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AN APPROACH TO THE STEREOSPECIFIC TOTAL SYNTHESIS OF 5,6-DIDEOXY-5-AMINO-HEXONIC ACIDS AND RELATED COMPOUNDS

by

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Fulfillment of the Requirements for the
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October, 1961.

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PREFACE

In recent years, the chemistry and biochemistry of aminosugars has attracted a great deal of interest because of their frequent occurrence in a variety of natural products such as the antibiotics, antigenic polysaccharides, cell wall constituents, etc... In many cases, the aminosugars are difficultly accessible by synthesis, a situation which stems from the multiplicity of reactive functional groups as well as the contiguity of asymmetric centers in carbohydrates. It is this latter characteristic in particular which would appear to have discouraged efforts directed at the total synthesis of carbohydrates and their derivatives, there being little hope of achieving stereochemical control when creating a sequence of contiguous asymmetric centers. For this reason, the stereospecific total synthesis of a carbohydrate-like structure has thus far never been accomplished and because of our special interest in the biochemistry of aminosugars, an effort has been made to design novel methods of approach giving access to certain hexosaminic acids through the application of stereospecific reactions. Of special interest is our selection as starting material of a six-carbon compound carrying no asymmetric center. The key step of this approach involves a Diels-Alder addition of a nitrosoalkane to methyl

sorbate, a reaction which proceeds in such a way as to eventually lead to a carbohydrate-like structure carrying an amino group on carbon atom 5 of the molecule. A search of the literature revealed that 5-deoxy-5-amino hexoses represent an as yet unknown class of compounds, so that no historical introduction can be given. During the course of our investigations, some important new knowledge about the mechanism of the Diels-Alder reaction has been acquired, thereby making it worth whileelaborating on this aspect of our work in the present thesis. It is our opinion that the research described below offers some new perspectives in the field of synthetic and theoretical organic chemistry and makes available unusual structures of biochemical interest.

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ABSTRACT

An approach to the stereospecific synthesis of polyhydroxy-5-aminohexanoic acids was designed. It was found that 1-chloro-1-nitrosocyclohexane undergoes a Diels-Alder reaction with methyl sorbate to give one stereoisomer of 3-methyl 3,6-dihydro-1,2-oxazine-6-carboxylic acid methyl ester. A number of derivatives of this latter compound are described. Catalytic hydrogenation afforded one isomer only of 2-hydroxy-5-aminohexanoic acid, a novel amino acid. Hydroxylation of the Diels-Alder adduct (as the N-benzoyl derivative) with osmium tetroxide followed by hydrolysis and hydrogenation afforded what is tentatively regarded as 5,6-dideoxy-5-aminotalonic acid. Epoxidation of the adduct with peroxytrifluoroacetic acid gave a 50:50 mixture of crystalline epoxides which were separated. The configuration of these epoxides was deduced from a study of their reaction with hydriodic acid. Pure stereoisomeric iodohydrins were obtained which were assigned configurations on the basis of their behavior under conditions of methanolysis. Similarly, chlorohydrins were obtained and assigned configurations by analogy with the course of iodohydrin formation. Reaction of the oxides with formic acid followed by methanolysis afforded a single mixture of trans-diols (3,4,5,6-tetrahydro-

3-methyl-4,5-dihydroxy-1,2-oxazine-6-carboxylic acid methyl ester), which are useful potential precursors of additional aminosugar-like compounds. Spectroscopic (IR and NMR) properties of several of the compounds are reported. Mechanistic considerations lead to the conclusion that the formation of the starting adduct probably proceeds by way of a two-step process, a course of reaction which is without precedent.

INTRODUCTION

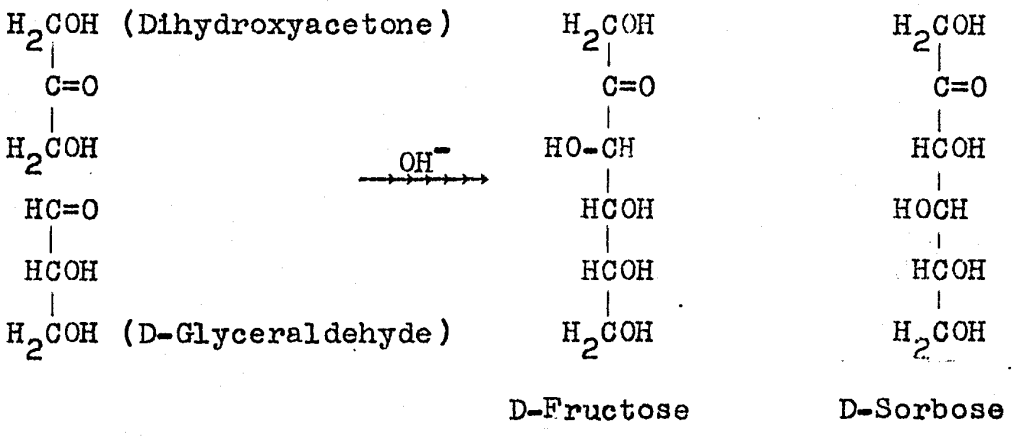
It has been discovered in recent years that amino-sugars occur as key constituents of several important classes of natural products such as the antibiotics, antigenic polysaccharides, bacterial cell wall constituents, etc... These subjects have been reviewed recently and it is apparent that their biochemistry is as yet poorly defined although much has been learned about their chemistry. More specifically, much of the present and past interest in this field has been focused on the synthesis of a variety of aminosugars with a view to establishing the structure of natural products containing such molecules as building blocks.[1,2,3,4,5] The most widely occurring type of aminosugars are those having the amino group in position 2 of the carbohydrate molecule (I),[6,7,8,9] although the occurrence of 3-deoxy-3-amino and 6-deoxy-6-aminosugars[10] has been noted. Such compounds have been made available through partial synthesis using as starting material one of the more common and readily available carbo-hydrates. A particularly elegant and novel method of synthesis has been recently developped by Baer and Fisher and leads to the difficultly accessible 3-deoxy-3-aminosugars.[11] In the case of the 2- and 6-deoxy-aminosugars, the application of the usual substitution reaction whereby a suitable leaving

group is displaced by ammonia or one of its derivatives (such as hydrazine) has found wide acceptance as a preparative method. A survey of the literature readily reveals that total synthesis of hexoses from precursors carrying no pre-formed asymmetric centers has never been given consideration as a potentially useful preparative approach presumably because of the presence in such structures of four contiguous asymmetric centers which contribute eight racemic modifications or sixteen optical isomers all of which have been obtained either from natural sources or by partial synthesis. Unless highly stereospecific syntheses become available, total synthesis poses an insurmontable problem from the practical standpoint and it is for this reason that such an approach has thus far been only of academic interest especially since a number of hexoses are readily available from natural sources and frequently easily interconvertible through well established reaction sequences. The partial synthesis of aminosugars is however much less flexible and imposes serious limitations to the general availability of these less common structures. Because of the extraordinary progress in the field of stereochemistry over the past fifteen years or so, it was thought worthwhile taking a second look at the potentialities of modern synthetic organic chemistry as applied to the problem of the stereospecific total synthesis of aminohexose-like structures. A brief historical account of

previous attempts in this field may be pertinent at this point in order that comparisons may be drawn with the approach making the subject of the present thesis.

The synthesis of D-glucose, D-mannose and D-fructose from α-acrose was first reported by Fisher and Tafel in 1887.[12] Some fifty years later, Fisher and Baer[13] found that a mixture of D-fructose and D-sorbose is formed when D-glyceraldehyde and dihydroxyacetone are condensed in aqueous barium hydroxide solution (Chart 1). In this process, no appreciable quantities

