hydroxy group and the oxygen of the pyranose ring. Certainly, the so-called "anomeric effect" which relates to the greater stability of the glycopyranoside

which has the aglycon in axial orientation rather than in equatorial orientation (36) must contribute appreciably to the stability of the conformation X for the anhydroriboside.

As it was said above, Newth suggested that the main product of the reactions of 1,2-anhydrosugars will have its origin in the more stable conformation of the anhydrosugar. Curtin (37) pointed out that the relative rates of the two reactions in such situations where the ground state is common to both transition states, are related only to the difference in the stabilities for the two transition states unless the barrier to the conformational change is equal in magnitude to the free energy of activation for the reaction.

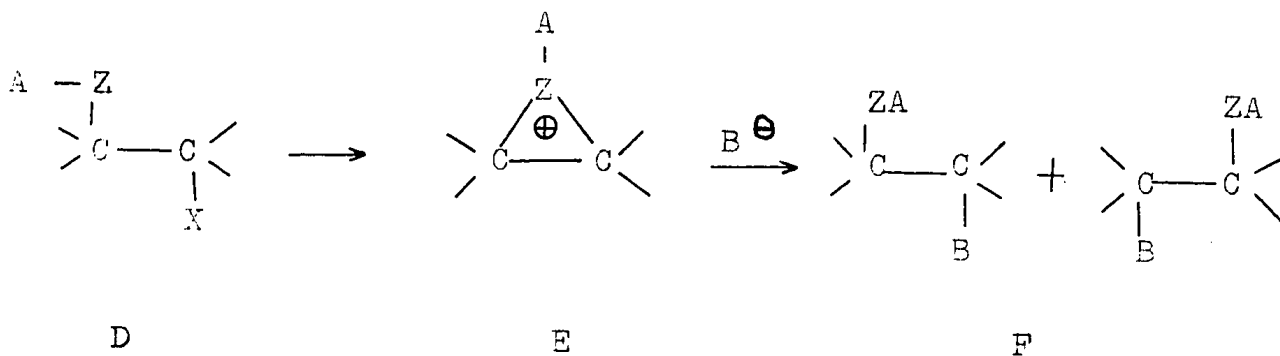
Schaub and coworkers (38) have suggested that the preferential opening of the oxide ring of methyl 2,3-anhydro-pentofuranosides is related mainly to the relative facility for the two carbons of the α -epoxide ring to split ionically. Cookson (32) has suggested that this may be important in the opening of 2,3-epoxide rings in monocyclic anhydropyranosides. However, Angyal (39) has disputed this point of view and in general conformational aspects are considered more important.

A main purpose of this thesis was to obtain information on these subjects through a study of relatively simple model compounds. The 3-methyl and 3-methoxy cyclohexene oxides were chosen for this purpose.

B. The Neighboring Groups in Solvolytic Displacement Reactions

As already mentioned, a purpose of this investigation was to compare the reaction properties of 3-substituted cyclohexene oxides with those of 3-substituted cyclohexene acetoxonium, iodonium and sulfonium ions. The purpose of this section is to describe briefly previous studies relating to these ions which are pertinent to the thesis.

The role of neighboring groups in solvolytic displacement reactions of halides and tosylates has been extensively studied in the last two decades by Winstein and numerous coworkers and by other investigators. The situation may be formulated in the following way.



Participation of the neighboring group - ZA in the displacement of X^- yields the cyclic intermediate, E, the ring of which is opened by attack of a solvent moiety, B, to yield the final products, F.

Numerous groups were found capable of participating in solvolytic displacement reactions and are discussed in reviews by Winstein in 1951 (40) and by Streitwieser in 1956 (41). The most common participating groups are those in which the atom Z of the group ZA in formula D has an unshared pair of electrons; for example the oxygen atom of an hydroxy-, methoxy- or acetoxy group, the nitrogen atom of an amino - or alkyl amino group, the sulfur atom of an alkyl - or aryl thio group, etc.

The requirement for neighboring group participation in solvolytic displacement reactions is that the neighboring group, - ZA, and the departing group, X, in the formula D can acquire a near linear relationship with the reacting center.

Three principal methods have been used to detect neighboring group participation. If neighboring group participation is significant in a given system, the rate of reaction must be greater than the rate of solvolysis in the absence of such participation. The rate enhancement, consequently, is one criterion for participation but only if the participation is significant in the transition state of the rate-determining step. When participation takes place, the over-all replacement process involves two Walden inversions. One inversion takes place on the carbon-atom carrying the departing group in the process of the ring closure and a second inversion occurs on the same carbon - or on the other carbon atom of the ring, in the ring opening stage. As a

result of the two Walden inversions, the product of the reaction has the same configuration as the reacting compound, either if the intermediate cyclic ion is symmetrical or if the ring-opening occurs at the same center as was involved in the ring closure. If the intermediate cyclic ion is unsymmetrical and ring-opening takes place at the position which originally carried the participating group, then both centers will be inverted in the course of the reaction. Thus, such rearrangements are also diagnostic of neighboring group participation.

(1) Neighboring acetoxy group

The role of a neighboring acetoxy group in solvolytic displacement reactions has been studied extensively and it can be illustrated by the acetolysis of trans-2-acetoxycyclohexyl tosylate investigated by Winstein and coworkers (42,43,44). Winstein showed that the rate-determining step in the course of this reaction was the formation of the resonance stabilized intermediate cyclohexene acetoxonium ion(XIV) as a result of the participation of the acetoxy group in the ionization of the molecule. This conclusion was based on the following facts. The ratio of the rate constants for the acetolysis of the cyclohexyl tosylate, trans-2-acetoxycyclohexyl tosylate and cis-2-acetoxycyclohexyl tosylate was found to be 1:0.3: 4.5 $\times 10^{-4}$ (45). The slow reaction rate of the cis-isomer was

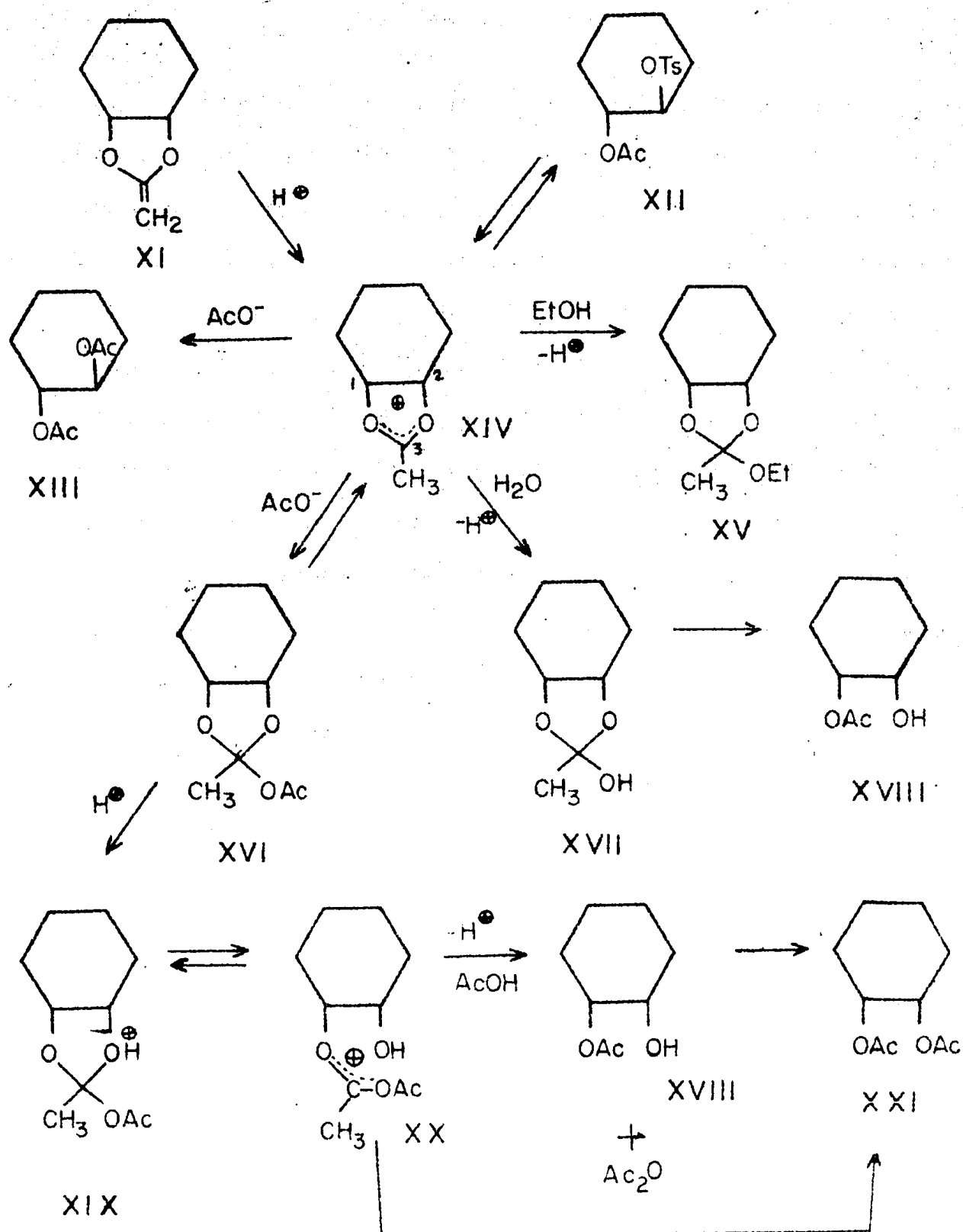
attributed to the electron-withdrawal of the acetoxy group inhibiting the departure of the tosyloxy group. The great difference in reactivities between the cis- and trans-isomers was ascribed to participation of the acetoxy group in the latter compound. The formation of the intermediate acetoxonium ion XIV was also inferred from the products of the solvolysis of the trans-compound in media of different compositions (see p. 18). The product of the acetolysis of the trans-2-acetoxycyclohexyl tosylate (XII) in dry acetic acid and in the presence of potassium acetate was found to be the trans-1,2-diacetoxycyclohexane (XIII) (42,45). This result amounts for an overall retention of configuration. When optically active XII was used (42) a racemic mixture of trans-1,2-diacetoxycyclohexane was the product of the above mentioned reactions. These results are consistent with the postulate of an intermediate having the structure XIV. Subsequent reaction of this intermediate by attack of the acetate ion or the acetic acid molecule at the 1- or 2-carbons yields the observed products. Structure XIV is symmetrical and must lead to racemic products.

Solvolysis of the trans-2-acetoxycyclohexyl tosylate (XII) in wet acetic acid (42) gave the monoacetate of the cis-1,2-cyclohexanediol XVIII. This result was interpreted (42) as a reaction of the acetoxonium ion XIV with water at the 3-carbon to yield to orthoacid XVII which is the tautomeric

form of the monoacetate XVIII. Solvolysis of XII in dry ethanol gave the ethylorthoacetate XV in good yields (46). This result was rationalized to mean that the acetoxonium ion XIV reacted with ethanol at the 3-carbon.

Finally, it was shown by Winstein and coworkers (47) that the ketene acetal of the cis-1,2-cyclohexanediol (XI) could be solvolized in media of various composition to yield the same products as these obtained by reactions of trans-2-acetoxycyclohexyl tosylate(XII) in the same media. Thus, acetolysis of the ketene acetal XI in dry basic or neutral acetic acid (with or without potassium acetate) gave the trans-1,2-diacetoxycyclohexane(XIII) and in moist acetic acid yielded the monoacetate of the cis-1,2-cyclohexanediol (XVIII). Solvolysis of the ketene acetal XI in dry ethanol gave the ethyl orthoacetate XV. These results were interpreted (47) to mean that the first step in the course of these reactions was the formation of the acetoxonium ion XIV by protonation of the ketene acetal XI. Subsequent reaction of the acetoxonium ion with the solvent yields the observed products.

The acetoxonium ion XIV, as it was pointed above, has three possibilities for reaction with the nucleophilic species. That is, the nucleophile can attack at either the 1-, 2- or 3-positions. It was assumed by Winstein (47) that the rate of reaction is much greater at the 3- than at the 1-, or 2-carbons. The preferential reaction of the cyclo-

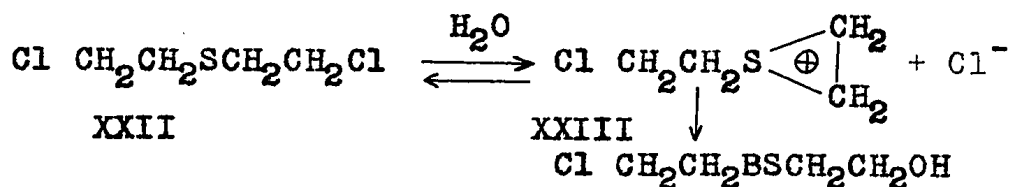


hexeneacetoxonium ion XIV with water or ethanol at the 3-carbon was mentioned above. The ion XIV also undergoes preferential attack at the 3-carbon by acetate ion or acetic acid to lead to the orthodiacetate XVI. While this is the first product of the reaction in dry acetic acid, with or without added potassium acetate, the orthodiacetate has only a short life and dissociates rapidly to the acetoxonium ion XIV. The latter undergoes nucleophilic attack at the 1- or 2-carbon to form the trans-diacetate XIII.

Whereas ionization of the orthodiacetate XVI in neutral or basic media involves essentially only dissociation of the acetate group at the 3-carbon, ionization in acid media may also involve dissociation of a C3 to ring-oxygen bond. Thus, the acetolysis of trans-2-acetoxycyclohexyl tosylate(XII) and of the ketene acetal XI in dry acetic acid containing p-toluene-sulfonic acid yielded a mixture of the cis- and trans-1,2-diacetoxycyclohexanes with the cis-isomer the major component. This result was taken to mean (47) that the orthodiacetate XVI forms the conjugate acid XIX which subsequently ionizes to the ionic species XX. The latter is a powerful acetylating agent and cis-diacetate XXI is formed by intramolecular acetylation of the free hydroxyl group. An alternative route from the ionic species XX to diacetate XXI would involve formation of acetic anhydride and the monoacetate XVIII, followed by acetylation of the monoacetate by the acetic anhydride (47).

(2) Neighboring Sulfur

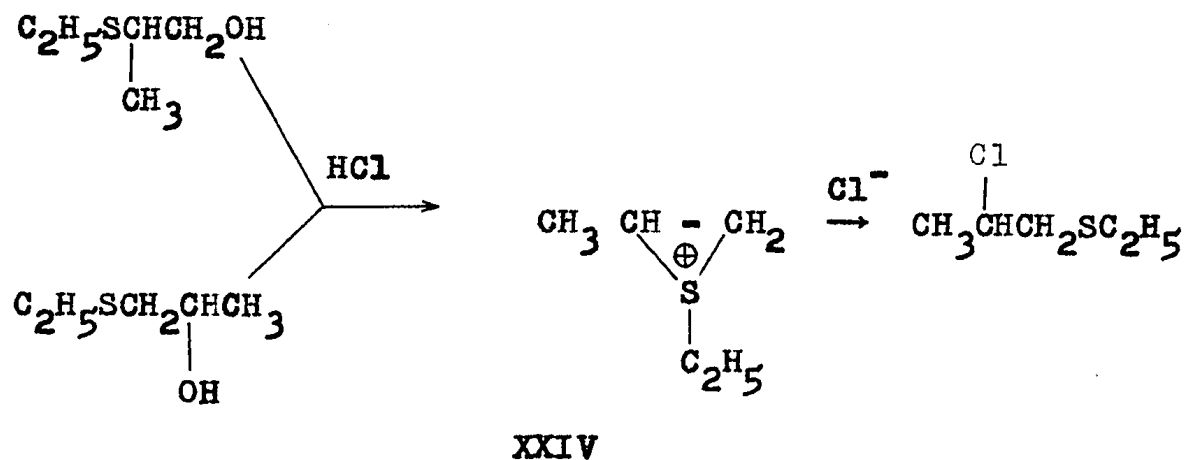
The solvolysis of halides having an alkyl-, or arylthio group at the β -position/ ^{proceeds} by a mechanism which involves the participation of the alkyl- or arylthio group in the rate determining step of the reaction to give a three-membered cyclic sulfonium cationic intermediate. The most extensively studied compound of this type is β, β' -dichlorodiethylsulfide XXII (mustard gas) (48,49,50). The hydrolysis of XXII in aqueous sodium hydroxide, in its initial stages, was found to be first order in XXII and independent of the concentration of added alkali.



The rate constant decreases with time because of the reverse reaction with the liberated chloride ion. When thiosulfate ion or certain other nucleophilic reagents were added to the reaction mixture, they reacted quantitatively but without changing the rate constant of the reactions. These results were taken as evidence that the rate determining step in the hydrolysis of mustard gas is a unimolecular process involving the formation of an intermediate ionic species. The fact that this intermediate can react with small quantities of

other nucleophiles in preference to the water, which is present in much greater concentration, was taken as evidence that the intermediate cation has considerable stability. It was assumed that the intermediate is the cyclic sulfonium ion XXIII since a free carbonium ion would be too reactive to display such a high degree of discrimination in its reactions with nucleophiles.

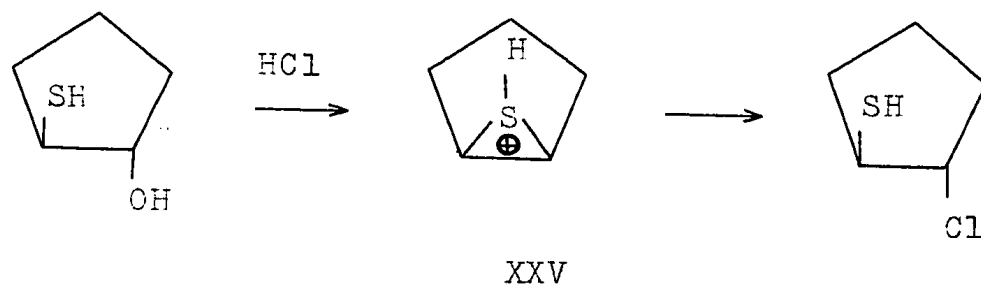
A sulfonium ion intermediate was also assumed by Fuson, Price, and Burness (51) to be the intermediate in the reactions of 2-ethylthio-1-propanol and 1-ethylthio-2-propanol with hydrochloric acid. Both alcohols on treatment with



hydrochloric acid yielded 1-ethylthio-2-chloropropane. These results were taken as evidence that both reactions involve the same intermediate sulfonium ion XXIV which opens with a chloride ion at the secondary position to give the product.

Van Tamelen (52) studied the reaction of trans-2-hydroxycyclopentanethiol with hydrochloric acid. The only product of the reaction was found to be the trans-2-chlorocyclopentanethiol. This result indicated that a double

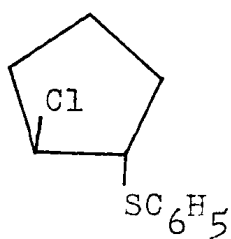
Walden inversion took place in the course of the reaction with hydrochloric acid and is consistent with the assumption that



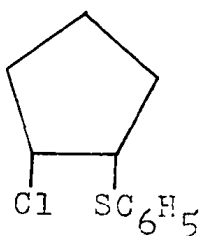
the sulfonium ion XXV is the intermediate cationic species in this reaction.

Neighboring sulfur participation also demonstrated by Goering and Hower (53) in the solvolysis of 2-chlorocyclopentyl and 2-chlorocyclohexyl phenyl sulfides in aqueous ethanol. The ratios of the rate constants of the solvolyses of cyclopentylchloride, trans-2-chlorocyclopentylphenyl sulfide (XXVI) and cis-2-chlorocyclopentylphenyl sulfide XXVII were found to be 1: 1.1×10^4 : 6.7×10^{-2} .

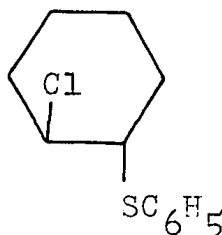
Under similar reactions conditions the ratios of the rate constants for the solvolysis of cyclohexylchloride, trans-2-chlorocyclohexyl phenyl sulfide (XXVIII), and cis-2-chlorocyclohexyl phenyl sulfide (XXIX) were found to be 1: 7×10^4 : 0.16 (53). The much greater reactivities of the trans-compounds were taken to mean that these isomers solvolyze exclusively by participation of the sulfur atom.



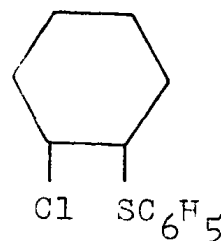
XXVI



XXVII

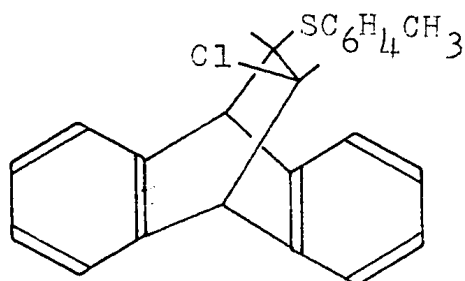


XXVIII

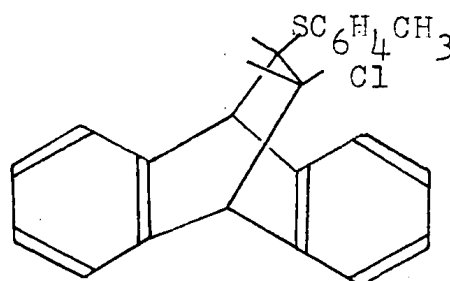


XXIX

Cristol and Arganbright (54) have studied the rates of the solvolyses of XXX and XXXI in 85% ethanol and found



XXX

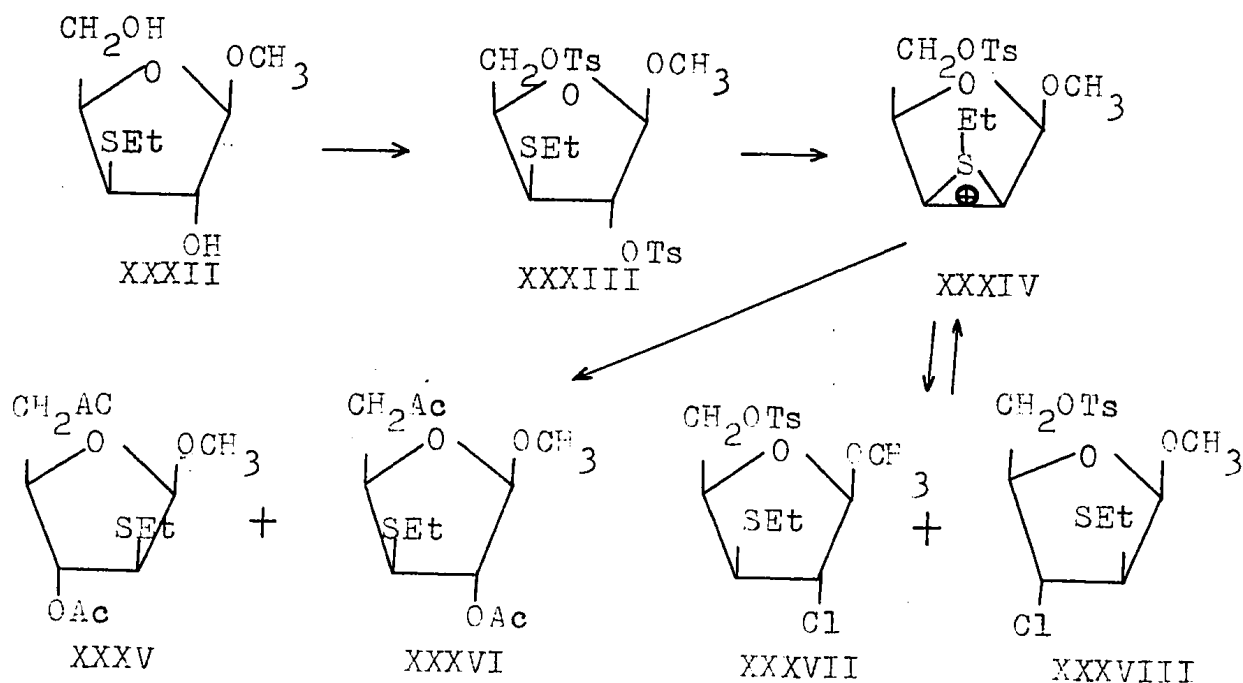


XXXI

that the trans-chlorosulfide XXX was only 4 times more reactive than the cis-isomer XXXI. The trans-isomer (XXX) solvolyzes at approximately the same rate as cyclohexyl chloride under the same reaction conditions (53). These results clearly show the lack of participation of the phenylthio group. Lack of participation in the case of the trans-isomer (XXX) was assigned to the fact that the carbon to sulfur and carbon to chlorine bonds cannot achieve the coplanarity required by the transition state for reaction with participation (54).

Baker and coworkers (55) have found that the tosylation of 3-deoxy-3-ethylthio- β -D-xylofuranoside (XXXII) in pyridine yields a mixture of monochloro-monodeoxy-monotosyl

derivatives XXXVII and XXXVIII. The formation of this mixture was explained (55) to arise by displacement of the 2-tosyloxy



group of the initially formed 2,5-ditosylate XXXIII with participation of the sulfur atom to form the sulfonium ion XXXIV. The intermediate XXXIV, then, reacted with the chloride ion present in the reaction mixture to produce the compounds XXXVII and XXXVIII. Treatment of the mixture of the chlorides XXXVII and XXXVIII with potassium acetate in methylcellosolve gave methyl-3,5-di-O-acetyl-2-deoxy-2-ethylthio- β -D-arabofuranoside (XXXV) as the main product of the reaction (80%) together with some XXXVI. Again the sulfonium ion XXXIV was considered an intermediate.

Baker and coworkers (56) have also demonstrated the

participation of the sulfur atom in reactions of trans-2-(methylthio)-cyclopentanol.

Participation of alkyl- and arylthio groups has also been shown to take place in the solvolysis of the aliphatic halides in which the thio group is situated at the γ , $-\delta-$, and ϵ -positions. In these cases five-, six-, and seven-membered cyclic sulfonium cations are formed (57,58).

EXPERIMENTAL

Melting points were determined with the Leitz microstage apparatus and are uncorrected.

Infrared spectra were obtained with a Perkin-Elmer infracord spectrometer.

Unless otherwise stated, the nuclear magnetic resonance spectra were obtained with a high resolution Varian spectrometer operating at 60 Mc/s. at room temperature. The signal of chloroform was taken as the reference signal for the determination of the chemical shifts.

The vapour phase chromatographic analyses were made with either the Burrell Kromo-Tog or the Perkin-Elmer 154 instruments. The columns for vapour phase chromatography were prepared as described by James and Martin (75).

3-Methoxycyclohexene (XXXIX)

3-Methoxycyclohexene (XXXIX) was prepared by reaction of trans-1,2-dibromocyclohexane with sodium methoxide as described by Gogek and coworkers (59). Yield 60%; b.p. 138-139° (760), n_D^{25} 1.4520. Gogek and coworkers (59) reported the b.p. 138.7-138.8° (757), Berlande (60) reported the b.p. 139, n_D^{20} 1.4530.

3-Methylcyclohexene (LXXIV)

3-Methylcyclohexene (LXXIV) was synthesized by

reaction of 3-bromocyclohexene (61) with methylmagnesium iodide following the directions given by Berlande (62). The yield was 56%; b.p. 101.5-102.5° (760 mm), n_D^{25} 1.4422. Berlande (62) reported b.p. 103-104° (760 mm), n_D^{26} 1.4332; the homogeneity of the compound was confirmed by vapour phase chromatography using an Apiezon M vacuum stopcock grease column.

Cyclohexene Oxide

Cyclohexene oxide was prepared in 80% yield by alkaline hydrolysis of crystalline trans-2-bromocyclohexanol (63) as described by Guss and Rosenthal (64). The compound had the physical constants, b.p. 130-131° (760 mm), n_D^{25} 1.4506. The physical constants reported in the literature are, b.p. 129-130°, n_D^{20} 1.4528 (64); b.p. 130°, n_D^{25} 1.4498 (63).

The purity of the compound was verified by vapour phase chromatography using a silicon oil D.C.-200 column (Perkin-Elmer column 154-0013-C).

Trans-2-Methoxycyclohexanol (LVIIa)

A mixture of 1.96 g (20 mm) of cyclohexene oxide and 20 ml of 1 N methanolic solution of sodium methoxide, protected from atmospheric moisture and carbon dioxide, was refluxed for 44 hrs. The reaction mixture was first treated with water and then neutralized with solid carbon dioxide.

The methanol was removed under vacuum and the residue dissolved in water and extracted with chloroform. After drying over sodium sulfate, the chloroform was removed under reduced pressure. The remaining product was distilled from a small glass bulb at 90° (air bath temperature) and 15 mm pressure to yield 2.2 g (60%) of trans-2-methoxycyclohexanol, n_D^{25} 1.4580. The 3,5-dinitrobenzoate melted at 101-102°. Winstein (65) reported the following physical constants for trans-2-methoxycyclohexanol, b.p. 72.5-73.5° (10 mm), n_D^{25} 1.4586. The 3,5-dinitrobenzoate was reported to melt at 101-102° (65).

Trans-2-Methylcyclohexanol (LXXXIII) and cis-3-Methylcyclohexanol (LXXXV)

Trans-2-Methylcyclohexanol (LXXXIII) was obtained from 2-methylcyclohexanol (a commercial mixture of cis- and trans-2-methylcyclohexanols made by the Eastman Kodak Co., Rochester, N.Y.) by esterification with phthalic anhydride and fractional crystallization of the esters as described by Gough and coworkers (66). The trans-2-methylcyclohexyl hydrogen phthalate melted at 123-125°. This compound is reported to melt at 124-125° (66), at 122-123° (67), and at 123.5-124.5° (27). Alkaline hydrolysis of the trans-2-methylcyclohexyl hydrogen phthalate yielded the trans-2-methylcyclohexanol (LXXXIII).

Cis-3-Methylcyclohexanol (LXXXV) was prepared from

3-methylcyclohexanol (a commercial mixture of cis- and trans-3-methylcyclohexanols made by the Eastman Kodak Co., Rochester, N.Y.) by esterification with p-nitrobenzoyl chloride and fractional crystallization of the p-nitrobenzoates as described by Gough and coworkers (66). The p-nitrobenzoate of the cis-3-methylcyclohexanol melted at 57-58°, in agreement with the melting point, 58°, reported (66) for the compound now known (27,109) to have cis-configuration. Alkaline hydrolysis of the p-nitrobenzoate gave the cis-3-methylcyclohexanol.

1,2-Iodo-acetoxy-3-methoxycyclohexanes

(1) Prevost reaction

A mixture of 200 ml glacial acetic acid, 8 ml of acetic anhydride and 16.7 g (100 mM) of silver acetate was refluxed for 3 hrs. The mixture was cooled to room temperature and 25.4 g (100 mM) of iodine was added with vigorous stirring. After all of the iodine had dissolved, 11.2 g (100 mM) of 3-methoxycyclohexene (XXXIX) was added in portions and stirring continued for 6 hrs. more at room temperature. The precipitate was gathered by filtration and thoroughly washed with benzene. The filtrate and washings were combined, diluted with an equal volume of water and extracted with benzene. The benzene solution was washed with water, then with a saturated solution of sodium bicarbonate and this was

followed by a wash with 2% sodium thiosulfate solution. Finally, the benzene solution was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent by evaporation at reduced pressure left a brown syrup, 27 g, 90% yield, which decomposed on standing at room temperature with the liberation of iodine. A quantity of 21 g of this syrup was crystallized from 40 ml of 60% ethanol-water to give 11.5 g (54.8%) of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII), m.p. 40-43°. Two recrystallizations from the same solvent system gave the analytical sample, m.p. 40.5-41.5°. The mother liquor from the first crystallization was evaporated to dryness and a 2.24 g sample of the residue was fractionated by adsorption chromatography on Magnesol-Celite (5:1) (68) as follows. The adsorbent was suspended in benzene and the slurry was introduced into a column 24 cm long and 7.5 cm in internal diameter. Pressure was applied to obtain uniform packing. The sample was applied to the column as a solution in a small amount of benzene and the chromatogram was developed with reagent grade benzene by applying pressure. The eluate was collected in a fraction collector and after testing, the following fractions were combined.

Fraction 1. - 200 - 750 ml of eluate.

Evaporation gave 1 g of 1 α -acetoxy-2 β -iodo-3 α -methoxycyclohexane (XLIII), m.p. 60-67°.

One recrystallization from 60% ethanol-water and two recrystallizations from petroleum ether (65-110°) gave 0.7 g of an analytical sample, m.p. 67-68.5°.

Fraction 2. - 750 - 2140 ml of eluate.

Evaporation gave 0.524 g of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII), m.p. 38-40.5°.

Extraction of the column of adsorbent with boiling ethanol gave a non-crystallizable syrup, 0.6 g, which was soluble in ethanol and water but insoluble in ether or benzene. The substance was not investigated further.

The total yield of 1 β ,2 α ,3 α -compound (XLII) was 65% and that of the 1 α ,2 β ,3 α -isomer (XLIII) was 14%.

Anal. Calc. for C₉H₁₅IO₃: C, 36.25; H, 5.07; I, 42.57.

Found: compound (XLII), C, 35.59; H, 5.18; I, 42.15

compound XLIII, C, 35.56; H, 4.95; I, 42.15.

The N.M.R. spectra for these compounds are reproduced in Fig. 3, p.108.

(2) Reaction of trans-3-Methoxycyclohexene Oxide (XLVI) with Acetyl Iodide

To a solution of 2.20 g (17.1 mM) of trans-3-methoxycyclohexene oxide (XLVI) in 30 ml of benzene, 3 g (17.6 mM) of acetyl iodide was added. The mixture was allowed to stand at room temperature for 1 hr. The dark

brown solution was washed first with water, then with sodium thiosulfate solution and finally with water. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure to yield 4.5 g (86%) of a brown syrup which crystallized from petroleum ether (80-100°). The yield of 1 α -iodo-2 β -acetoxy-3 α -methoxycyclohexane (XLV), m.p. 48-56°, was 0.80 g (18%). Two recrystallizations from 70% ethanol-water were used to prepare the analytical sample, m.p. 58.5-59.5°.

Anal. Calc. for $C_9H_{15}IO_3$: C, 36.25; H, 5.07; I, 42.57

Found: C, 36.97; H, 4.94; I, 41.73

The N.M.R. spectrum of this compound is shown in Fig. 3, p.108.

A small amount of the iodide XLV was treated with silver acetate in moist acetic acid and the product was hydrolysed with ethanolic sodium hydroxide. 3 α -Methoxy-1 β ,2 β -cyclohexanediol (XLVIII) was identified as the product by paper chromatography.

3-Methoxy-1,2-cis-cyclohexanediols

(1) Prevost reaction of 3-methoxycyclohexene

A mixture of 3.67 g (22mM) of silver acetate and 5.37 g (22 mM) of iodine in 70 ml of glacial acetic acid was stirred at room temperature until all the iodine had dissolved (1 hr.). An amount of 2.46 g (22 mM) of 3-methoxy-

cyclohexene (XXXIX) was added and the reaction mixture was left at room temperature with continued stirring for two hrs. more. Then, 10 ml of water and 3.67 g (22 mM) of silver acetate were added and the mixture was heated at 125° with stirring for 24 hrs. After this time, the mixture was cooled, filtered and the precipitate was washed with acetic acid. The solvent was removed under reduced pressure. The brown syrup which remained was saponified with 1 N alcoholic sodium hydroxide. The ethanol was removed under reduced pressure and the residue was adsorbed on 2 g of Celite. The resulting powder was transferred to the top of a small chromatographic column prepared from 10 g of wet Celite and extracted with chloroform (69). Evaporation of the chloroform left a pale yellow syrup, 2.2 g, (69%), which was examined by paper chromatography using the xylene-methylethylketone-water (1:1:1) system, and the ammoniacal silver nitrate spray described by Lemieux and coworkers for the same compounds (70). Authentic samples of 3 α -methoxy-1 α ,2 α -cyclohexanediol (XLVII) and 3 α -methoxy-1 β ,2 β -cyclohexanediol (XLVIII) were spotted on the same chromatogram for the identification of the components in the reaction mixture. The chromatogram showed the 3 α , 1 β ,2 β -diol (XLVIII) to be the major component and the 3 α -1 α ,2 α -diol (XLVII) to be the minor component. The same solvent system was employed for quantitative separation of

the compounds by partition chromatography on Celite (71). A quantity of 1.55 g of the syrupy mixture of diols was fractionated through a column 19.8 cm long and 5.4 cm internal diameter, packed with 134 g of Celite and prepared in the usual manner (71). The eluate was collected in a fraction collector and after testing, the following fractions were combined.

Fraction 1. - 680 - 1300 ml of eluate.

Evaporation of the solvent gave 1.03 g of pure 3 α -methoxy-1 β , 2 β -cyclohexanediol (XLVIII).

Fraction 2. - 1300 - 1960 ml of eluate.

Removal of the solvent by evaporation gave 0.05 g of a mixture of XLVIII and XLVII.

Fraction 3. - 1960 - 2700 ml of eluate.

Evaporation of the solvent gave 0.20 g of pure 3 α -methoxy-1 α , 2 α -cyclohexane diol (XLVII).

The purity of the compound in each fraction was tested by paper chromatography. These experiments indicated that the percentage of the 3 α , 1 β , 2 β -compound (XLVIII) in the mixture was 84% and that of the 3 α , 1 α , 2 α -isomer (XLVII) was 16%.

(2) Solvolysis of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII) in moist acetic acid in the presence of silver acetate

A mixture of 1.4 g (8.4 mM) of silver acetate, 30 ml of glacial acetic acid, 2 ml of water and 2 g (6.71 mM) of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII) was heated at 90-95° with continual stirring for 13 hrs. The precipitate collected, washed with ethanol and the washings were combined with the filtrate. The solvent was removed by evaporation at reduced pressure and the residual syrup was saponified with 1 N alcoholic sodium hydroxide solution. The glycol, 0.615 g (62%) isolated in the manner described above and was found to be identical to an authentic sample of 3 α -methoxy-1 β ,2 β -cyclohexanediol (XLVIII) both by paper chromatography and infrared spectroscopy.