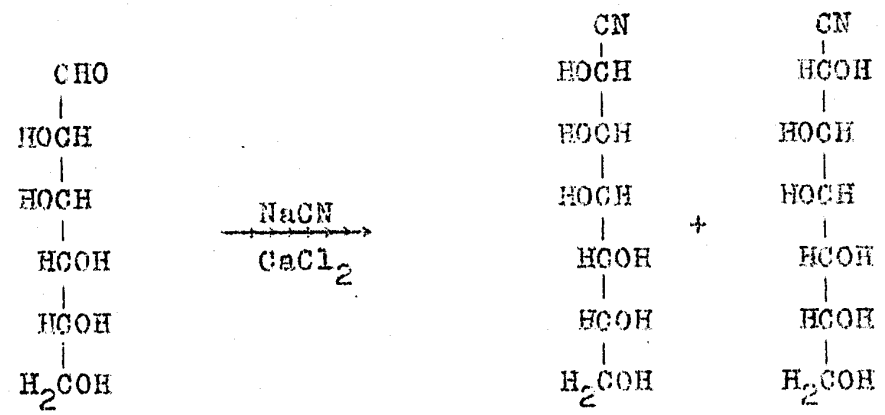
Chart 1



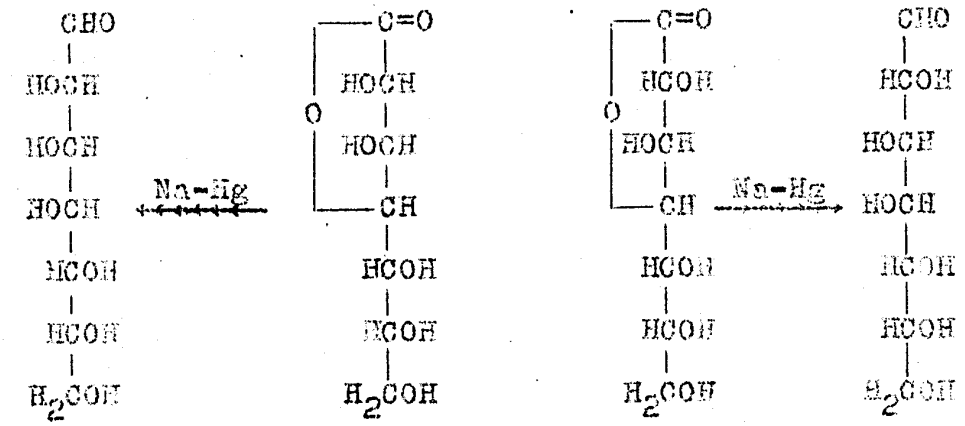
of D-tagatose and D-psicose appeared to be produced. It should be noted here that precursors possessing an asymmetric center have been used as starting material and the yields of pure products are to say the least prohibitive, thus making these approaches of academic interest only. The conversion of a reducing sugar to a higher homolog can be accomplished much more successfully through the application of the classical

Kiliani synthesis. In this process which involves the intermediacy of cyanohydrins, good stereochemical control is usually possible because of the strong directive influence of the pre-formed asymmetric centers on the course of the reaction (Chart 2). The subsequent discovery by Fisher that

Chart 2

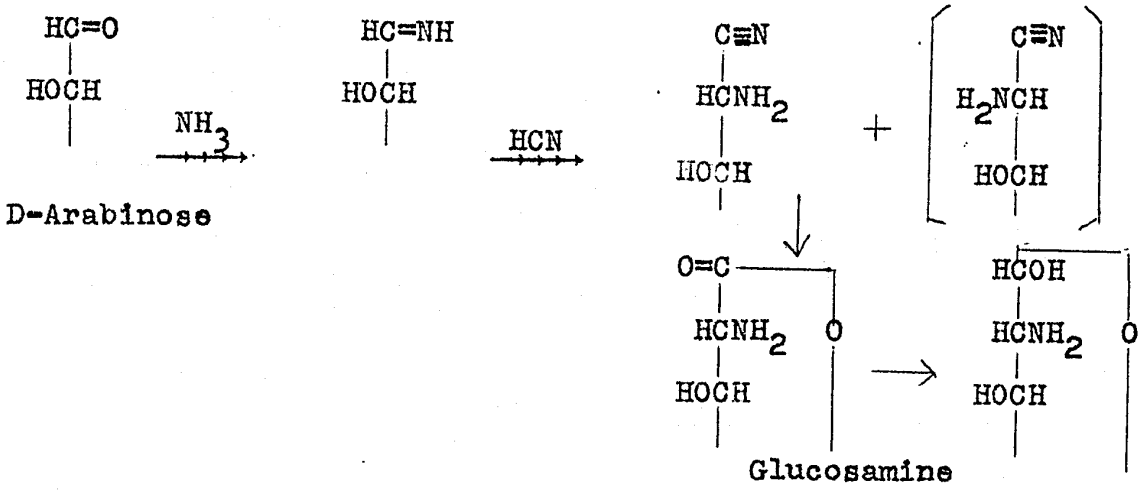


D-Mannose Epimeric D-mannoheptonic nitriles



the lactones derivable from Kiliani's cyanohydrins are reducible by sodium amalgam to aldoses[14] (Chart 2) still constitutes a

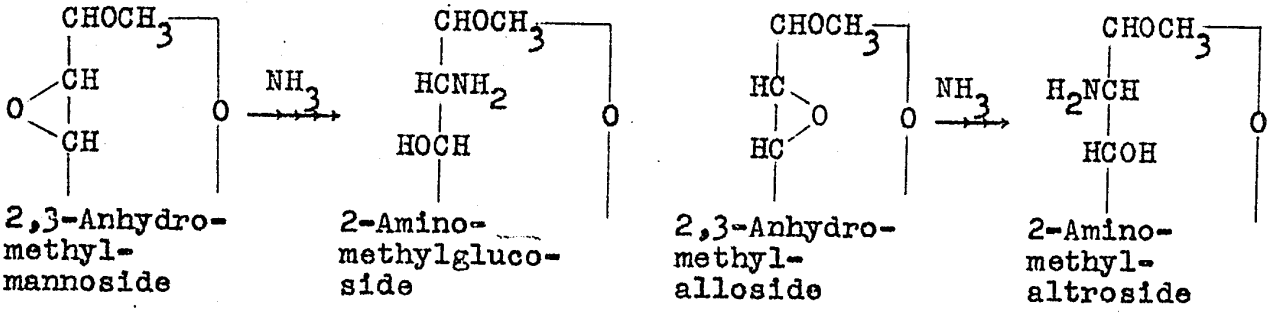
Chart 3



practical route for the partial synthesis of carbohydrates.

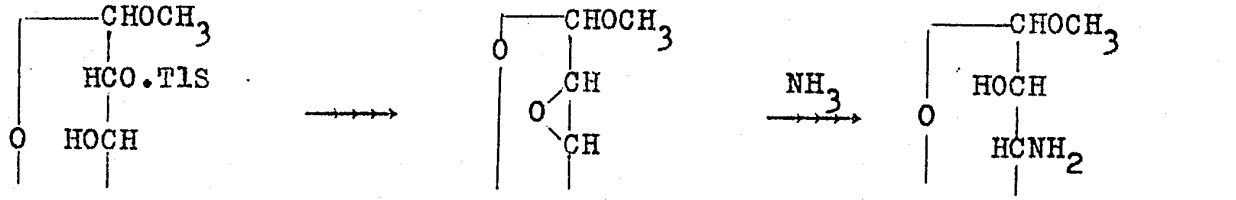
With regard to the synthesis of aminosugars, the subject has been reviewed and here again no attempt has as yet been made to obtain these structures by total synthesis. The most commonly employed routes of partial synthesis involve aminonitrile intermediates (Chart 3). The opening of suitable anhydro derivatives with ammonia (Chart 4),

Chart 4



direct displacement reactions (Chart 5) and insertion of nitro-

Chart 5



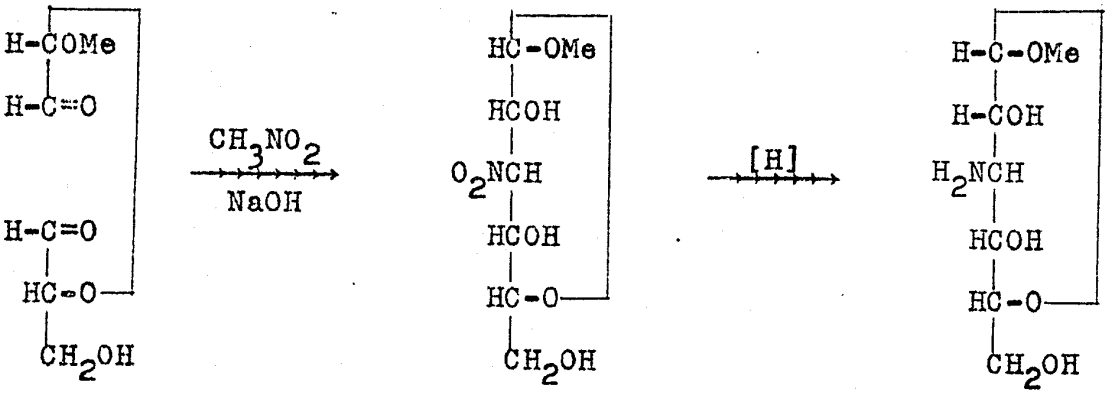
2-Tosyl methyl-glucoside

2,3-Anhydro-methylmannoside

3-Aminomethyl Altroside (methyl epi-glucosamine

methane by reaction with dialdehydes derivable from pyranosides through periodate cleavage (Chart 6).[11]

Chart 6



As will become evident in another section of this thesis, derivatives of 5-deoxy-5-aminosugars have been obtained for the first time, and represent a class of compounds for which no method of partial synthesis appears to have been reported as yet.