(3) Solvolysis of 1 α -acetoxy-2 β -iodo-3 α -methoxycyclohexane (XLIII) in moist acetic acid in the presence of silver acetate

The procedure followed was the same as that above for the solvolysis of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane. The reaction mixture was made up of 15 ml of glacial acetic acid, 1 ml of water, 0.140 g (0.84 mM) of silver acetate and 0.200 g (0.67 mM) of 1 α -acetoxy-2 β -iodo-3 α -methoxycyclo-

hexane (XLIII). The mixture was heated at 100° for 24 hrs. The glycol obtained, 39 mg (40%), was identified as 3 α -methoxy-1 α ,2 α -cyclohexanediol (XLVII) both by paper chromatography and infrared spectroscopy.

Trans-3-methoxycyclohexene oxide (XLVI)

To an ice-cold solution of 40 g (134.2 mm) of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII) in 180 ml ethanol, 290 ml of 1 N aqueous sodium hydroxide solution was added portionwise with shaking over a period of 30 minutes. The reaction mixture was allowed to stand at 0° for 14 hrs. After this time, the solution was neutralized with 2 N sulfuric acid, divided into five equal portions and these were extracted countercurrently six times with 50 ml portions of chloroform. The combined extracts were dried over anhydrous magnesium sulfate and the chloroform was removed by fractional distillation using an efficient column at atmospheric pressure. The residue was transferred to a small flask and distilled at reduced pressure using a 20-cm Vigreux column to yield 15 g (88%) of trans-3-methoxycyclohexene oxide (XLVI), b.p. 68-69° (18 mm), n_D^{20} 1.4520. McRae et al (72) reported the compound to boil at 67-69° (15 mm) and n_D^{20} 1.4532. Bannard and Hawkins (73) reported the physical constants, b.p. 54-55° (10 mm) and n_D^{25} 1.4512.

The identity of the oxide XLVI was verified by vapour

phase chromatography using a Silicon oil D.C.-200 column (see p. 60). The chromatogram consisted of a single band which had identical retention volume as that of an authentic sample of trans-3-methoxycyclohexene oxide. Under the same chromatographic conditions, the product of perbenzoic acid epoxidation of 3-methoxycyclohexene (see p. 60) showed two bands on the chromatogram corresponding to cis- and trans-3-methoxycyclohexene oxides.

3-Methoxy-1,2-trans-cyclohexanediols

(1) Dry Prevost reaction of 3-methoxycyclohexene

A mixture of 87 g (0.38 M) of thoroughly dried freshly prepared silver benzoate, 48.3 g (0.19 M) of iodine and 600 ml of dry benzene was refluxed with stirring until all the iodine had dissolved. 3-Methoxycyclohexene (XXXIX), 21.3 g (0.19 M) was then added and the mixture kept at the refluxing temperature with vigorous stirring for 24 hrs. After cooling to room temperature, the reaction mixture was filtered and the precipitate was washed with benzene. The filtrate and washings were combined and washed with water, saturated solution of sodium bicarbonate, sodium thiosulfate solution, and finally with water. After drying over anhydrous sodium sulfate, the benzene was removed by evaporation under reduced pressure. The remaining syrup, 57 g (85%), was

crystallized from ethanol to yield the dibenzoate of 3 α -methoxy-1 α ,2 β -cyclohexanediol, 25 g, m.p. 117.5-120.5°. The mother liquors were shown to contain combined iodine. No attempt was made to isolate other isomeric dibenzoates of the other isomeric glycols. Recrystallization of the dibenzoate of the 3 α -methoxy-1 α ,2 β -cyclohexane diol from ethanol yielded the analytical sample, m.p. 121-122°, which possessed the saponification equivalent, 177, expected for this compound. Alkaline hydrolysis of the dibenzoate gave a glycol which was identical to an authentic sample of 3 α -methoxy-1 α ,2 β -cyclohexanediol (LI). The identity was demonstrated by paper chromatography using the methylethylketone-xylene-water (1:1:1) system (70) and by infrared spectroscopy.

(2) Solvolysis of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII) in dry acetic acid in the presence of silver acetate.

Glacial acetic acid, 50 ml, 5 ml acetic anhydride, and 3.5 g silver acetate, were added to a three-neck, 150 ml flask, equipped with a mechanical stirrer and a condenser. The mixture, protected from atmospheric moisture, was refluxed for 20 hrs. After this time the temperature of the reaction mixture was adjusted to 90-95° and 5 g (17 mM) of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII) was

introduced. The mixture was allowed to remain at 90-95° with stirring for 24 hrs. After cooling and filtration to remove the solids, the solvent was removed in vacuo. The residual syrup was hydrolyzed with base in the manner described on p. 33 for the preparation of glycols from the product of the wet Provost reaction with 3-methoxycyclohexene. The yield of glycols was 1.36 g (55%). Analysis by paper chromatography using methylethylketone-xylene-water (1:1:1) (70) showed the presence of 3 α -methoxy-1 β , 2 β -cyclohexanediol (XLVIII), 3 α -methoxy-1 α , 2 β -cyclohexanediol (LI) and 3 α -methoxy-1 β , 2 α -cyclohexanediol (LII). The quantities of the three glycols in the mixture were determined by Celite partition chromatography (see p. 34). An amount of 0.510 g of the glycol mixture was chromatographed using a column 26.5 cm long and 1.6 cm in inside diameter prepared from 50 g of Celite. The eluate was collected in fraction collector and after testing the following fractions were combined.

Fraction 1. - 180 - 312 ml of eluate.

Evaporation of the solvent gave 0.089 g of
3 α -methoxy-1 β , 2 β -cyclohexanediol (XLVIII).

Fraction 2. - 312 - 372 ml of eluate.

Evaporation of the solvent gave 0.045 g of
3 α -methoxy-1 β , 2 α -cyclohexanediol (LII).

Fraction 3. - 390 - 750 ml of eluate.

Evaporation of the solvent gave 0.314 g of

3 α -methoxy-1 α ,2 β -cyclohexanediol (LI).

The composition of the mixture of the glycols, based on the amounts of the three compounds recovered in the above chromatographic analysis, was: XLVIII, 20%; LII, 10%; LI, 70%.

(3) Solvolysis of 1 α -acetoxy-2 β -iodo-3 α -methoxycyclohexane (XLIII) in dry acetic acid in the presence of silver acetate

A mixture of 100 mg of XLIII, 1 ml of glacial acetic acid, 0.1 ml of acetic anhydride and 70 mg of silver acetate was treated in the manner described in the preparation of glycols given above. Alkaline hydrolysis of the product and examination of the hydrolyzate by paper chromatography showed the presence of 3 α -methoxy-1 β ,2 α -cyclohexanediol (LII), 3 α -methoxy-1 α ,2 β -cyclohexanediol (LI) and 3 α -methoxy-1 α ,2 α -cyclohexanediol (XLVII). As it was estimated from the intensities of the spots on the chromatogram, the relative amounts of the glycols were: LII, 80%; LI, 10%; XLVII, 10%.

Reaction of trans-3-Methoxycyclohexene oxide (XLVI) with Sodium Thioethoxide

The procedure followed was that described by Baker and coworkers for the reaction of cyclopentene oxide with sodium thioethoxide (56).

Sodium, 4.92 g (214 mM), was reacted with 50 ml absolute methanol and the solution was added, over a 30 min. period with stirring, to an ice-cold solution of 13.30 g (214 mM) of ethanethiol in 35 ml absolute methanol. The stirring was continued for one more hour. trans-3-Methoxycyclohexene oxide (XLVI), 13.7 g (107 mM), was added dropwise with stirring to the chilled solution. The reaction mixture was allowed to stand at 0° for one hour more after the addition was completed. The stirring was then discontinued and the mixture was left at room temperature for 15 hrs. Cold water, 150 ml, was added and the solution was neutralized with 2 N sulfuric acid. The precipitate was collected by filtration and washed first with 30 ml methanol and then with 50 ml chloroform. The filtrates were combined and the solution was divided into two equal portions and these were extracted countercurrently five times with 50 ml portions of chloroform. The chloroform extracts were combined, washed with saturated sodium bicarbonate solution, then with water and dried over anhydrous sodium sulfate. The solvent was removed by evaporation at reduced pressure and the residual liquid was distilled from a 20 cm long Vigreux column at 102-106° (1 mm) to yield 18.5 g (92%) of a mixture of 1 α -ethylthio-3 α -methoxy-2 β -cyclohexanol (LVa) and 2 α -ethylthio-3 α -methoxy-1 β -cyclohexanol (LVia).

Anal. Calc. for $C_9H_{18}O_2S$: C, 56.79; H, 9.53; S, 16.84

Found: C, 56.51; H, 9.83; S, 17.03

A 0.975 g sample of the above material (LVa and LVia) was reacted with 3.5 g of 3,5-dinitrobenzoyl chloride in pyridine and the product was isolated in the usual manner. A syrup, 1.7 g (90%), was obtained which crystallized from ethanol to yield 1.02 g (62%) of 1 α -ethylthio-2 β -(3,5-dinitrobenzoyloxy)-3 α -methoxycyclohexane (LVc), m.p. 117-120°. Three recrystallizations from ethanol were used to prepare the analytical sample, m.p. 120-121.5°.

Anal. Calc. for $C_{16}H_{20}O_7N_2S$: C, 49.96; H, 5.24; S, 8.34; N, 8.04

Found: C, 49.99; H, 5.26; S, 8.06; N, 7.35

A 0.98 g sample of the thioethers (LVa and LVia) was acetylated with acetic anhydride and sodium acetate in the conventional method. The reaction product was distilled from a small glass bulb at 115-130° air bath temperature and at 3.2 mm pressure to give 1.1 g (91%) of a syrupy product (LVb and LVib) possessing a saponification equivalent 229 (theory 232.3).

Anal. Calc. for $C_{11}H_{20}O_3S$: C, 56.86; H, 8.67; S, 13.79

Found: C, 56.76; H, 8.71; S, 15.04

A 0.87 g sample of the above acetates (LVb and LVib) was heated under reflux with 20 ml ethanol and 3.5 g of freshly prepared Raney Nickel catalyst (p. 870 of ref. 74) for 2.5 hrs. After this time, a test for sulfur was negative. The ethanolic

solution was separated by decantation and the catalyst was washed four times with 5 ml portions of boiling ethanol. The filtrate and washings were combined and the ethanol was removed by distillation using a 20 cm long Vigreux column at atmospheric pressure. The residue was transferred to a small glass bulb and distilled at 100-110° (air bath temperature) and 20 mm pressure, to give 0.350 g (55%) of a liquid product. The distillate was analysed by vapour phase chromatography using the Burrell Kromo-Tog apparatus. A 6 ft, 6 mm internal diameter column, packed with dioctyl phthalate-Celite 545, 80-100 mesh, (1:4 w/w) was used. The operating temperature was 150° and the rate of gas flow was 62 ml of helium per minute. The chromatogram consisted of two bands. One band was identified as trans-2-methoxycyclohexyl acetate (LVIIb) (identical retention volume as that of an authentic sample of LVIIb). The other band was assumed to be trans-3-methoxycyclohexyl acetate (LVIIIb). The percentages of the two compounds LVIIb and LVIIIb in the mixture were 90% and 10%, respectively, as estimated from the areas under the two bands. The retention volumes of these compounds relative to that of 3-acetoxycyclohexene are given in Table I, p. 44. These experiments indicated that the opening of trans-3-methoxycyclohexene oxide (XLVI) with sodium thiothoxide yielded 90% of 1 α -ethylthio-3 α -methoxy-2 β -cyclohexenol (LVa) and 10% of 2 α -ethylthio-3 α -methoxy-1 β -cyclohexanol (LVia).

TABLE I

Relative Retention Volumes of 2- and 3-Methoxycyclohexyl
Acetates

Column length, 6 ft.; stationary phase, dioctyl phthalate; temperature 150°; flow rate, 62 ml helium per minute.

<u>Compound</u>	<u>Relative Retention</u> <u>Volume</u>
3-acetoxycyclohexene	1
<u>trans</u> -2-methoxycyclohexyl acetate (LVIIb)	2.20
<u>trans</u> -3-methoxycyclohexyl acetate (LVIIIb)	2.56

1 α -Ethylthio-2 β -acetoxy-3 α -methoxycyclohexane (LVb)

A 0.190 g sample of 1 α -ethylthio-3 α -methoxy-2 β -cyclohexanol (LVa), obtained from the corresponding 3,5-dinitrobenzoyl derivative (LVc) by alkaline hydrolysis, was acetylated with acetic anhydride and sodium acetate in the usual manner. The acetate (LVb) was a liquid which resisted crystallization. Reductive desulfurization of this compound with Raney Nickel gave trans-2-methoxycyclohexyl acetate (LVIIb). The latter compound was identified by vapour phase chromatography as described in the previous experiment.

The N.M.R. spectrum of the acetate LVb is shown in Fig. 4-A, p. 123.

Reaction of the Mixture of 3-Methoxycyclohexene Ethylthio hydrins (LVa) and (LVia) with Concentrated Hydrochloric Acid

A 3.21 g sample (16.9 mM) of the mixture of LVa and LVia was kept with 15 ml of concentrated hydrochloric acid in a sealed tube, at 95° for 15 min. and at room temperature for 2.5 hrs. The reaction mixture, was transferred to a separatory funnel, 25 ml of water was added and the solution was extracted three times with 25 ml portions of chloroform. The chloroform solution was washed with water, then with saturated sodium bicarbonate

solution, and finally with water. After drying, the chloroform was distilled through a 20 cm long Vigreux column at atmospheric pressure and the residual liquid was simply distilled in vacuo to yield 3.1 g (90%) of product, b.p. 85-92 (1.6 mm). The completeness of the reaction was shown by the absence of a band for hydroxy group in the infrared spectrum. The N.M.R. spectrum of this substance showed it to be a mixture of approximately 80% of 1β -chloro- 2α -ethylthio- 3α -methoxycyclohexane (LXI) and 20% of 1α -ethylthio- 2β -chloro- 3α -methoxycyclohexane (LX). This could be ascertained from the relative intensities of the two bands for the methoxy groups.

Anal. Calc. for $C_9H_{17}ClOS$: C, 51.78; H, 8.14; Cl, 16.98; S, 15.36
Found: C, 51.94; H, 8.03; Cl, 17.19; S, 15.46

Solvolysis of the Chloride Mixture LX and LXI in Dry Acetic Acid in the Presence of Silver Acetate

A mixture of 15 ml of glacial acetic acid, 1 ml of acetic anhydride and 1.8 g (10.7 mM) of silver acetate was heated at 120° for 2 hrs. and then cooled to $50-60^\circ$. A 1 g (4.85 mM) quantity of the mixture of chlorides (LX and LXI) was added and the reaction mixture was kept at $50-60^\circ$ with stirring for 20 hrs. After this time, reaction was complete as shown by a test for combined chlorine. A small amount of water was then added to decompose the

excess of acetic anhydride and the solution was allowed to cool to room temperature. The precipitate was collected, and extracted with chloroform. The filtrate and extracts were combined and washed first with water, then with sodium bicarbonate saturated solution and, finally, with water. After drying the chloroform was removed by evaporation under reduced pressure. The remaining liquid was transferred to a glass bulb for distillation at 115-130° (air bath temperature) and 1.8 mm pressure. A 0.935 g (84%) yield of a liquid mixture of 1 α -ethylthio-2 β -acetoxy-3 α -methoxycyclohexane (LVb) and 1 β -acetoxy-2 α -ethylthio-3 α -methoxycyclohexane (LVIIb) was obtained.

Anal Calc. for C₁₁H₂₀O₃S: C, 56.86; H, 8.67; S, 13.79

Found: C, 56.76; H, 8.71; S, 15.04

A 0.450 g sample of the mixture of the acetates LVb and LVIIb was crystallized from ethanol to yield 0.350 g (78%) of 1 β -acetoxy-2 α -ethylthio-3 α -methoxycyclohexane (LVIIb), m.p. 49-52°. Two recrystallizations from the same solvent were used to prepare the analytical sample, m.p. 52.5-53.5°. The N.M.R. spectrum of LVIIb is given in Fig. 4-B, p.123. A small amount of the acetate LVIIb was desulfurized with Raney Nickel catalyst to give trans-3-methoxycyclohexyl acetate (LVIIIb).

Anal. Calc. for C₁₁H₂₀O₃S: C, 56.86; H, 8.67; S, 13.79

Found: C, 57.25; H, 8.52; S, 13.50.

A 0.33 g quantity of the mixture of the acetates LVb and LVIIb was treated with 1.5 g of Raney Nickel catalyst in 10 ml of ethanol in the same manner as that described on p. 42. The product, 0.150 g (61%), was analyzed by vapour phase chromatography (see p. 43) and found to be composed of 96% of trans-3-methoxycyclohexyl acetate (LVIIIb) and 4% of trans-2-methoxycyclohexyl acetate (LVIIb).

Reaction of trans-3-Methoxycyclohexene Oxide (XLVI) with Lithium Aluminum Hydride in Ether

trans-3-Methoxycyclohexene oxide (XLVI), 0.103 g, was allowed to react with 0.100 g of lithium aluminum hydride in 4 ml of boiling absolute ether for 16 hrs. The reaction mixture was first treated with 0.3 ml of water and then with 2.5 ml of 4 N sulfuric acid. The ethereal layer was separated and the aqueous phase was extracted three times with 2 ml portions of ether. The ethereal extracts were combined and dried over anhydrous magnesium sulfate. The solution was analyzed by vapour phase chromatography using the Burrell Kromo-Tog instrument. An 8 ft, 6 mm internal diameter column, packed with glycerol-Celite fire brick (1:4 w/w) was used. The operating temperature was 100° and the rate of gas flow was 114 ml of helium per minute; the chromatogram showed the presence of trans-2-methoxycyclohexanol (LVIIa), 97%, and trans-3-

methoxycyclohexanol (LVIIIa), 3%. The retention volumes of these compounds relative to cis-3-methoxycyclohexanol are given in Table II, p. 50.

Reaction of cis-3-Methoxycyclohexene Oxide (LXII) with Lithium Aluminum Hydride

The quantities and the procedure were the same as those described above for the reduction of the trans-3-methoxycyclohexene oxide (XLVI). Analysis of the reaction product by vapour phase chromatography on a glycerol column (see previous experiment) indicated that the product was a mixture of cis-2-methoxycyclohexanol (LXIII) (98%) and cis-3-methoxycyclohexanol (LXIV) (2%). The retention volumes of LXIII and LXIV are given in Table II, p. 50.

Reaction of cis-3-Methoxycyclohexene Oxide (LXII) with Sodium Thioethoxide

Cis-3-Methoxycyclohexene oxide (LXII), 0.640 g (5 mM), was treated with 4 ml of 2.5 N methanolic solution of sodium thioethoxide as was described on p.40 for the reaction of trans-3-methoxycyclohexene oxide (XLVI). The product was distilled from a small glass bulb at 100° (air bath temperature) and 1 mm pressure to yield 0.850 g (90%) of a liquid product which was a mixture of 1 β -ethylthio-3 α -methoxy-2 α -cyclohexanol (LXVa) and 2 β -ethylthio-3 α -methoxy-1 α -cyclohexanol (LXVIa).

TABLE II

Relative Retention Volumes of 2- and 3-Methoxycyclohexanols

Column length, 8 ft.; stationary phase, glycerol;
temperature, 100°; flow rate, 114 ml helium per minute.

<u>Compound</u>	<u>Relative Retention Volume</u>
<u>cis</u> -3-methoxycyclohexanol (LXIV)	1
<u>cis</u> -2-methoxycyclohexanol (LXIII)	1.48
<u>trans</u> -3-methoxycyclohexanol (LVIIIa)	1.61
<u>trans</u> -2-methoxycyclohexanol (LVIIa)	2.46

Anal Calc. for $C_9H_{18}O_2S$: C, 56.79; H, 9.53; S, 16.84

Found: C, 56.69; H, 9.74; S, 16.86

A 0.380 g sample of the above product (LXVa and LXVIa) was treated with 3 ml of acetic anhydride and 1 g of anhydrous sodium acetate in the usual manner. The product was distilled at 100-110° (air bath temperature) and 1 mm pressure to give 0.427 g (86%) of the acetates LXVb and LXVIb. The completeness of the acetylation was shown by the absence of a band for hydroxy group in the infrared spectrum.

A 0.385 g quantity of the above acetates (LXVb and LXVIb) in 5 ml of ethanol was treated with half a teaspoonful of Raney nickel and heated at the refluxing temperature for 4 hrs. The ethanolic solution was separated by decantation and the catalyst was washed four times with 2 ml portions of boiling ethanol. The ethanolic solution was saponified with potassium hydroxide, neutralized with solid carbon dioxide and concentrated to half its volume by distillation. Analysis of the ethanolic solution by vapour phase chromatography under the conditions described on p.49 showed the product to be a mixture of 98% of cis-2-methoxycyclohexanol (LXIII) and 2% of cis-3-methoxycyclohexanol (LXIV).

Reaction of the Mixture of 3-Methoxycyclohexene Ethylthiohydrins (LXVa and LXVIa) with Concentrated Hydrochloric Acid

A 0.376 g sample of the mixture of LXVa and LXVIa

was treated with 4 ml of concentrated hydrochloric acid at 95-100° for 1 hr., as was described on p. 45, The product was distilled at 100-110° (air bath temperature) and 1 mm pressure to yield 0.370 g (90%) of dichlorocompounds. No hydroxyl group absorption was present in the infrared spectrum of this product.

Anal. Calc. for $C_8H_{14}SCl_2$: S, 15.04; Cl, 33.26

Found: S, 15.46; Cl, 31.60

Solvolysis of Above Dichlorocompounds in Dry Acetic Acid
in the Presence of Silver Acetate

A mixture of 5 ml glacial acetic acid, 0.3 ml acetic anhydride and 0.5 g of silver acetate was heated at 120° for two hrs. and cooled to 60-70°. The dichlorocompounds, 0.27 g, was added and the mixture was allowed to stand at 60-70° for 15 hrs. The product of the reaction was isolated in the manner described on p. 46 and was distilled from a small glass bulb at 110-120° (air bath temperature) and 1 mm pressure to yield 0.27 g of 1 α ,3 α -diacetoxy-2 β -ethylthiocyclohexane (LXXIII). The N.M.R. spectrum of this product is shown in Fig. 5, p. 132.

Anal. Calc. for diacetate $C_{12}H_{20}O_4S$: C, 55.35; H, 7.74;

S, 12.31; Sapon. equiv.; 130.1

Found: C, 55.15; H, 8.25; S, 12.66; Sapon equiv. 125.

1,2-Iodo-(3,5-dinitrobenzoyloxy)-3-methylcyclohexanes

Into a round-bottomed flask equipped with a mechanical stirrer was added 100 ml of benzene, 5.08 g (20 mM) of finely pulverized iodine, and 6.38 g (20 mM) of freshly prepared (76) silver 3,5-dinitrobenzoate. The mixture was stirred at room temperature until all the iodine was dissolved (1 hour) and was then cooled to 0°. To the ice-cold reaction mixture was added 1.92 g (20 mM) of 3-methylcyclohexene (LXXIV) with stirring and the mixture was maintained at 0° for 9 hrs. and at room temperature for one hr. It was then filtered and the cake was extracted several times with benzene. The combined filtrate and extracts were washed with water, then with saturated sodium bicarbonate solution, then with sodium thiosulfate solution and finally with water. After drying over sodium sulfate, the benzene was removed under reduced pressure at 30° to yield 7.6 g (87%) of a thick brown syrup. This was dissolved in hot chloroform (1 ml per g) and an equal volume of hot ethanol was added. Crystalline 1 β -(3,5-dinitrobenzoyloxy)-2 α -iodo-3 α -methylcyclohexane (LXXIX), 3.24 g (42.6%) separated on cooling, m.p. 132-134°. Two recrystallizations from the same solvent system and one from ethyl acetate did not change the melting point. The mother liquors from the recrystallizations were combined the solvent was removed at reduced pressure and the residue,

4.93 g, was chromatographed on Magnesol-Celite (5:1) containing Rhodamine 6 G as an internal indicator in the following manner.

Five parts of Magnesol (greater than 200 mesh), a commercial hydrated magnesium acid silicate manufactured by the Westvaco chlorine Products Co., South Charleston, West Virginia, was mixed with 1 part of acid washed Celite 535 (greater than 200 mesh), a commercial filter aid prepared from diatomaceous earth and manufactured by the Johns-Mansville Co., New York, N.Y. The mixture was extracted with acetone and dried at room temperature. An amount of 420 g of this mixture was dispersed in 1.5 liter of methanol and a solution of 45 mg of Rhodamine 6 G (Calcozine red 6 G extra, Color Index no. 752) in 50 ml of methanol was added with stirring. The slurry was filtered on a Buchner funnel, and left on the funnel until dripping ceased. It was then transferred to a pan and dried in a vacuum oven at 100-120° (about 20 mm) for 24 hrs. The dry adsorbent was stored in a tightly capped bottle. It was pink in daylight and showed a yellow fluorescence under ultraviolet light.

A quantity of 190 g of the above adsorbent was suspended in petroleum ether (80-100°) and the slurry was introduced into a column 28 cm long and 4.5 cm in inside diameter. Pressure was applied to obtain uniform packing.

The sample, 2.735 g, was applied to the column as a solution in a small amount of chloroform. Petroleum ether (80-100°) and mixtures of the petroleum ether and diethyl ether were used to develop the column in the following amounts: 500 ml of petroleum ether, followed by 4,000 ml of 2% ether in petroleum ether and, finally, 1,800 ml of 5% ether in petroleum ether.

Air pressure of about 40 cm of mercury was applied to the top of the column to increase the rate of development. Three bands appeared on the column. These bands were visible in daylight due to their deep pink colour on the light pinkish background. Ultraviolet radiation showed the adsorbed bands as dark zones on a bright fluorescence background. Development was continued until the two first bands were washed through. Then, the column of the adsorbent was extracted with 20% ethanol in benzene. The following fractions of eluate were collected:

- Fraction 1. - 4500 - 4970 ml of eluate yielded upon evaporation 0.095 g of the 1 α -iodo-2 β - (3,5-dinitrobenzoyloxy)-3 α -methylcyclohexane (LXXX), m.p. 188.5-189°, after three recrystallization from 1:1 chloroform-ethanol.
- Fraction 2. - 4970 - 5100 ml of eluate yielded 0.044 g of non-crystallizable syrup.
- Fraction 3. - 5100 - 6150 ml of eluate yielded 0.623 g

of 1 β -iodo-2 α -(3,5-dinitrobenzoyloxy)-
3 α -methylcyclohexane (LXXVIII) m.p. 134-136°,
after two recrystallizations from 1:1 chloro-
form-ethanol.

Extraction of the column of the adsorbent with
20% ethanol in benzene gave, after evaporation of the
solvent, 1.90 g of a non-crystallizable syrup which was a
mixture of two isomeric iodides. This syrup was rechroma-
tographed under the conditions described above. A 20 cm
long, 4 cm in internal diameter column was used. The ether
content of the eluent was progressively increased in
increments of 2% for every 2 liters of solvent, to a
maximum of 20%. During the developing process, a broad
band was developed. The eluate was collected in 50 ml tubes.
Each tube was evaporated to dryness and the residue was
weighed. A weight-total volume of eluent plot indicated
that the broad band observed on the column actually consisted
of two overlapping bands of equal amounts of material. A
fraction of the eluate, 5650-6100 ml, was evaporated to
dryness to give 1 β -(3,5-dinitrobenzoyloxy)-2 α -iodo-3 α -
methylcyclohexane (LXXIX), m.p. 132-134, after three
recrystallizations from 1:1 chloroform-ethanol. Another
fraction of the eluate, 7000-9000 ml, after evaporation
yielded 1 α -(3,5-dinitrobenzoyloxy)-2 β -iodo-3 α -methylcyclo-
hexane (LXXVII), m.p. 156-158°, after three recrystallizations

from 1:1 chloroform-ethanol.

Consequently, the approximate percentage composition of the initial reaction product was: LXXIX, 61%; LXXX, 2-3%; LXXVIII, 14%; LXXVII, 19%.

The N.M.R. spectra of the four isomers are shown in Figs. 6 and 7, pp. 137 and 138.

Anal. Calc. for $C_{14}H_{15}IN_2O_6$: C, 38.72; H, 3.48; I, 29.22

Found: compound LXXIX, C, 38.55; H, 3.84; I, 29.44

LXXX, C, 38.56; H, 3.71; I, 29.29

LXXVIII, C, 38.93; H, 3.77; I, 29.31

LXXVII, C, 38.81; H, 3.82; I, 29.65

Trans-3-methylcyclohexene Oxide (LXXXI)

To an ice-cold solution of 5.43 g (97 mM) of potassium hydroxide in 100 ml of 97% ethanol, was added 20 g (46 mM) of 1β -(3,5-dinitrobenzoyloxy)- 2α -iodo- 3α -methylcyclohexane (LXXIX) and the mixture was kept at 0° with stirring for 24 hours. It was then filtered. The filtrate was diluted with 150 ml of water, and then distributed equally in five separatory funnels and countercurrently extracted five times with 20 ml portions of chloroform. The extracts were combined and dried over anhydrous magnesium sulfate. The chloroform was removed by distillation using a fractionating column packed with glass helices at atmospheric pressure. The residue was distilled from a

20 cm long Vigreux column to yield 1.85 g (36%) of trans-3-methylcyclohexene oxide (LXXXI), b.p. 133-134° (750 mm) n_D^{31} 1.4445.

Anal. Calc. for $C_7H_{12}O$: C, 74.95; H, 10.78

Found: C, 74.91; H, 10.78

The above product was analyzed by vapour phase chromatography on the Burrel Kromo-Toe instrument. An 8 ft., 5 mm in inside diameter column, packed with glycerol-Celite fire brick (1:4 w/w) was used. The operating temperature was 55° and the rate of gas flow was 46 ml of helium per minute. The chromatogram consisted of a single band. Under the same chromatographic conditions, the product of the perbenzoic acid oxidation of 3-methylcyclohexene (see next experiment) showed two bands on the chromatogram corresponding to cis- and trans-3-methylcyclohexene oxides.

Perbenzoic Acid Epoxidation of 3-Methylcyclohexene (LXXIV)

To a solution of 35.5 g (257 mM) of perbenzoic acid in 450 ml chloroform (p. 808 of reference 74) at -5° was added 20 g (208 mM) of 3-methylcyclohexene (LXXIV) over one-half hour. Throughout the addition the temperature of the mixture was maintained at 0°. It was then allowed to stand at this temperature for five days. After this time, the reaction was complete as indicated by titration of the unreacted perbenzoic acid using the sodium thiosulfate

method (p. 809 of reference 74). The reaction mixture was washed three times with saturated sodium bicarbonate solution, then one each with potassium iodide solution, sodium thiosulfate solution, and water. After drying, over sodium sulfate, the chloroform and the reaction products were separated by distillation at atmospheric pressure using a column packed with glass helices. The yield was 15 g (70%) of material b.p. 144-145.5° (760 mm), n_D^{26} 1.4467; Kotz (77) reported, b.p. 143-144°C (760 mm). Mousseron and coworkers (78) reported, b.p. 142° (760 mm), n_D^{25} 1.4467.

The product of the reaction was found to contain two components by vapour phase chromatographic analysis under the conditions described in the previous experiment. The slower moving compound had the same retention volume as trans-3-methylcyclohexene oxide (LXXXI). The other band was assumed to be that for the cis-3-methylcyclohexene oxide (LXXXII). On this basis, the chromatographic analysis showed the mixture to contain 53% of the trans-oxide (LXXXI) and 47% of the cis-isomer (LXXXII). The retention volumes of the trans-oxide relative to that of the cis-oxide was 1.11. The identity of the cis-oxide was clearly established by lithium aluminum hydride reduction of the mixture as described later on (see p. 60).

Anal. Calc. for $C_7H_{12}O$: C, 74.95; H, 10.78

Found: C, 74.91; H, 10.78

Perbenzoic Acid Oxidation of 3-Methoxycyclohexene (XXXIX)

A 1.12 (10 mM) sample of 3-methoxycyclohexene (XXXIX) was treated with 3.6 g (26 mM) of perbenzoic acid in 25 ml chloroform in the manner described in the previous experiment for the oxidation of 3-methylcyclohexene, with the exception that the oxides were not separated from the chloroform. The solution of the oxides in chloroform was analyzed by vapour phase chromatography using the Perkin-Elmer instrument. A 6 ft., 7 mm internal diameter column with silicone oil D.C.-200 as the stationary phase (Perkin-Elmer column 154 0013-C) was used. The operating temperature was 160° and the rate of gas flow was 54 ml of helium per minute. The chromatogram consisted of two bands which were identified as the cis- and trans-3-methoxycyclohexene oxides, by comparison of their chromatographic properties with those of authentic samples. The mixture was found to be composed of 18% of cis-3-methoxycyclohexene oxide (LXII) and 82% of trans-3-methoxycyclohexene oxide (XLVI). The retention volumes of the two isomeric oxides relative to cyclohexene oxide as were determined at 184° are shown in Table III.

Reduction of the Mixture of cis-and trans-3-Methylcyclohexene Oxides (LXXXII and LXXXI) with Lithium Aluminum Hydride

To a solution of 1 g of lithium aluminum hydride

TABLE III

Relative Retention Volumes of some Trisubstituted Cyclohexanes

Column length, 6 ft.; stationary phase, Silicone oil D.C-200 (Perkin-Elmer column 154-0013-C); temperature 184°; flow rate 46 ml helium per minute.

<u>Compound</u>	<u>Relative Retention Volume</u>
cyclohexene oxide	1
<u>trans</u> -3-methylcyclohexene oxide (LXXXI)	1.24
<u>cis</u> -3-methylcyclohexene oxide (LXXXII)	1.24
1 α -methoxy-3 α -methyl-2 β -cyclohexanol (LXXXVIIa)	2.05
2 α -methoxy-3 α -methyl-1 β -cyclohexanol	2.25
<u>trans</u> -3-methoxycyclohexene oxide (XLVI)	1.68
<u>cis</u> -3-methoxycyclohexene oxide (LXII)	1.98
1 α ,3 α ,-dimethoxy-2 β -cyclohexanol	3.14
2 α ,3 α -dimethoxy-1 β -cyclohexanol	3.14
1 β ,3 α -dimethoxy-2 α -cyclohexanol	2.79
2 β ,3 α -dimethoxy-1 α -cyclohexanol	2.79
<u>trans</u> -2-methoxycyclohexanol (LVIIa)	1.73

in 30 ml dry ether was added 1 g of the mixture of cis- and trans-3-methylcyclohexene oxides (LXXXII and LXXXI). After the addition, the reaction mixture was allowed to reflux for 18 hrs.. It was then treated first with water and then with dilute sulfuric acid. The ether layer was separated and the aqueous phase was extracted four times with 25 ml portions of ether. The ether extracts were combined and dried over magnesium sulfate. Removal of the ether at reduced pressure at 0° left 0.92 g (92%) of material. This product was analyzed by vapour phase chromatography using the Burrell Kromo-Tog instrument. An 8 ft., 6 mm internal diameter column, packed with glycerol-Celite fire brick (1:4 w/w) was used.. The operating temperature was 102° and the rate of gas flow was 66 ml helium per minute.. The chromatogram consisted of four bands corresponding to cis-2-, cis-3-, trans-2- and trans-3-methylcyclohexanols (LXXXIII-LXXXVI). The identities of the four components were established through a comparison of their retention volumes with those of authentic samples. The percentages of the four isomers in the mixture, as determined by a comparison of the areas of the four bands on the chromatogram, were: trans-2-methylcyclohexanol (LXXXIII), 18%; trans-3-methylcyclohexanol (LXXXIV), 34%; cis-2-methylcyclohexanol (LXXXVI), 43%; cis-3-methylcyclohexanol (LXXXV), 5%. It is to be noted that the ratio of trans to cis isomers would require the

mixture of oxides to contain 52% and 48% of the trans- and cis-3-methylcyclohexene oxides, respectively. As seen on p. 59 , actual analysis of the mixture of oxides showed it to contain 53% and 47% of these compounds, respectively. This agreement clearly justifies the contention that, with the aid of vapor phase chromatography, the mixture of oxides can be profitably used to study the reaction properties of the cis-isomer. The retention volumes of the four isomeric methylcyclohexanol (LXXXIII-LXXXVI) relative to cis-3-methylcyclohexanol (LXXXV) are listed in Table IV, p. 64.

Reduction of trans-3-Methylcyclohexene Oxide (LXXXI) with Lithium Aluminum Hydride

The procedure followed was that described in the previous experiment. The reaction mixture contained 0.10 g of trans-3-methylcyclohexene oxide (LXXXI), 0.4 g of lithium aluminum hydride and 10 ml of dry ether. The product of the reaction was analyzed by vapour phase chromatography under the conditions described above. The analysis showed the products to contain 34% of trans-2-methylcyclohexanol (LXXXIII) and 66% of trans-3-methylcyclohexanol (LXXXIV). This ratio of trans-2-methyl- to trans-3-methylcyclohexanol, 0.52, agrees well with that determined above, 0.53, in the reaction product from the reduction of the mixture of cis- and trans-oxides. Thus, these results lend further support to the above

TABLE IV

Relative Retention Volumes of 2- and 3-Methylcyclohexanols

Column length, 8 ft.; stationary phase glycerol;
temperature, 102°; flow rate, 66 ml helium per minute.

<u>Compound</u>	<u>Relative Retention Volume</u>
<u>cis</u> -2-methylcyclohexanol (LXXXVI)	1
<u>trans</u> -2-methylcyclohexanol (LXXXIII)	1.33
<u>trans</u> -3-methylcyclohexanol (LXXXIV)	1.43
<u>cis</u> -3-methylcyclohexanol (LXXXV)	2.02

contention relating the reliability of the analytical methods based on vapour phase chromatography.

Reaction of the trans-3-Methoxycyclohexene Oxide (XLVI) with Dimethylmagnesium

(A) Preparation of the Ethereal Solution of Dimethylmagnesium

The method described by Kullman (79) for the preparation of ethereal diethylmagnesium solution was followed. Into a one-liter, three-neck flask equipped with a condenser, a stirrer through a mercury seal and dropping funnel, 24.5 g of magnesium turnings, 250 ml of absolute ether and a crystal of iodine were added. A solution of 142 g (1 mole) of methyl iodide in 150 ml absolute ether was added slowly through the separatory funnel with stirring, at such a rate as to keep the reflux under control. When all the magnesium was dissolved, a mixture of 92 g (1.05 M) of dry dioxane and 80 ml of absolute ether was added in three equal portions at 24 hour intervals. Before each addition, the reaction mixture was cooled in an ice-water bath. The dioxane was added over period of 1 hr. and the reaction mixture was allowed to stand at room temperature until the next addition. After the additions were completed, the apparatus was so arranged that the reaction mixture could

be transferred using nitrogen pressure, under anhydrous conditions, from the three-neck flask to a sintered glass funnel for filtration into a dry flask. The filtrate, 250 ml, was analyzed by titration with standard acid and phenolphthalein as indicator (80). It was found to contain 2.001 milliequivalents of magnesium per ml. Determination of the iodide by the Volhard's method (p. 457 of reference 81) showed the solution to contain 0.0177 milliequivalents of iodide per ml. This indicated that the magnesium was combined to an extent 99.1% as dimethylmagnesium.

(B) Reaction of trans-3-Methoxycyclohexene Oxide with Dimethyl Magnesium

The above solution of dimethyl magnesium, 10 ml (20 m.E), was added to a 50 ml round-bottomed flask equipped with a condenser. A solution of 1.28 g (10 mM) of trans-3-methoxycyclohexene oxide (XLVI) in 20 ml dry ether was then added and the mixture, protected both from atmospheric moisture and carbon dioxide, was allowed to stand at room temperature for 17 hrs. It was then refluxed for 2 hrs. After cooling to 0°, a few drops of water added and this was followed by the addition of 20 ml 2 N hydrochloric acid in portions. The ethereal layer was separated and the aqueous phase was extracted twice with 15 ml volumes of ether. The extracts were combined and washed first with saturated

sodium bicarbonate solution and then with water. After drying over magnesium sulfate, the ether was removed under reduced pressure at room temperature. The residue was distilled from a small glass bulb at 75-95° (air bath temperature) and 8 mm pressure to yield 1 g (70%) of a liquid material. The product was analyzed by vapour phase chromatography on a Burrel Kromo-Tog instrument. A 4 ft., 6 mm in inside diameter column, packed with Apiezon M vacuum stopcock grease-Celite 545, 100 mesh, (1:4 w/w) was used. The operating temperature was 108° and the rate of gas flow was 56 ml of helium per minute. The analysis showed the product to contain 54% of 1 α -methyl-3 α -methoxy-2 β -cyclohexanol (LXXXVIIa) and 46% of 2 α -methyl-3 α -methoxy-1 β -cyclohexanol (LXXXVIIIa). The retention volumes of the compounds LXXXVIIa and LXXXVIIIa relative to trans-3-methoxycyclohexene oxide (XLVI) are shown in Table V, p. 68.

A 1 g (6.9 mM) sample of the above product (LXXXVIIa and LXXXVIIIa) was esterified with 1.85 g (10 mM) of p-nitrobenzoyl chloride in pyridine and the esters were isolated in the usual manner. A thick syrup, 1.83 g (90%), was obtained. Crystallization from petroleum ether (80-100°) gave 1 α -methyl-2 β -p-nitrobenzoyloxy-3 α -methoxycyclohexane (LXXXVIIb) m.p. 97-100°. Two recrystallizations from the same solvent yielded 0.400 g (22%) of the analytical sample, m.p. 101-102°. The mother liquors were combined and

TABLE V

Relative Retention Volumes of 1 α -Methyl-3 α -methoxy-2 β -cyclohexanol (LXXXVIIa) and 2 α -Methyl-3 α -methoxy-1 β -cyclohexanol (LXXXVIIIa)

Column length, 4 ft.; stationary phase, Apiezon M vacuum stopcock grease; temperature, 108 $^{\circ}$; flow rate, 56 ml helium per minute.

<u>Compound</u>	<u>Relative Retention Volume</u>
<u>trans</u> -3-methoxycyclohexene oxide (XLVI)	1
1 α -methyl-3 α -methoxy-2 β -cyclohexanol (LXXXVIIa)	1.40
2 α -methyl-3 α -methoxy-1 β -cyclohexanol (LXXXVIIIa)	1.88

evaporated to dryness. The residue, 1.040 g, was chromatographed on silicic acid-Celite (2:1 w/w) containing Rhodamine 6G as an internal indicator (82). The adsorbent, 60 g, was dispersed in petroleum ether (80-100°) and packed into a column 15 cm long and 3.5 cm in inside diameter. The sample was applied to the column as a solution in a small amount of chloroform and the chromatogram was developed under pressure with 5% ether in petroleum ether (80-100°). During the developing process, two well separated bands appeared on the chromatogram. Their location on the column could be followed visually from their pink colour on a pinkish background. Under ultraviolet radiation, the bands appeared as dark zones on a fluorescence background. The development of the chromatogram was continued until both bands had passed through the column. The following fractions were obtained.

Fraction 1. - 500 - 1000 ml of eluate gave, after removal of the solvent, 0.570 g of 1 β -p-nitrobenzoyloxy-2 α -methyl-3 α -methoxycyclohexane (LXXXVIIIb), m.p. 68.5-69.5°, after two recrystallizations from petroleum ether (80-100°).

Fraction 2. - 1000 - 2000 ml of eluate yielded, after evaporation of the solvent, 0.001 g of a non-crystallizable syrup.

Fraction 3. - 1200 - 2200 ml of eluate yielded, after evaporation of the solvent, 0.296 g of

1 α -methyl-2 β -p-nitrobenzoyloxy-3 α -methoxy-cyclohexane (LXXXVIIb), m.p. 101-102° after two recrystallizations from petroleum ether (80-100°).

These experiments indicated that the mixture of the p-nitrobenzoates contained 55% of LXXXVIIb and 45% of LXXXVIIIb. This was in good agreement with the results obtained by analysis of the alcohols LXXXVIIa and LXXXVIIIa using vapour phase chromatography.

Anal Calc. for C₁₅H₁₉NO₅: C, 61.42; H, 6.53

Found: for compound LXXXVIIb, C, 61.62; H, 6.65

LXXXVIIIb, C, 61.12; H, 6.53

The N.M.R. spectra of LXXXVIIb and LXXXVIIIb are given in Fig. 8, p. 152.

3-Methyl-1,2-trans-cyclohexanediols

(1) Demethylation of 1 α -Methoxy-3 α -methyl-2 β -cyclohexanol (LXXXVIIa)

Pure 1 α -methoxy-3 α -methyl-2 β -cyclohexanol (LXXXVIIa) 50 mg, prepared by alkaline hydrolysis of the corresponding p-nitrobenzoate (LXXXVIIb), was heated in a sealed tube at 80° for 2 hrs. with 3 ml of 55% hydriodic acid. The content of the tube was neutralized with saturated bicarbonate solution and was extracted 5 times with 5 ml volumes of chloroform.

The chloroform solution was dried, the solvent was removed at reduced pressure to leave a syrup, 20 mg, (45%). Crystallization from ethyl acetate yielded a hygroscopic sample of 3a-methyl-1a,2 β-cyclohexanediol (LXXXIXa), mlp. 46-47.5°. The glycol LXXXIXa was converted to the di-p-dinitrobenzoate (LXXXIXb) which melted at 123.5-125.5° after one recrystallization from ethyl acetate. The latter compound was identical (mixed m.p. and infrared spectra) with the di-p-nitrobenzoate (see the foregoing experiment) of one of the glycols which were obtained by alkaline hydrolysis of the mixture of 3-methylcyclohexene oxides.

Anal. Calc. for $C_{21}H_{26}N_2O_8$: C, 58.87; H, 4.71

Found: C, 57.84; H, 4.78

(2) Alkaline Hydrolysis of the Mixture of 3-Methylcyclohexene Oxides (LXXXI and LXXXII)

A mixture of 3-methylcyclohexene oxides (LXXXI, 53%, LXXXII, 47%), 1.06 g (9.6 mM), 10 ml of 1 N aqueous sodium hydroxide and 10 ml of 1,4-dioxane was refluxed for 60 hrs. The reaction mixture was then neutralized with solid carbon dioxide and the solvent was removed under reduced pressure. The residue was dissolved in 10 ml of water and extracted four times with 20 ml volumes of chloroform. The solvent was removed by evaporation at reduced pressure and the remaining syrup was distilled from a small glass bulb at 130-140° (air

bath temperature) and 2 mm pressure, to give 0.875 g (70%) of product. Crystallization of this product from ethyl acetate gave 3a -methyl-1 β ,2 α -cyclohexanediol (XCa) which was purified by two recrystallization from the same solvent to afford an analytical sample, 0.476 g (55%), m.p. 94.5-96°. A sample of the glycol XCa was converted to the di-p-nitrobenzoate (XCb) which melted at 164.5-166.5° after two recrystallizations from ethyl acetate.

Anal. Calc. for $C_7H_{14}O_2$: C, 64.58; H, 10.83

Found: C, 64.48; H, 10.57

The mother liquors from recrystallization of the glycol XCa were combined and evaporated to dryness. The residue, 0.35 g, was esterified with p-nitrobenzoyl chloride in pyridine and the product was isolated in the usual manner. The yield was 1.05 g (91%). This product was chromatographed on Magnesol-Celite (5:1) containing Rhodamine 6G as an internal indicator. The preparation of the adsorbent and the chromatographic procedure followed were the same as described on p. 54. A 28 cm long, 2.7 cm in inside diameter column packed with 65 g of the adsorbent was used. The sample, 1.05 g, was applied to the column as a solution in a small amount of chloroform. The chromatogram was developed with mixtures of ether in petroleum ether (80-100°). The concentrations of ether and amounts of solvent were as follows: 5% ether in petroleum ether, 1000 ml; 10% ether in petroleum ether,

1000 ml; 15% ether in petroleum ether, 1000 ml. During the developing process, two well separated bands could be distinguished either in the daylight, due to their deep pink colour on a light pinkish background, or under ultra-violet light due to their dark colour on a fluorescent background. The elution of the column was continued until the first band had passed through the column. Then, the column was extracted with 5% ethanol in chloroform. The following fractions were obtained.

Fraction 1. - 2000 - 2750 ml of eluate yielded, after evaporation, 0.643 g of di-p-nitrobenzoate of 3 α -methyl-1 α , 2 β -cyclohexanediol (LXXXIXb), m.p. 123.5-125.5° (after three recrystallizations from ethyl acetate).

Fraction 2. - 2750 - 2950 ml of eluate gave, after evaporation of the solvent, 6 mg of a syrup.

Fraction 3. - Extraction of the column with 5% ethanol in chloroform gave, after evaporation to dryness, 0.372 g of di-p-nitrobenzoate of the 3 α -methyl-1 β , 2 α -cyclohexanediol (XCb), m.p. 164.5-166.5°, (after three recrystallizations from ethyl acetate).

Anal. Calc. for $C_{21}H_{20}N_2O_8$: C, 58.87; H, 4.71

Found: for compound LXXXIXb, C, 58.32; H, 4.79

XCb, C, 53.34; H, 4.97

These experiments showed that the product of the alkaline hydrolysis of the mixture of 3-methylcyclohexene oxides (LXXXI and LXXXII) contained 75% of 3 α -methyl-1 β , 2 α -cyclohexanediol (XCa) and 25% of 3 α -methyl-1 α , 2 β -cyclohexanediol (LXXXIXa).

(3) Alkaline Hydrolysis of trans-3-Methylcyclohexene Oxide (LXXXI)

A mixture of 55 mg of trans-3-methylcyclohexene oxide (LXXXI), 0.5 ml of 0.5 N aqueous sodium hydroxide and 0.5 ml of 1,4-dioxane was heated in a sealed tube at 100° for 60 hrs. The product, isolated in the way described in the previous experiment, was analyzed by vapour phase chromatography on the Burrel Kromo Tog instrument. A 4 ft., 6 mm internal diameter column, packed with sorbitol-Celite fire brick (1:4 w/w) was used. The operating temperature was 120° and the rate of gas flow was 90 ml helium per minute. The analysis showed the mixture to contain 55% of 3 α -methyl-1 β , 2 α -cyclohexanediol (XCa) and 45% of 3 α -methyl-1 α , 2 β -cyclohexanediol (LXXXIXa).

3 α -Methyl-1 β , 2 β -Cyclohexanediol

(1) By Reaction of trans-3-Methylcyclohexene Oxide (LXXXI) with Acetyl Chloride and Subsequent Acetolysis in Moist Acetic Acid.

A mixture of 0.136 g of trans-3-methylcyclohexene

oxide (LXXXI) and 1 ml of acetyl chloride was heated in a sealed tube at 100° for 64 hrs. The content of the tube was transferred in a small flask and the unreacted acetyl chloride was removed by evaporation under reduced pressure at room temperature. The residue was distilled from a small glass bulb at 80°-100° (air bath temperature) and 1 mm pressure to yield 0.180 g (80%) of chlorocompounds (XCIII).
Anal. Calc. for $C_9H_{15}ClO_2$: C, 56.69; H, 7.92; Cl, 18.59
Found: C, 57.00; H, 7.89; Cl, 18.59

A mixture of 0.163 g of the above chlorocompounds (XCIII), 3 ml of 90% acetic acid-water and 0.5 g of silver acetate was refluxed for four days. The reaction mixture was filtered and the precipitate was washed with 15 ml chloroform. The chloroform layer of the combined filtrates was washed first with water then with saturated sodium bicarbonate solutions and finally with water. After drying over sodium sulfate, the chloroform was removed by evaporation at reduced pressure. The residue, 0.120 g, represented a yield of 81% based on the assumption that this product was a mixture of the monoacetates of 3 α -methyl-1 β ,2 β -cyclohexanediol (XCIV). The above product (XCIV) was hydrolyzed with sodium hydroxide and the glycol was isolated in the manner described on p. 71. The yield was 30 mg of 3 α -methyl-1 β ,2 β -cyclohexanediol (XCIA), m.p. 82.5-83.5°, after two recrystallizations from n-hexane. The low yield of XCIA was

due primarily to accidental loss. The di-p-nitrobenzoate (XCIIb) of the glycol (XCIIa) melted at 136-138° after recrystallization from chloroform-ethanol 1:1.

(2) By Wet Prevost Reaction of 3-Methylcyclohexene

A mixture of 13.36 g (80 mM) of silver acetate, 80 ml of glacial acetic acid, 0.87 ml (40 mM) of water and 8.13 g (32 mM) of iodine was stirred at room temperature until all the iodine was dissolved. 3-Methylcyclohexene (LXXIV), 3.07 g (32 mM), was then added and the reaction mixture was stirred first at room temperature for 6 hrs. and then at the reflux temperature for 5 days. The mixture was then filtered and the filter cake washed with chloroform. The filtrate and washings were combined, diluted with 100 ml of water and extracted four times with 60 ml volumes of chloroform. The chloroform solution was washed first with water then with saturated solution of sodium bicarbonate and finally with water and dried. Removal of the chloroform under reduced pressure left a syrup 2.5 g which gave a positive test for combined iodine. Distillation of this product from a small glass bulb at reduced pressure gave 2.3 g of a liquid. Some high boiling material was left in the distillation apparatus which contained iodine. The distillate was saponified with ethanolic sodium hydroxide to give 1.6 g (39%) of easily crystallizable material. Two recrystallizations of this product from ethyl acetate and one from ethanol

yielded 0.6 g of 3 α -methyl-1 β ,2 β -cyclohexanediol (XCIIa), m.p. 82.5-83.5°. The glycol was identical (mixed m.p. and infrared spectra) with the glycol obtained in the previous experiment by way of the reaction of trans-3-methylcyclohexene oxide with acetyl chloride.

Anal. Calc. for C₇H₁₄O₂: C, 64.58; H, 10.83

Found: C, 64.59; H, 11.17

A sample of the glycol (XCIIa) was converted to di-p-nitrobenzoate (XCIIb) which after two recrystallizations from 1:1 ethanol-chloroform, melted at 136-138°. This compound was identical (mixed m.p. and infrared spectra) with the di-p-nitrobenzoate of the glycol obtained in the previous experiment by way of the reaction of trans-3-methylcyclohexene oxide with acetyl chloride.

Anal. Calc. for C₂₁H₂₀N₂O₈: C, 58.87; H, 4.71

Found: C, 59.09; H, 5.08

Reaction of the Mixture of 3-Methylcyclohexene Oxides (LXXXI and LXXXII) with Sodium Thioethoxide

The procedure followed was the same as that described on p. 40 for the reaction of trans-3-methoxycyclohexene oxide with sodium thioethoxide. The reaction mixture consisted of 4.03 g (36 mM) of 3-methylcyclohexene oxides (trans, 53%; cis, 47%) and 30 ml of 2.4 N methanolic solution of sodium thioethoxide. The yield of thioethers XCIVa-XCVIIIa

was 5.7 g (90%), b.p. 108-115° (10 mm).

Anal. Calc. for $C_9H_{18}OS$: C, 62.01; H, 10.40; S, 18.39

Found: C, 61.90; H, 10.58; S, 18.40

A 1 g (5.74 mM) quantity of the above product (XCVa-XCVIIIa) was acetylated with acetic anhydride and sodium acetate in the usual way to give 1.18 g (95%) of the acetylated product. The substance possessed a saponification equivalent of 211, in good agreement with the theoretical value of 216.3.

A sample, 0.58 g, of the above acetylated product was treated, with approximately 1.5 g of Raney nickel catalyst in 10 ml of ethanol in the way described on p. 42 . The ethanolic solution of the desulfurized product was treated with 0.160 g of sodium hydroxide. The ethanol was removed under reduced pressure at room temperature and the residue was diluted with 10 ml of water. The aqueous solution was extracted four times with 20 ml volumes of ether and the extracts were dried. The ether was removed under reduced pressure at room temperature to yield 0.150 g (50%) of a liquid product. Analysis of this product by vapour phase chromatography, under the conditions described on p. 62 , indicated that it was a mixture of the following composition: trans-2-methylcyclohexanol (LXXXIII), 34%; trans-3-methylcyclohexanol (LXXXIV), 20%; cis-2-methylcyclohexanol (LXXXVI), 44%; and cis-3-methylcyclohexanol (LXXXV), 2%.

On the basis of this analysis the mixture of trans- and cis-3-methylcyclohexene oxides contained 54% and 46% of the two oxides, respectively (compare with the results on pp.59 and 62). These experiments showed that the product of the reaction of 3-methylcyclohexene oxides (LXXXI and LXXXII) with sodium thioethoxide contained the following compounds: 1 α -ethylthio-3 α -methyl-2 β -cyclohexanol (XCVa), 34%; 2 α -ethylthio-3 α -methyl-1 β -cyclohexanol (XCVIa), 20%; 2 β -ethylthio-3 α -methyl-1 α -cyclohexanol (XCVIIa), 2%; 1 β -ethylthio-3 α -methyl-2 α -cyclohexanol (XCVIIIa), 44%.

Reaction of 3-Methylcyclohexene Ethylthiohydrins (XCVa-XCVIIIa) with Concentrated Hydrochloric Acid

The procedure followed was the same as the one described on p. 45 . The mixture of XCVa-XCVIIIa, 1 g, was mixed with 15 ml of concentrated hydrochloric acid. The resulting heterogeneous mixture was heated at 100° for 2 hours in a sealed tube with occasional shaking. The product of the reaction (XCIX-CII) was 0.90 g (82%). The fact that the infrared spectrum of this compound showed no hydroxyl band indicated that the reaction was complete.

Anal. Calc. for $C_9H_{17}ClS$: C, 56.07; H, 8.88; S, 16.63;

Cl, 18.39

Found:

C, 55.92; H, 9.23;

Cl, 15.56

Reaction of the Mixture of the above Chlorocompounds (XCIX-CII) with Silver Acetate in Dry Acetic Acid

The procedure was the same as the one described on p. 46 . A quantity of 0.748 g of the chlorides (XCIX-CII) was reacted with a mixture of 6 ml acetic acid, 0.3 ml acetic anhydride and 1.3 g silver acetate. The reaction product was distilled from a small glass bulb at 85-100° (air bath temperature) and 1 mm pressure to yield 0.600 g (71%), of a mixture of the acetates XCVb-XCVIIIb.

Anal. Calc. for $C_{11}H_{20}SO_2$: C, 61.07; H, 9.31; S, 14.82;

Saponification equivalent, 216.33

Found:

C, 61.17; H, 9.38; S, 15.02;

Saponification equivalent, 214.

The above product (XCVb-XCVIIIb), 0.5 g, was reacted with half a teaspoonful of Raney nickel catalyst in 5 ml of ethanol in the way described on p. 42 . The ethanolic solution of the methylcyclohexyl acetates was treated with potassium hydroxide in the manner described on p. 78 . The resulting ethanolic solution of methyl cyclohexanols was analyzed by vapour phase chromatography using a glycerol column as described above. The analysis indicated the following composition for the mixture: trans-2-methylcyclohexanol (LXXXIII), 2.5%; trans-3-methylcyclohexanol (LXXXIV), 49.5%; cis-3-methylcyclohexanol (LXXXV), 22%; cis-2-methylcyclohexanol (LXXXVI), 26%. These

experiments indicated that the product of the acetolysis of the chlorocompounds XCIX-CII was of the following composition:

1 α -ethylthio-2 β -acetoxy-3 α -methyleyclohexane (XCVb), 2.5%;
1 β -acetoxy-2 α -ethylthio-3 α -methyleyclohexane (XCVIb), 49.5%;
1 α -acetoxy-2 β -ethylthio-3 α -methyleyclohexane (XCVIIb), 22%;
1 β -ethylthio-2 α -acetoxy-3 α -methyleyclohexane (XCVIIIb), 26%.

Di-O-Methyl-1,2,3-Cyclohexanetriols

A mixture of 1.28 g (10 mm) of trans-3-methoxycyclohexene oxide (XLVI) and 20 ml of 0.5 N methanolic solution of sodium methoxide, protected from atmospheric moisture and carbon dioxide, was heated at 55° for five days. The reaction mixture was first treated with a few drops of water and then neutralized with solid carbon dioxide. The methanol was removed by evaporation under reduced pressure at room temperature. The residue was dissolved in 10 ml water and extracted four times with 20 ml portions of chloroform. After drying over magnesium sulfate, the chloroform was removed under reduced pressure at room temperature to give 1.064 g (66%) of material.

A 1.064 g sample of the above material was esterified with p-nitrobenzoyl chloride in pyridine to give 1.647 g (81%) of the ester. Crystallization of the ester from ethanol and two recrystallizations from the same solvent yielded 1.19 g of 1 α ,3 α -dimethoxy-2 β -p-nitrobenzoyloxy-

cyclohexane, m.p. 106-107°. The compound was identical (mixed m.p., infrared spectra) with the p-nitrobenzoate of an authentic sample of 1 α ,3 α -dimethoxy-2 β -cyclohexanol (70). The mother liquors from the crystallizations were combined and evaporated to dryness. The residue, 0.454 g, was chromatographed on Magnesol-Celite (5:1) containing Rhodamine 6G as an internal indicator. The preparation of the adsorbent and the chromatographic procedure followed were the same as described on p. 54. A column of 14.5 cm long, 3.5 cm in inside diameter packed with 50 g of the adsorbent, was used. The chromatogram was developed with 5% ether in petroleum ether (80-100°) into which progressively increasing amount of ethanol as follows: 0.05% ethanol in ether-petroleum ether, 1,400 ml; 0.1% ethanol in ether-petroleum ether, 4,000 ml; 0.15% ethanol in ether-petroleum ether, 2,000 ml. During the process of elution, the positions of the two bands on the column could be followed by their deep pink colour on a light pinkish background or by their deep blue colour under ultraviolet light. The following fractions were obtained:

Fraction 1. - 5,600 - 6,500 ml of eluate gave after evaporation to dryness 0.081 g of 2 α ,3 α -dimethoxy-1 β - p-nitrobenzoyloxycyclohexane as a non-crystallizable syrup.

Fraction 2. - Extraction of the column with 10% ethanol-

chloroform solution gave, after evaporation to dryness, 0.340 g of 1 α ,3 α -dimethoxy-2 β -p-nitrobenzoyloxycyclohexane, m.p. 105-107°.

This experiment indicated that the mixture of esters contained approximately 95% of the 1 α ,2 β ,3 α -compound and 5% of the 1 β ,2 α ,3 α -isomer. The N.M.R. spectrum of the 2 α ,3 α -dimethoxy-1 β -p-nitrobenzoyloxycyclohexane is shown in Fig. 1. The two signals at 234 and 238 c/s obviously arise from the axial and equatorial methoxy groups, respectively, and leave no doubt regarding the 1 β ,2 α ,3 α -configuration of the compound. Anal. Calc. for C₁₅H₁₉NO₆: C, 58.24; H, 6.19; Found: for the 1 α ,2 β ,3 α -compound, C, 58.24, H, 6.19

Kinetics of the Methanolysis of 3-Substituted Cyclohexene Oxides

The method used to determine the rates of methanolysis was the following. To a weighed sample of oxide (1 mM) contained in a 4 ml glass bulb was added 2 ml of a freshly prepared standard 0.5 N methanolic solution of sodium methoxide at room temperature. The container was then closed with a Neoprene cup and introduced into a constant temperature bath. The time of immersion of the container was taken as the zero time of reaction. At various times

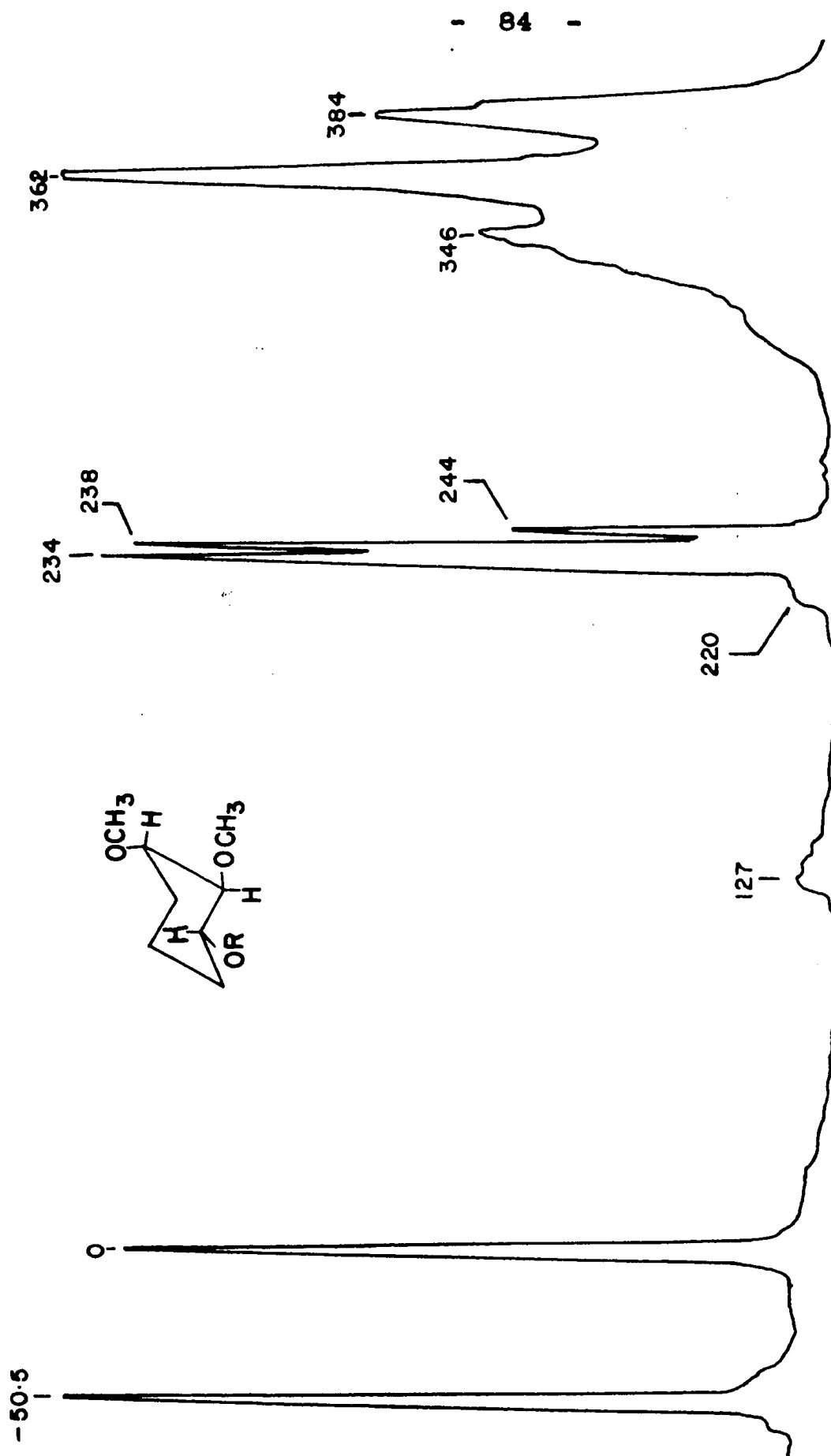


Fig. 1. - The nuclear magnetic resonance spectrum of 2α,3α-dimethoxy-1β-p-nitrobenzoyloxycyclohexane measured in carbon tetrachloride at room temperature. Chloroform was used as an external standard (reference signal).

thereafter, 100 ml samples were taken by means of an hypodermic microsyringe which was introduced through the neoprene seal. The reaction was immediately quenched by neutralization with glacial acetic acid using phenolphthalein indicator. The resulting solution was analyzed by vapour phase chromatography. A 6 ft., 6 mm internal diameter column, with silicon oil D.C.-200 as the stationary phase, (Perkin-Elmer column 154 0013-C) was used. The operating temperature was varied from 150° to 180° depending on the mixture being analyzed and the rate of gas flow was 60 ml of helium per minute. The retention volumes of the oxides studied and those of the products of the methanolyses are given in Table III, p. 61. Before each analysis, the accuracy of the operation of the instrument was established using a standard methanolic solution of cyclohexene oxide and trans-2-methoxycyclohexanol. The bands on the chromatogram corresponding to the reactants and products were identified and traced on paper of uniform weight. The tracings were cut out and weighed. In the foregoing discussion the weights of cut-outs for the oxides and the products are symbolized by W_o and W_p , respectively. The rate constants, given in Tables VI - XIII, were calculated as first-order rate constants, k , using the standard expression,

$$k = \frac{2.3}{t} \log \frac{a}{a-x} ,$$

TABLE VI

Methanolysis of Cyclohexene Oxide at 33.6°

The initial concentrations of the oxide and sodium methoxide, in pure methanol, were 0.5 and 0.53 moles per liter, respectively.

Time (min.)	$\frac{a}{a-x}$	$\log \frac{a}{a-x}$	$k \times 10^6$ (sec. ⁻¹)
<u>First run</u>			
375	1.302	0.1146	11.7
600	1.571	0.1962	12.5
810	1.788	0.2524	11.9
900	1.883	0.2748	11.7
1,380	2.556	0.4076	11.3
1,620	2.775	0.4433	10.4
1,920	3.272	0.5148	<u>10.3</u>
		Average	11.4
<u>Second run</u>			
240	1.190	0.0755	12.0
450	1.349	0.1300	11.1
1,085	2.075	0.3170	11.2
1,260	2.219	0.3462	10.5
1,500	2.566	0.4093	<u>10.4</u>
		Average	11.0
<u>Third run</u>			
300	1.212	0.0835	10.6
520	1.416	0.1511	11.1
720	1.584	0.1998	<u>10.6</u>
		Average	10.8

TABLE VII

Methanolysis of Cyclohexene Oxide at 54.5°

The initial concentrations of the oxide and sodium methoxide, in pure methanol, were 0.5 and 0.53 moles per liter, respectively.

Time (min.)	$\frac{a}{a-x}$	$\log \frac{a}{a-x}$	$k \times 10^6$ (sec. ⁻¹)
<u>First run</u>			
60	1.283	0.1082	69.1
90	1.519	0.1815	77.3
120	1.645	0.2162	69.0
180	2.055	0.3128	66.6
240	2.642	0.4219	67.3
		Average	68.0
<u>Second run</u>			
50	1.232	0.0906	69.4
100	1.501	0.1764	67.6
150	1.862	0.270	69.0
200	2.270	0.356	68.2
250	2.704	0.4320	66.5
		Average	68.1

TABLE VIII

Methanolysis of trans-3-Methylcyclohexene Oxide (LXXXI) at
33.6°

The initial concentrations of the oxide and sodium methoxide in pure methanol were 0.5 and 0.53 M per liter, respectively.

Time (min.)	$\frac{a}{a-x}$	$\log \frac{a}{a-x}$	$k \times 10^6$ (sec. ⁻¹)
<u>First run</u>			
1,385	1.073	0.0306	0.84
2,890	1.156	0.0630	0.84
5,785	1.329	0.1235	0.82
6,480	1.370	0.1367	0.81
7,800	1.458	0.1638	<u>0.81</u>
		Average	0.82
<u>Second run</u>			
1,515	1.079	0.0334	0.84
2,760	1.430	0.0580	0.80
4,270	1.215	0.0846	0.76
5,570	1,293	0.1116	<u>0.79</u>
		Average	0.80
<u>Third run</u>			
2,880	1.142	0.0577	0.77
4,320	1.233	0.0909	0.81
5,760	1,327	0.1229	0.81
7,200	1.411	0.1495	<u>0.79</u>
		Average	0.79

TABLE IX

Methanolysis of trans-3-Methylcyclohexene Oxide (LXXXI)
at 54.5°

The initial concentrations of oxide and sodium methoxide in pure methanol were 0.5 and 0.53 moles per liter, respectively.

Time (min.)	$\frac{a}{a-x}$	x (mol/lit.)	$\log \frac{a}{a-x}$	$k \times 10^6$ (sec. ⁻¹)
<u>First run</u>				
412	1.150	0.065	0.0607	5.65
1,325	1.589	0.185	0.2011	5.37
1,865	1.950	0.243	0.290	5.95
2,955	2.818	0.322	0.4499	5.83
			Average	5.70
<u>Second run</u>				
810	1.367	0.134	0.1357	5.73
1,620	1.789	0.220	0.2526	5.45
2,280	2.268	0.280	0.3556	5.97
4,325	4.465	0.388	0.6498	5.76
			Average	5.72

TABLE X

Methanolysis of the Mixture of trans and cis-3-Methylcyclohexene oxides (trans, 53%; cis, 47%) at 54.5°C

The initial concentrations of the oxide mixture and sodium methoxide were 0.991 and 0.53 moles per liter, respectively.

Time (min.)	$\frac{x}{a}$	$\frac{x}{a}$ (mol./lit.)
60	0.085	0.084
90	0.150	0.149
120	0.175	0.173
180	0.236	0.234
240	0.298	0.295
310	0.350	0.345
780	0.560	0.554
1,320	0.675	0.668
1,940	0.755	0.747

TABLE XI

Methanolysis of trans-3-Methoxycyclohexene Oxide (XLVI)
at 33.6°

The initial concentrations of the oxide and sodium methoxide were 0.5 and 0.53 moles per liter, respectively.

Time (min.)	$\frac{a}{a-x}$	$\log \frac{a}{a-x}$	$k \times 10^6$ (sec. ⁻¹)
<u>First run</u>			
1,445	1.078	0.0326	0.86
2,880	1.155	0.0626	0.83
4,320	1.217	0.0853	0.76
5,760	1.294	0.1119	0.74
7,200	1.390	0.1430	<u>0.76</u>
		Average	0.79
<u>Second run</u>			
2,396	1.122	0.050	0.80
2,760	1.179	0.0715	1.00
4,270	1.210	0.0828	0.74
5,560	1.288	0.1099	<u>0.75</u>
		Average	0.82

TABLE XII

Methanolysis of trans-3-Methoxycyclohexene Oxide (XLVI)
at 54.5°

The initial concentrations of the oxide and sodium methoxide were 0.5 and 0.53 moles per liter, respectively.

Time (min.)	$\frac{a}{a-x}$	$\log \frac{a}{a-x}$	$k \times 10^6$ (sec. ⁻¹)
407	1.166	0.0667	6.27
805	1.335	0.1255	5.97
1,320	1.550	0.1903	5.52
1,620	1.707	0.2322	5.49
1,860	1.811	0.2579	5.31
2,280	2.068	0.3155	5.30
2,950	2.537	0.4043	5.25
Average			5.58

TABLE XIII

Methanolysis of cis-3-Methoxycyclohexene Oxide (LXII) at
54.5°

The initial concentrations of the oxide and sodium methoxide were 0.5 and 0.53 moles per liter, respectively.

Time (min.)	$\frac{a}{a-x}$	$\log \frac{a}{a-x}$	$k \times 10^6$ (sec. ⁻¹)
60	1.296	0.1126	71.9
90	1.481	0.1705	72.6
120	1.700	0.2304	73.5
150	1.943	0.2885	73.6
180	2.223	0.3469	73.8
240	2.846	0.4542	72.5
Average			73.0

where t is the time in seconds, a is the initial concentration of the oxide in moles per liter, and $a-x$ is the concentration of the oxide after the reaction time t . The ratio $\frac{a}{a-x}$ was taken as related to the weights of the cut-outs using the following expression,

$$\frac{a}{a-x} = \frac{W_o + W_p}{W_o}.$$

cis-3-Methylcyclohexene oxide (LXXXII) was not available in a pure state for kinetic studies. The rate of methanolysis of this compound was determined through a study of the methanolysis of a mixture of cis- and trans-3-methylcyclohexene oxides (cis, 47%; trans, 53%). The chromatogram consisted of three bands; a single band for the two oxides, W_o , one band for the products of the methanolysis of the cis-oxide, W_{p_1} , and one band for the products of the reaction of the trans-oxide, W_{p_2} . It was evident, from the values of W_{p_1} and W_{p_2} that the cis-oxide was more reactive than the trans-oxide. The concentration of the products (x) at various times was determined using the relationship,

$$\frac{W_{p_1} + W_{p_2}}{W_{p_1} + W_{p_2} + W_o} = \frac{x}{a}.$$

where a is the initial concentration (moles/liter) of the mixture of oxides. Values of $\frac{x}{a}$ and x obtained in this way are given in Table X. A plot of the concentrations of the

products (x) against t for the above reaction is shown in Fig. 2, p. 96. In the same figure is shown a plot of concentrations of the products (x) against t for the methanolysis of pure trans-3-methylcyclohexene oxide (LXXXI). Substraction of the two plots gives a plot for the methanolysis of the cis-3-methylcyclohexene oxide (LXXXII). From this plot, the half-life of the reaction, $\tau = 228$ min., was determined. The rate constant, k, was calculated from the expression

$$k = \frac{2.3}{\tau} \log 2.$$

In the case of trans-3-methylcyclohexene oxide (LXXXI), the two products of the reaction, 1 α -methoxy-3 α -methyl-2 β -cyclohexanol (LXXXVIIa) and 2 α -methoxy-3 α -methyl-1 β -cyclohexanol, appeared on the chromatogram as well separated bands. The two bands were identified by comparison of their retention volumes with that of an authentic sample of LXXXVIIa (see p. 66). It was found that the above reaction at 54.5° gave the 1 α ,3 α ,2 β -compound (LXXXVIIa) in 75.5% and the 2 α ,3 α ,1 β -isomer in 24.5%. In all other cases the two products of the reaction appeared as a single band in the chromatogram.