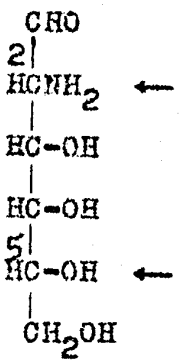
To summarize, previous synthetic work in this field has always relied on the use of carbohydrates or suitable

fragments as starting material. It is the purpose of this thesis to describe the results of an approach which allows the stereospecific total synthesis of hexonic acid type of structures in which the four contiguous asymmetric centers are built stereospecifically from a starting material containing none.

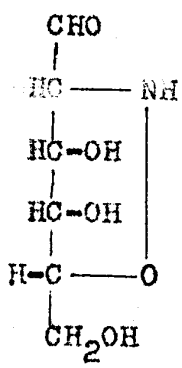
Description of the Approach

A wide variety of substances in the open-chain aliphatic series could be considered as potential starting materials for the synthesis of hexose-like structures. However, if stereochemical control of the synthetic approach is to be achieved, open-chain intermediates are undesirable as they hardly provide for stepwise configurational control due to the occurrence of free rotation which tends to minimize the operation of steric effects. Because of the extraordinary progress in the field of the stereochemistry of six-membered rings, more specifically cyclohexane derivatives, during the course of the past decade or so, it was thought that the use of six-membered cyclic intermediates should offer a better chance of achieving stereochemical control of a sequence of steps especially since steric effects are greatly magnified in small-ring compounds by comparison with their open-chain counterparts. Examination of an open-chain hexosamine (I) suggested to us that a theoretically convenient way of conferring cyclohexane-like geometry to such a molecule would consist in linking the two functional groups

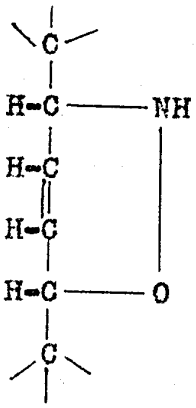
on carbons 2 and 5 respectively, to obtain the heterocycle (II). There is a very specific reason why this mode of formal ring closure of (I) to (II) should be preferred over a number of alternative modes; it is because the nitrogen-oxygen bond of (II) should be cleaved readily under hydrogenating conditions to give (I), thus greatly simplifying the necessary ultimate transition from cyclic to open-chain geometry. Given an appropriate precursor such as (III) which should have cyclohexene-like



(I)



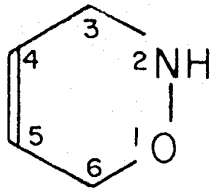
(II)



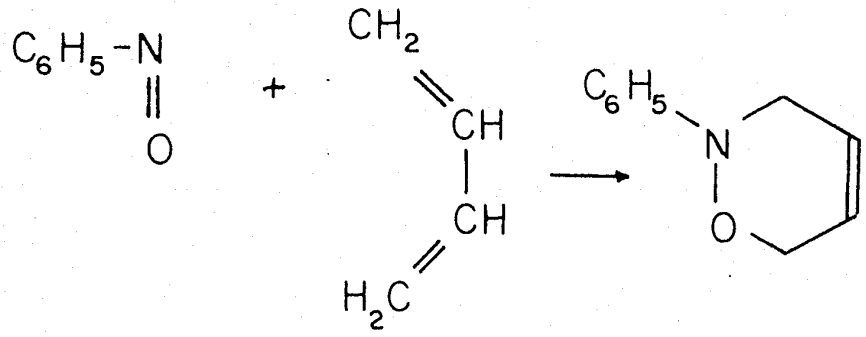
(III)

geometry, it becomes entirely conceivable that the two additional asymmetric centers of (II) could be introduced stereospecifically and when followed by reduction, totally synthetic (I) would result. There remains to examine the possible existence and synthetic availability of an appropriate precursor of type (III), whose ring system is that of a dihydro-1,2-oxazine (IV). No comprehensive review of the

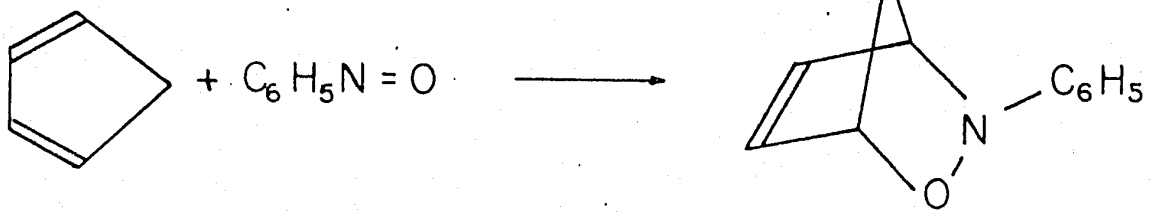
chemistry of this heterocyclic ring system is available,[15] although it is mentioned briefly in "Organic Chemistry" by Richter.[16] It is comparatively recently that derivatives of the sought-for ring system (IV) have become accessible and this through the ingenious application of the Diels-Alder reaction to suitable organic nitroso derivatives. It had been noted early by W. Dilthey[17] that nitrosobenzene (V) can act as an excellent dienophile and as an example its reaction with butadiene (VI) has been shown to afford readily the corresponding 1,2-oxazine (VII).[18] The structure of the diene can be varied and in this way some substituted 1,2-oxazines have been also prepared. A most recent example of this has been provided by Kresge and Schulz[19] who reacted cyclopentadiene (VIII) with nitrosobenzene whereby high yields of the bicyclic oxazine (IX) have been obtained. Although these examples provide us with the desired type of ring system in a most convenient manner, the use of nitrosobenzene as the dienophile is out of consideration for our specific purposes since there exist no simple method allowing the ultimate removal of the phenyl group in the desired end-products. Clearly, a different type of organic nitroso compound is required which would permit the facile generation of an appropriate 1,2-oxazine with an unblocked nitrogen as in (IV). It is in this connection that the recent investigations of Wichterle on the behavior



(IV)



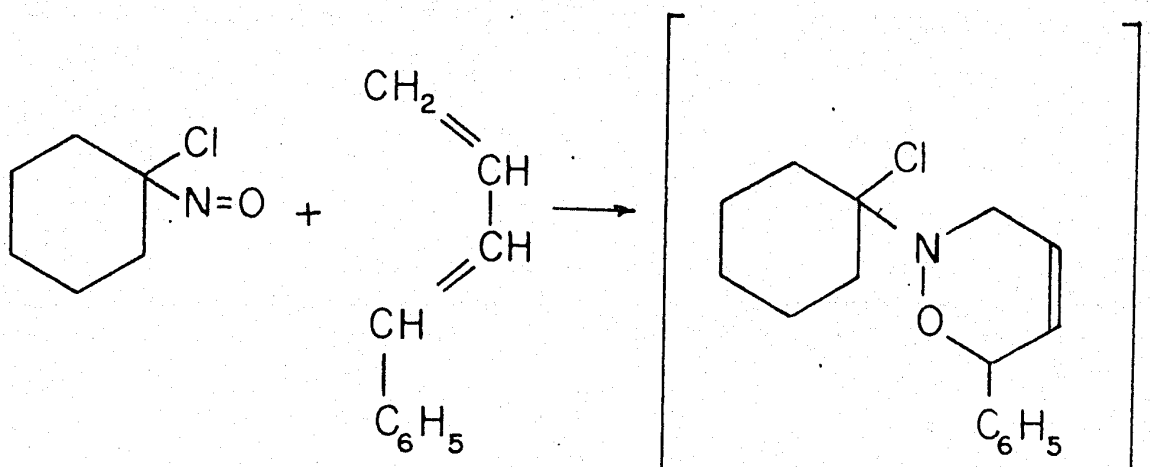
(V) (VI) (VII)



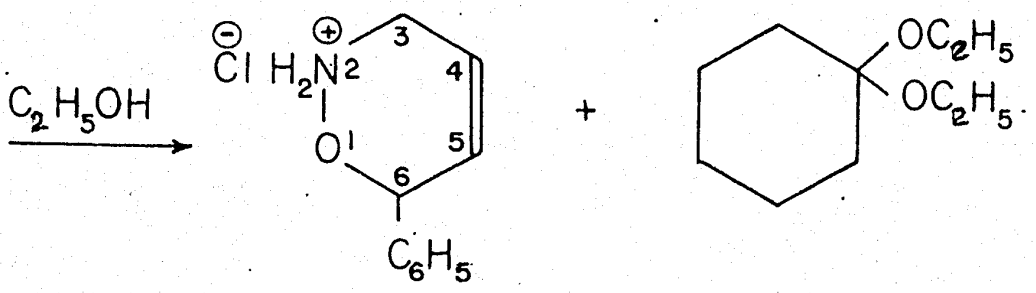
(VIII) (V) (IX)

of certain nitrosoalkanes in the Diels-Alder reaction acquire a critical importance. Of particular interest are his observations on the addition of 1-chloro-1-nitrosocyclohexane (X) to 1-phenylbutadiene (XI), a reaction which leads smoothly to 6-phenyl-3,6-dihydro-1,2-oxazine hydrochloride (XIII)[20] when carried out in ether-ethanol as the solvent. The presence of an electronegative substituent such as chlorine in a position alpha to the nitroso group (X) is believed to increase the dienophilic character of the latter. It is clear that (XII) must be an intermediate in this process but since it reacts with ethanol to produce cyclohexanone diethyl ketal (XIV), the only end product isolated is the crystalline hydrochloride (XIII) which separates from the solution as the reaction proceeds. The starting chloronitroso derivative (X) is readily prepared from cyclohexanone oxime by chlorination. This extension of the Diels-Alder reaction as imagined and applied by Wichterle certainly represents the most practical and elegant method of synthesis of 1,2-oxazine derivatives with an unblocked nitrogen and supplies us with the sought-for approach to the preparation of 1,2-oxazines of potential use in our projected total synthesis of hexosamine-like compounds.

It should be pointed out that Wichterle[21] has also shown that 1-cyano-1-nitrosocyclohexane (XV) can be substituted



(X) (XI) (XII)

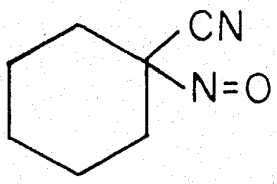


(XIII) (XIV)

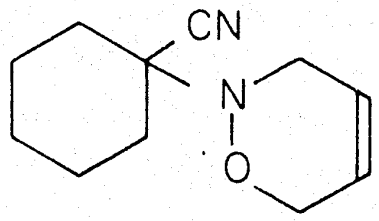
for the chloro derivative (X) in this reaction although in this case, the first intermediate adduct (XVI) can be isolated and characterized. The reaction has been applied to a number of dienes and adducts for which the constitutions (XVII), (XVIII), (XIX) and (XX) were suggested, have been obtained. It appears however that the position of the substituents in these adducts has been assigned on arbitrary grounds so that no weight should be attached to the actual direction of the addition reaction with the unsymmetrical dienophilic nitroso group. However, Wichterle has presented evidence for the position of the phenyl group in adduct (XIII), the product resulting from hydrogenation and hydrogenolysis having been shown to be identical with an authentic specimen.

Mechanism and Stereochemistry of the Reaction

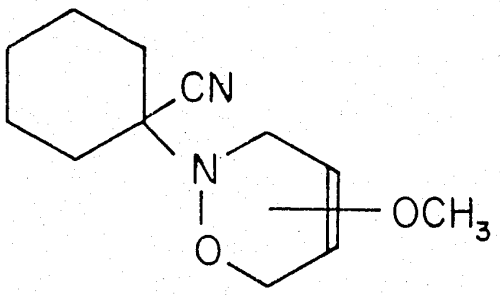
Examination of structure (III) reveals that should it be derivable from the appropriate corresponding diene, then two of the eventual total of four asymmetric centers present in (I) would be simultaneously created upon reaction with the dienophile. It is therefore of paramount importance to achieve stereochemical control at that stage in order for the synthesis to be simple and expedient. It is a virtue of the Diels-Alder readtion to allow for the simultaneous construction of two asymmetric centers from a starting material containing none and it is appropriate at this point to discuss briefly the



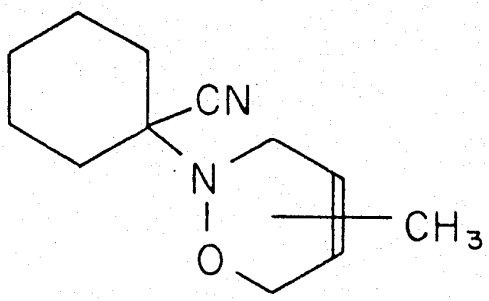
(XV)



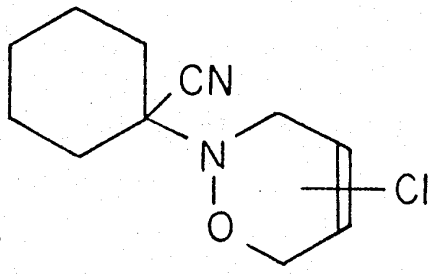
(XVI)



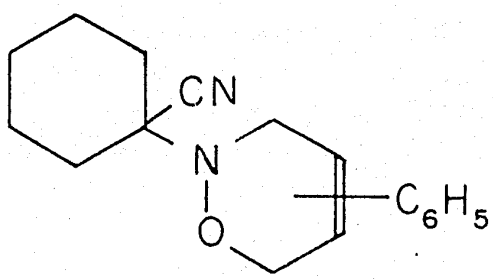
(XVII)



(XVIII)



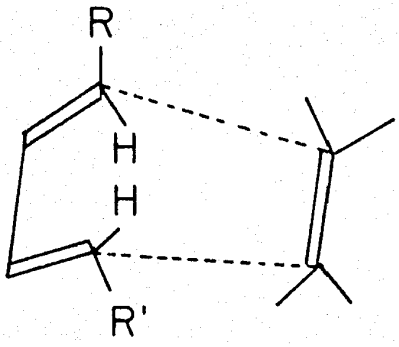
(XIX)



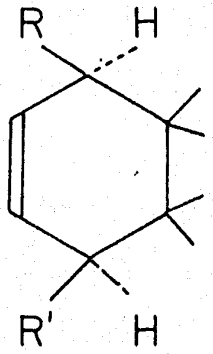
(XX)

mechanism of the reaction in order that predictions of configuration in the adducts can be made.

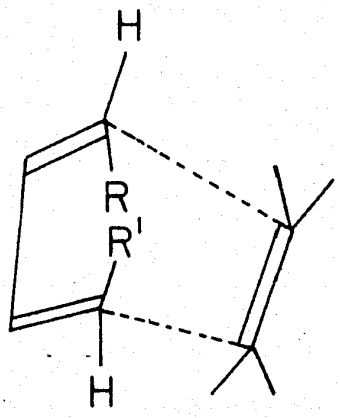
It has been known for some time that the relative configuration of substituents in a Diels-Alder adduct is governed by the geometry of the diene as well as the dienophile. In the particular case of nitrosoalkanes acting as dienophiles one needs to consider only the configuration of the substituted diene and it is well-established that if a diene possesses the trans-trans configuration as in (XXI) or cis-cis-configuration as in (XXIII), the substituents R and R' will assume the cis-configuration in the adduct (XXII). A recent example of this can be found in the addition of acrylate to trans-trans-1,4-diacetoxy-butadiene (XXIV), the resulting adduct (XXV) having its acetoxyl substituents arranged in the cis fashion.[21a] It is a stereochemical consequence of this type which has been used as evidence for a one step mechanism in the Diels-Alder reaction, i.e. the process would involve the simultaneous formation of two new single bonds. A two-step mechanism could hardly accommodate the stereochemical outcome, as free rotation in the first formed intermediate would allow the second step to favor the production of the trans-configuration in the resulting adduct. Since a comprehensive discussion of the mechanism of the Diels-Alder reaction has recently been given by Woodward and Katz,[22] it would be superfluous to elaborate on this subject. It should suffice to mention that



(XXI)

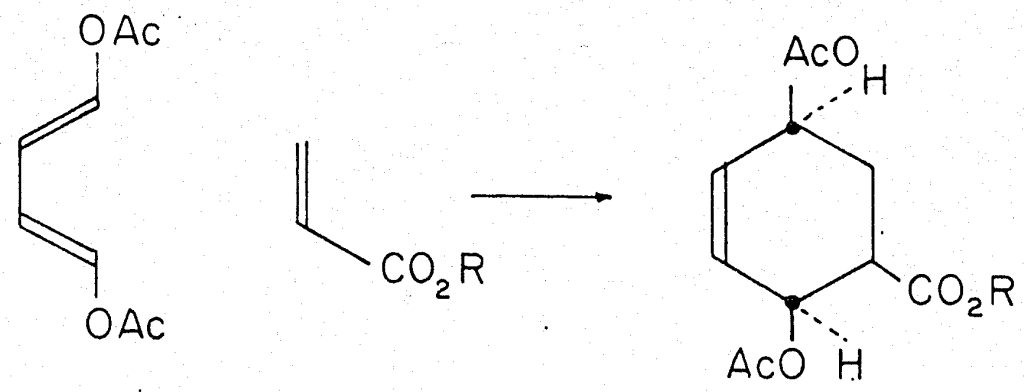


(XXII)