The product of the methanolysis of trans-3-methoxycyclohexene oxide (XLVI) at 54.5° was analysed by adsorption chromatography (see pp. 81-83) and found to

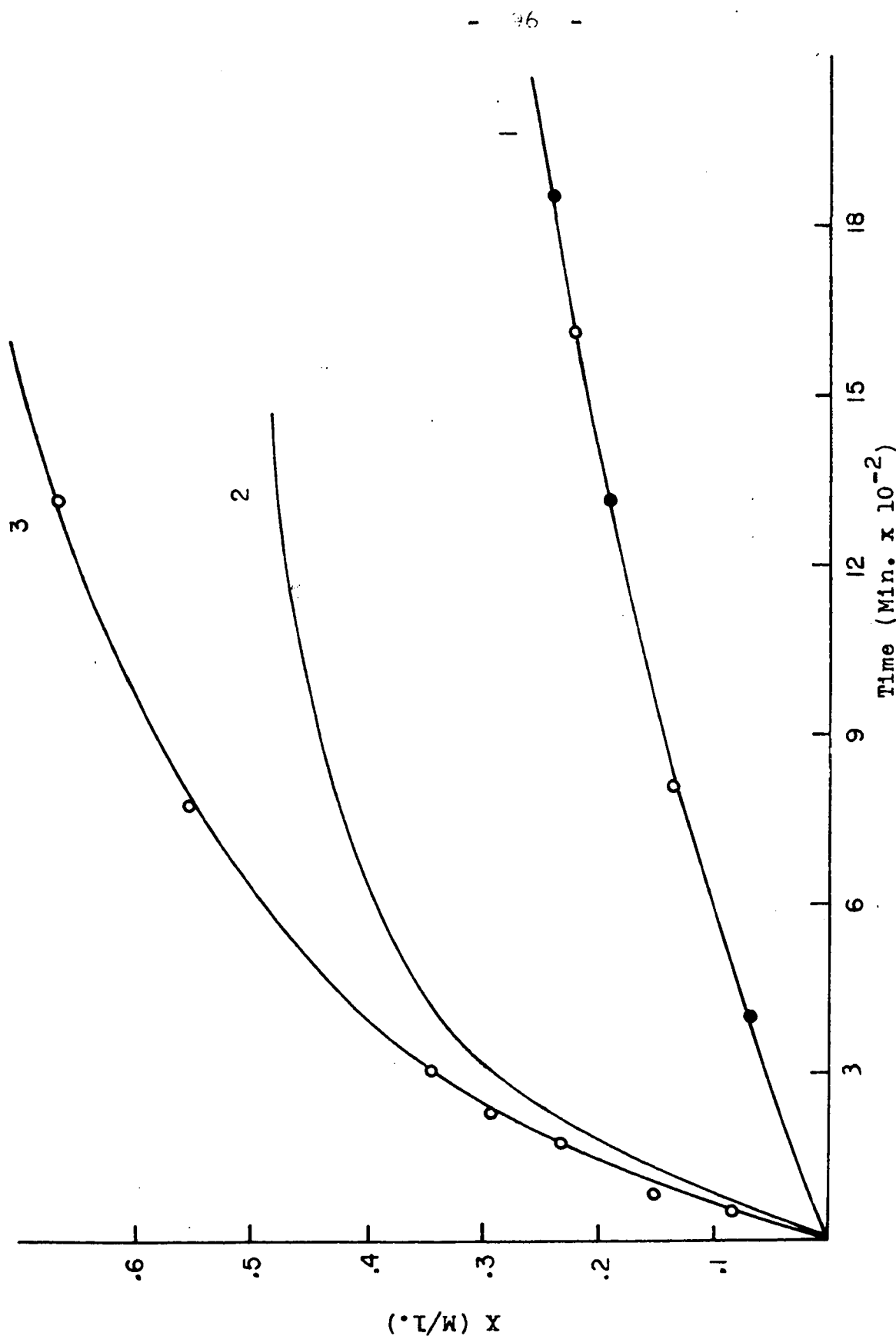


Fig. 2. - Plots of the concentrations of the products (X) of the methanolysis of 3-methylcyclohexene oxides at 54.5° against time. 1. Methanolysis of trans-3-methylcyclohexene oxide (LXXI). 3. Methanolysis of a mixture of the 3-methylcyclohexenes oxides (cis, 47%; trans, 53%). 2. The Methanolysis of cis-3-methylcyclohexene oxide as derived by subtraction of the plot 1 and 3.

consist of 95% 1 α ,3 α -dimethoxy-2 β -cyclohexanol and 5% of 2 α ,3 α -dimethoxy-1 β -cyclohexanol.

trans-1-Acetoxy-2-iodocyclohexane (CXVI)

This compound was prepared by way of reaction of cyclohexene with equimolar amounts of silver acetate and iodine in glacial acetic acid as described on p. 29.

The reaction mixture contained 150 ml glacial acetic acid, 16.7 g (100 mM) silver acetate, 25.4 g (100 mM) iodine and 8.2 g (100 mM) of cyclohexene. This mixture was stirred at room temperature for 10 min. The product of the reaction, isolated as described on p. 29, was distilled at 88-89° (1 mm) to give 10.7 g (40%) of trans-1-acetoxy-2-iodocyclohexane (CXVI).

Anal. Calc. for C₈H₁₅IO₂: I, 47.35

Found: I, 46.95

Kinetic Studies of the Acetolysis of trans-1-Acetoxy-2-iodocyclohexane (CXVI), 1 β -Acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII) and 1 α -Acetoxy-2 β -iodo-3 α -methoxycyclohexane (XLIII)

The procedure used for the determination of the rates of the acetolysis of the above compounds was the following. A sample of the iodoacetate, approximately 0.5 millimoles, was weighed accurately into a 10 ml volumetric

flask and dissolved in a 0.97% solution of potassium acetate in commercial glacial acetic acid. After making up to volume, 1 ml portions of this solution were transferred to glass vials (10 x 75 mm) and the tubes sealed. The vials were simultaneously submerged in a constant temperature bath. After an appropriate time interval, a vial was removed and chilled in ice-water mixture. The vial was opened and the contents were transferred quantitatively to a 50 ml glass stoppered conical flask with the aid of about 25 ml. of distilled water. It was found necessary to remove the coloured material from the aqueous solution by adding 10 ml of chloroform prior to analysis. After shaking, the potassium iodide in the mixture was determined, using Fajans method (p. 457 of reference 81) which involves standard silver nitrate solution (0.1 N) and eosin as indicator. The titrations were performed with a calibrated syringe-type microburette. The first-order rate constants, $k \text{ sec}^{-1}$, given in Tables XIV - XVIII, were calculated in the usual manner.

TABLE XIV

Acetolysis of trans-1-Acetoxy-2-iodocyclohexane (CXVI)
at 117.5°

The initial concentrations of the iodo-compound (CXVI) were 0.0536 and 0.0524 moles per liter for the first and second runs, respectively.

Time (min.)	x (mole/liter)	$\log \frac{a}{a-x}$	$k \times 10^7$ (sec. ⁻¹)
<u>First run</u>			
180	0.0253	0.2774	580
360	0.0280	0.3203	340
375	0.0324	0.4028	412
465	0.0362	0.4885	402
550	0.0400	0.5955	<u>414</u>
		Average	430
<u>Second run</u>			
58.3	0.0076	0.0678	445
121.7	0.0147	0.1427	449
181	0.0177	0.179	380
241	0.0205	0.2153	<u>342</u>
		Average	404

TABLE XV

Acetolysis of 1 β -Acetoxy-2 α -iodo-3 α -methoxycyclohexane
(XLII) at 117.5°

The initial concentration of the iodo-compound
(XLII) was 0.0511 mole per liter for both the runs.

Time (min.)	x (mole/liter)	$\log \frac{a}{a-x}$	$k \times 10^7$ (sec. ⁻¹)
<u>First run</u>			
1,260	0.0086	0.0799	24.2
1,515	0.0095	0.0892	22.5
2,880	0.0203	0.2198	29.5
2,955	0.0219	0.2425	31.4
5,460	0.035	0.5016	38.2
7,155	0.040	0.663	35.5
9,780	0.0457	0.979	<u>38.3</u>
		Average	31.4
<u>Second run</u>			
1,460	0.0111	0.1062	28.2
2,700	0.0176	0.183	25.8
3,600	0.0248	0.2882	30.6
6,000	0.0371	0.5635	<u>36.0</u>
		Average	30.1

TABLE XVI

Acetolysis of 1 α -Acetoxy-2 β -iodo-3 α -methoxycyclohexane
(XLIII) at 117.5°

The initial concentrations of the iodo-compound
(XLIII) were 0.0509 and 0.0510 mole per liter for the first
and second runs, respectively.

Time (min.)	x (mole/liter)	$\log \frac{a}{a-x}$	$k \times 10^7$ (sec. ⁻¹)
<u>First run</u>			
2,940	0.0056	0.0507	6.6
4,320	0.0100	0.0955	11.2
5,775	0.0132	0.1303	8.7
7,340	0.0163	0.1682	8.9
10,080	0.0225	0.2526	<u>9.6</u>
		Average	9.0
<u>Second run</u>			
5,670	0.0122	0.1186	8.0
8,660	0.0164	0.1689	7.5
11,640	0.0225	0.2534	8.3
14,410	0.0280	0.3450	9.2
20,920	0.0358	0.5265	<u>9.6</u>
		Average	8.5

TABLE XVII

Acetolysis of 1β -Acetoxy- 2^a -iodo- 3^a -methoxycyclohexane
(XLIII) at 98.5°

The initial concentration of the iodo-compound
(XLIII) was 0.0503 mole per liter.

Time (min.)	x (mole/liter)	$\log \frac{a}{a-x}$	$k \times 10^7$ (sec. ⁻¹)
7,190	0.0078	0.0733	3.91
10,080	0.0113	0.1102	4.18
14,400	0.0167	0.1749	<u>4.65</u>
Average			4.25

TABLE XVIII

Acetolysis of 1 α -Acetoxy-2 β -iodo-3 α -methoxycyclohexane
(XLIII) at 98.5°

The initial concentration of the iodo-compound
(XLIII) was 0.05106 mole per liter.

Time (min.)	x (mole/liter)	$\log \frac{a}{a-x}$	$k \times 10^7$ (sec. ⁻¹)
17,280	0.0035	0.0310	0.688
18,780	0.0031	0.0273	0.558
21,000	0.0048	0.0394	<u>0.720</u>
Average			0.65

DISCUSSION

The main purpose of this research was to gain information on the effect of a substituent at the 3-position of a 1,2-bridged cyclohexane derivative on the relative rates of attack at the 1- and 2-positions to bring about opening of a 1,2-bridge. This approach for a study of neighboring group effects was felt of interest since it would take advantage of the fact that the freedom of rotation in a six-membered ring is so restricted that it is possible to envisage with considerable confidence the conformations for the compound. That is, it should be possible to predict the location in space of the 3-substituent when either the 1- or the 2-position of the cyclohexane ring undergoes reaction. Thus, the results of such a study should be amenable to conformational analysis without undue speculation. It was particularly desired to acquire information on the effect of changing the polarity of the 3-substituent since considerable evidence has accumulated that the conformational analysis of reactions must take into consideration the relative orientations in space of the dipoles of polar bonds as well as the bulk of the groups involved (36,83). Obviously, the polar effects must be anticipated to be of prime importance amongst the factors which control the conformations and reaction properties of carbohydrate molecules. In order to gain information on these matters, it was decided to compare the reaction

properties of a number of derivatives of 3-methylcyclohexane with those of 3-methoxycyclohexane. The main problem confronting such a study was the lack of known compounds which have suitable structural features. It was therefore necessary to synthesize a rather large number (fifteen) of new compounds and to gain information as to their precise structures and configurations. The success encountered in this work was to a very large measure made possible by the powerful new tools of vapor phase chromatography and nuclear magnetic resonance spectroscopy.

The general plan of this discussion is to present first of all the syntheses with the arguments for the structures and configurations of the compounds obtained. After the identities of all the model compounds studied have been established, the results obtained which are related to their reaction properties will be discussed.

A. Derivatives of Methoxycyclohexane

The physical constants of the compounds reported in this section are collected in Table XIX, p. 106.

The system of nomenclature used to describe the trisubstituted cyclohexanes is that proposed by Lemieux and coworkers (70).

TABLE XIX

Physical Constants of Some 1,2,3-Trisubstituted Cyclohexanes

<u>Compound</u>	<u>M.p.</u>
1 α -Acetoxy-2 β -iodo-3 α -methoxycyclohexane (XLIII)	67 - 68.5°
1 β -Acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII)	40.5- 41.5°
1 α -Iodo-2 β -acetoxy-3 α -methoxycyclohexane (XLV)	58.5- 59.5°
1 α -Ethylthio-2 β -(3,5-dinitrobenzoyloxy)-3 α -methoxycyclohexane (LVc)	120 -121.5°
1 β -Acetoxy-2 α -ethylthio-3 α -methoxycyclohexane (LVib)	52.5- 53.5°
1 α -Methyl-2 β -p-nitrobenzoyloxy-3 α -methoxycyclohexane (LXXXVIIb)	101 -102°
1 β -p-Nitrobenzoyloxy-2 α -methyl-3 α -methoxycyclohexane (LXXXVIIIb)	68.5- 69.5°
3 α -Methyl-1 α ,2 β -cyclohexanediol (LXXXIXa)	46 - 47.5°
bis-p-Nitrobenzoate of LXXXIXa (LXXXIXb)	123.5-125.5°
3 α -Methyl-1 β ,2 α -cyclohexanediol (XCa)	94.5- 96°
bis-p-Nitrobenzoate of XCa (XCb)	164.5-166.5°
3 α -Methyl-1 β ,2 β -cyclohexanediol (XCia)	82.5- 83.5°
bis-p-Nitrobenzoate of XCia (XCib)	136 -138°
1 β -(3,5-Dinitrobenzoyloxy)-2 α -iodo-3 α -methylcyclohexane (LXXIX)	132 -134°
1 α -(3,5-Dinitrobenzoyloxy)-2 β -iodo-3 α -methylcyclohexane (LXXVII)	156 -158°
1 α -Iodo-2 β -(3,5-dinitrobenzoyloxy)-3 α -methylcyclohexane (LXXX)	188.5-189°
1 β -Iodo-2 α -(3,5-dinitrobenzoyloxy)-3 α -methylcyclohexane (LXXVIII)	134 -136°
<u>trans</u> -3-Methylcyclohexene oxide (LXXXI)	(B.p. 133 -134° (750 mm.); n _D ³¹ = 1.4445)

(1) 3-Methoxycyclohexene iodohydrins and related compounds

Reaction of 3-methoxycyclohexene (XXXIX) with equimolar amounts of iodine and silver acetate in dry acetic acid at room temperature (see p. 109) gave a mixture of 3-methoxy-1,2-iodoacetoxycyclohexanes in 90% yield. Crystallization of the mixture from 60% ethanol-water gave the isomer XLII, m.p. 40.5 - 41.5°, in 54% yield. Fractionation of the compounds in the mother liquor by adsorption chromatography on Magnesol-Celite (5:1) (68) gave the isomer XLIII, m.p. 67-68.5°, in 14% yield and a further 11% yield of XLII. Thus, the total yield of XLII was 65%.

The structures and configurations of the isomeric 3-methoxy-1,2-iodoacetoxycyclohexanes (XLII and XLIII) were established by nuclear magnetic resonance spectroscopy (N.M.R.) and by chemical means. The N.M.R. spectra of these compounds are given in Fig. 3, p. 108. In all of the foregoing interpretations of N.M.R. spectra, the chemical shifts between the coupled hydrogens being considered are large as compared to the coupling constant. Therefore it is possible (84) for the present purposes to interpret the spectra on the basis of simple, first order perturbation theory (85).

The signal at low field, 106 c/s, in the spectrum for the compound XLII, (spectrum A) can be assigned to the hydrogen on the carbon which is bonded to the acetoxy group. This type of hydrogen is well established to produce signals

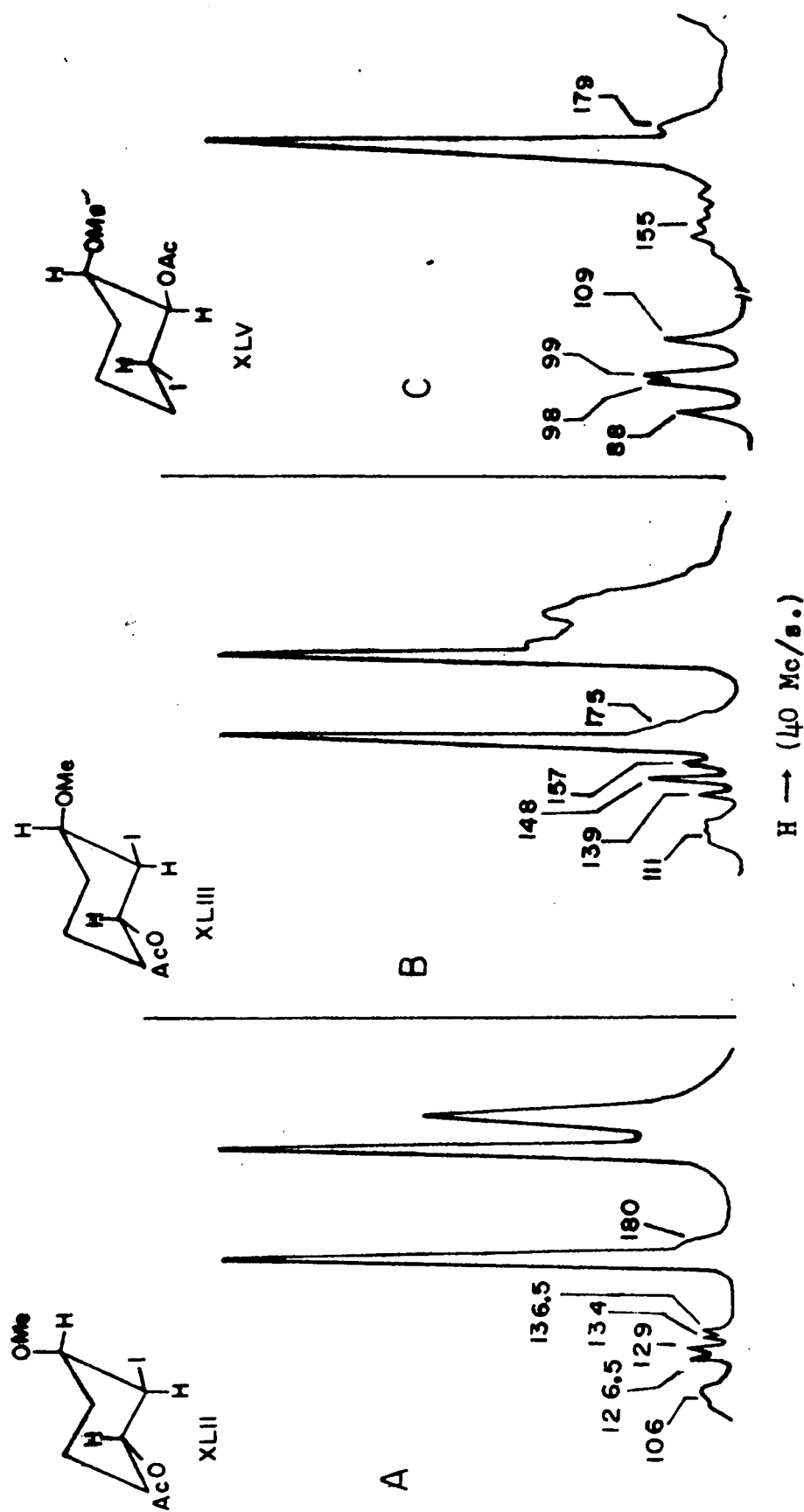
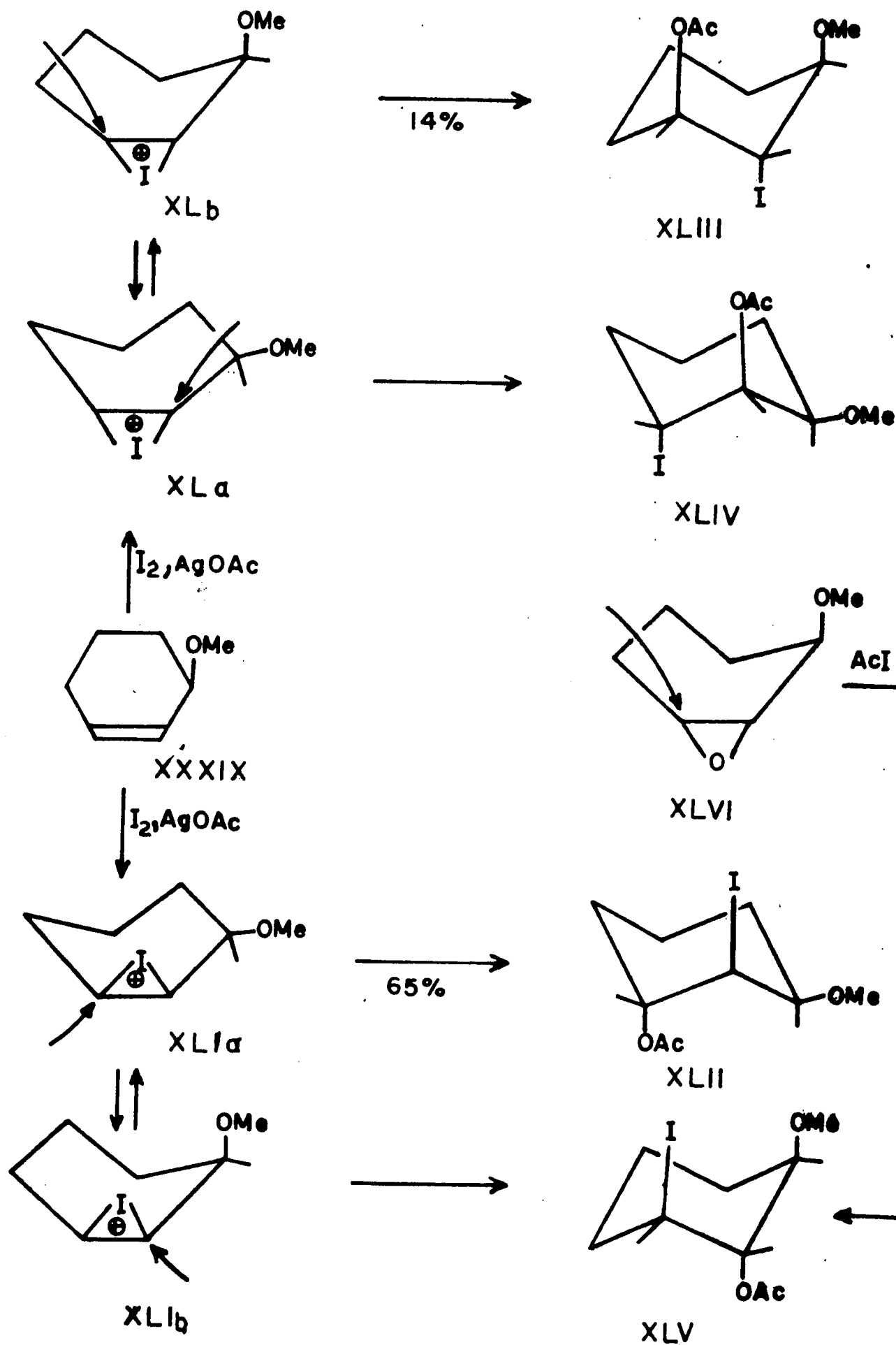


Fig. 3. - The nuclear magnetic resonance spectra of 3-methoxy-1,2-iodoacetoxybicyclohexanes, XLII, XLIII and XLV, measured in chloroform (reference signal) with the Varian spectrometer operating at 40 Mc/s. at room temperature.



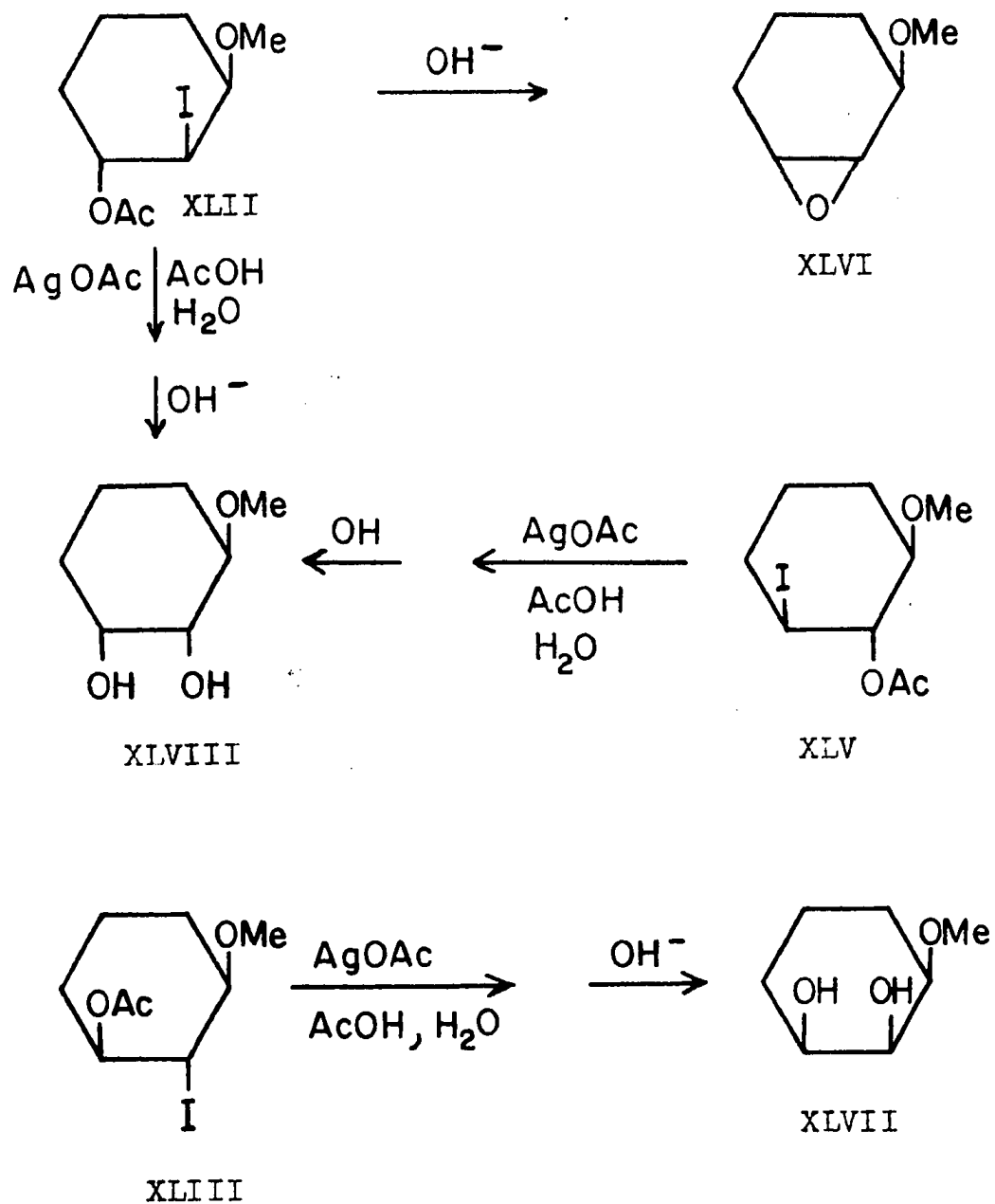
in this region from chloroform (internal standard) (86,87). The complexity of this signal is such that the hydrogen cannot be coupled only with two other hydrogens in the molecule (70,84). Therefore, the quartet at 126.5-136.5 c/s must arise from the 2-hydrogen and this hydrogen must be on the same carbon as the iodine atom. Thus, the compound is a 1-acetoxy-2-iodo-3-methoxycyclohexane. The structure of the signal for the 2-hydrogen allows an assignment of configuration since the observed coupling constants of 2.5 and 7.5 c/s require the 2-hydrogen to be in a gauche relationship with one of the neighboring hydrogens and trans to the other (70,86). The method by which XLII was synthesized requires the iodine atom and the acetoxy group to be in trans-relationship. Therefore, the iodine atom and the methoxy group must be in a cis-relationship and the compound XLII is 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane. This conclusion is supported in part by the fact that treatment of XLII with sodium hydroxide in aqueous ethanol at 0° gave the trans-3-methoxycyclohexene oxide (XLVI) in 88% yield (see page 113). The identity of the latter compound was established by comparisons of boiling points, refractive indices and retention volumes on vapour phase chromatography with an authentic sample. The oxide XLVI was synthesized by McRae and coworkers (72) and its configurations was established by Lemieux and coworkers (70). The configuration of the oxide obtained requires the iodoacetate XLII to have

the iodine atom and the methoxy group on the same side of the cyclohexane ring as was required by the N.M.R. spectrum.

The spectrum B in Fig. 3 is that for the 3-methoxy-1,2-iodoacetoxycyclohexane XLIII. The signal for the hydrogen on the carbon which is attached to the acetoxy group (111 c/s) is in the form of an unresolved multiplet and therefore must be the 1-hydrogen in the molecule. On this basis the compound must be a 1-acetoxy-2-iodo-3-methoxycyclohexane. This conclusion is confirmed by the triplet observed at 139-157 c/s for the signal of the 2-hydrogen in the region expected for a hydrogen on a carbon which is attached to an iodine atom. The spacing of this triplet indicates coupling constants of 9 c/s for the coupling of the 2-hydrogen with the vicinal hydrogens. These coupling constants require the 2-hydrogen to be in axial orientation and to be coupled with two neighboring axial hydrogens. Therefore the compound must be 1 α -acetoxy-2 β -iodo-3 α -methoxycyclohexane. This assignment of configuration was partially confirmed by the observation that compound XLIII on solvolysis in moist acetic acid and in the presence of silver acetate (see p. 113) gave after hydrolysis the glycol XLVII which was identical (infrared spectra and paper chromatography) with an authentic sample of 3 α -methoxy-1 α ,2 α -cyclohexanediol. The configuration of the glycol XLVII requires the iodoacetate XLIII to have the acetoxy group and the methoxy group in a cis-relationship.

The formation of the 3-methoxy-1,2-iodoacetoxycyclohexanes (XLII and XLIII) from the reaction of 3-methoxycyclohexene (XXXIX) with equimolar amounts of silver acetate and iodine is well understood in view of the mechanism of the reaction. Many years ago, the reaction of the silver salts of carboxylic acids and iodine (88) in ether or benzene was shown by Simonini (89) to give an active complex intermediate, $(R\text{COO})_2\text{AgI}$, which could be isolated. Birckenbach (90) later established that reaction of equimolar amounts of silver acetate and iodine in ether at -80° yielded a filtrate which added IOAc to cyclohexene to give the acetate of trans-2-iodo-cyclohexanol. Carlsohn (91) established that the positive part of the substances IOCOR is the iodine. In the presence of an alkene, the positive iodine of the substance IOAc attacks the double bond and forms an intermediate iodonium ion (92) which then opens through an attack by acetate ion to give the trans-iodoacetate. With regard to the present preparation (see p.109) the attack of I^+ on the 3-methoxycyclohexene (XXXIX) would yield the intermediates $\text{XLa} \rightleftharpoons \text{XLb}$ and $\text{XLIIa} \rightleftharpoons \text{XLIIb}$ which would then be opened through attack by the acetate ion to form compounds XLII - XLV depending on which of the 1- and 2-positions is attacked.

A third isomeric 3-methoxy-1,2-iodoacetoxycyclohexane, XLV, m.p. $58.5-59.5^\circ$, was prepared by the reaction

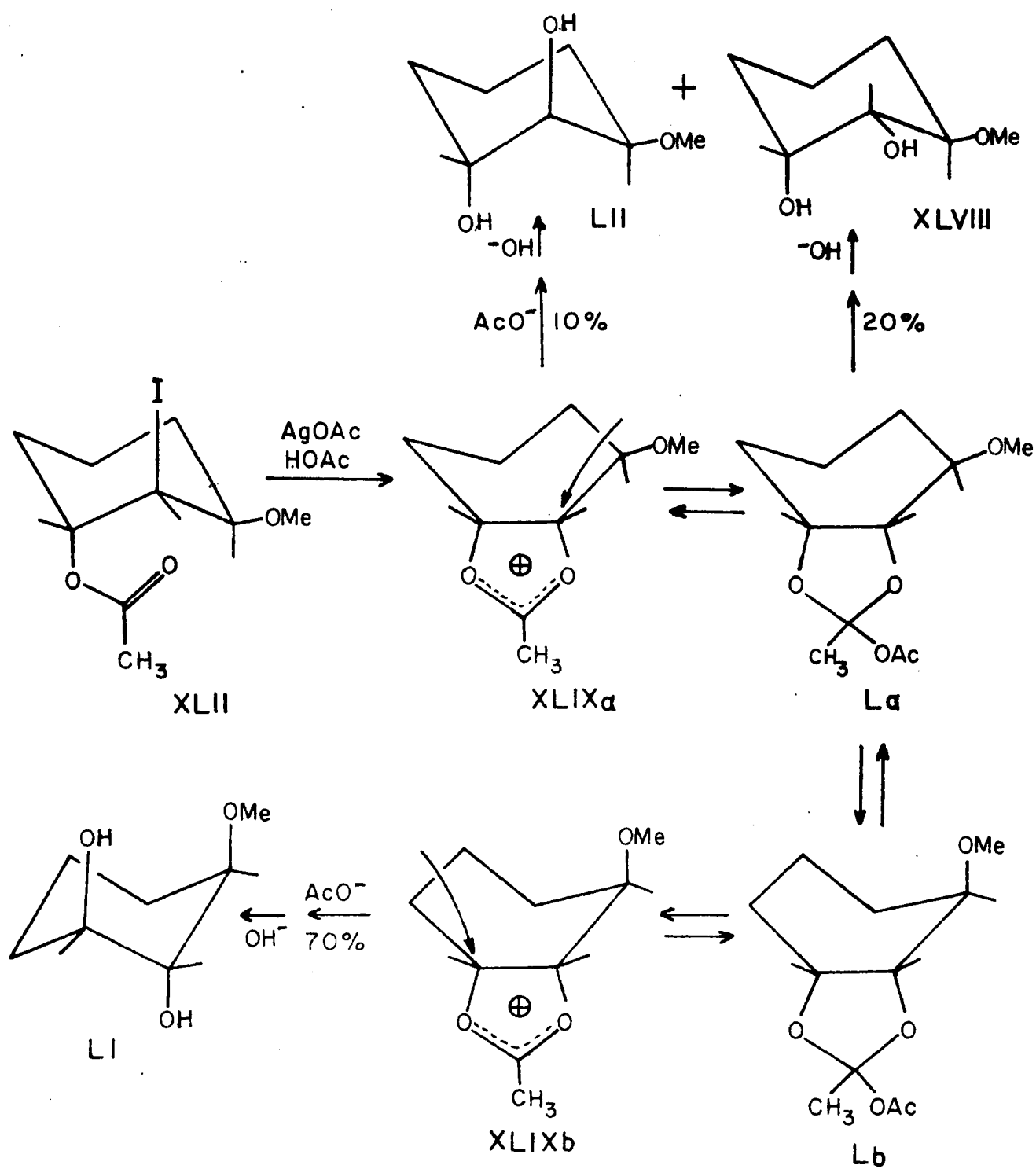


of trans-3-methoxycyclohexene oxide (XLVI) with acetyl iodide in benzene at room temperature (see p. 109). The structure and configuration of XLV was also established by N.M.R. spectroscopy. The spectrum for this compound is given in Fig. 3-c. The signal for the hydrogen on the carbon bonded to the iodine atom (155 c/s) is in the form of an unresolved multiplet. This fact indicates that this hydrogen is the 1-hydrogen in the molecule. The signal for the hydrogen on the carbon bonded to the acetoxy group (88-109 c/s) is in the form of a quartet resulting from coupling with the 1- and 3-hydrogens. The spacing of the lines in the quartet requires coupling constants of 10 and 11 c/s. Therefore, the compound must have the 1-, 2- and 3-hydrogens all in axial orientation and must be 1 α -iodo-2 β -acetoxy-3 α -methoxycyclohexane. The product of the solvolysis of XLV (see p. 113) supports this assignment of configuration. Treatment of XLV with moist acetic acid in the presence of silver acetate gave, after hydrolysis, a glycol (XLVIII) which was identical (infrared spectra and paper chromatography) with an authentic sample of 3 α -methoxy-1 β ,2 β -cyclohexanediol. The configuration of the glycol XLVIII requires the acetoxy- and the methoxy groups in XLV to be in a trans-relationship.