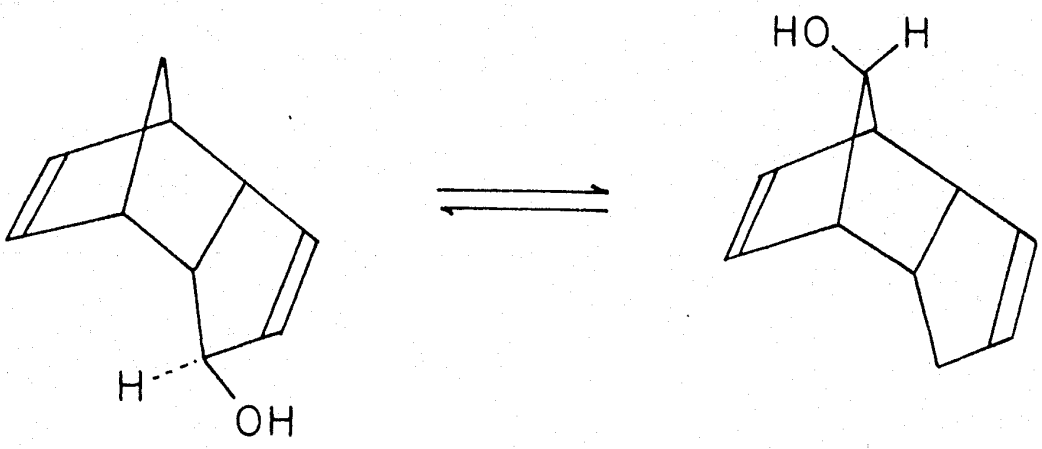


(XXIII)

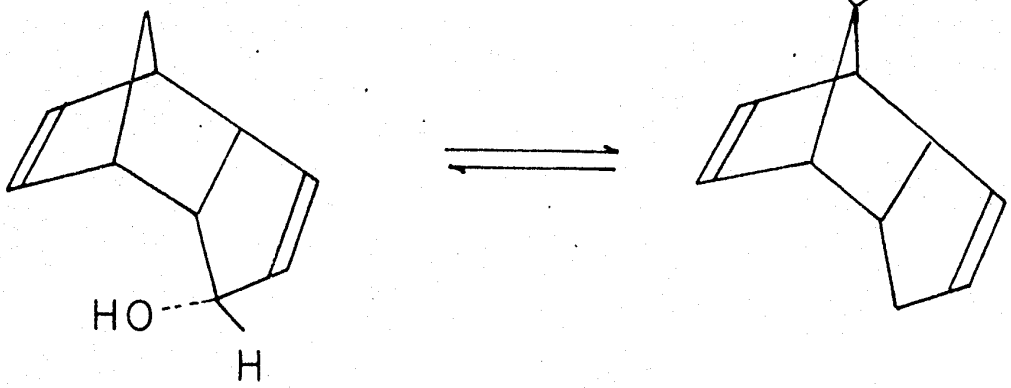
these authors have produced convincing evidence for a two-stage mechanism taking place for all practical purposes in a single overall step. The subtleties inherent to this interpretation have been revealed through a study of the thermal interconversions of α-and β-1-hydroxydicyclopentadiene (XXVI) and (XXVIII) with syn- and anti-8-hydroxydicyclopentadiene respectively (XXVII and XXIX), with retention of optical activity. The only reasonable interpretation of these remarkable observations that could be conceived by Woodward and Katz is that during the interconversions, the molecules must pass through a stage (XXX) in which one bond is in process of formation while another is suffering cleavage. On that basis, the new theory was proposed that the rate-controlling process in the Diels-Alder reaction consists in the formation of a single bond between one terminus of the diene system and one of the unsaturated centers of the olefin. After passage of the barrier to the formation of that first single bond, the reaction proceeds with the construction of a second full bond. In order to accommodate the stereochemical consequences of the reaction, it is necessary that no intermediate of finite life be formed thus suggesting that traversal of the two consecutive barriers cannot be widely separated in time and probably even overlap in most cases. It may be pointed out that Lutz and Roberts[23] have recently



(XXIV) (XXV)



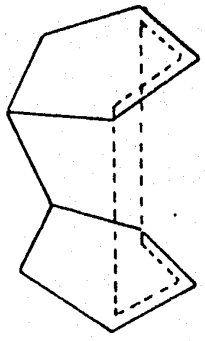
(XXVI) (XXVII)



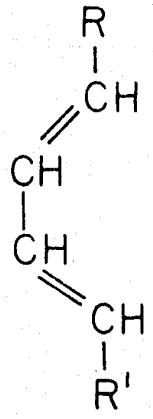
(XXVIII) (XXIX)

confirmed Woodward's and Katz's views using methacrolein dimer as a substrate. Since no new insight into the mechanism of the reaction has been acquired in these latter studies, no further comment would appear necessary. Of interest however are the recent reports on the catalytic influence of Friedel-Craft catalysts on the Diels-Alder reaction,[24,25] this can be taken as concrete evidence that polar species or intermediates are involved and would appear to exclude free radical species at least when Lewis acids are used as promoters.

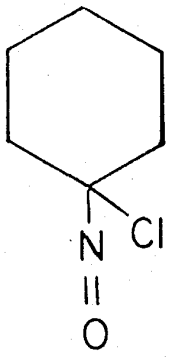
Extending these considerations and concepts to the reaction of nitrosoalkanes with dienes, we would appear to be on safe grounds when expecting stereochemical consequences similar to those of the classical Diels-Alder reaction. More specifically, the reaction of a trans-trans-disubstituted diene (XXXI) with 1-chloro-1-nitrosocyclohexane (X) should lead to the dihydro-1,2-oxazine (XXXII) in which the substituents R and R' have the cis configuration. This expectation would not be justified if the above mechanistic generalizations cannot be extrapolated to the case of dienophilic nitroso-compounds. We would hope however that they apply because the adduct (XXXII) has the thermodynamically least stable configuration, a feature which would theoretically provide an entry into the alternative more stable trans-configuration through the application of suitable equilibration conditions. Since this stereochemical sequence could not be applied in



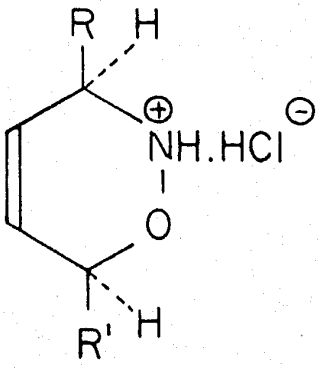
(XXX)



(XXXI)



(X)

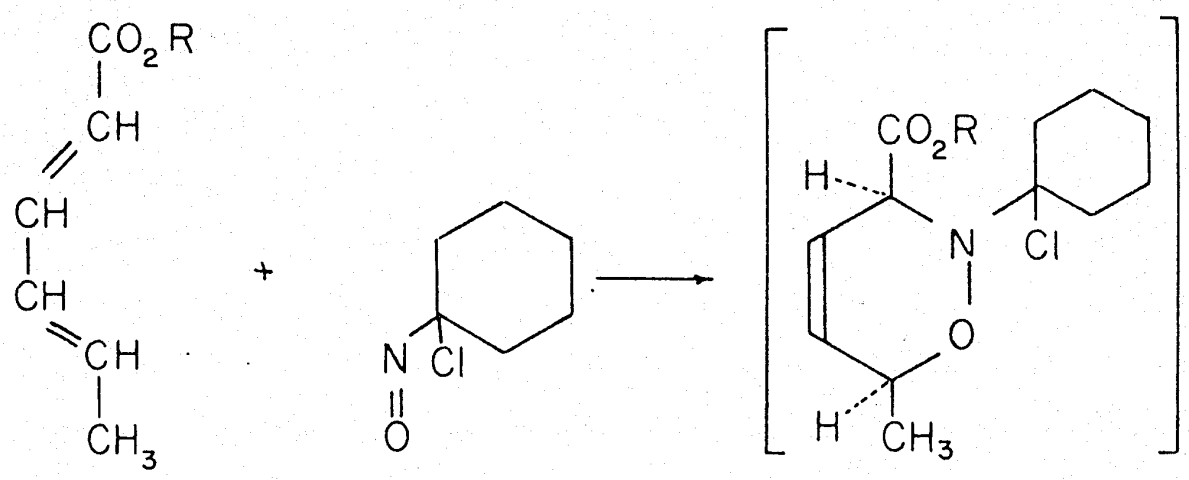


(XXXII)

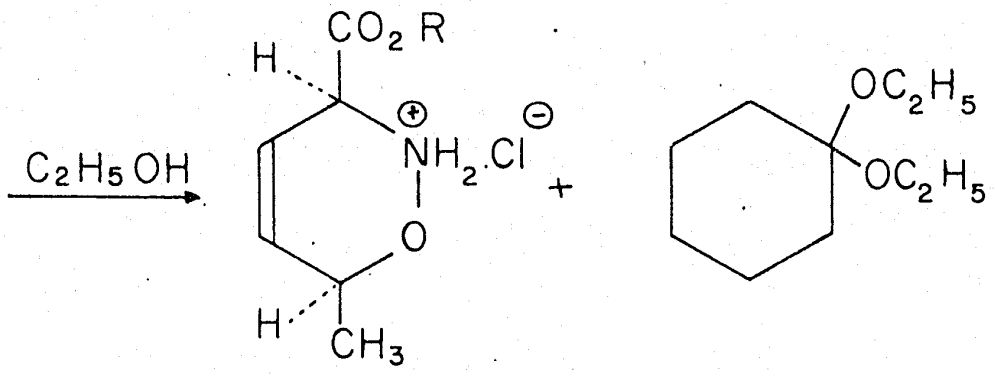
reverse, a trans-configuration in the adduct (XXXII) would eliminate the possibility of obtaining four out of the eight ultimately possible racemates that would result once the four contiguous asymmetric centers are constructed. In spite of this remote but possible limitation it was deemed desirable to explore the approach summarized in equations (XXXI)⟶(XXXII) since a stereospecific total synthesis of four or even less racemates would nevertheless constitute a precedent in the field and should eventually serve some useful purpose.

Selection of Starting Material and Directive Effects in the Diels-Alder Reaction

In order to test the applicability of 3,6-dihydro-1,2-oxazines such as (XXXII) as intermediates in the synthesis of deoxy-aminohexose-like structures it would suffice to equate the substituents R and R' to simple entities commonly encountered in the carbohydrate field, and then proceed with the introduction of two more asymmetric centers at the site of the double bond. It is immediately apparent that if R = CO_2H and R' = CH_3, not only are such groups of frequent natural occurrence but they can theoretically be built into the adduct (XXXII) from a cheap and readily available diene acid, sorbic acid (XXXIII, R = H). This commercially available diene acid has the trans-trans-configuration and should reaction with 1-chloro-1-nitroso-cyclohexane (X) occur, it would be expected that the

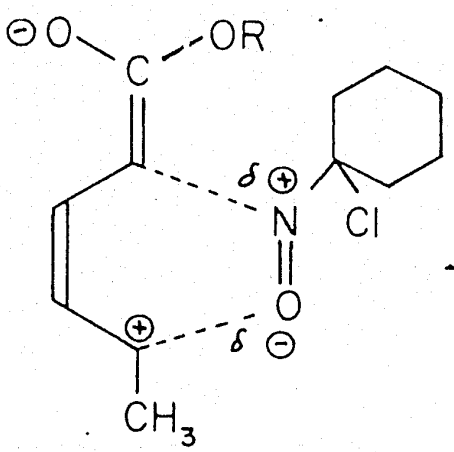


(XXXIII) (X) (XXXIV)



(XXXV)

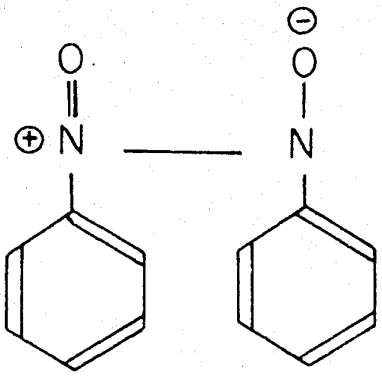
oxazine-acid (XXXV, R = H) might be formed in which the 3 and 6-substituents would be cis-oriented for reasons already discussed above and in which the nitrogen would occupy the position α- to the carboxyl group rather than the alternative δ-position as in (XXXIX). This latter structural point brings us to discuss briefly directive effects in such Diels-Alder reaction and as will become evident, expectations regarding the orientation of the N-O bond in the adduct can hardly be based on acceptable precedents. The operation of resonance in sorbic acid leads largely to polarization as shown in (XXXVI). Now, because we are unaware of the electronic transition of lowest energy in nitroso alkanes such as (X), we would be inclined to predict on the basis of the empirical fact that oxygen is more electronegative than nitrogen, that electrons would be localized on the oxygen, and thus would favor the formation of complex (XXXVI) conducive to adduct (XXXV). It may be said that in this case, the oxygen of the nitroso group acts as the donor of electrons. However, it is a well recognized fact that nitroso compounds dimerize readily and the structure of such a dimer has recently been elucidated. It was shown that the dimer of nitrosobenzene has the structure (XXXVII) which reveals obviously that the nitrogen of a molecule of nitroso-benzene donated electrons to the nitrogen of another molecule. Hence, the nitrogen of nitroso compounds can act as electron



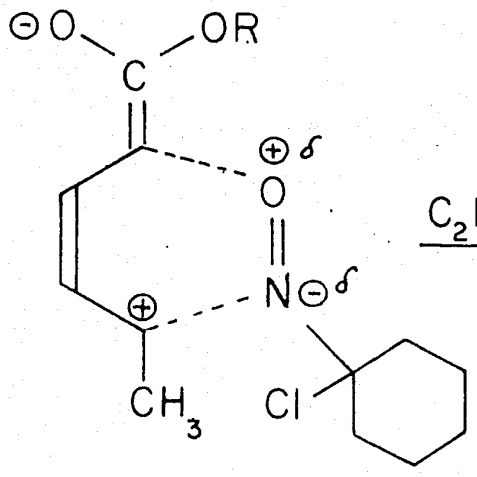
C_2H_5OH

(XXXV)

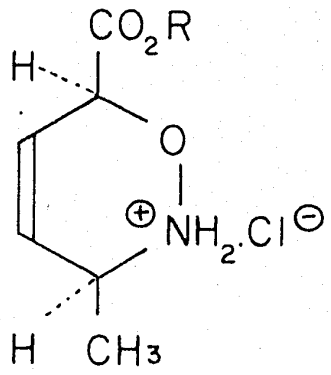
(XXXVI)



(XXXVII)



C_2H_5OH



(XXXVIII)

(XXXIX)

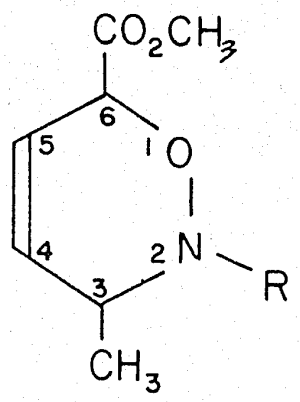
donor although in the case of (XXXVII) it is also a nitrogen which appears as the acceptor. Reasoning by analogy, it would also seem justifiable therefore to expect the formation of complex (XXXVIII) in which the nitrogen acts as the donor, an eventuality which would lead to adduct (XXXIX). Comparison of this latter array with structures (II) and (I) shows that (XXXIX) would be theoretically conducive to a 5-deoxy-5-amino-hexose-like substance, a class of aminosugars never encountered previously either in nature or in the laboratory. For the reasons just exposed above, it would appear presumptuous to select either (XXXV) or (XXXIX) as the product of the reaction, although it must be admitted that we intuitively preferred (XXXV) over (XXXIX). We soon discovered however that this intuition verged on pure practical reasoning, adduct (XXXV) offering the possibility of achieving synthetic correlations with naturally occurring products. Finally, it should be noted that in both (XXXV) and (XXXIX) the predictable cis-orientation of the 3,6-substituents uniquely provides for the theoretical production of all possible stereoisomers in that series and this by virtue of the expectable convertibility of the cis to the trans-configuration.

Methods and Results

The preparation of the required 1-chloro-1-nitroso-cyclohexane (X) was accomplished according to Wichterle. It

has the appearance of a deep blue liquid with lacrymatory properties and which can be stored at 0°C. We initially attempted to condense it with sorbic acid in ether-ethanol but without success, the starting materials being recovered unchanged. However, when methyl sorbate was used instead, a homogeneous crystalline adduct slowly deposited, the yield reaching 70% after 10 to 12 days. Empirical analysis, infrared spectrum (major characteristic bands at 1740 cm^{-1}, and 1590 cm^{-1}), and NMR spectrum (Fig. 1) definitely established that its structure corresponded to (XXXV, R = CH_3 or XXXIX, R = CH_3); however, no evidence for the cis-configuration could be adduced from these data. As will become evident below, the structure must be represented by (XL). It was characterized by the formation of a benzoate (XLI) which gave IR and NMR (Fig. 2) spectra in agreement with its constitution. The N-carbobenzoxy derivatives could also be readily obtained but not in the crystalline state.