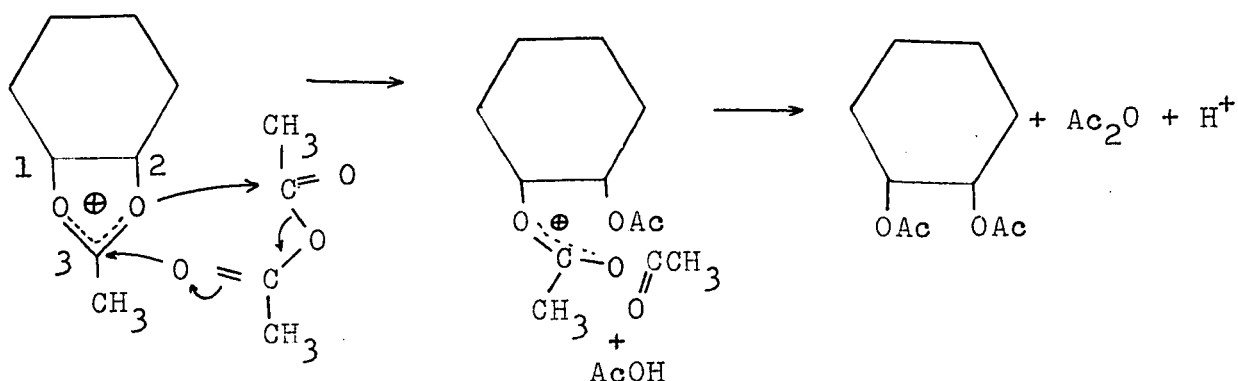
(2) 3-Methoxy-1,2-cyclohexanediols and related compounds

Solvolysis of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII) in dry acetic acid in the presence of acetic

anhydride and silver acetate at 90-95° gave after hydrolysis a mixture of 3-methoxy-1,2-cyclohexenediols in 60% yield (see p.116). The mixture was analyzed by paper chromatography using the methylethylketone-xylene-water (1:1:1) system and the ammoniacal silver nitrate spray described by Lemieux and coworkers (70). The chromatogram showed the presence of 3 α -methoxy-1 α ,2 β -cyclohexanediol (LI), 3 α -methoxy-1 β ,2 α -cyclohexanediol (LII) and 3 α -methoxy-1 β ,2 β -cyclohexanediol (XLVIII) identified by comparison of their R_f -values with those of authentic samples obtained from Lemieux and coworkers (70). A quantitative estimation of the glycols in the mixture was made by partition chromatography on Celite (71) using the same solvent system as that used for the paper chromatograms. The mixture was thus found to contain 70% of LI, 10% of LII and 20% of XLVIII. The acetolysis of XLII would be expected to involve first the formation of the acetoxonium ion (XLIXa $\rightleftharpoons$ XLIXb). The 1- and 2-positions would then compete for nucleophilic attack by the acetic acid. Attack at the 1- and 2-positions would yield the diacetates of the glycols LI and LII, respectively. The above results show that the reaction at the 1- takes place more readily than at the 2-position. The presence of the glycol XLVIII in the reaction product was unexpected since the reaction was carried out under strictly anhydrous conditions and in the presence of acetic anhydride.



However, Winstein (42) and also Kullnig (93) have observed similar anomalies. For example, Kullnig has found that the solvolysis of 1 -tosyloxy-2 -acetoxy-3 ethoxycyclohexane in dry acetic acid and in the presence of acetic anhydride and potassium acetate gave the acetates of the three glycols LI, LII and XLVIII and the solvolysis of trans-2-acetoxycyclohexyl tosylate under the same conditions gave the diacetates of cis- and trans-1,2-cyclohexanediols, with the trans-isomer as the major product of the reaction. Kullnig rationalised the formation of the cis-glycol XLVIII on the basis of an opening of the acetoxonium ion ring through coordination of the ion with acetic anhydride as formulated below.



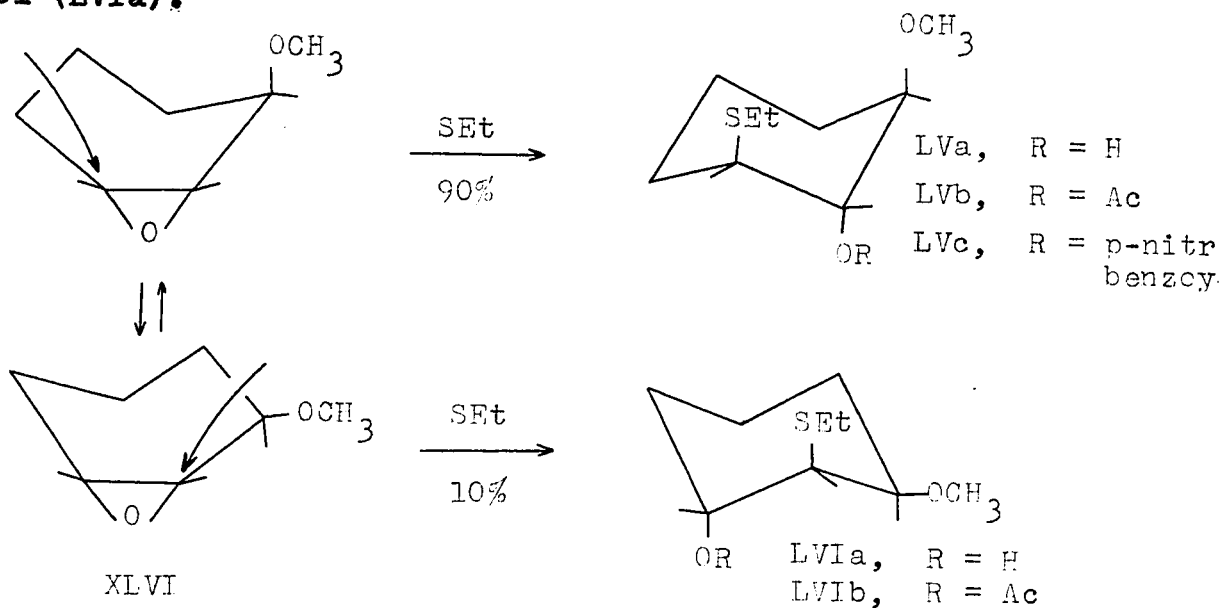
Thus, this route of reaction does not appear to require strong acid catalysis as suggested by Winstein (see introduction p. 19).

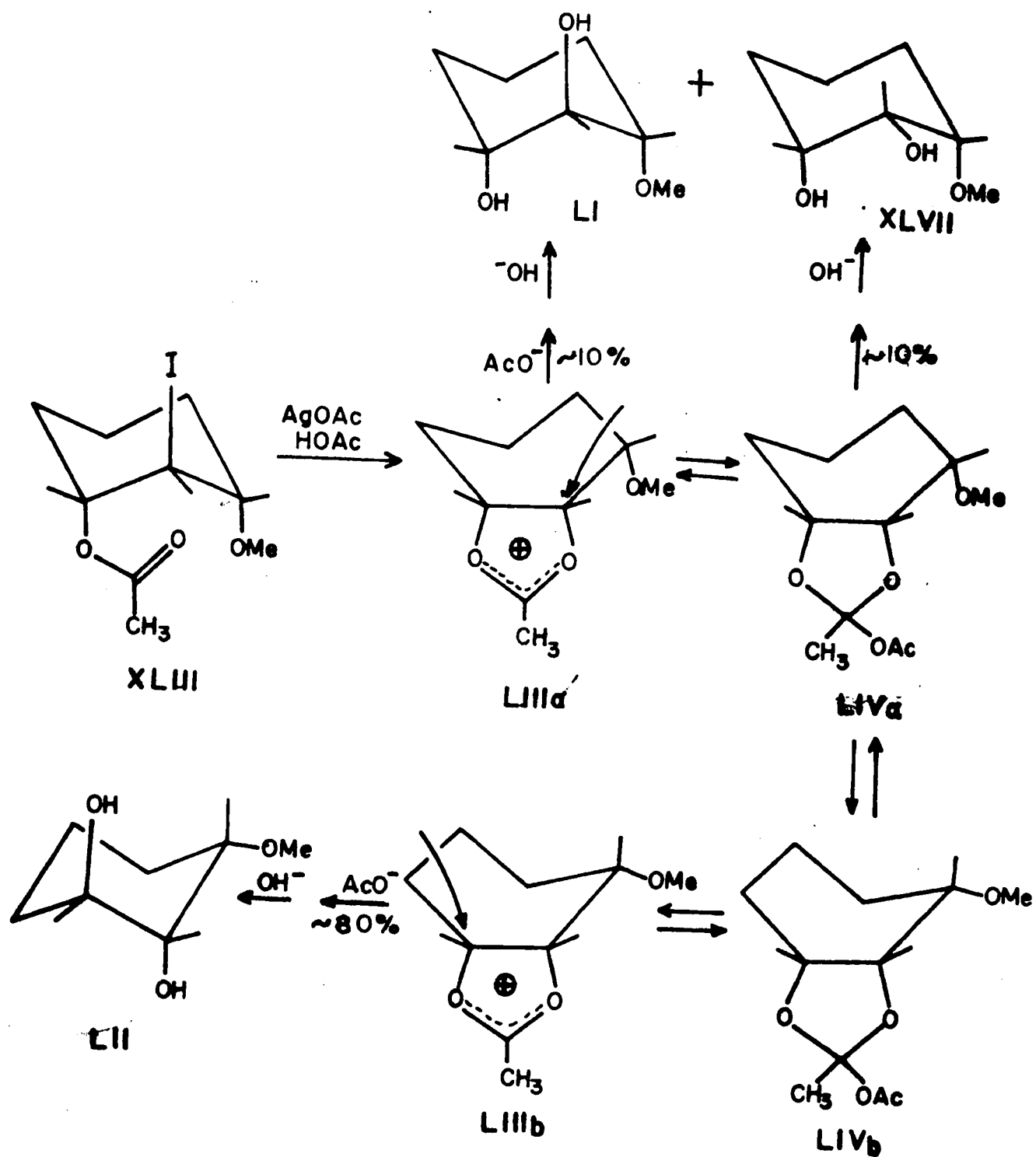
The solvolysis of 1 α -acetoxy-2 β -iodo-3 α -methoxy

cyclohexane (XLIII) in dry acetic acid in the presence of acetic anhydride and silver acetate at 90-95° (see p. 119) also provided after alkaline hydrolysis a cis-glycol (XLVII) as well as the two trans-glycols LI and LII. The presence of these glycols in the product was demonstrated by paper chromatography. The trans-glycol LII was definitely the major product (about 80%) of reaction as gauged by the intensity of the spots on the sprayed chromatogram. Therefore it can be concluded that the intermediate acetoxonium ion (LIIa $\rightleftharpoons$ LIIb) opens preferentially by attack at the 1-position.

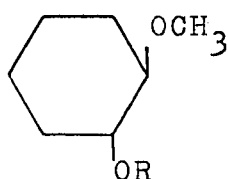
(3) 3-Methoxycyclohexene ethylthiohydrins and related compounds

Reaction of the trans-3-methoxycyclohexene oxide (XLVI) with sodium thioethoxide in methanol at 0° gave a 92% yield of a mixture of 1 α -ethylthio-3 α -methoxy-2 β -cyclohexanol (LVa) and 2 α -ethylthio-3 α -methoxy-1 β -cyclohexanol (LVia).



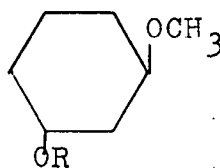


The mixture of thioethers, LVa and LVia, could not be analysed by vapour phase chromatography. The compounds were therefore acetylated and reductively desulfurized to the 1,2- and 1,3-methoxycyclohexyl acetates (LVIIb and LVIIIb) prior to analysis by vapour phase chromatography on a dioctyl



LVIIa, R = H

LVIIb, R = Ac



LVIIIa, R = H

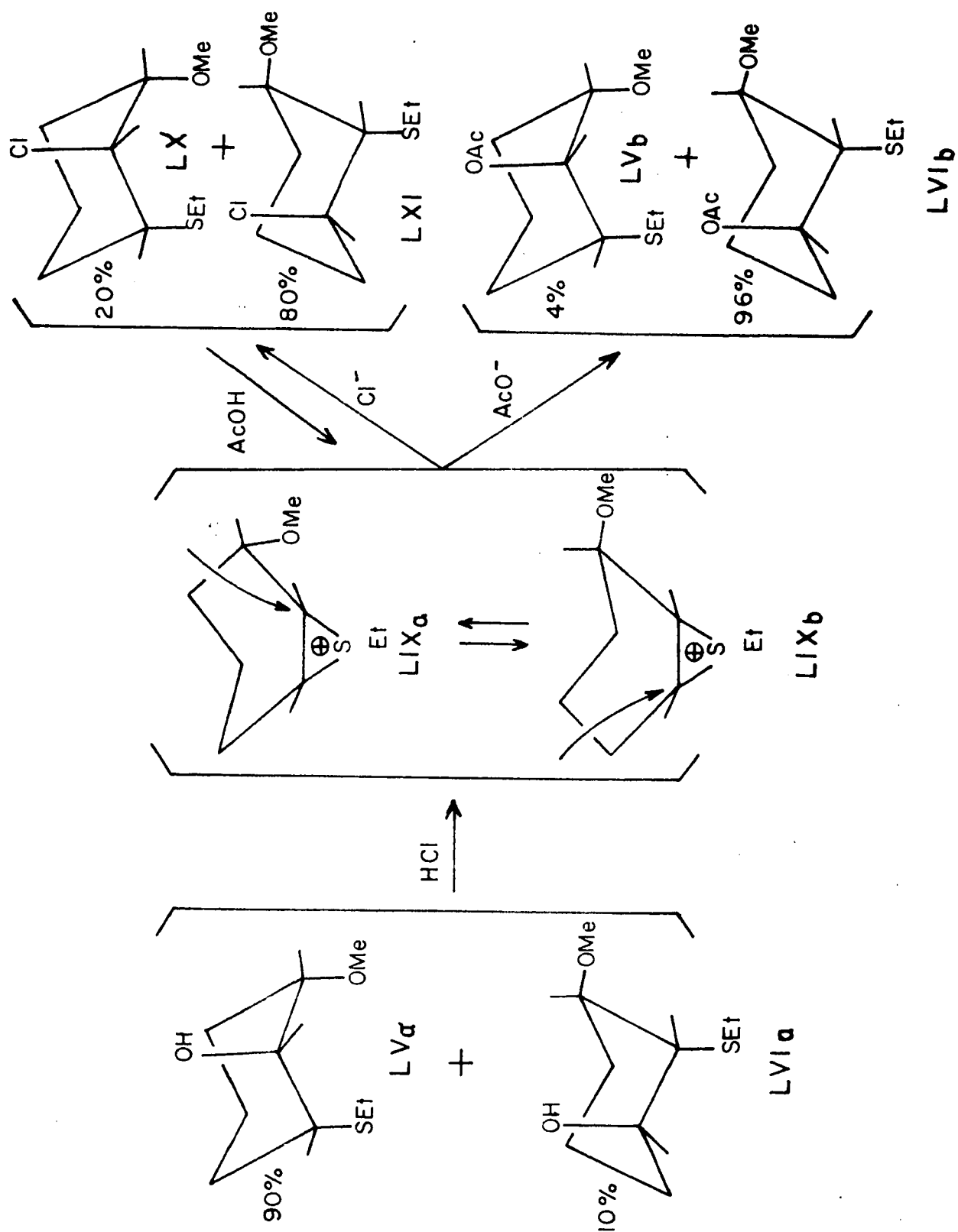
LVIIIb, R = Ac

phthalate column. The mixture was thus found to contain 90% of LVIIb and 10% of LVIIIb. The same result was obtained in other experiments where the methoxycyclohexyl acetates LVIIb and LVIIIb were hydrolysed to methoxycyclohexanols LVIIa and LVIIIa and the mixture of alcohols was analysed by vapour phase chromatography on a glycerol column. Therefore, it can be concluded that the product of reaction of trans-3-methoxycyclohexene oxide (XLVI) with sodium thioethoxide contained about 90% of 1 α -ethylthio-3 α -methoxy-2 β -cyclohexanol (LVa) and about 10% of 2 α -ethylthio-3 α -methoxy-1 β -cyclohexanol (LVia).

A sample of the mixture of the thioethers (LVa and LVia) was esterified with 3,5-dinitrobenzoyl chloride in pyridine. Crystallization of the product from ethanol gave

1 α -ethylthio-2 β (3,5-dinitrobenzoyloxy)-3 α -methoxycyclohexane (LVc), m.p. 120-121.5 $^{\circ}$, in 62% yield. Alkaline hydrolysis of LVc gave the compound LVa which on acetylation gave the acetate LVb. The structure of the latter compound was established unequivocally through its transformation to trans-2-methoxycyclohexanol by the reductive desulfurization procedure. The N.M.R. spectrum of the acetate LVb is shown in Fig. 4a, p. 123. The spectrum as would be expected, is in complete agreement with the structure assigned for the compound. The band in the region 148.5-167.5 c/s can be assigned to the signal of the hydrogen atom on the carbon atom bonded to the acetoxy group. This signal is in the form of a quartet with the two central lines very close together. The spacing of this quartet indicates coupling constants of 9 and 10 c/s. These facts require that the hydrogen be in axial orientation and coupled with two other neighboring axial hydrogen atoms.

Reaction of the mixture of the thioethers (LVa and LVia) with concentrated hydrochloric acid at 95 $^{\circ}$ for 15 minutes gave a 90% yield of a mixture of 1 α -ethylthio-2 β -chloro-3 α -methoxycyclohexane (LX) (20%) and 1 β -chloro-2 α -ethylthio-3 α -methoxycyclohexane (LXI) (80%) (see p. 122). The composition of the mixture was estimated by a comparison of the intensities of signals for the methoxy groups in the N.M.R. spectrum of the mixture. The mechanism for the



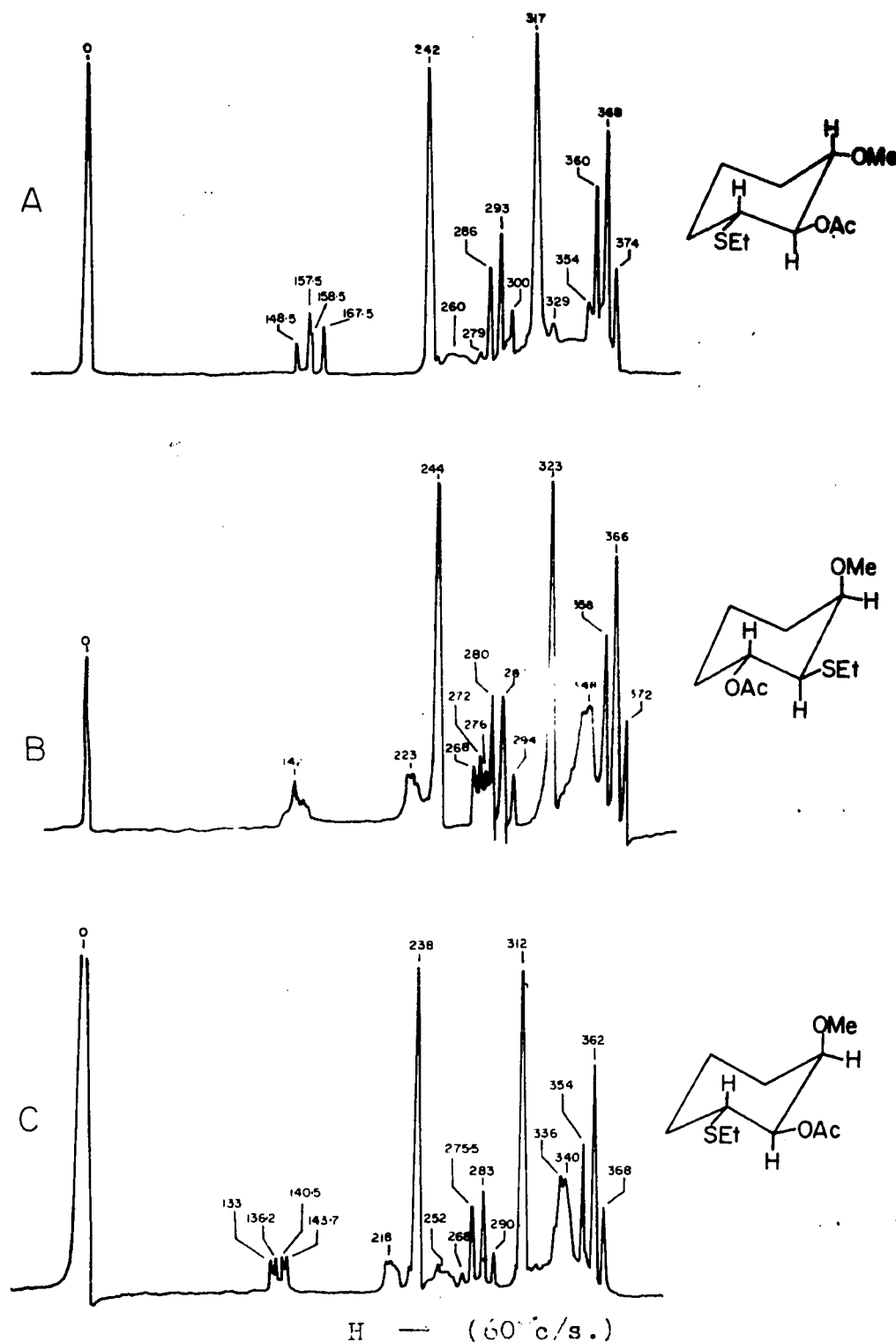


Fig. 4. - The nuclear magnetic resonance spectra of the 3-methoxy-1,2-acetoxy-ethylthiocyclohexanes LVb, LVib and LXVb, measured in carbon tetrachloride at room temperature. Chloroform was used as an external standard.

formation of the chlorocompounds LX and LXI in the above reaction is well understood. The displacement of the hydroxy group proceeds with participation of the ethylthiogroup to form the sulfonium cation ($\text{LIXa} \rightleftharpoons \text{LIXb}$) which then reacts with chloride ion at the 1- and 2-positions. The results show that the opening of the sulfonium ion by chloride ion took place at the 1-position preferentially.

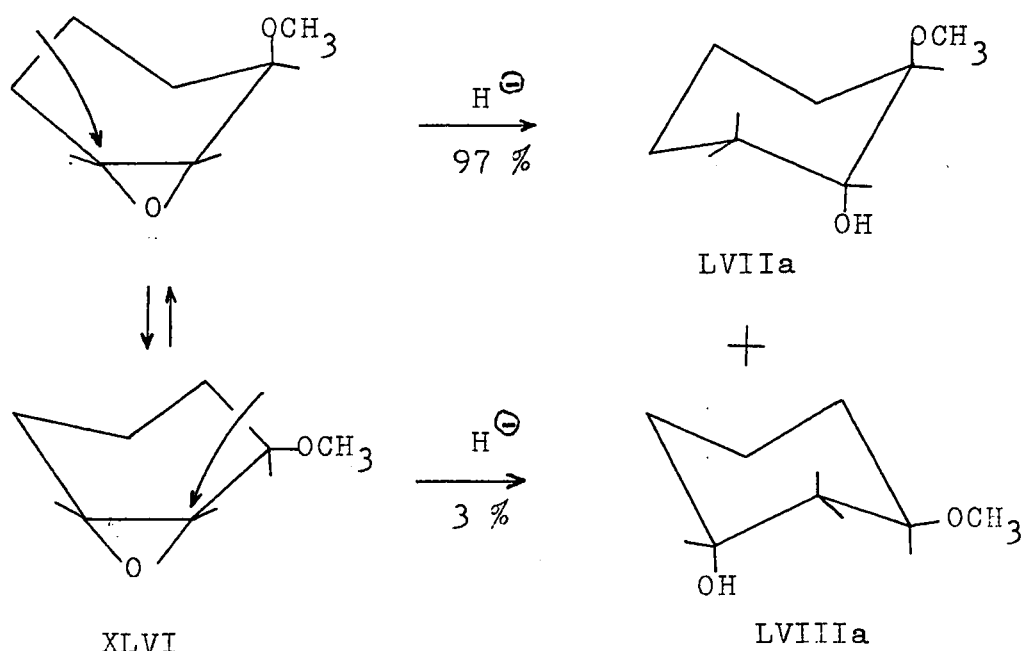
Solvolysis of the mixture of the chlorides (LX and LXI) in dry acetic acid containing silver acetate at 50-60° gave a mixture of 1 α -ethylthio-2 β -acetoxy-3 α -methoxycyclohexane (LVb) and 1 β -acetoxy-2 α -ethylthio-3 α -methoxycyclohexane (LVib) in 84% yield (see p. 122). The procedure of reductive desulfurization and vapor phase chromatography was used to analyze the mixture. The results showed the mixture to contain 4% of LVb and 96% of LVib. Therefore, the sulfonium ion intermediate showed a high degree of preference for reaction at the 1-position over the 2-position.

A sample of the mixture of acetates (LVb and LVib) was crystallized from ethanol to afford (LVib), m.p. 52.5-53.5°, in 78% yield. The fact that the solvolysis of the chlorides (LX and LXI) could yield only two isomers and the configuration of one of them, LVb, was established requires that the second isomer, LVib, to be 1 β -acetoxy-2 α -ethylthio-3 α -methoxycyclohexane. This conclusion was confirmed by reductive desulfurization and hydrolysis to produce trans-

3-methoxycyclohexanol (LVIIIIa). The identity of the latter compound was established by vapour phase chromatographic comparison with an authentic sample of trans-3-methoxycyclohexanol which was obtained by lithium aluminum hydride reduction of trans-3-methoxycyclohexene oxide (XLVI). The N.M.R. spectrum of LVIIb confirmed its identity. The spectrum (Fig. 4B) shows an unresolved multiplet in the region of 142 c/s which can be assigned to the hydrogen on the carbon bonded to the acetoxy group. This observation suggests that the acetoxy group is at the 1-position. The band in the region 268-280 c/s can be assigned to the signal for the hydrogen on the carbon bonded to ethylthio group. This band is in the form of a quartet with the line at highest field (280 c/s) undoubtedly overlapped by part of the signal from the methylene group of the ethylthio group (compare with the spectrum A for LVb). The structure of this signal indicates that the coupling constants for its interaction with the neighboring hydrogens are 4 c/s and 8 c/s, respectively. Thus, the hydrogen must be axial and coupled with one axial and one equatorial hydrogen as required by the structure (LVIIb) assigned to the compound.

As was seen above, trans-3-methoxycyclohexene oxide (XLVI) was reduced with lithium aluminum hydride to afford a mixture of the 1,2- and 1,3-trans-methoxycyclohexanols (LVIIa and LVIIIIa). The reaction product was

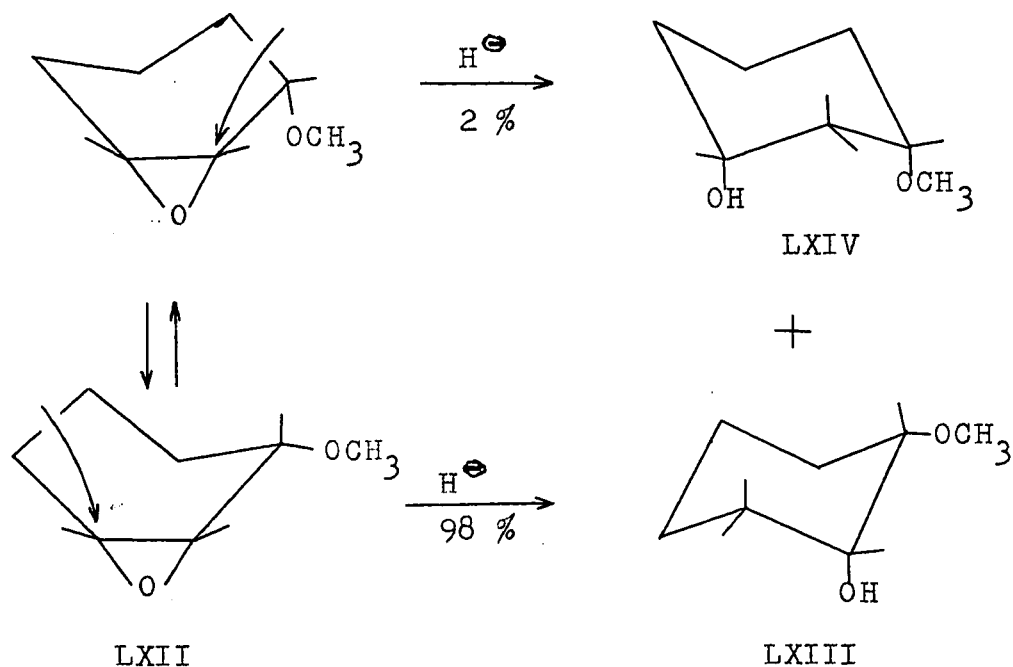
analyzed by vapour phase chromatography using a glycerol



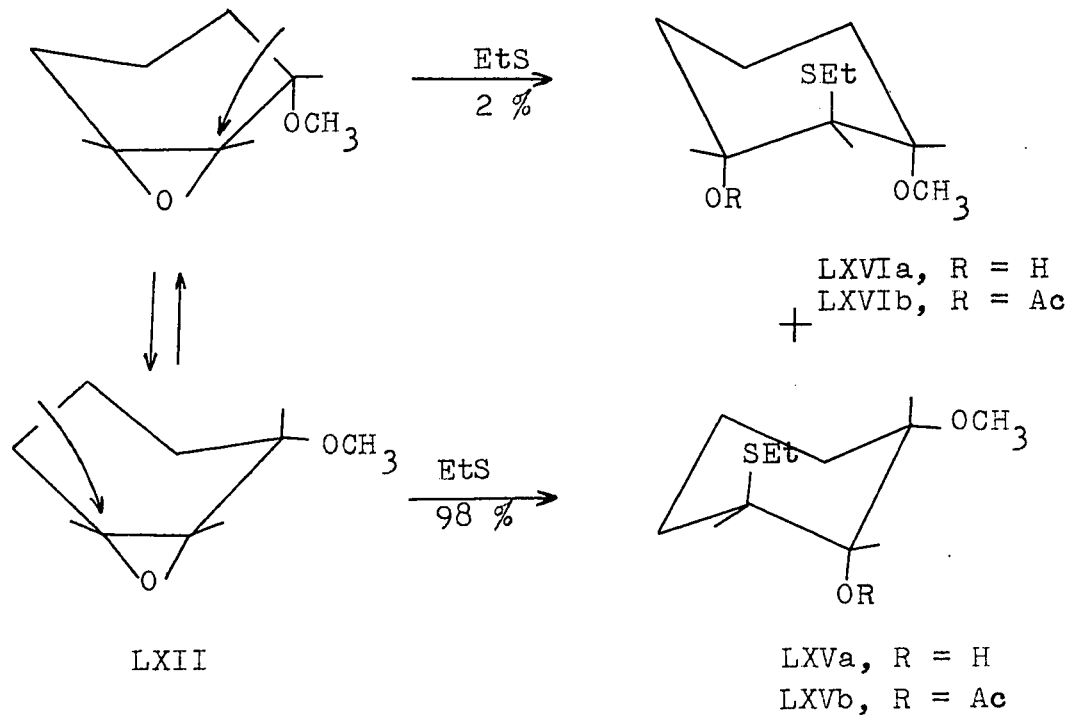
column and found to contain 97% and 3% of the 1,2- and 1,3-isomers, respectively. The zones in the chromatogram were identified by comparison of their retention volumes with that of an authentic sample of trans-2-methoxycyclohexanol prepared by methanolysis of cyclohexene oxide.

Reduction of the cis-3-methoxycyclohexene oxide (LXII) with lithium aluminum hydride gave a mixture of cis-2-methoxycyclohexanol (LXIII) and cis-3-methoxycyclohexanol (XLIV). The mixture was found to contain 98% of the 1,2-isomer (LXIII) and 2% of the 1,3-isomer (XLIV) by vapour phase chromatography on a glycerol column. The identities of these isomers could be deduced from the results of the

foregoing experiments related to the mercaptolysis of cis-3-methoxycyclohexene oxide.



Reaction of the cis-3-methoxycyclohexene oxide (LXII) with sodium thioethoxide in methanol at 0° gave a

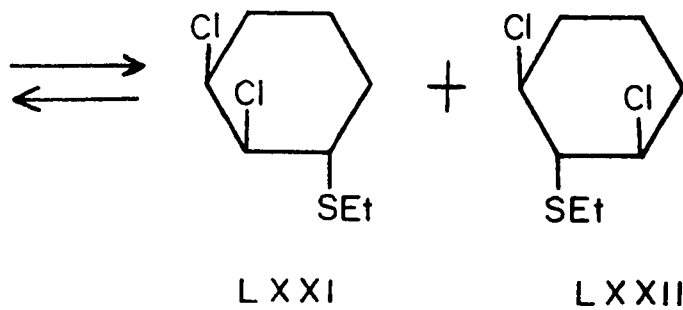
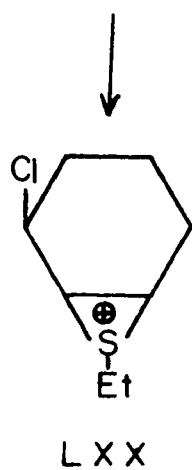
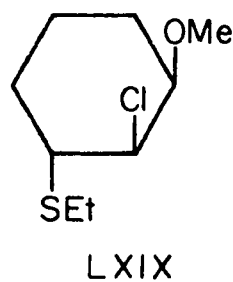
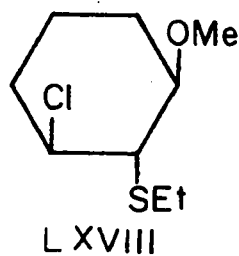
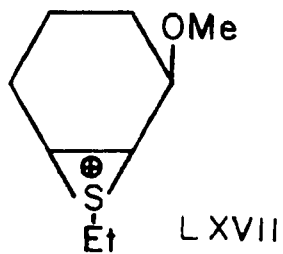
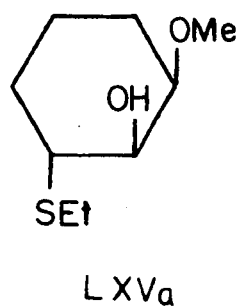
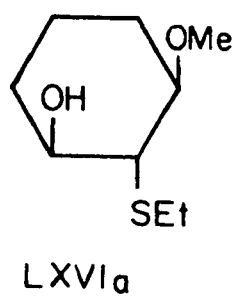


90% yield of a mixture of 1β -ethylthio- 3α -methoxy- 2α -cyclohexanol (LXVa) and 2β -ethylthio- 3α -methoxy- 1α -cyclohexanol (LXVIa). Acetylation of the mixture with acetic anhydride in the presence of anhydrous sodium acetate yielded a mixture of acetates LXVb and LXVIb. The N.M.R. spectrum of the mixture of the acetates LXVb and LXVIb (Fig. 4-C, p. 123) indicated that this product contained almost exclusively one of the isomeric compounds. The signal for the hydrogen on the carbon attached to the acetoxy groups (133-143.7 c/s) is in the form of a quartet. Therefore, this hydrogen is the 2-hydrogen in the molecule and the compound must be 1-ethylthio-2-acetoxy-3-methoxycyclohexane. The spacing of the lines in the quartet requires coupling constants of 3.2 and 7.5 c/s for the coupling of the 2-hydrogen with the 1- and 3-hydrogen. Consequently, this hydrogen must be in axial orientation and coupled with one axial and one equatorial neighboring hydrogens and the compound must be 1β -ethylthio- 2α -acetoxy- 3α -methoxycyclohexane (LXVb). A quantitative estimation of the acetates LXVb and LXVIb in the mixture, was achieved by the reductive desulfurization procedure described before followed by hydrolysis to produce cis-2-methoxycyclohexanol (LXIII) and cis-3-methoxycyclohexanol (LXIV). The mixture (LXIII and LXIV) was then analyzed by vapour phase chromatography using a glycerol column and found to contain 98% of

LXIII and 2% of LXIV. These results indicated that the product of the reaction of cis-3-methoxycyclohexene oxide with sodium thioethoxide contained approximately 98% of 1 β -ethylthio-3 α -methoxy-2 α -cyclohexanol (LXVa) and 2% of 2 β -ethylthio-3 α -methoxy-1 α -cyclohexanol (LXVIa).

Reaction of the mixture of thioethers (LXVa and LXVIa) with concentrated hydrochloric acid at 95° for one hour gave a chlorocompound which contained two chlorine atoms. The formation of a dichlorocompound was indicative that both the hydroxy and the methoxy groups in the thioethers LXVa and LXVIa were displaced by chlorine during the reaction process. The displacement of these groups could be rationalized on the basis of ethylthio groups participation as formulated on p. 130.

Although the structures and configurations of the dichlorocompounds were not established it is assumed, on the basis of mechanistic considerations, that the main product is 2 β -ethylthio-1 α ,3 α -dichlorocyclohexane (LXXII). That is, displacement of the hydroxy group would be expected to proceed via the sulfonium cation LXVII. The latter, on reaction with chloride ion, would open at the 1- or 2-positions to give LXVIII and LXIX, respectively. In view of the reactions of trans-3-methoxycyclohexene acetoxonium and iodonium ions and of trans-3-methoxycyclohexene oxide with nucleophiles, it can be expected that the sulfonium ion LXVII



opens preferentially at the 1-position. Therefore, it seems likely that the main initial product of reaction is LXVIII. The formation of LXVIII and LXIX are reversible processes and hence, LXVIII and LXIX can be expected to be interconvertible. Therefore, any of the compound LXIX formed in the initial stages of the overall reaction must be expected to undergo further reaction by way of LXVIII. Displacement of the methoxy group of LXVIII with participation of the sulfur atom would yield the sulfonium cation LXX. Reaction of LXX with chloride ion at the 1- and 2-positions would yield the chlorocompounds LXXI and LXXII, respectively. In view of the reversibility of this latter reaction and if equilibrium was achieved the main product should be the all equatorial compound LXXII. It must be stressed however, that the composition of the product was not established.

Solvolysis of the above chlorocompounds (LXXI and LXXII) in dry acetic acid containing silver acetate (see p. 134) gave a compound which possessed two acetoxy groups. The N.M.R. spectrum of this product is shown in Fig. 5, p. 132. The band in the region of 154 c/s is obviously the signal of the hydrogen on the carbon attached to the acetoxy group. The intensity of this band indicates the presence of two such hydrogens. This band is in the form of an unresolved multiplet, a fact which indicates that the acetoxy groups are located at the 1- and 3-positions of the molecule.

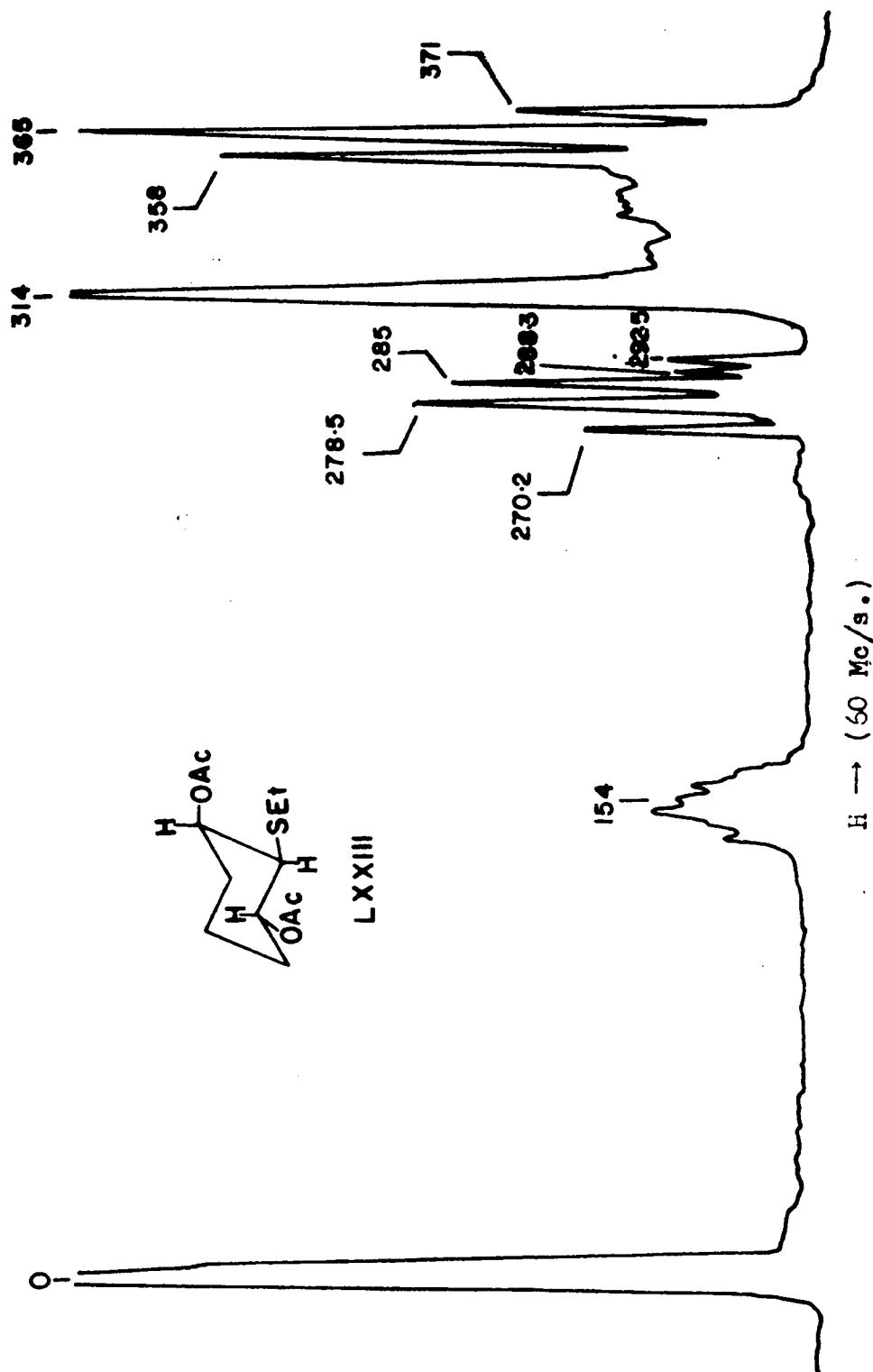
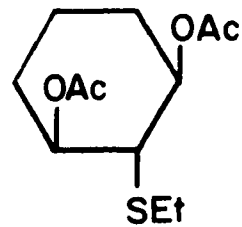
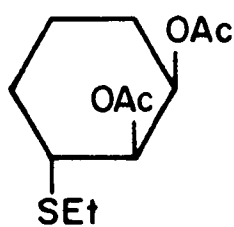
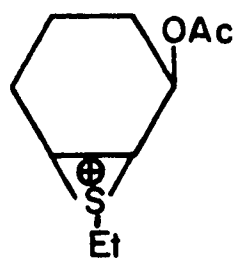
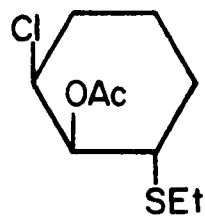
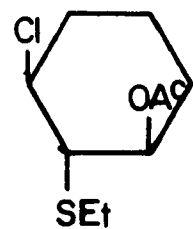
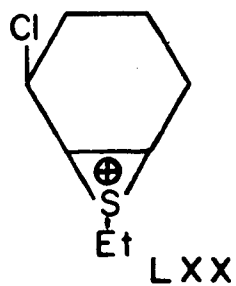
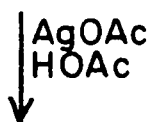
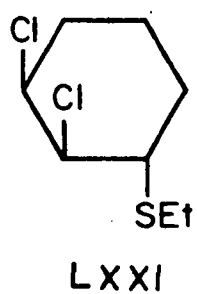
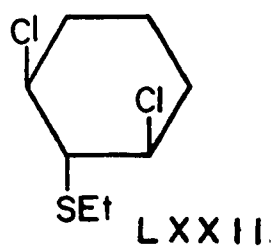


Fig. 5. - The nuclear magnetic resonance spectrum of 1 α ,3 α -diacetoxy-2 β -ethylthiocyclohexane measured in chloroform (reference signal) at room temperature.

A comparison of this spectrum with the spectra for the thioethers LVb, LVib and LXVb (see Fig. 4, p. 123) clearly shows that the bands at 270.2, 278.5, 285 and 292.5 c/s constitute the quartet of the methylene hydrogens of the ethylthio group. The relative intensities of the bands at 270.2 and 278.5 c/s are such (compare with spectra A,B,C Fig. 4) as to indicate that they overlap with two other bands. This situation is taken as an evidence that a triplet exists in the spectra with the signals at 270.2, 278.5 and 288.3 c/s and which arises from the hydrogen on the carbon which is attached to the ethylthio group. The spacing of this triplet requires this hydrogen to be strongly coupled, 8.3 - 9.8 c/s, with the two neighboring hydrogens. Consequently, this hydrogen must be axial and coupled with two axial neighboring hydrogen. On this basis, the compound is assumed to be 1 α ,3 α -diacetoxy-2 β -ethylthiocyclohexane (LXXIII). The reaction route of the solvolysis of the mixture of the chlorocompounds LXXI and LXXII leading to LXXIII is shown on p. 134. The formation of LXXIII in high yield clearly suggests that the sulfonium ion derived from the dichloride LXXII reacts preferentially at the 1-position in the conformation that has the chlorine atom in axial orientation. Attack of the sulfonium ion at the 2-position would be expected to hinder participation of the ethylthio group in the replacement of the chlorine in the second stage



LXXIII

of the reaction .

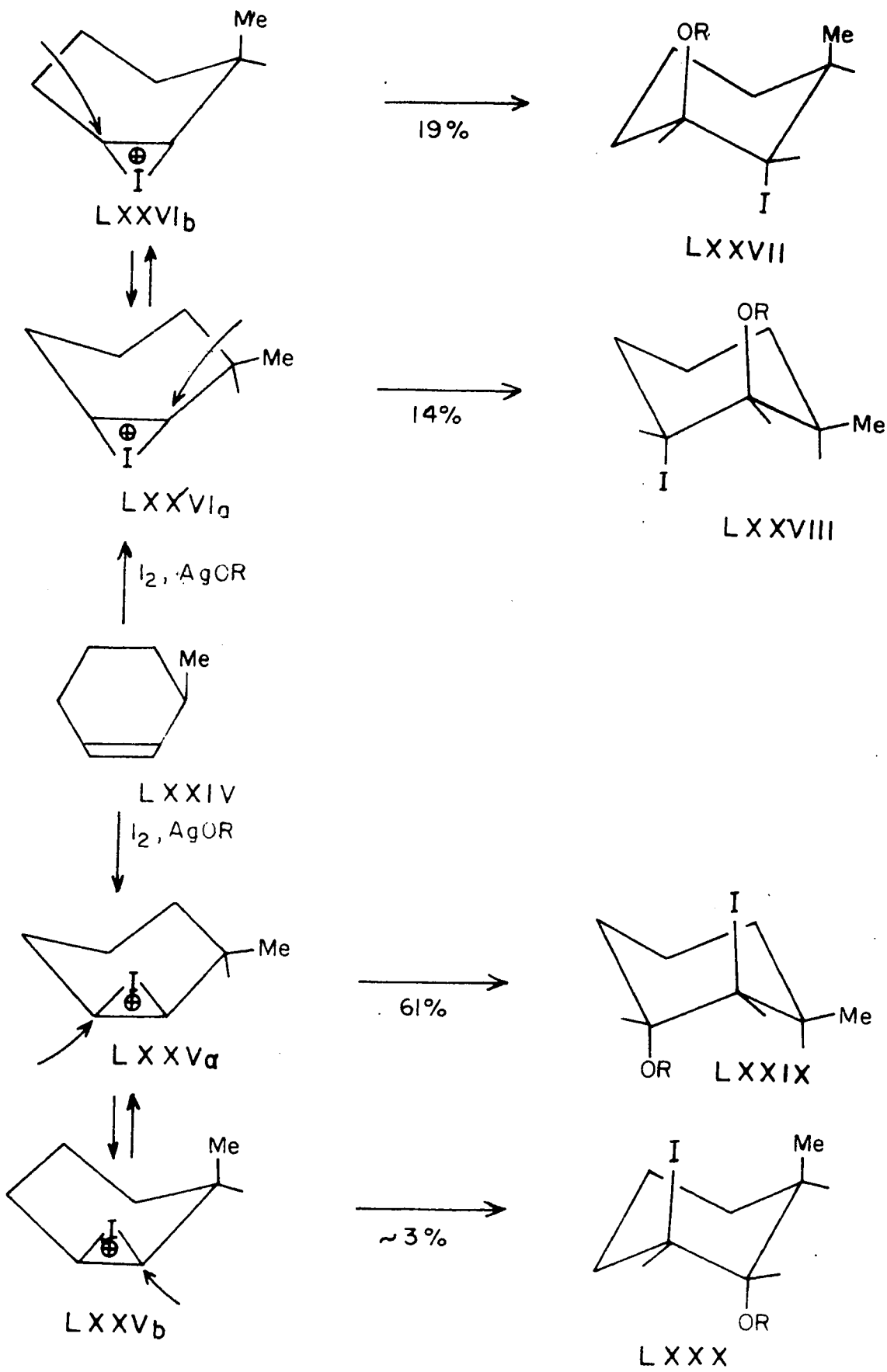
B. Derivatives of Methylcyclohexene

(1) 3-Methylcyclohexene iodohydrins and related compounds

Reaction of 3-methylcyclohexane (LXXIV) with equimolar amounts of silver 3,5-dinitrobenzoate and iodine in benzene at 0° gave a syrupy mixture of 3-methyl-1,2-iodo-(3,5-dinitrobenzoyloxy) cyclohexanes in 87% yield (see p.136). Crystallization of the mixture from ethanol-chloroform (1:1) gave the compound LXXIX, m.p. 132-134°, in 43% yield. The compounds in the mother liquor were fractionated by adsorption chromatography on Magnesol-Celite (5:1) containing Rhodamine 6G as an internal indicator for the detection of the zones. The total yields of the compounds obtained are as follows; LXXIX, m.p. 132-134, 61%; LXXVII, m.p. 156-158, 19%; LXXVIII, m.p. 134-136°, 14%; LXXX, m.p. 188.5-189, 2-3%.

The structures and configurations of these compounds were established by N.M.R. spectroscopy. The spectra for the various isomers are given in Figs. 6 and 7.

The spectrum for compound LXXVIII (Fig. 6A) shows a quartet at 107-117.2 c/s which must arise from the hydrogen on the carbon bonded to 3,5-dinitrobenzoyloxy group. The fine structure of this signal implies that this hydrogen is the 2-hydrogen in the molecule. The coupling constants of 3.6 and 6.6 c/s indicate that the 2-hydrogen must be axial



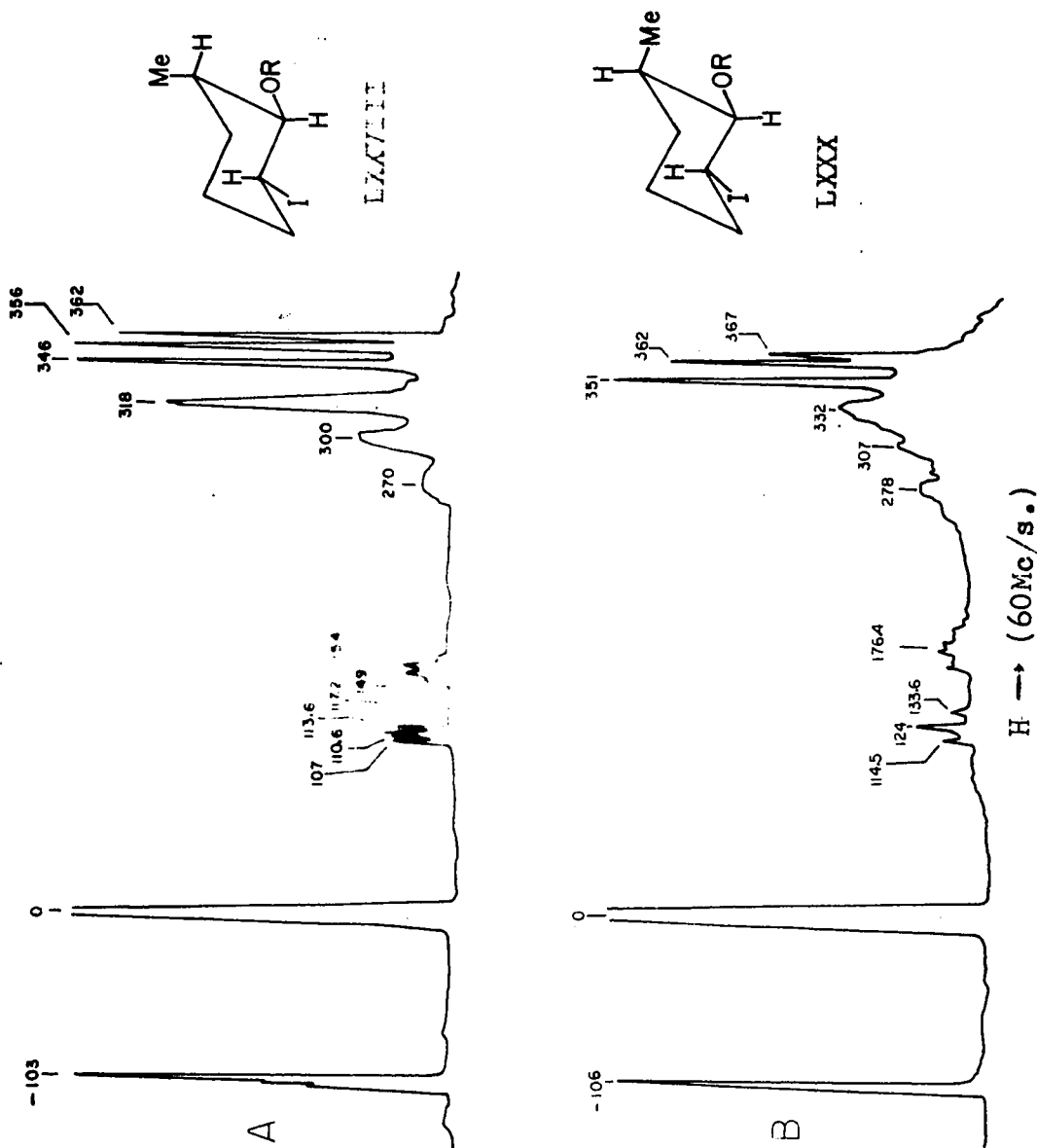


Fig. 6. - The nuclear magnetic resonance spectra of 1-iodo-2-(3,5-dinitrobenzoyloxy)-3-methylcyclohexanes. LXXVIII and LXXX (R = 3,5-dinitrobenzoyl) measured in chloroform (reference signal) at room temperature.

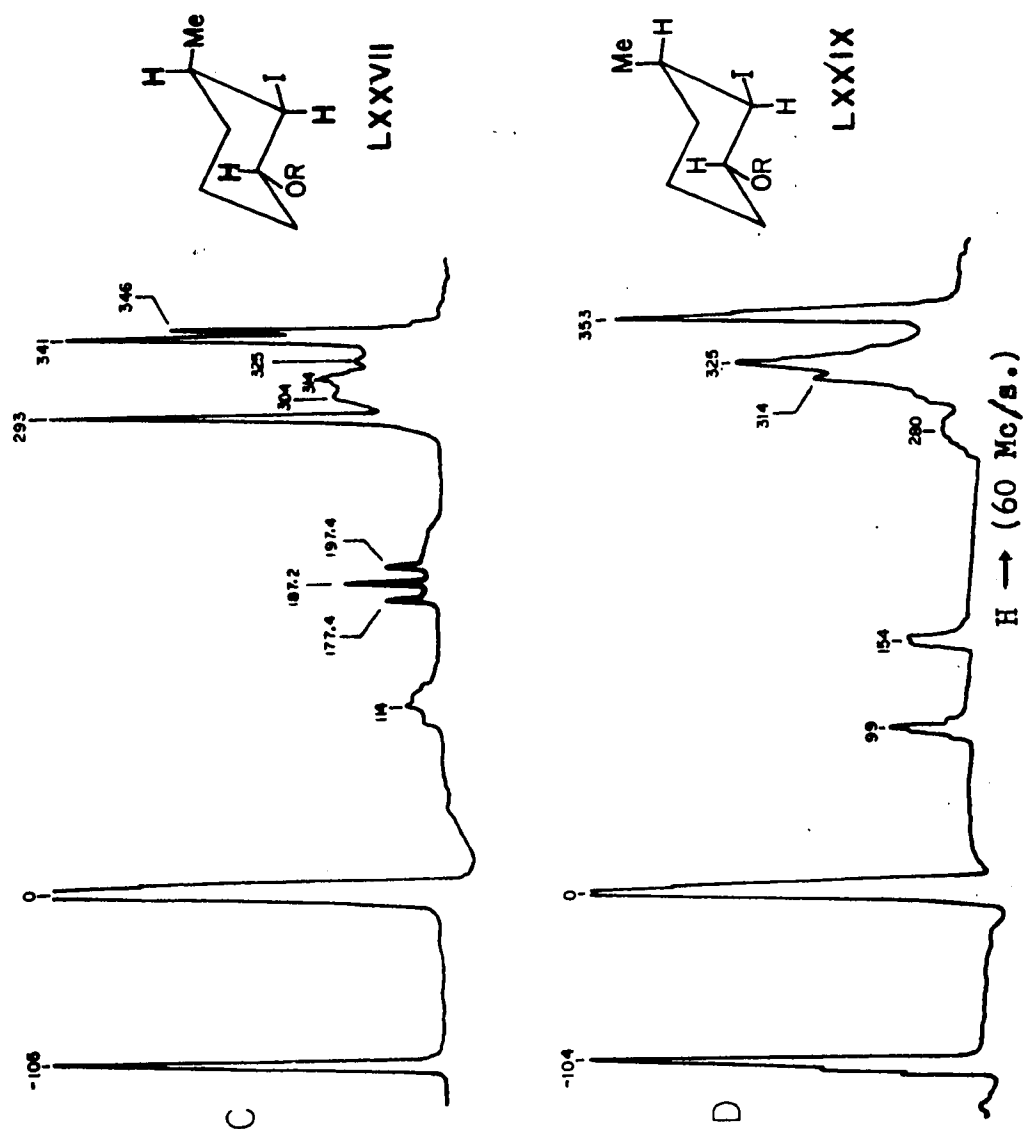


Fig. 7. - The nuclear magnetic resonance spectra of the 1-(3,5-dinitrobenzoyloxy)-2-iodo-3-methylcyclohexanes, LXXVII and LXXIX, (R = 3,5-dinitrobenzoyl) measured in chloroform (reference signal) at room temperature.

and coupled with one axial and one equatorial neighboring hydrogen. The method of synthesis of LXXVIII requires the iodine atom and the 3,5-dinitrobenzoyloxy group to be on the opposite side of the cyclohexane ring. Therefore, the methoxy group and the 3,5-dinitrobenzoyloxy group must be on the same side of the ring and the configuration of the compound must be 1β -iodo- 2α -(3,5-dinitrobenzoyloxy)- 3α -methylcyclohexane.

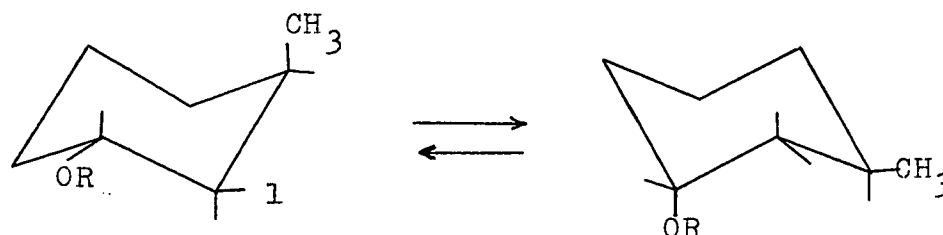
The spectrum for compound LXXX is that reported in Fig. 6 . The signal for the hydrogen on the carbon attached to the 3,5-dinitrobenzoyloxy group (114.5-133.6 c/s) is in the form of a triplet which must represent a quartet resulting from almost equal coupling of the 2-hydrogen with the neighboring 1- and 3-hydrogens. The spacing in the signal requires coupling constants of about 9.5 c/s. Therefore, the 2-hydrogen in the molecule must be in an axial orientation and coupled with two neighboring axial hydrogens. Consequently, the configuration of LXXX must be 1α -iodo- 2β -(3,5-dinitrobenzoyloxy)- 3α -methylcyclohexane.

Spectrum C in Fig. 7 is that for the compound LXXVII. The signal for the hydrogen on the carbon bonded to the iodine (177.4-197.4 c/s) is in the form of a triplet and therefore this hydrogen must be at the 2-position in the molecule. This triplet must represent a quartet with two central lines nearly superimposed. The spacing of the lines

in the triplet requires that the 2-hydrogen is coupled strongly, about 10 c/s, with the 1- and 3-hydrogens. Therefore, the 1-, 2- and 3-hydrogens must all be axially oriented and compound LXXVII must be 1 α -(3,5-dinitrobenzoyloxy)-2 β -iodo-3 α -methylcyclohexane.

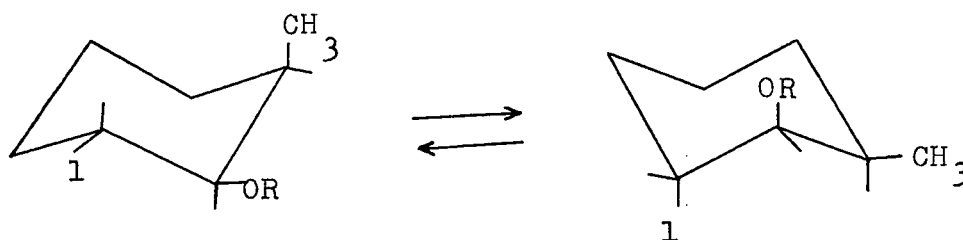
Spectrum D in Fig. 7 is that obtained for compound LXXIX. In view of the above experience with the isomeric compounds, the bands at 99 and 154 c/s can be assigned to the signals for the hydrogens on the carbons bonded to the 3,5-dinitrobenzoyloxy group and the iodine atom, respectively. Neither signal could be resolved. However, the half-band widths of the above signals 10 and 9 c/s respectively indicate that both these hydrogens must be predominantly in axial orientations and coupled with at least one axial hydrogen. This result requires that either the 1- and 2- or the 2- and 3-hydrogens be in trans-relationship. In view of the mode of preparation, it can be assumed that the trans-relationship is between the 3,5-dinitrobenzoyloxy group and the iodine atom. The fact that only four diastereoisomers are possible for the 1,2-trans-(iodo-3,5-dinitrobenzoyloxy)-3-methylcyclohexanes and the configurations of three of these were established (compounds LXXVII, LXXVIII, LXXX) requires that the fourth isomer (LXXIX) to be 1 β -(3,5-dinitrobenzoyloxy)-2 α -iodo-3 α -methylcyclohexane. The spectrum of this compound can be rationalized on the basis that it exists to

appreciable amounts in both the chair forms. It should be



noted in this respect that trans-cyclohexene dibromide exists as an almost equimolar mixture of both the chair conformations (94,95,96) and the destabilization brought on by an axial methyl group is rather great, about 1.8 kcal/mole (97). The spectra for the isomeric compounds supports this contention. The isomers LXXVII and LXXX, which have all the large substituents equatorial, show coupling constants of 9.5-10.2 c/s for the axial 2-hydrogen with the axial 1- and 3-hydrogens. The actual coupling constants are probably somewhat smaller than these values since the central lines were not resolved. Certainly, these coupling constants are in good agreement with the 9.2 c/s value calculated by Karplus for the coupling constant for neighboring hydrogens that define a dihedral angle of 180° (98). Therefore, compounds LXXVII and LXXX can be considered conformationally pure. However, in the case of the 1 β -iodo-2 α -(3,5-dinitrobenzoyloxy)-3 α -methyl-

cyclohexane (LXXVIII) the coupling constant for the 1- and 2-hydrogens is only 6.6 c/s. This result requires a substantial contribution to the spectrum by both the chair conformations. The chemical shifts observed for the 1- and



2-hydrogens are also in agreement with the conclusion that compounds LXXVIII and LXXIX are conformationally impure. Lemieux and coworkers (87) have shown that a hydrogen in equatorial orientation will produce its signal at lower field than a chemically similar hydrogen in axial orientation. The 2-hydrogens of compounds LXXVII and LXXIX can be considered similar and the fact that the signal for the 2-hydrogen in LXXVII is at 187.2 c/s while that for LXXIX is at 154 c/s can therefore be taken as evidence that the 2-hydrogen of LXXIX has more "equatorial character" than that of LXXVII. Similarly, the 2-hydrogen of LXXVIII must have more "equatorial character" than that of LXXX since its signal is at lower field (112 c/s) than that (124 c/s) for LXXX. The

same considerations apply to the signals for the 1-hydrogens. A number of other features are evident in the spectra for compounds LXXVII - LXXX which deserved brief mentioning since they may be of interest to theoretical spectroscopists. The doublets at high field in spectra A, B (Fig. 6) and in spectrum C (Fig. 7) undoubtedly arise from the 3-methyl group which is coupled with the 3-hydrogen. The fact that the methyl group signal is not split in the case of compound LXXIX (Fig. 7-D) is likely related to a small chemical shift between the largely equatorial 3-hydrogen and one of the 4-hydrogens. In such a situation⁽¹¹⁰⁾ the methyl group cannot be simply considered as coupled only with the 3-hydrogen. This interpretation is supported by the fact that it was not possible to resolve the signal for the 2-hydrogen into a simple quartet. The sharp signals of intensity approximately 2 which are at positions 346, 351 and 293 in spectra A, B (Fig. 6) and spectrum C (Fig. 7) cannot be assigned in a simple manner. These almost surely arise from hydrogens in one or more of the methylene groups. It is of interest to note that the sharpness of these signals is suggestive of the type of signal observed for methyl groups which are not coupled with other hydrogens. Thus, the presently unaccountable occurrence of these sharp signals in the spectra for the compounds point up a possible source for error when making deductions regarding structure from the N.M.R. spectra of

organic compounds.

(2) 3-Methylcyclohexene Oxides

Reaction of 1β -(3,5-dinitrobenzoyloxy)- 2α -iodo- 3α -methylcyclohexane (LXXIX) with sodium hydroxide in aqueous ethanol at 0° gave the epoxide LXXXI, b.p. $133-134^\circ$ (750 mm), n_D^{31} 1.4445, in 36% yield. The structure and configuration of the oxide LXXXI was established by lithium aluminum hydride reduction to a mixture of trans-2-methylcyclohexanol (LXXXIII) and trans-3-methylcyclohexanol (LXXXIV). The latter mixture was characterized by a comparison of their retention volumes on vapour phase chromatography using a glycerol column with the retention volumes observed with authentic samples of the cis and trans forms for 2- and 3-methylcyclohexanols. The formation of the methylcyclohexanols LXXXIII and LXXXIV by reduction of the oxide LXXXI provides unambiguous evidence that the oxide is the trans-3-methylcyclohexene oxide.

Perbenzoic acid epoxidation of 3-methylcyclohexene (LXXIV) gave a preparation, 3-methylcyclohexene oxide, substantially with the same physical constants (b.p. $144-144.5^\circ$ (760 mm), n_D^{26} 1.4467) as that reported in the literature (77,78). Vapour phase chromatographic analysis showed it to be a mixture of trans-3-methylcyclohexene oxide (LXXXI) (53%) and cis-3-methylcyclohexene oxide (LXXXII) (47%).

That the product was in fact a mixture of the cis and trans oxides was shown by lithium aluminum hydride reduction to a mixture of methylcyclohexanols LXXXIII - LXXXVI (see p.148). The oxide with greater retention volume showed vapor phase chromatographic properties identical to the authentic sample of trans-3-methylcyclohexene oxide (LXXXI) mentioned above.

Kötz and Hoffmann (77) and also Mousseron and coworkers (78) have reported the synthesis of 3-methylcyclohexene oxide by perbenzoic acid epoxidation of 3-methylcyclohexene but did not give any information as to the homogeneity and the configuration of this compound. It is now evident from the above results that the oxide obtained by these investigators was an about equimolar mixture of the trans- and cis-3-methylcyclohexene oxides.

The formation of the cis-oxide (LXXXII) in about equal amount to the trans-isomer (LXXXI) was unexpected in view of Henbest's (99) results on the effect of a 3-substituent on the perbenzoic acid epoxidation of 3-substituted cyclohexenes. Henbest and coworkers (99) have found that the reaction of 3-acetoxycyclohexene with perbenzoic acid gave trans-3-acetoxycyclohexene oxide as the main product of the reaction. They interpreted their results in terms of steric hindrance exerted by the acetoxy group on the entering perbenzoic acid molecule when the latter approaches the

double bond from the same side of the ring where the acetoxy group is located. On this basis, one could expect the bulkier methyl group on the 3-methylcyclohexene molecule to hinder a cis-approach of the perbenzoic acid molecule even more than the acetoxy group, and therefore the 3-methylcyclohexene would be expected to yield the trans-oxide even more preferentially than 3-acetoxycyclohexene. However, this was not the case. It seems likely that the main effect of the 3-substituent in this reaction is other than steric. For this purpose the reaction of 3-methoxycyclohexene with perbenzoic acid was studied. The product of the reaction was analysed by vapour phase chromatography on a Silicon Oil D.C.-200 column (Perkin-Elmer column 154-0013-C) and found to contain 82% of trans-3-methoxycyclohexene oxide (XLVI) and 18% of cis-3-methoxycyclohexene oxide (LXII).

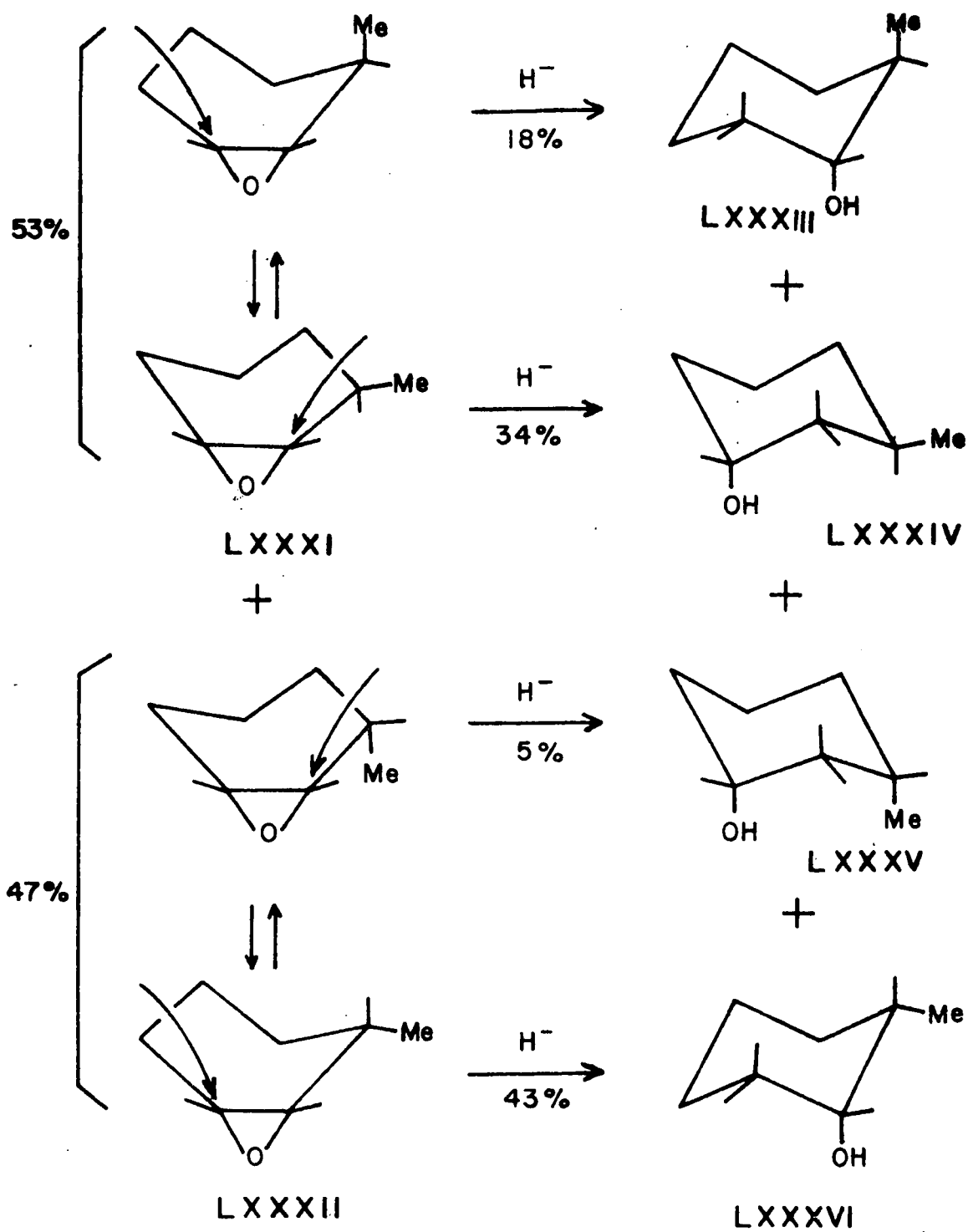
From these results it seems likely that the nature rather than the size of the 3-substituent controls the stereochemical path of the reaction of 3-substituted cyclohexenes with perbenzoic acid. Obviously, the polar bonds are more favorably disposed in trans-3-methoxycyclohexene oxide than in the cis-isomer. It is reasonable to expect that this situation will also be present in the transition states for the formation of these oxides. On this basis, the preferential formation of the trans-oxides in the perbenzoic acid epoxidation of the 3-acetoxy and

3-methoxycyclohexenes, but not in the case of 3-methylcyclohexene, appears reasonable.

Reduction of the mixture containing 53% of trans-3-methylcyclohexene oxide (LXXXI) and 43% of the cis-isomer (LXXXII) with lithium aluminum hydride in ether at 35° produced a mixture of the four isomeric 1,2- and 1,3-methylcyclohexanols (LXXXIII-LXXXVI) in 92% yield. The mixture was resolved by vapour phase chromatography on a glycerol column into four well separated zones. The compound in each zone was identified by comparison of its retention volume with that of an authentic sample. The two trans-methylcyclohexanols LXXXIII and LXXXIV obviously were formed from the trans-oxide (LXXXI). It was estimated from the areas of the zones on the chromatogram that the mixture contained 34% of the 1,2-trans-compound (LXXXIII) and 66% of the 1,3-trans-isomer (LXXXIV). Similarly, it was estimated that the cis-3-methylcyclohexene oxide gave rise to a 90% yield of the cis-2-methylcyclohexanol (LXXXVI) and 10% yield of the cis-3-methylcyclohexanol (LXXXV). Thus, in the case of the trans-oxide the hydride ion was accepted at the 2-position in preference to the 1-position whereas in the case of cis-oxide the 1-position was attacked preferentially.

(3) 3-Methylcyclohexene 1,2-glycols and related compounds

The hydrolysis of a 3-methylcyclohexene oxide must



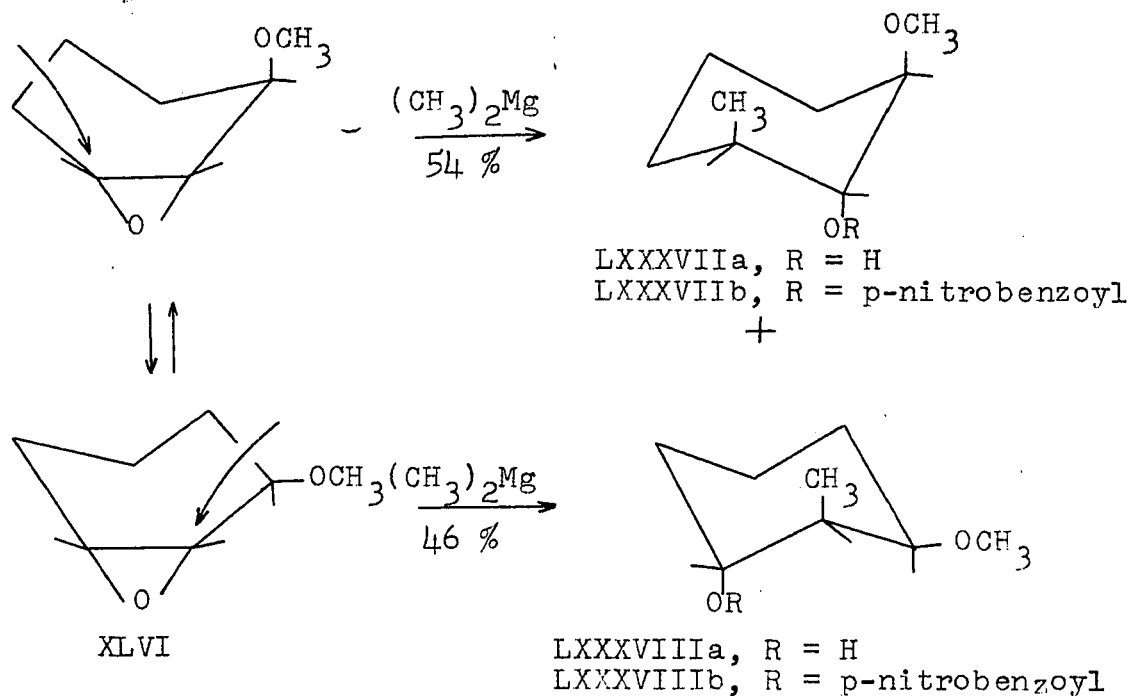
be expected to yield both the possible 3-methyl-1,2-trans-cyclohexanediols regardless of the configuration of the oxide. In order to study the hydrolysis of the oxides it was first necessary to characterize and to establish the configurations of the 3-methylcyclohexene 1,2-glycols. It was decided to approach this problem by alkylation of trans-3-methoxycyclohexene oxide (XLVI) using dimethylmagnesium.