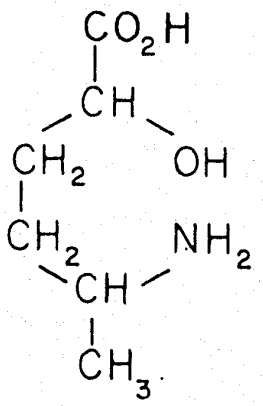
The direction of the addition of the nitroso group to methyl sorbate was established by submitting the adduct hydrochloride to catalytic hydrogenation over Adam's catalyst in acetic acid as the solvent. Two molar equivalents of hydrogen are rapidly absorbed and lead to the isolation of a crystalline amino acid which must have constitution (XLIII) rather than (XLIV) on the basis of the fact that its reaction



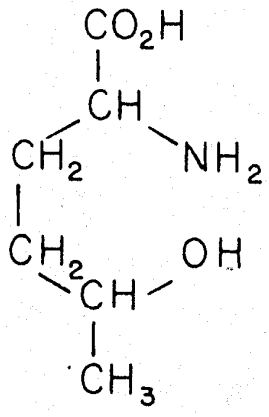
(XL, R=H.HCl)

(XLI, R=C_6H_5CO)

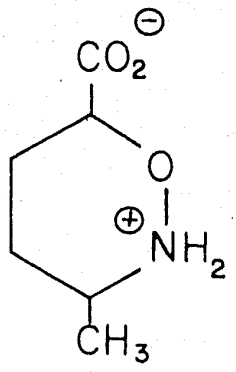
(XLII, R=$C_6H_5CH_2OCO$)



(XLIII)



(XLIV)



(XLV)

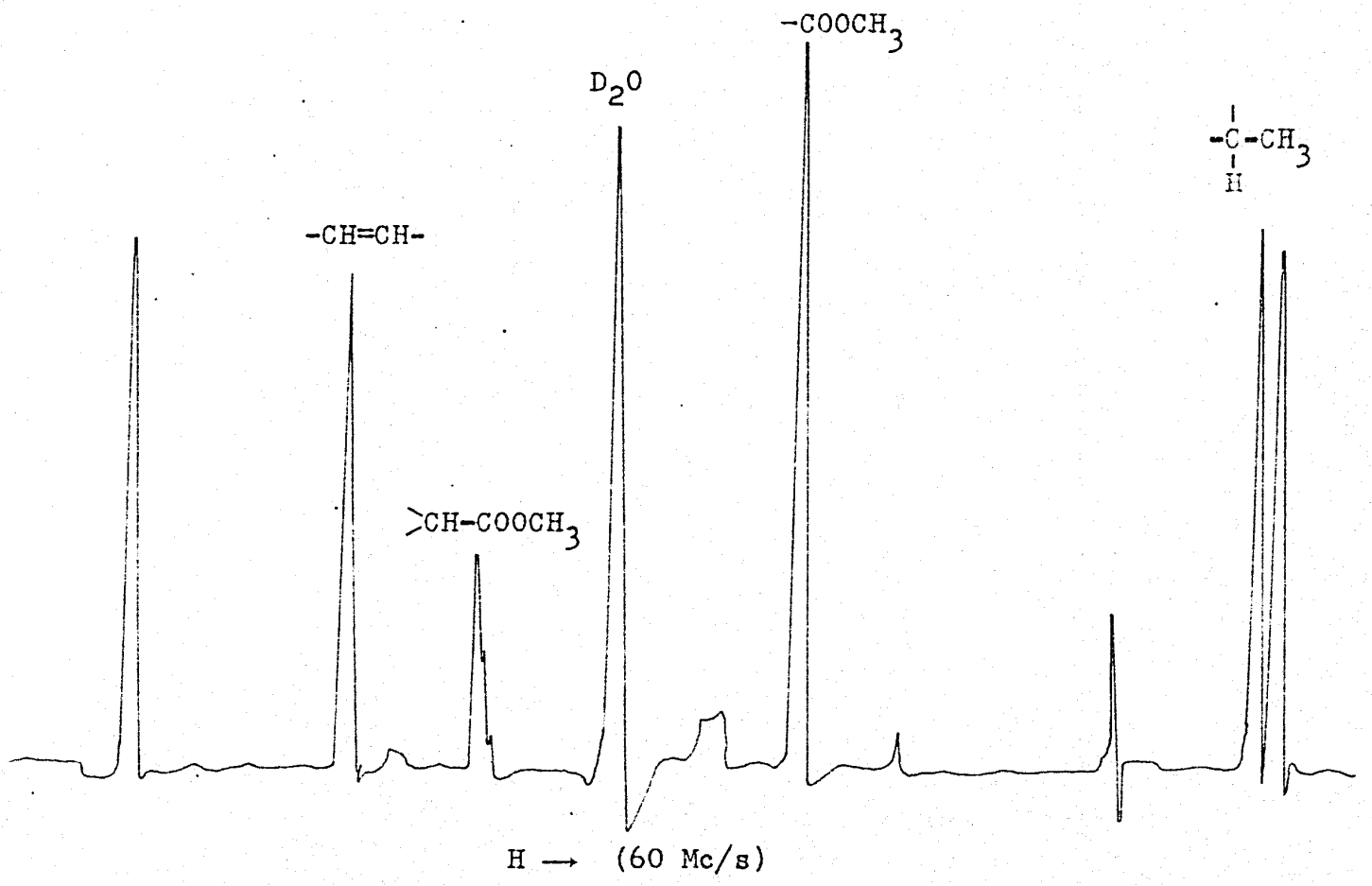


Fig. 1. The NMR spectrum of 1,2-oxazine hydrochloride derivative (XL) measured in D_2O.

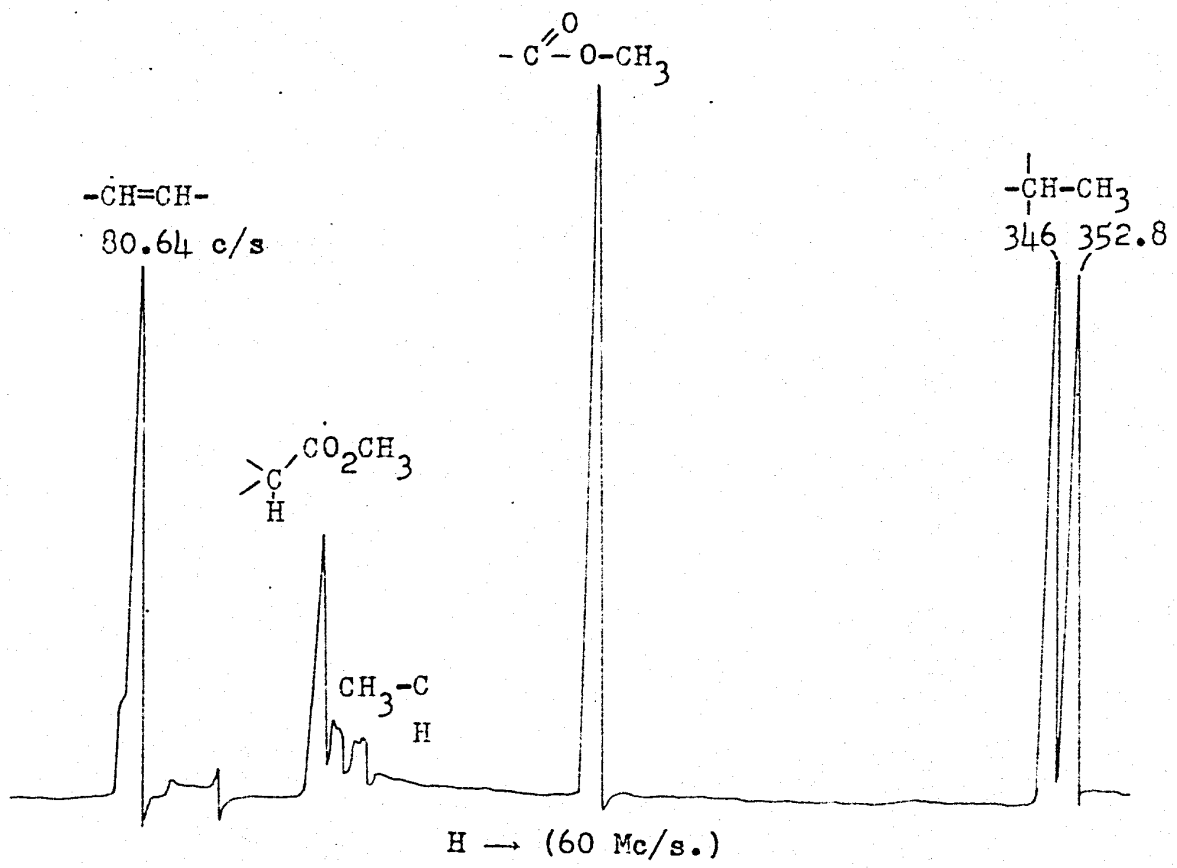


Fig. 2. The NMR spectrum of N-benzoyl derivative (XLI) measured in chloroform.

with phenylisocyanate affords only the corresponding ureide and not the hydantoin. This excludes structure (XLIV) and the additional observation that the amino acid reacts sluggishly with ninhydrin by comparison with a number of conventional α-amino acids, confirms structure (XLIII). It should be noted that this synthesis of the novel compound (XLIII) is entirely stereospecific. The question of the configuration of the 3,6-substituents in adduct (XL) and hence in (XLIII) can only be inferred at this time, the evidence being as yet incomplete and indirect as will be shown in a later section (see Discussion of Results).