Bartlett and Berry in 1934 (67) showed that the reaction of cyclohexene oxide with dialkylmagnesium proceeds normally and gives trans-2-alkylcyclohexanol in contrast to the reaction of the same oxide with alkylmagnesium halide which proceeds with ring contraction to form methylcyclopentyl carlinol (100).

An ethereal solution of diethylmagnesium can be obtained which contains a sufficiently low concentration of magnesium halide by the method of Noller and Hilmer (101) to be useful for reaction with cyclohexene oxide to form trans-2-ethylcyclohexanol in good yields (67). However, Noller and Hilmer's method when applied for the preparation of ethereal solution of dimethylmagnesium gave a reagent that was of no value for the preparation of trans-2-methylcyclohexanol (67). In the present work it was found possible to prepare an ethereal solution of dimethylmagnesium in high concentration (2N) and low magnesium

halide content using the procedure described by Kullman (79) for the preparation of ethereal solutions of diethylmagnesium.

Reactions of the trans-3-methoxycyclohexene oxide (XLVI) with dimethylmagnesium at room temperature gave a mixture in 70% yield of 1 α -methyl-3 α -methoxy-2 β -cyclohexanol (LXXXVIIa) and 2 α -methyl-3 α -methoxy-1 β -cyclohexanol (LXXXVIIIa). The assignments of these structures and configurations are discussed below. Vapor phase chromatographic analysis using an Apiezon M vacuum stopcock grease



column, showed the mixture to contain 54% of LXXXVIIa and 46% of LXXXVIIIa. The separation of the two compounds was achieved through their p-nitrobenzoyl derivatives LXXXVIIb

and LXXXVIIb. Esterification of the mixture of LXXXVIIa and LXXXVIIIa with p-nitrobenzoyl chloride in pyridine gave a mixture of the esters in 90% yield. 1 α -Methyl-2 β -(p-nitrobenzoyloxy)-3 α -methoxycyclohexane (LXXXVIIb), m.p. 101-102°, was obtained directly by crystallization from petroleum ether. Fractionation of the compounds in the mother liquor by adsorption chromatography on silicic acid - Celite (2:1) mixture enabled the isolation of 1 β -(p-nitrobenzoyloxy)-2 α -methyl-3 α -methoxycyclohexane (LXXXVIIIb), m.p. 68.5-69.5°.

It is to be expected that an inversion of the reacting center will take place in the opening of the oxide ring. Therefore, assuming no participation of the methoxy group, the p-nitrobenzoyloxy groups and the methyl groups in compounds LXXXVIIb and LXXXVIIIb would be in a trans-relationship and the p-nitrobenzoyloxy group would be on the same side of the cyclohexane ring as that formerly occupied by the oxide-ring oxygen atom. The N.M.R. spectra obtained for compounds LXXXVIIb and LXXXVIIIb are shown in Fig. 8, p. 152. The spectrum for the ester LXXXVIIb (spectrum A) is seen to possess a band in the region of 138-156 c/s which can be assigned, from its position in the field, to the hydrogen on the carbon which is bonded to p-nitrobenzoyloxy group. This band being in the form of a triplet, can be assumed to arise from the 2-hydrogen in

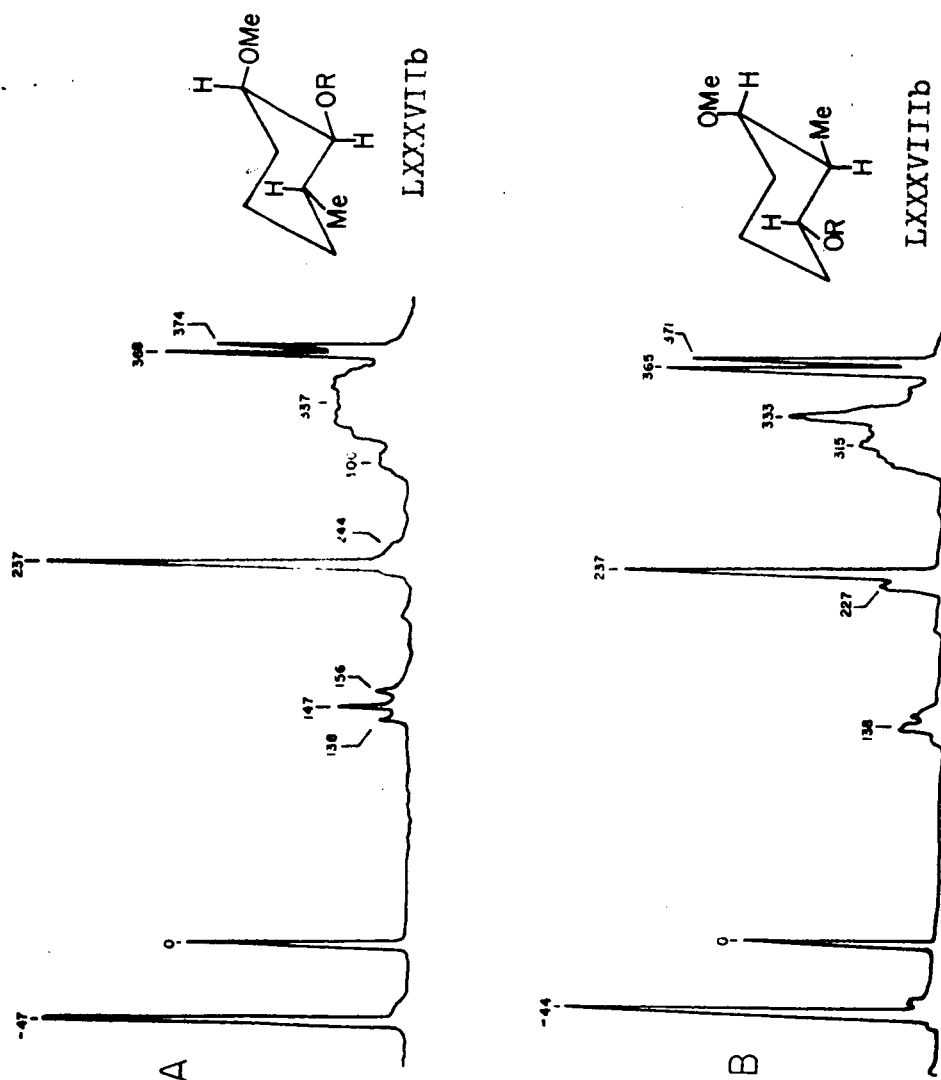


Fig. 8. - The nuclear magnetic resonance spectra of 1 α -methyl-2 β -(p-nitro-benzoyloxy)-3 α -methoxycyclohexane (LXXXVIIb) and 1 β -(p-nitro-benzoyloxy)-2 α -methyl-3 α -methoxycyclohexane (LXXXVIIIb) measured in carbon tetrachloride at room temperature. Chloroform was used as an external standard (reference signal).

the molecule. Furthermore, the spacing of the lines in the signal, 9 c/s, requires the 2-hydrogen to be oriented axially and to be coupled with two neighboring axial hydrogen atoms. Therefore, compound LXXXVIIb must be 1 α -methyl-2 β -p-nitrobenzoyloxy-3 α -methoxycyclohexane.

The spectrum for the ester LXXXVIIIb (spectrum B) has a signal in the region of 138 c/s which is in the form of an unresolved multiplet. This fact suggests that the hydrogen which is on the same carbon as the p-nitrobenzoyloxy group is the 1-hydrogen in the molecule. The presence of a signal for a methoxy group at 237 c/s and the doublet for the C-methyl group at 365 and 371 c/s clearly indicates that the compound is isomeric to LXXXVIIb. The signal at 227 c/s arises from the hydrogen atom situated on the same carbon as the methoxy group. The half-band width of this signal is clearly much less than that which spreads below the signal for the methoxyl group in LXXXVIIb at about 244 c/s which is due to the axial 3-hydrogen. The 3-hydrogen in LXXXVIIIb would be equatorial and therefore less strongly coupled in accordance with these results. These spectral features together with the close correspondence of the chemical shifts (except for the 3-hydrogens which can be expected to be at lower field in the case of LXXXVIIIb since it is equatorially oriented) strongly support the contention that LXXXVIIIb is in fact 1 β -p-nitrobenzoyloxy-2 α -methyl-3 α -methoxycyclo-

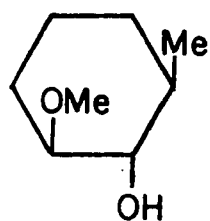
hexane. Unequivocal proof that the compound is not an isomer of LXXXVIIb which formed with participation of the methoxy group either with ring contraction or methoxy group migration was not obtained. The main purpose of the reaction was to obtain LXXXVIIb for the foregoing configurational confirmations.

The reactions used for the syntheses and to obtain evidence for the structures and configurations of 3-methyl-1,2-cyclohexanediols (LXXXIXa, XCa and XCIIa) are summarized on p. 156.

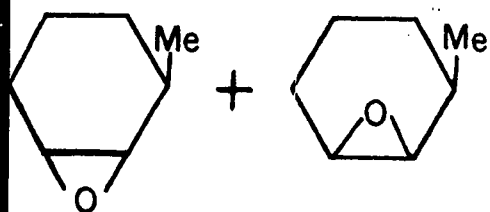
Pure 1 α -methoxy-3 α -methyl-2 β -cyclohexanol (LXXXVIIa) (obtained by alkaline hydrolysis of the p-nitrobenzoyl derivative LXXXVIIb) was treated with 55% hydroiodic acid at 80° for two hours to provide 3 α -methyl-1 α ,2 β -cyclohexanediol (LXXXIXa), m.p. 46-47.5°; di-p-nitrobenzoate (LXXXIXb) melted at 123.5-125.5°. This glycol (LXXXIXa) must have the structure indicated if no inversion took place during the demethylation reaction. A good deal of evidence exists (59,70,72) that the expected glycol is always obtained. Surely, cleavage of the carbon to methoxy group bond to form a glycol cannot be expected to be an important reaction route.

Alkaline hydrolysis of the mixture containing 53% trans-3-methylcyclohexene oxide (LXXXI) and 47% of the cis-isomer (LXXXII) in aqueous dioxane at 100° gave a

mixture of 3-methyl-1,2-cyclohexanediols (LXXXIXa) and (XCa) in 70% yield. Crystallization of the mixture from ethyl acetate gave the glycol XCa, m.p. 94.5-96° in 55% yield; the di-p-nitrobenzoyl derivative (XCb) melted at 164.5-166.5°. The compounds in the mother liquor were converted to p-nitrobenzoyl derivatives and the product was fractionated on Magnesol-Celite (5:1) containing Rhodamine 6G as an internal indicator for the detection of the zones. The chromatographic separation afforded a di-p-nitrobenzoate LXXXIXb, m.p. 123.5-125.5°, which was identical (mixed m.p. and infrared spectra) with the di-p-nitrobenzoyl derivative of 3 α -methyl-1 α , 2 β -cyclohexanediol, and di-p-nitrobenzoate XCb, m.p. 164.5-166.5°, which was identical (mixed m.p. and infrared spectra) with the di-p-nitrobenzoyl derivative of the glycol XCa. It was estimated from the above chromatographic analysis that the product of the alkaline hydrolysis of the mixture of cis- and trans-3-methylcyclohexane oxides contained 75% of the glycol XCa and 25% of the glycol LXXXIXa. The synthesis of the glycol LXXXIXa by two different ways confirms the assigned structure for this compound and can leave no doubt as to the identity of LXXXVIIa. The isomeric glycol XCa, m.p. 94.5-96.5°, therefore must be 3 α -methyl-1 β , 2 α -cyclohexanediol since only two isomeric glycols can be expected to form on the hydrolysis of the mixture of the oxides LXXXI and LXXXII.

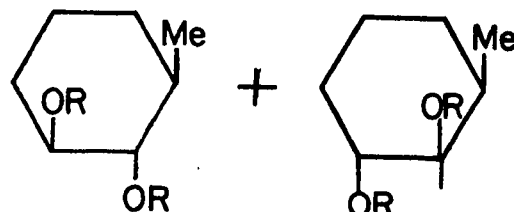
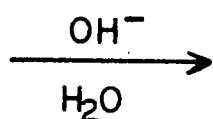


LXXXVIIa



LXXXI

LXXXII



LXXXIXa, R=H

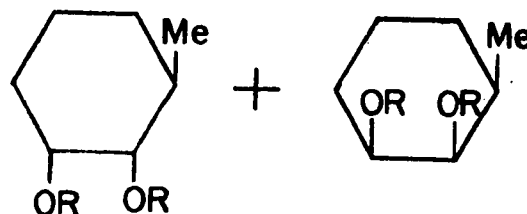
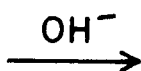
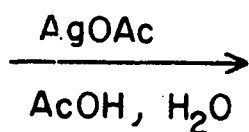
XCa, R=H

LXXXIXb, R=COC₆H₄NO₂

XCb, R=COC₆H₄NO₂



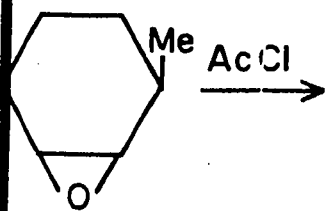
LXXIV



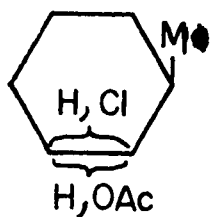
XCIa, R=H

XCII, R=H

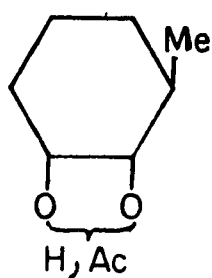
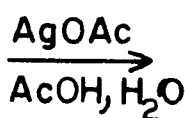
XCIb, R=COC₆H₄NO₂



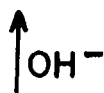
LXXXI



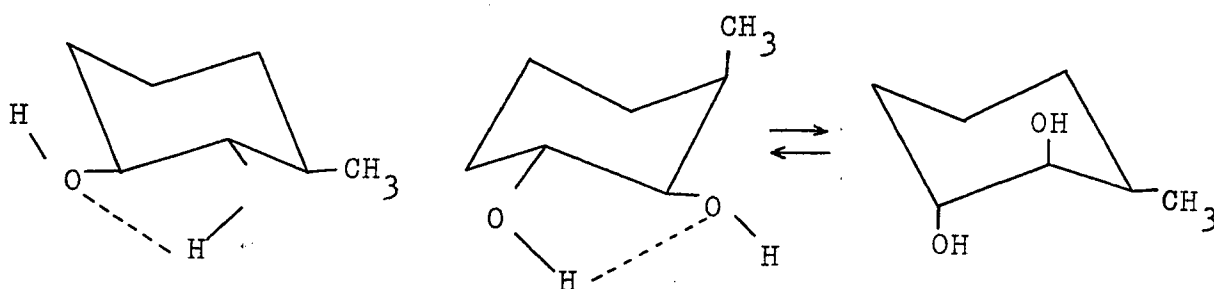
XCIII



XCIV



The above conclusions regarding the structures of the glycols LXXXIXa and XCa are supported by their infrared spectra in highly diluted carbon tetrachloride solutions. The glycol LXXXIXa must be expected to exist entirely in the conformation with all the groups equatorially



LXXXIXa

XCa

oriented, whereas the glycol XCa must exist as a mixture of the two conformations. Since intra-molecular hydrogen bonding in trans-1,2 diols can take place only when the two hydroxyl groups are in a gauche relationship (102) it can be predicted that the intramolecular hydrogen bonding will be more pronounced in the case of glycol LXXXIXa than in the case of glycol XCa. The infrared spectra that were obtained for the two glycols in carbon tetrachloride solution (0.005 M) are shown in Fig. 9, p. 158. The bands at 3640 and 3599 cm^{-1} are associated with the O-H stretching vibrations of the unbonded and bonded hydroxyl groups, respectively. It is seen that, as expected, the relative intensity of absorption in bonded over non-bonded regions

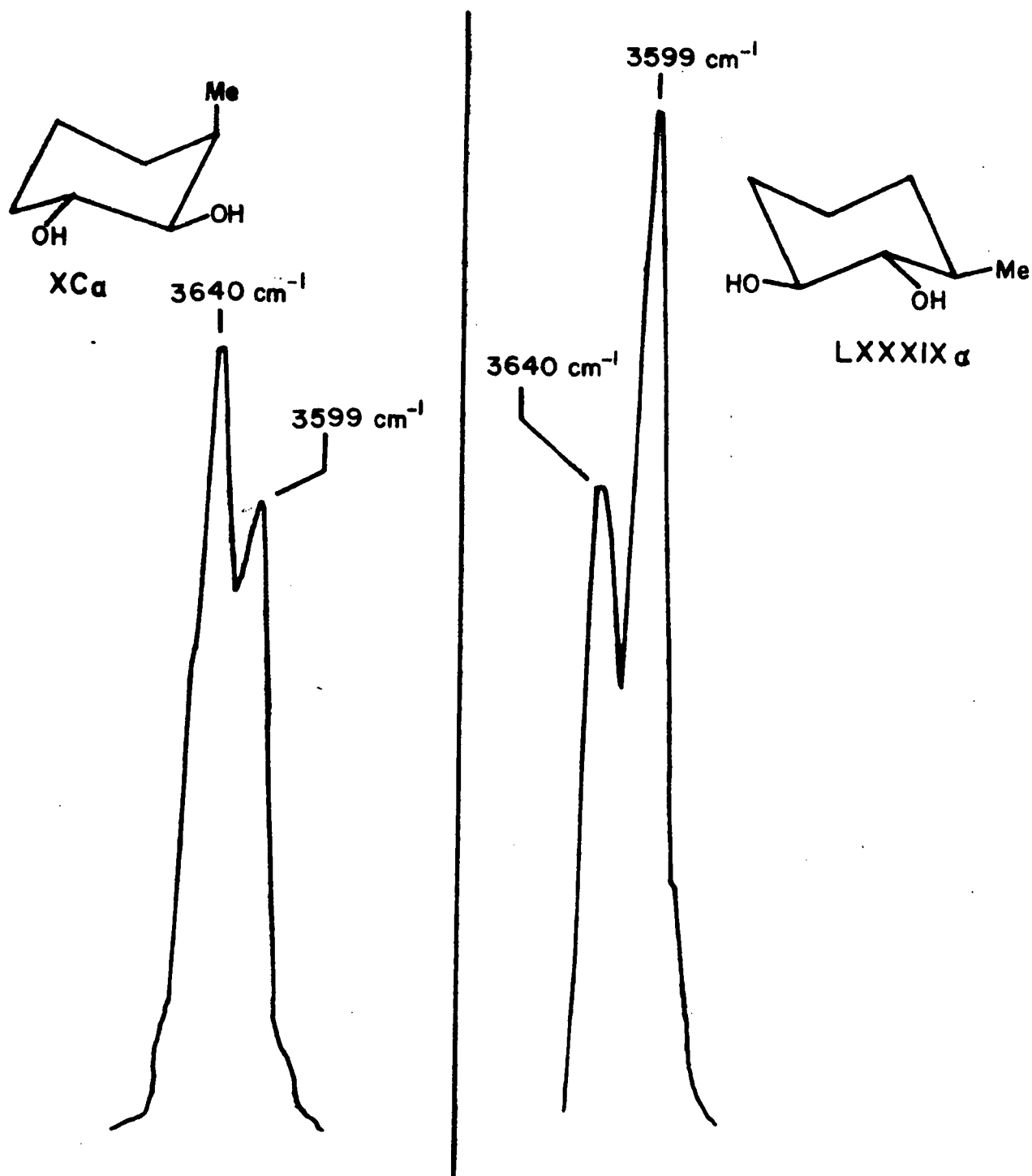


Fig. 9. - The infrared spectra of 3-methyl-1,2-trans-cyclohexanediol isomers LXXXIXα and XCa, in 0.005 M carbon tetrachloride solutions, measured with the Beckman DU spectrometer.

is much greater of the all-trans glycol (LXXXIXa).

Mousseron and coworkers (78) have reported the synthesis of a 3-methyl-1,2-cyclohexane diol, m.p. 90-91°, from the acid hydrolysis of 3-methylcyclohexene oxide, but did not provide information as to the configuration of this compound, other than it was a trans-1,2-diol. In view of the above discussion regarding the structures and configurations of the glycols LXXXIXa and XCa it is evident that the glycol obtained by Mousseron and coworkers is the 3 α -methyl-1 β ,2 α -cyclohexanediol (XCa).

The alkaline hydrolysis of the trans-3-methylcyclohexene oxide (LXXXI) in aqueous dioxane solution at 100°, gave a mixture of the glycols LXXXIXa and XCa consisting of 45% of the former and 55% of the latter compound as established by vapour phase chromatography on a sorbitol column. From these results and from the relative proportions of the glycols LXXXIXa and XCa (25% of LXXXIXa and 75% of XCa) formed on the alkaline hydrolysis of a mixture of 52-53% trans- and 47-48% cis-3-methylcyclohexene oxides, it is estimated that the cis-3-methylcyclohexene oxide (LXXXII) reacts almost quantitatively at the 1-position (97-99%) with hydroxide ion.

Reaction of trans-3-methylcyclohexene oxide (LXXXI) with acetyl chloride in a sealed tube at 100° (see p.156) gave a mixture of the chlorides (XCIII) in 80% yield.

Solvolysis of the mixture XCIII in moist acetic acid and in the presence of silver acetate (see p. 156) gave a syrup (81% yield based on the monoacetate XCIV) which after alkaline hydrolysis yielded crystalline 3 α -methyl-1 β , 2 β -cyclohexanediol (XCIA), m.p. 82.5-83.5°; the di-p-nitrobenzoate (XCIB) melted at 136-138°. The structure of the glycol XCIA is required by the fact that the opening of the oxide LXXXI with acetyl chloride involves an attack by chloride ion with inversion of the configuration of the reacting carbon. Consequently, the chlorine atom and the acetoxy group in the mixture of chlorides XCIII must be in trans-relationship and the acetoxy group must be on the same side of the cyclohexane ring as that formerly occupied by the oxide-ring oxygen atom. Since acetolysis of the chlorides XCIII would proceed by participation of the acetoxy groups, the acetoxonium ion formed in each case would lead in the presence of water to the monoacetate XCIV, which, on hydrolysis, would provide XCIA in the configuration shown.

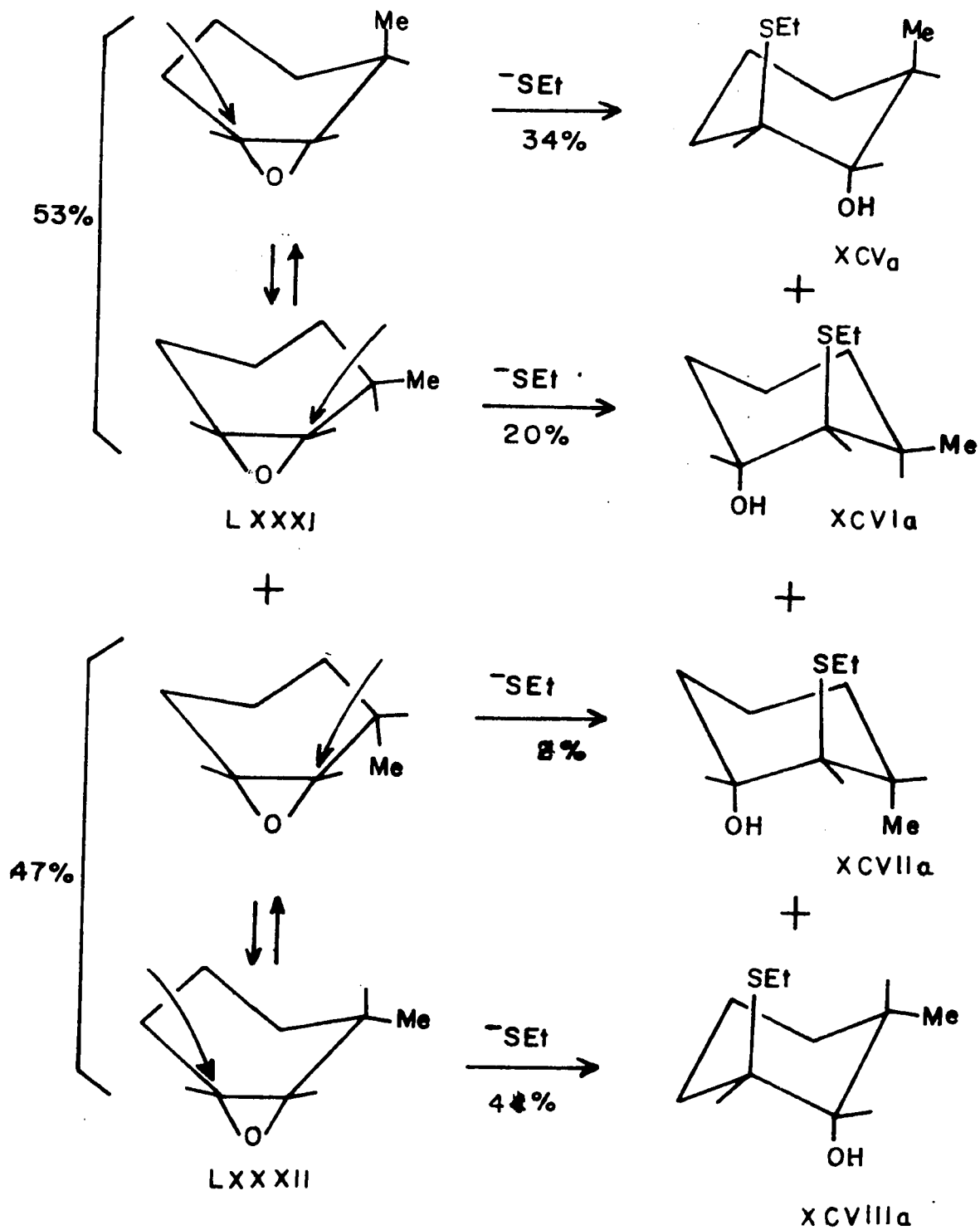
Reaction of 3-methylcyclohexene (LXXIV) with silver acetate and iodine in moist acetic acid (see p. 156) gave after alkaline hydrolysis a product in 39% yield. Crystallization from ethyl acetate yielded a glycol XCIA, m.p. 82.5-83.5°, in 29% yield which was identical (mixed m.p. and infrared spectra) with the glycol XCIA obtained above by way of the reaction of trans-oxide (LXXXI) with

acetyl chloride. The cis-diol XCII could not be obtained in a crystalline state.

Mousseron and coworkers (78) have prepared a 3-methyl-1,2-cis-cyclohexane diol, m.p. 81-82°, by permanganate oxidation of 3-methylcyclohexene. They reported that this glycol was cis-1,2-glycol but they did not provide any information regarding the configurational relationship between methyl and the hydroxy groups. Lemieux, Kullnig and Moir (70) have predicted that this compound should be 3 α -methyl-1 β , 2 β -cyclohexanediol. The close correspondence of the melting point of XCIIa, (m.p. 82.5-83.5°), and that noted above for Mousseron's compound supports this prediction.

(4) 3-Methylcyclohexene ethylthiohydrins and related compounds

Reaction of the mixture of trans- and cis-3-methylcyclohexene oxides (trans-, 53%; cis-, 47%;) with sodium thioethoxide in methanol at 0° gave in 90% yield a mixture of 3-methylcyclohexene ethylthiohydrins XCVa - XCVIIIa (see p. 162). The mixture was converted to the methylcyclohexanols LXXXIII - LXXXVI by reductive desulfurization and the resulting mixture of 1,2- and 1,3-methylcyclohexanols was analyzed by vapour phase chromatography. The results indicated that the cis-oxide (LXXXII) reacted to an extent of 66% at the 1-position while the trans-oxide (LXXXI) reacted to an extent of 63% at the 1-position.

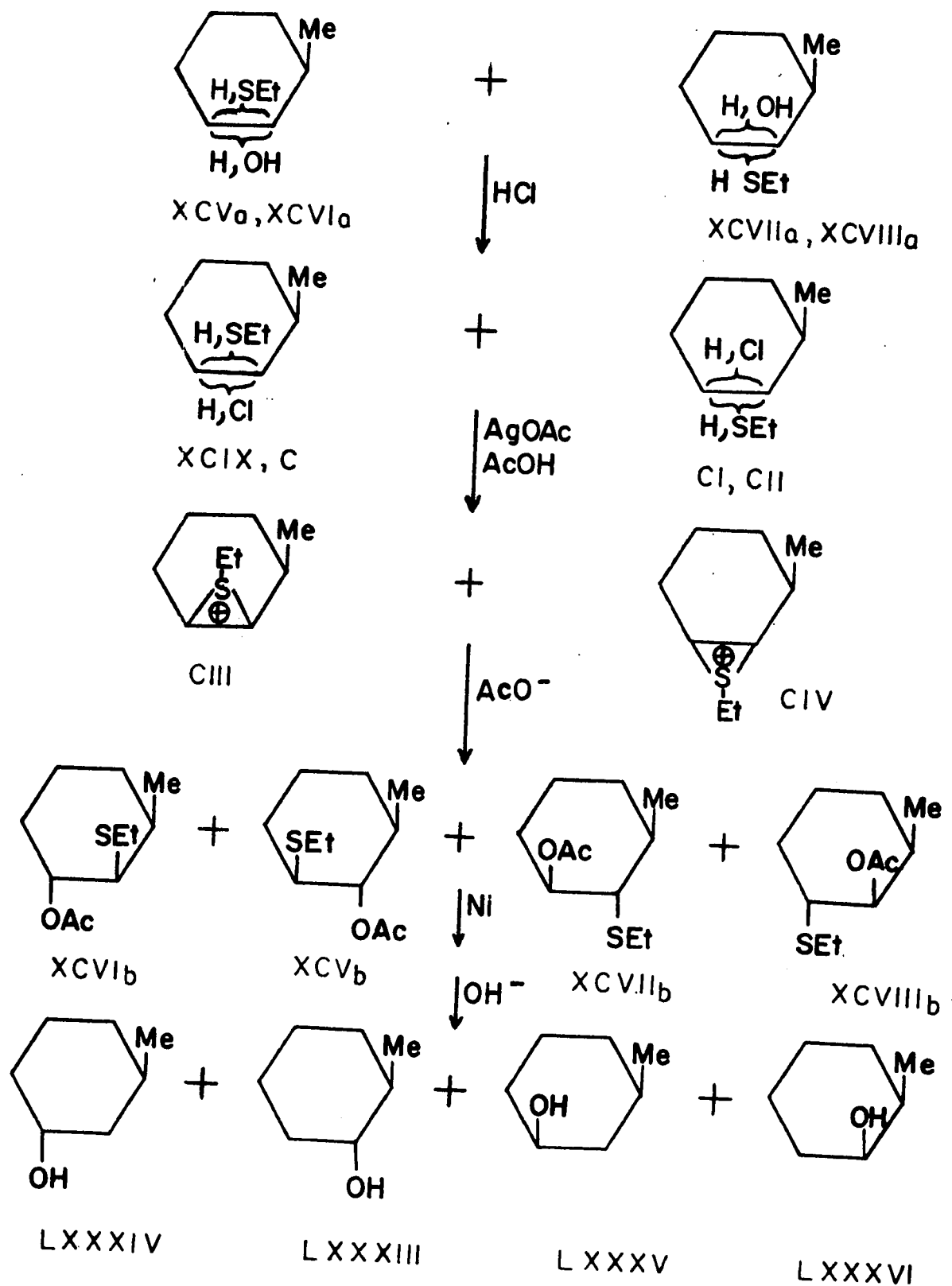


The mixture of ethylthio-3-methylcyclohexanols XCVA - XCVIIIA was converted, by treatment with concentrated hydrochloric acid, to the mixture of chlorocompounds XCIX - CII in 82% yield (see p.164). It was not possible to analyze this mixture by vapour phase chromatography. The mixture was subjected to acetolysis in dry acetic acid and in the presence of silver acetate at 50-60° (see p.164). Reactions by way of the sulfonium cations CIII and CIV led to a mixture of the thiocompounds XCVb - XCVIIb in 71% yield and this mixture was reductively desulfurized to the methylcyclohexanols LXXXIII - LXXXVI for analysis by vapor phase chromatography. The results of the analysis showed that the cis-sulfonium cation CIII underwent reaction to an extent of 95% at the 1-position while the trans-sulfonium cation (CIV) reacted at the 1-position to the extent of only 45%.

C. Methanolysis of the 3-Methyl- and 3-Methoxycyclohexene Oxides

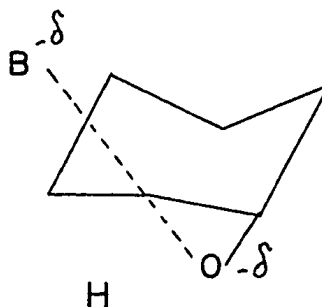
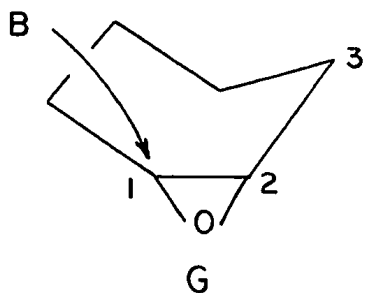
It appears well established (see p.4 introduction) that base catalyzed opening of an oxide ring involves nucleophilic attack by the entering basic group with the strain of the oxide ring providing an important driving force for the reaction (8). Kinetic investigations of such reactions have shown them to be first order in base and in oxide.

As was seen earlier, Ottar (3) has shown that the



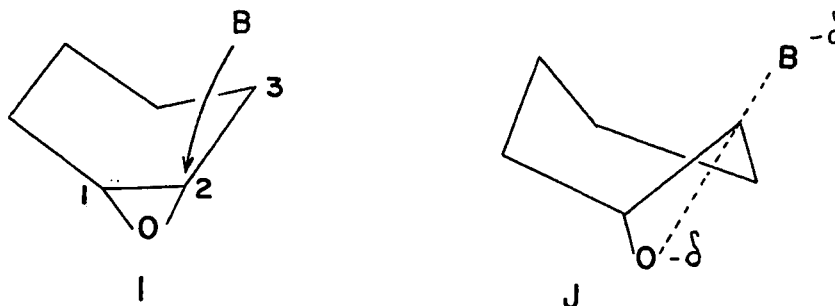
cyclohexene oxide molecule is in the form of the dissymmetric conformations I Ia and I Ib (p. 2) and in a given conformation the two carbon atoms in the oxide ring are not equivalent. However, in the reactions of cyclohexene oxide the two carbons could be regarded as chemically equivalent to the extent that the rate for conformational change ($I Ia \rightleftharpoons I Ib$) is very large as compared to the rate of reaction.

According to the Fürst and Plattner rule (28), cyclohexene oxide in a given conformation should tend to undergo reaction at the center which, on inversion, will possess the new substituent in axial orientation. This preferred route of reaction is undoubtedly related to the fact that attack at the 1-position as shown in formula G. leads to the transition state H. This structure for the transition state allows room for both the entering and leaving

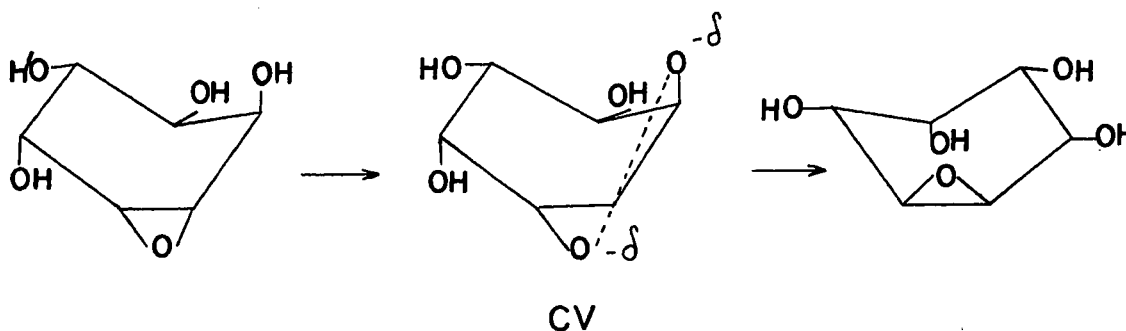


group to be in a linear arrangement with the reacting center and the six-membered ring to possess as much as possible the favorable features of the chair conformation. Reaction at the 2-position on the other hand as shown in formula I would require a transition state J in which the six-membered ring

has a boat-like conformation and which, therefore, must be expected to be relatively unfavorable. The fact that



Angyal and coworkers (103) have observed oxide ring migrations in anhydroinositols as shown below suggests that an attack



at the 2-position of I can take place without undue distortions of the half chair conformation if the entering group could approach the 3-position very closely. As close an approach as is present in the oxide ring migration undoubtedly is not possible for reactions involving an external base. Nevertheless, it can be anticipated that the geometry of the transition state for nucleophilic attack

at the 2-position of I will be intermediate to those of J and CV and probably substantially more stable than would be expected from considerations based on the structures J and CV.

The 3-substituted cyclohexene oxides will be also expected to exist as an equilibrium mixture of the two conformations corresponding to the two half-chair conformations of the six-membered ring. Studies on the opening of the oxide ring when situated in conformationally rigid structures clearly show that the attack which leads to diaxial product take place 8 to 10 times faster than the attack at the other position. For this reason, as the best first approximation, all oxide ring-opening reactions of 3-substituted cyclohexene oxides will be considered to follow the Fürst-Plattner rule only.

A kinetic study of the reaction of such a substituted cyclohexene oxide must take into account the relative rates of reaction at the two centers (1- and 2-positions). The comparison of the rate of reaction at one of these centers with that of a center in cyclohexene oxide must be based on half the rate of the reaction of the latter compound under comparable reaction conditions. In the foregoing discussions, k_0 refers to half the rate constant of cyclohexene oxide and k_1 and k_2 refer to the actual rate constants for reactions at the 1- and 2-positions of

3-substituted cyclohexene oxides. For a given oxide, the observed rate constant k_T is related to k_1 and k_2 by the equation (1)

$$k_T = k_1 + k_2 \quad (1)$$

The rate constants k_1 and k_2 are related to the percentage of reaction P_1 and P_2 at 1- and 2-positions by equation (2)

$$\frac{k_1}{k_2} = \frac{P_1}{P_2} \quad (2)$$

From the equations (1) and (2) the values of k_1 and k_2 can be determined.

(1) Reaction of trans-3-Substituted Cyclohexene Oxides

The observed rate constants k_T , for the reaction of cyclohexene oxide and its trans-3-methyl and trans-3-methoxy derivatives with sodium methoxide in methanol at 33.6° and 54.5° are reported in Tables VI - XIII and summarized in Table XX. The values of k_1 and k_2 reported in Table XX for the trans-3-methyl and trans-3-methoxycyclohexene oxides were established by chromatographic analyzes of the products of the reactions (see p. 95). The observed rate constants, k_T , for the reaction of cis-3-methyl and cis-3-methoxycyclohexene oxides with sodium methoxide in methanol at 54.5° are also reported in Table XX.

TABLE XX

Summary of the First Order Rate Constants for the Methanolysis of Cyclohexene Oxide and 3-substituted Cyclohexene Oxides.

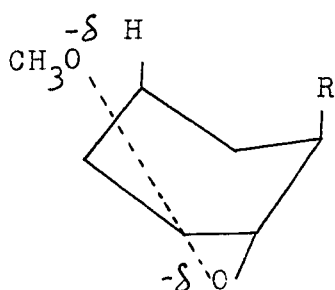
Equimolar amounts (0.5 M) of the oxide and sodium methoxide were reacted in pure methanol.

Compound	Temp., C°	Rate Constants, sec. ⁻¹		
		$k_T \times 10^6$	$k_1^{(a)} \times 10^6$	$k_2^{(a)} \times 10^6$
Cyclohexene Oxide	33.6	11	5.5	5.5
	54.5	68	34	34
<u>trans</u> -3-Methylcyclohexene Oxide (LXXXI)	33.6	0.8		
	54.5	5.71	4.3	1.40
<u>trans</u> -3-Methoxycyclohexene oxide (XLVI)	33.6	0.8		
	54.5	5.58	5.33	0.25
<u>cis</u> -3-Methylcyclohexene oxide (LXXXII)	54.5	50	50	
<u>cis</u> -3-Methoxycyclohexene oxide (LXII)	54.5	73	73	

(a) The rate constants k_1 and k_2 are related to rates of reaction at 1- and 2-positions of the oxide and $k_T = k_1 + k_2$.

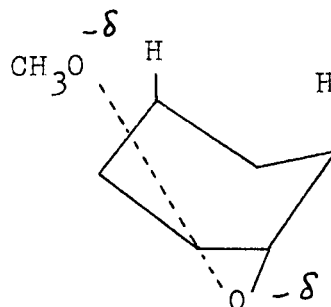
The relative rates of reaction of one position in cyclohexene oxide (set as 100) and each of the positions in trans-3-methyl, and trans-3-methoxycyclohexene oxides are given in Table XXI. The relative reactivities are also expressed in terms of $\Delta\Delta F^\ddagger$'s.

Inspection of Table XXI shows that the introduction of a substituent at the 3-position of the cyclohexene oxide molecule lowers the reactivity of both the 1- and 2-position. Let us consider first of all the reaction at the 1-position. The transition states can be represented by formula CVI and CVII. It is seen that, in view of the above considerations, the reactions at the 1-position should proceed mainly in



CVI, $R = CH_3$

CVII, $R = OCH_3$



CVIII

that conformation where the 3-substituent is in a quasi-axial orientation. This consideration alone can account for the lesser reactivities of the 1-positions of the 3-substituted compounds as compared to the reactivity of one of the positions of cyclohexene oxide (transition state CVIII). The transition

TABLE XXI

Rates for the Methanolysis of trans-3-substituted Cyclohexene Oxides at 54.5° Relative to Cyclohexene Oxide

Compound	Position of Reaction	Relative rate (a)	$\Delta\Delta F^\ddagger$ (b) kcal/mole
Cyclohexene Oxide	1	100	0
	2	100	0
<u>trans</u> -3-Methylcyclohexene Oxide	1	12.6	1.35
	2	4.2	2.07
<u>trans</u> -3-Methoxycyclohexene Oxide	1	15.6	1.21
	2	0.8	3.14

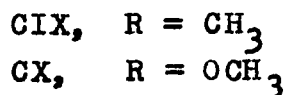
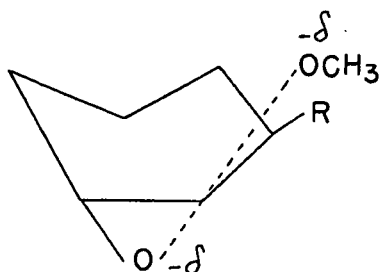
(a) Relative rate = rate constant for the position of the 3-substituted cyclohexene oxide undergoing reaction divided by one half the rate constant for the reference compound, cyclohexene oxide.

(b) $\Delta\Delta F^\ddagger = RT \ln k_r$ where k_r is the relative rate of the reaction.

states CVI and CVII can be expected to have the cyclohexane ring in a near half-chair conformation. If the oxygen atoms of the methoxide ion and of the oxide ring and the carbon of the reacting center are in a near linear arrangement, obviously the distance between the oxygen of the entering methoxide ion and the 3-substituent in the transition states CVI and CVII must be greater than in the case where the transition states have the cyclohexane ring in a chair conformation with the 3-substituent and the entering methoxide ion both axial. This is reflected by the rather low values of $\Delta\Delta F^\ddagger$ for the ring opening at the 1-position. A 1,3-diaxial interaction between two oxygen atoms can be expected (104) to be about 2 kcal/mole and an oxygen-methyl group 1,3-diaxial interaction should be at least nearly as great. Assuming that only 1,3-interactions are important in fixing the stabilities of the transition states relative to the ground states and taking into consideration the facts that a gauche interaction between a methyl and a methylene group is 0.9 kcal/mole (97) and that between an oxygen atom and a methylene group is 0.2-0.4 kcal/mole, (104,105) it would follow that the interactions between the quasi-axial R groups and the entering methoxide ion in the transition states CVI and CVII would be about 0.45 kcal/mole of the 3-methylcyclohexene oxide reaction and 0.8-1.0 kcal/mole for the 3-methoxycyclohexene oxide reaction. Such a situation may be

the case since the repulsion between two opposed oxygen atoms may be largely electrostatic in origin and thus fall off with only the square of the distance while a steric interaction such as can be assumed between a methyl group and an oxygen atom would fall off with about the ninth power of distance.

Turning now to a consideration of the relative rates of reaction at the 2-positions, a consideration of the geometry of the most likely transition states CIX and CX seems illuminating. If the two oxygen atoms and the



2-carbon are in a linear arrangement in the transition state, a study of a model shows clearly that the entering methoxy group and the R group must be strongly eclipsed. On steric grounds only, since the Van der Waal radii for an oxygen atom and a methyl group are 1.4 Å and 2.0 Å, respectively, it would be expected that the trans-3-methylcyclohexene oxide would undergo reaction at the 2-position less readily than trans-3-methoxycyclohexene oxide. It is seen in

Table XX, however, that the reverse is true; the latter compound undergoing reaction at a rate six times less than the former. This amounts to a difference in $\Delta\Delta F^\ddagger$'s for the reactions of about 1.1 kcal/mole. The errors inherent in the determination of the free energies of activation for these reactions do not allow conclusions regarding the contribution of the entropies of activation toward this difference. It seems likely that change in entropy considerations would favor reaction of the 3-methyl over the 3-methoxy compound since the latter compound is undoubtedly conformationally less pure and, consequently, stabilized to a greater extent through entropy of mixing and the achievement of its transition state will require the methyl group of the methoxy group to be directed away from the entering group - an effect which will tend to decrease the entropy of activation relative to the situation when the R group is methyl. Nevertheless, it seems likely that the non-bonded interaction between the entering methoxide ion and the R-group is not greatly different whether the R group in methoxy or methyl. The apparently anomalously great effect of the methoxy group may be due to its electronegativity. Parker and Isaaks (8) and also Lemieux and coworkers (70) have suggested that the inductive effect (-I) of the methoxy group may render it more difficult for the reacting center to achieve the carbonium ion character at the transition state. On the other hand, the electrostatic

repulsions between the C₂-O and C₃-O bonds may be much greater when one of the oxygen atoms carries the much larger partial negative charge of the transition state than when two methoxy groups are nearly eclipsed in an electrically neutral molecule. Chu (36) has obtained evidence that the interaction energy (0.55 kcal/mole) for two oxygen atoms in gauche orientation is considerably greater than that (0.2 kcal/mole) for an oxygen atom in gauche orientation with a methylene group. On the other hand, Angyal and McHugh (104) have provided evidence that these interactions have values of 0.35 and 0.45 kcals/mole. The present results do not allow a decision on these matters.

The fact remains to note that for both the trans-oxides the 2-position is considerably less reactive than the 1-position especially in the case of the trans-3-methoxycyclohexene oxide. Thus, for these conformationally not highly rigid compounds, the preferred routes of reaction are by way of the less stable conformations for the oxides. This result requires strong interaction between the entering group and the 3-substituent when the attack is at the 2-position and therefore confirms the above expressed conclusion as to the structure of the transition state.

It would be predicted on the basis of this conclusion, that the 3-substituent and the entering group are strongly eclipsed in an attack at 2-position, that the larger

the attacking group, the more preferential would be the attack at the 1-position. This prediction is partially supported by data presented in Table XXII. It is seen that attack at the 2-position of 3-methylcyclohexene oxide, except for the reaction of sodium thioethoxide, seems preferred the smaller the entering group. The space requirements for a methoxide versus a thioethoxide ion in making a nucleophilic attack should be less for the methoxide ion since the Van der Waal radius for oxygen ($1.4 \text{ \AA}$) is less than that for sulfur ($1.85 \text{ \AA}$).

However, the situation here may be complicated for the kind of reasons advanced by Eliel (106) for the rather low gauche interaction of a bromine atom with a methyl group as compared to that between two methyl groups in spite of the fact that the Van der Waal's radii for a bromine atom and methyl group are about the same.

The courses of the reactions of trans-3-methoxycyclohexene oxide with a variety of nucleophilic reagents are summarized in Table XXIII. It is seen that all the reagents except for dimethyl magnesium showed a strong preference for reaction at the 1-position. In the case of dimethyl magnesium, it is not unlikely that the complex CXI is formed and this brings a methyl group in close proximity to the reacting center. Also, dimethyl magnesium may promote reaction by acting as a Lewis acid.

TABLE XXII

Reactions of trans-3-Methylcyclohexene Oxide with a Variety
of Nucleophilic Reagents

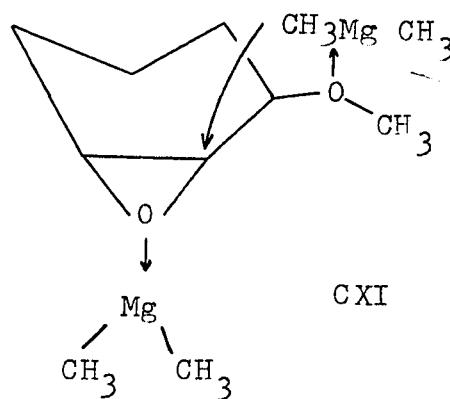
Reagent	Reaction conditions	Percentage opening	
		1-position	2-position
LiAlH_4	Ether at 35°	34.5	65.5
NaOH	Dioxane-water (1:1) at 100°	45	55
NaOCH_3	Methanol at 54.5°	77.5	24.5
NaSC_2H_5	Methanol at 0°	63	37

TABLE XXIII

Reactions of trans-3-Methoxycyclohexene Oxide with Various
Nucleophilic Reagents

Reagent	Reaction Conditions	Percentage opening	
		1-position	2-position
LiAlH_4	Ether at 35°	97	3
NaOH^*	Water at 100°	80	20
NaOCH_3	Methanol at 54.5°	95	5
NaSC_2H_5	Methanol at 0°	90	10
$(\text{CH}_3)_2\text{Mg}$	Ether at room temperature	54	46

* Values reported in the literature (70).



(2) Reaction of cis-3-Substituted Cyclohexene Oxides

The rate constants were determined for the reactions of cyclohexene oxide and of the cis-3-methyl and cis-3-methoxy-cyclohexene oxides with sodium methoxide in methanol at 54.5°. It was not possible to establish conditions for vapor phase chromatographic analysis that would allow the determination of the relative amounts of the two products resulting from the reaction of 3-substituted cyclohexene oxide. Judging from the results obtained in the reactions of these oxides with other reagents (see Tables XXIV and XXV), it can be assumed that the methanolysis occurred preponderantly (over 90%) at the 1-position. This result is not surprising from the point of view of conformational analysis. For a cis-3-substituted cyclohexene oxide to undergo reaction at the 2-position according to the Fürst-Plattner rule, the 3-substituent would have to be in a quasi-axial orientation and strongly compressed with the

TABLE XXIV

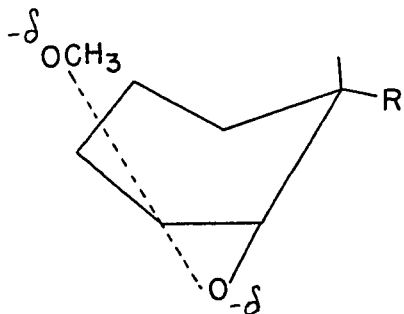
Reactions of cis-3-Methylcyclohexene Oxide with Various
Nucleophilic Reagents

Reagent	Reaction Conditions	Percentage opening	
		1-position	2-position
LiAlH_4	Ether at 35°	90	10
NaOH	Dioxane-water (1:1) at 100°	97-99	1-3
NaSC_2H_5	Methanol at 0°	96	4

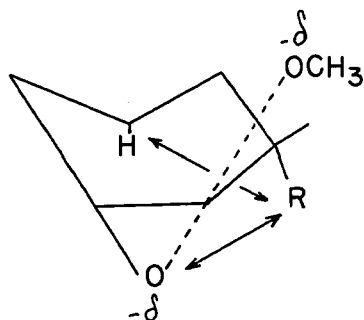
TABLE XXV

Reactions of cis-3-Methoxycyclohexene Oxide with Various
Nucleophilic Reagents

Reagent	Reaction Conditions	Percentage Opening		References
		1-position	2-position	
LiAlH_4	Ether at 35°	98	2	
NaOH	Water at 100°	81	19	(70)
NaOCH_3	Methanol at boiling temperature	only		(72)
NH_3	Water-ethanol at 100°	only		(73)
NaSC_2H_5	Methanol at 0°	99	1	



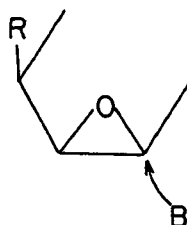
CXIV, R = CH₃
CXV, R = OCH₃



CXII, R = CH₃
CXIII, R = OCH₃

oxygen atom of the oxide ring as it is indicated by the formulas CXII and CXIII. Also, the quasi-axial 3-substituent would have a gauche interaction with the methylene group. On the other hand, attack at the 1-position would proceed through transition states CXIV and CXV in which the 3-substituent is in a quasi-equatorial orientation and on the side of the cyclohexane ring opposite to that of the entering group. Consequently, the reaction could be expected to proceed as readily as the reaction of cyclohexene oxide. In fact, the rate constants for the methanolysis of these oxides, given in Tables XX and XXI, show that both the cis-3-methyl and cis-3-methoxycyclohexene oxides underwent reaction at very much the same but somewhat more rapid a rate than half the rate of cyclohexene oxide. This result is in contrast to the ideas of Bose et al (107) for the effect of a 3-substituent cis to the epoxide ring on the reactivity of the 1-position. Bose et al (107) suggested that sugar epoxides, which have a substituent at the α -position cis to the epoxide oxygen, tend to avoid attack in the manner

shown by the formula below. Obviously, this is exactly



opposite to the present findings.

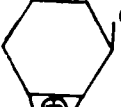
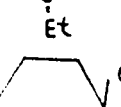
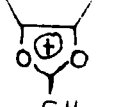
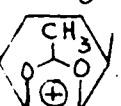
D. The Routes for the Reactions of a Number of
1,2-Bridged Cationic Derivatives of 3-Substituted
Cyclohexanes

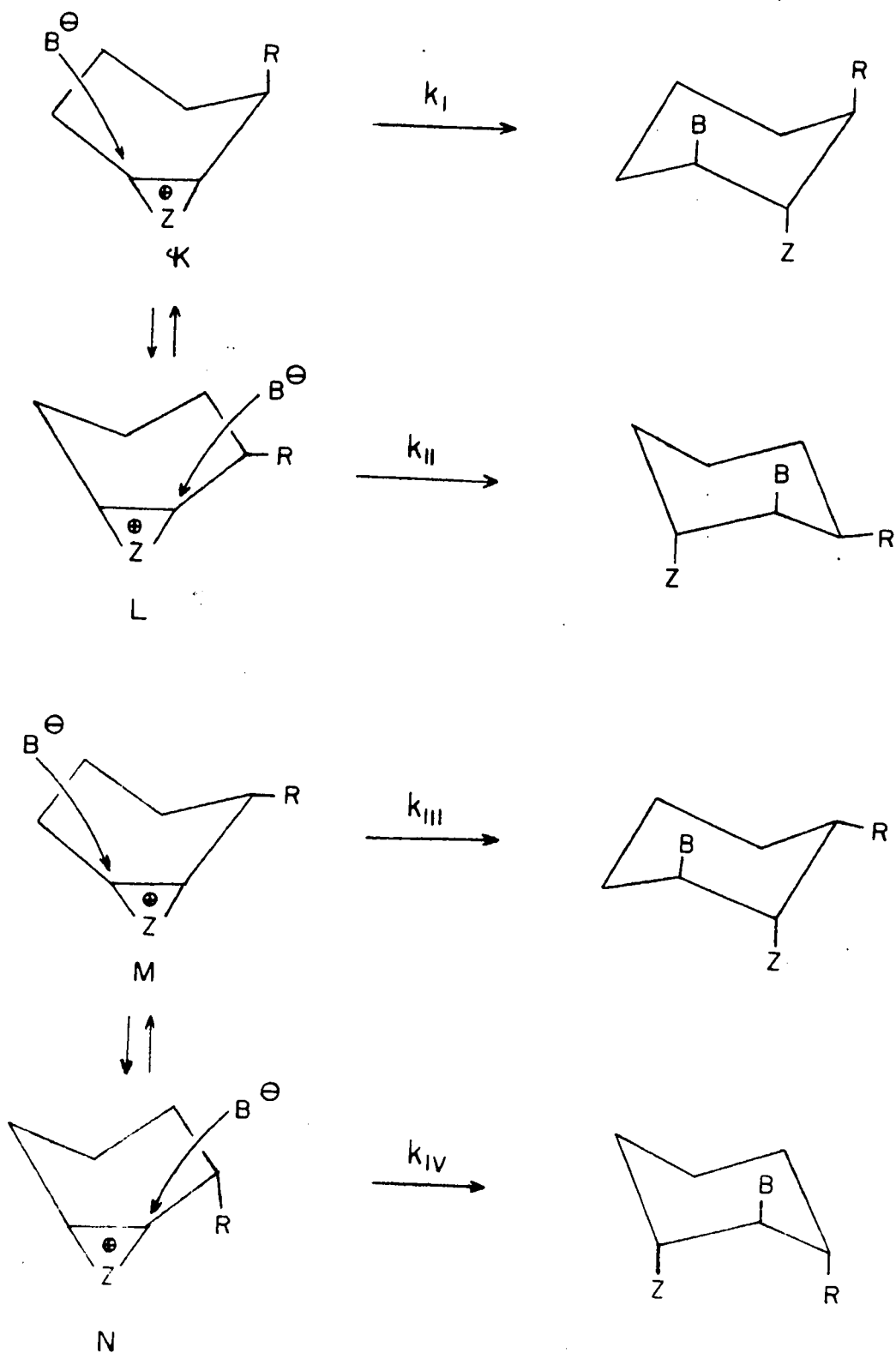
The directions of the ring openings of 1,2-bridged cationic derivatives of 3-substituted cyclohexenes are shown in Table XXVI.

In view of the results obtained from the study of the reactions of cis and trans-3-methylcyclohexene oxides and cis and trans-3-methoxycyclohexene oxides the reactive bridged cationic substances could be anticipated to have the following reaction properties since the structures of these compounds bear an obvious close relationship to the structures of the oxides. First of all, if the cationic species K - N are formed reversibly and do not differ appreciably in stability, it could be predicted that the relative rates of the ring-opening reactions would be

TABLE XXVI

Direction of Opening of the 3-substituted-1,2-bridged Cyclohexene Cationic Intermediates

Compound	Reagent	Percentage reaction	
		1-position	2-position
	AcOH or AcO ⁻	only	-
	AcOH or AcO ⁻	only	-
	3,5-dinitrobenzoate ion	97	3
	3,5-dinitrobenzoate ion	57	43
	AcOH or AcO ⁻	96	4
	AcOH or AcO ⁻	95	5
	AcOH or AcO ⁻	45	55
	AcOH or AcO ⁻	88	12
	AcOH or AcO ⁻	~ 90	~ 10
	AcOH or AcO ⁻	~ 90	~ 10



$k_{III} > k_I > k_{II} \geq k_{IV}$. This idea of course is based on the assumption that the Fürst-Plattner rule is maintained. Thus, it may have been anticipated that the main product of the reaction of 3-methoxycyclohexene with equimolar amounts of silver acetate and iodine (see p. 109) to form 3-methoxy-1,2-iodoacetoxycyclohexanes would be mainly the isomer derived from the iodonium ion (XLIIa) which corresponds to M in the generalized scheme. In accordance with this speculation, the reaction gave the 1β -acetoxy- 2α -iodo- 3α -methoxycyclohexane (XLII) in 65% yield. The other major product of the reaction (based on the course of the reactions of the 3-methoxycyclohexene oxides) would be the one derived from the iodonium ion (XLIIb) which corresponds to K in the generalized scheme. In fact this was the only other isomer isolated and this in 14% yield.

The results obtained from the reaction of 3-methylcyclohexene with equimolar amounts of silver 3,5-dinitrobenzoate and iodine in benzene (see p. 136) are also in agreement with expectations based on the course of the reactions of 3-methylcyclohexene oxides. Thus, the main product of this reaction was the 1β -(3,5-dinitrobenzoyloxy)- 2α -iodo- 3α -methylcyclohexane (LXXIX) (61%) which obviously was derived from the iodonium ion LXXVa (ion M in the generalized scheme). Two other products of this reaction were isolated, 1α -(3,5-dinitrobenzoyloxy)- 2β -iodo- 3α -

methylcyclohexane (LXXVII) in 19% yield, and 1 β -iodo-2 α -(3,5-dinitrobenzoyloxy)-3 α -methylcyclohexane (LXXVIII) in 14% yield. These compounds would arise from the iodonium ions LXXVIb and LXXVIa (see p. 136), respectively, which correspond to the ions K and L, respectively, in the generalized formulas. Furthermore, the compound, 1 α -iodo-2 β -(3,5-dinitrobenzoyloxy)-3 α -methylcyclohexane (LXXX) which would arise from the iodonium ion LXXVb (the same as N in the general scheme) was formed only in 3% yield, a result which agrees well with the expectations. The fact that the cis-3-methyl iodonium ion (LXXVa $\rightleftharpoons$ LXXVb) opened almost exclusively at the 1-position supports the contention that these cationic species open to form initially the diaxial product. Evidence for diaxial opening of halonium ionic intermediates was reported by Alt and Barton (108) with reference to the addition of halogens to unsaturated steroids.

The solvolysis of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII) in dry acetic acid in the presence of silver acetate (see p. 116) produced the diacetate of 3 α -methoxy-1 α ,2 β -cyclohexanediol (LI) as the main product of the reaction (70% yield). This fact indicates that the first formed acetoxonium ion (XLIXa) was converted to the conformational isomer (XLIXb) for reaction at the 1-position. This conversion could occur by simple conformational change

of the acetoxonium ion if its barrier to reaction is greater than that for the conformational change. It is clear however that the acetyl orthoacetate ($\text{La} \rightleftharpoons \text{Lb}$) is an unstable intermediate in these reactions (47) and the conformational change for the acetoxonium ions can proceed by way of this intermediate. The fact that the acetoxonium ion opened preferentially at the 1-position obviously parallels the reaction of the related trans-3-methoxycyclohexene oxide (XLVI). The acetolysis of 1 α -acetoxy-2 β -iodo-3 α -methoxycyclohexane (XLIII) in dry acetic acid in the presence of silver acetate (see p. 119) also followed the route of reaction predicted by the generalized scheme. Here again the acetoxonium ion presumably did not react in the conformation in which it was formed (LIIIIa). Instead it was converted to the conformational isomer LIIIIb which then underwent reaction at the 1-position to give the diacetate of 3 α -methoxy-1 β , 2 α -cyclohexenediol (LII). As will be seen later on, the rates for the acetolysis of the iodo-compounds (XLII, XLIII) can be interpreted to support the above contentions related to the conformational inter-conversions of acetoxonium ions.

The stereochemical results of the reactions of the thioethers LVa and LVIIa by way of the sulfonium ion ($\text{LIXa} \rightleftharpoons \text{LIXb}$) are also in agreement with the generalized scheme. The reaction of the mixture of 1 α -ethylthio-3 α -

methoxy-2 β -cyclohexanol (LVa) (90%) and 2 α -ethylthio-3 α -methoxy-1 β -cyclohexanol (LVia) (10%) with concentrated hydrochloric acid (see p. 122) gave a mixture containing 80% of 1 β -chloro-2 α -ethylthio-3 α -methoxycyclohexane (LXI) and 20% of 1 α -ethylthio-2 β -chloro-3 α -methoxycyclohexane (LX). Should the sulfonium ions react in the conformations in which they are formed, the overall reaction would take place with retention of the configurations of the reactants. That is, the chlorocompounds obtained would consist of 90% of 1 α ,2 β ,3 α -compound (LX) and 10% of the 1 β ,2 α ,3 α -isomer (LXI). However, almost the reverse was the case. Therefore, it must be concluded that interconversion of the two conformations of the sulfonium ion (LIXa $\rightleftharpoons$ LIXb) took place prior to their reaction and that the sulfonium ion LIXb reacts faster than the conformational isomer LIXa. This result is not surprising in view of the well known stability of sulfonium ions.

The routes of opening of the 3-methylcyclohexene sulfonium cations CIII and CIV are also in accordance to the routes of opening of the corresponding cis and trans-3-methylcyclohexene oxides. Thus, acetolysis of a mixture of 3-methyl-1,2-chloroethylthiocyclohexanes (XCIX-CII) (see p.164) indicated that the sulfonium cation CIII underwent opening at the 1-position to the extent of 95% and the sulfonium cation CIV opened at the 1-position to

the extent of 45%.

E. Kinetics of the Acetolysis of trans-1-Acetoxy-2-Iodo-cyclohexane (CXVI), 1 β -Acetoxy-2 α -Iodo-3 α -Methoxycyclohexane (XLII) and 1 α -Acetoxy-2 β -Iodo-3 α -Methoxycyclohexane (XLIII)

Winstein and coworkers (45) have shown that the ratios of the rate constants for the acetolysis of cyclohexyl tosylate, trans-2-acetoxycyclohexyl tosylate and cis-2-acetoxycyclohexyl tosylate were 1:0.3:4.5 x 10⁻⁴. The lower reactivity of the cis-1,2-isomer as compared to that of cyclohexyl tosylate was attributed to the electron withdrawing effect of the acetoxy group which inhibits the departure of the tosyloxy group to leave a carbonium ion. The much greater reactivity of the trans-1,2-compound over that of cis-1,2-isomer as was seen in p.16 is related to participation of the acetoxy group in the process of the dissociation.

The three above mentioned reactions are classified as S_N¹ reactions since in each case the rate determining stage involves the scission of the tosyloxy to carbon bond prior to nucleophilic attack by the acetate ion or the acetic acid molecule from the solvent. However, in the case of the reaction of the trans-2-acetoxycyclohexyl tosylate, the rate determining step involves nucleophilic attack by

the neighboring acetoxy group in the course of the dissociation of the tosyloxy to carbon bond. Consequently, the reacting center will not develop as high a carbonium ion character as in the case for the other two tosylates. It would therefore be predicted that the effect on the rate of introducing an electron-withdrawing group at the 3-position of the trans-1-acetoxy-2-tosyloxycyclohexane should be more like the rather small effects noted for S_N2 reactions than the large effects, as noted for example above, for the S_N1 reactions. The foregoing results substantiate this prediction.

The rate for the acetolysis of trans-1-acetoxy-2-iodocyclohexane (CXVI) at 117.5° and the rates of acetolysis of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII) and 1 α -acetoxy-2 β -iodo-3 α -methoxycyclohexane (XLIII) at 98.5° and 117.5° are given in Tables XIV - XVIII, pp. 99-103 and summarized in Table XXVII, p. 192. It is seen that the introduction of a methoxy group at the 3-position of CXVI decreases the rate of reaction in both the configurations for the resulting compound. This decrease at the rates could partly be arisen from the electron-withdrawing effect of the methoxy group. However, this effect is small in comparison with the effect of electronegative groups in S_N1 reactions which do not involve participation of neighboring groups.

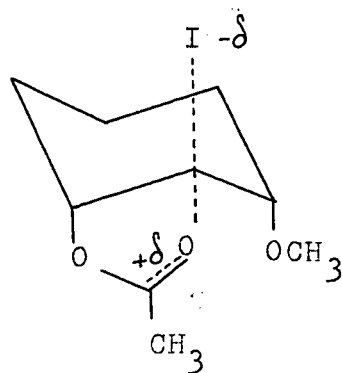
The lower reactivity (3.5 to 6 times) of the

TABLE XXVII

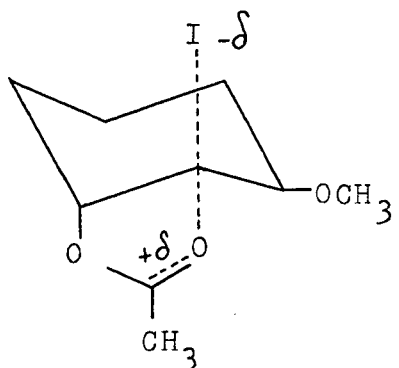
Summary of the First Order Rate Constants for the Acetolysis
of Some Substituted 2-Acetoxycyclohexyl Iodides

Compound	Temperature	$k \times 10^{-7}$ (sec. ⁻¹)
<u>trans</u> -1-acetoxy-2-iodocyclohexane	117.5°	417
1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane (XLII)	98.5°	4.25
	117.5°	30.7
1 α -acetoxy-2 β -iodo-3 α -methoxycyclohexane (XLIII)	98.5°	0.65
	117.5°	8.8

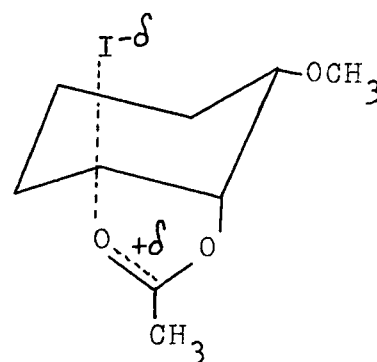
1 α ,2 β ,3 α -compound (XLIII) in comparison with that of the 1 β ,2 α ,3 α -isomer (XLII) can be rationalized by consideration of the transition states for the reactions of these compounds. In the transition state for the compound with the 1 α ,2 β ,3 α -configuration represented by formula CXVII must be a



CXVII



CXVIII



CXIX

strong interaction between the oxygen atoms of the participating group and the oxygen of the methoxy group. These interactions must be greatly reduced in the transition state CXVIII for the reaction of the 1 β ,2 α ,3 α -compound. The results clearly require a destabilization of the transition state CXVII which is brought on by the non-bonded interaction between the oxygen atoms. This interaction would be much less in the solvolysis of the isomeric 1 β -iodo-2 α acetoxy-3 α -methoxycyclohexane (XLIV) by way of the transition state CXIX. In other words, one would expect on steric grounds the transition state CXIX to be considerably more stable than the transition state CXVII and this can be assumed to

be the case regardless of the nature of the departing group. The electronegative methoxy group is removed to a greater extent from the reacting center in the case of the transition state CXIX and this fact would also favor a greater stability for CXIX than for CXVII. Thus, the high preference (over 80%) of cis-3-methoxycyclohexene acetoxonium ion to react at the 1-position over the 2-position, as already mentioned above (see p. 188) is confirmed by these kinetic investigations.

CLAIMS TO ORIGINAL RESEARCH

1. The following compounds were synthesized. Their structures and configurations were established using nuclear magnetic resonance spectroscopy as well as classical methods.
 1. 1 α -acetoxy-2 β -iodo-3 α -methoxycyclohexane
 2. 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane
 3. 1 α -iodo-2 β -acetoxy-3 α -methoxycyclohexane
 4. 1 α -ethylthio-2 β -(3,5-dinitrobenzoyloxy)-3 α -methoxycyclohexane
 5. 1 β -acetoxy-2 α -ethylthio-3 α -methoxycyclohexane
 6. 1 α -methyl-2 β -p.nitrobenzoyloxy-3 α -methylcyclohexane
 7. 1 β -p.nitrobenzoyloxy-2 α -methyl-3 α -methoxycyclohexane
 8. 3 α -methyl-1 α ,2 β -cyclohexanediol
 9. 3 α -methyl-1 β ,2 α -cyclohexanediol
 10. 3 α -methyl-1 β ,2 β -cyclohexanediol
 11. 1 β -(3,5-dinitrobenzoyloxy)-2 α -iodo-3 α -methylcyclohexane
 12. 1 α -(3,5-dinitrobenzoyloxy)-2 β -iodo-3 α -methylcyclohexane
 13. 1 α -iodo-2 β -(3,5-dinitrobenzoyloxy)-3 α -methylcyclohexane
 14. 1 β -iodo-2 α -(3,5-dinitrobenzoyloxy)-3 α -methylcyclohexane

15. trans-3-methylcyclohexene oxide

2. A method was developed for the synthesis of a cis-1,2-diol from an epoxide by reaction of the latter with acetyl chloride followed by acetolysis of the resulting product. The method is illustrated by the synthesis of 3 α -methyl-1 β ,2 β -cyclohexanediol from trans-3-methylcyclohexene oxide.
3. Concentrated solutions (2N) of dimethylmagnesium in ether were prepared. The high concentrations of these solutions now make possible use of this reagent for the synthesis of trans-2-methyl alcohols from 1,2-epoxides.
4. Perbenzoic acid oxidation of 3-methoxycyclohexene gave a mixture of cis- and trans-3-methoxycyclohexene oxides in which the trans-isomer was the main product (82%).
5. Perbenzoic acid oxidation of 3-methylcyclohexene gave an almost equimolar mixture of cis- and trans-methylcyclohexene oxides.
6. Polar effects seem to have a greater influence than steric effects on the stereochemical routes of the perbenzoic acid oxidations of 3-substituted cyclohexenes.
7. The rate constants of the methanolysis of cyclohexene oxide, trans-3-methoxycyclohexene oxide and trans-3-methylcyclohexene oxide, at 33.6 and 54.5°, and of cis-3-methoxycyclohexene oxide and cis-3-methylcyclohexene

oxide, at 54.5° , were determined. The relative rates of reaction of one position in cyclohexene oxide (set as 100.) and each of the positions (1- and 2-) in 3-substituted cyclohexene oxides were calculated. The effect of 3-substituent on the reactivity of the 1- and 2-positions of 3-substituted cyclohexene oxides was rationalized in terms of conformational analysis of the transition states for the reactions of these compounds.

8. trans-3-Methoxycyclohexene oxide reacted preferentially at the 1-position (more than 90%) with the following nucleophilic reagents: a) sodium thioethoxide in methanol b) sodium methoxide in methanol and c) lithium aluminum hydride in ether.
9. trans-3-Methoxycyclohexene oxide reacted with dimethylmagnesium in ether in almost equal amounts at the 1- and 2-positions. A theoretical interpretation of the apparent anomaly is described.
10. cis-3-Methoxycyclohexene oxide reacted almost exclusively at the 1-position (98%) with the following nucleophilic reagents: a) sodium thioethoxide in methanol and b) lithium aluminum hydride in ether.
11. The percentage reaction at the 1-position of trans-3-methylcyclohexene oxide with a variety of nucleophilic reagents was as follows: a) with lithium aluminum hydride in

- ether, ^{34.5}/b) with sodium hydroxide in dioxane-water, 45
- c) with sodium methoxide in methanol, 77.5 and
- d) with sodium thioethoxide in methanol, 63.
12. cis-3-Methylcyclohexene oxide reacted preferentially at the 1-position (90% or more) with the following nucleophilic reagents: a) sodium thioethoxide in methanol b) lithium aluminum hydride in ether and c) sodium hydroxide in dioxane-water.
13. trans-3-Methoxycyclohexene-1,2-iodonium ion was attacked in acetic acid containing acetate ion almost exclusively at the 1-position.
14. cis-3-Methoxycyclohexene-1,2-iodonium ion was attacked in acetic acid containing acetate ion almost exclusively at the 1-position.
15. The opening of trans-3-methylcyclohexene-1,2-iodonium ion with 3,5-dinitrobenzoate ion proceeded to extents of 57% and 43% at the 1- and 2-position, respectively.
16. cis-3-Methylcyclohexene-1,2-iodonium ion was attacked by 3,5-dinitrobenzoate ion mainly at the 1-position (97%).
17. trans-3-Methoxycyclohexene-1,2-acetoxonium ion was attacked in acetic acid containing acetate ion mainly at the 1-position (88%).
18. cis-3-Methoxycyclohexene-1,2-acetoxonium ion was attacked by acetic acid containing acetate ion mainly at the 1-position.

19. cis-3-Methoxycyclohexene-1,2-ethylsulfonium ion was attacked in acetic acid containing acetate ion mainly at the 1-position (96%).
20. cis-3-Methylcyclohexene-1,2-ethylsulfonium ion was attacked in acetic acid containing acetate ion mainly at the 1-position (95%).
21. The opening of trans-3-methylcyclohexene-1,2-ethylsulfonium ion with acetic acid containing acetate ion took place of the 1- and 2-positions to extents of 45 and 55%, respectively.
22. Treatment of 3 α -methoxy-2 β -ethylthio-1 α -cyclohexanol with concentrated hydrochloric acid resulted in the displacement of both the hydroxy and the methoxy groups by chlorine atoms.
23. The rate constants for the acetolysis of trans-1-acetoxy-2-iodocyclohexane at 117.5° and the rate constants of the acetolysis of 1 β -acetoxy-2 α -iodo-3 α -methoxycyclohexane and 1 α -acetoxy-2 β -iodo-3 α -methoxycyclohexane at 98.5 and 117.5° were determined.

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