The novel oxazine carboxylic acid (XLV) could also be prepared with relative ease by catalytic hydrogenation of the benzoate (XLI) followed by aqueous acid hydrolysis or methanolysis under mild conditions. The solubility behavior as well as the IR spectrum of XLI (major bands at 1640 cm^{-1} and 1750 cm^{-1}) clearly suggest a zwitterionic structure as would be expected. The NMR spectrum (Fig. 3) which will be discussed later (see Discussion section) confirmed constitution (XLV) and also gave an indication that the configuration of the substituents is probably trans. Whether this configuration is the result of an epimerization of the carboxyl group during methanolysis or is already present in the initial adduct has not been settled conclusively as yet. However, it was established that during the process of the formation of the adduct (XL),

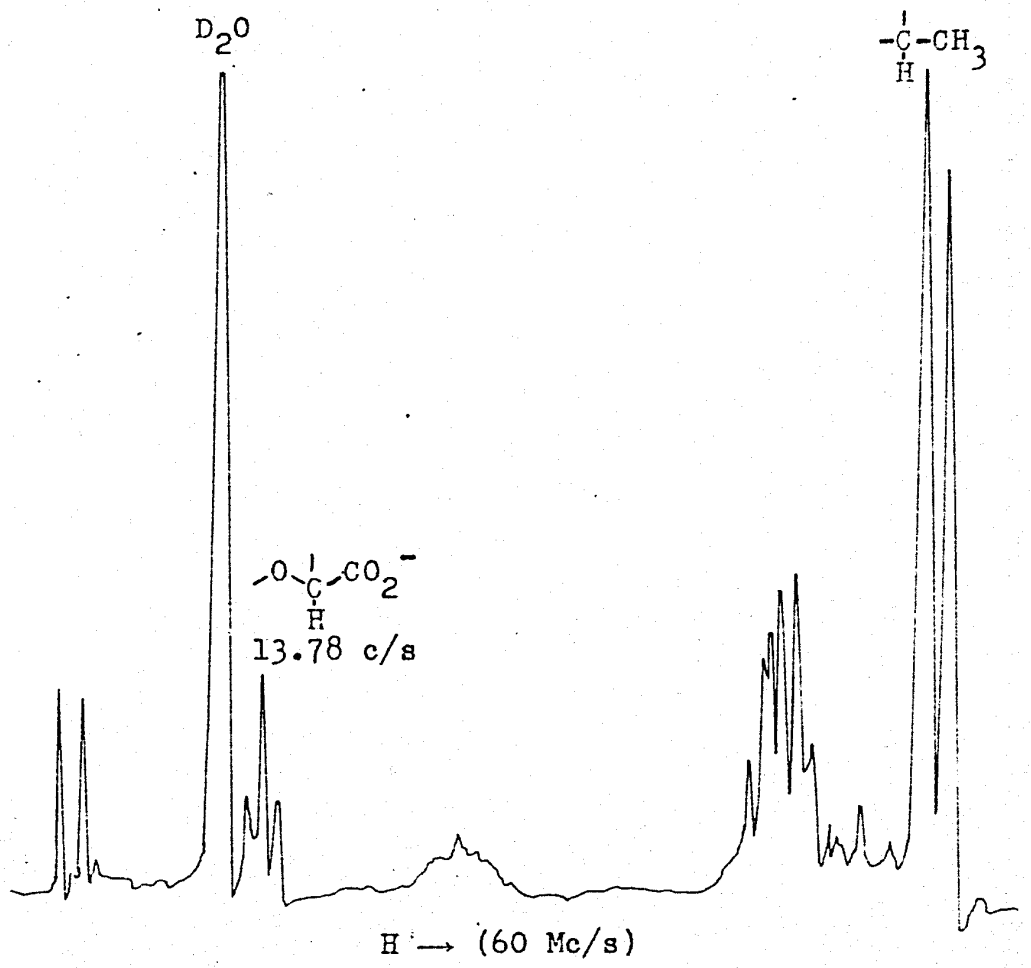


Fig. 3. The NMR spectrum of oxazine-carboxylic acid (LXXXIII) measured in D_2O.

no epimerization could have taken place (subsequent to the formation of XXXIV for instance) since the use of deuterated ethanol (C_2H_5OD) as the solvent in lieu of normal ethanol, did not lead to a detectable incorporation of deuterium on carbons 3 or 6 of the adduct. Furthermore, benzoylation of (XL) in deuterium oxide as the solvent also produced the deuterium-free benzoate (XLI). It follows that if epimerization has taken place in (XLV), it must be at the stage of hydrolysis, a possibility which is under investigation.

The next problem consisted in the construction of the last two asymmetric centers at positions 4 and 5 of (XL), the problem of the stereospecific introduction of the first two at positions 3 and 6 having been solved. The use of the cis-hydroxylating agent osmium tetroxide was selected for our purposes because of its marked steric requirements especially in the form of its complex with pyridine.[26] Treatment of the N-benzoyl derivative (XLI) with osmium tetroxide in ether-pyridine led within minutes to the quantitative precipitation of the corresponding osmate which when shaken for a few hours with aqueous sodium carbonate afforded in virtually quantitative yield the diol-acid (XLVI). That the alkaline medium used in the decomposition of the osmate did not cause epimerization of the carboxyl group was demonstrated by conducting the reaction in deuterium oxide. Under these conditions, no incorporation of deuterium in (XLVI) could be detected (as determined by

NMR analysis of the corresponding methyl ester; see "Discussion Section"). Reaction with diazomethane gave the corresponding crystalline methyl ester (XLVII) the NMR spectrum of which (Fig. 4) clearly established its homogeneity. Hence, the hydroxylation reaction proceeded with complete stereospecificity to give a single isomer and it is of interest to note at this point that in two basic steps only, the desired four contiguous asymmetric centers have been constructed stereospecifically. The relative configuration of the substituents in (XLVI) is discussed in a later section (see Discussion) where structure (XLVIII) is tentatively suggested as representing the correct stereochemistry.

To complete our total synthesis, it remained to submit (XLVI) to acid hydrolysis under mild conditions followed, without isolation, by catalytic hydrogenation over Adam's catalyst. These reactions proceeded normally to give finally the crystallin amino acid (XLIX) in good yields. Accepting our assignment of configuration as shown in (XLVIII), it follows that the novel aminoacid (XLIX), must be DL-5,6-dideoxy-5-aminotalonic acid. For purposes of comparison, the formula of D-talose is shown in (L). It is of interest, that 2,6-dideoxy-2-aminotalose, a position isomer of (XLIX) has recently been isolated from natural sources.[26a]

Attention was next turned to other hydroxylation methods with a view to obtain ultimately the other stereo-isomers of (XLIX). It may be recalled that assuming a <u>trans</u>-

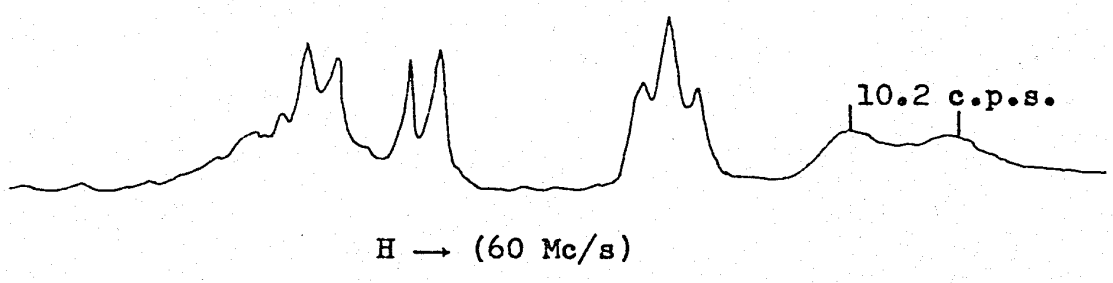
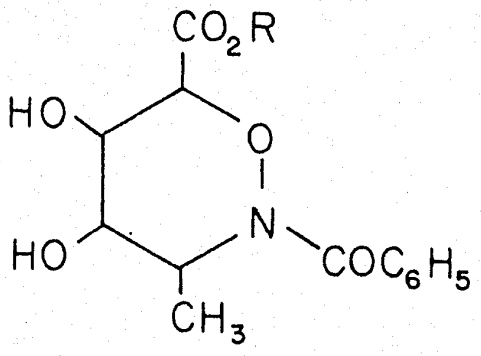
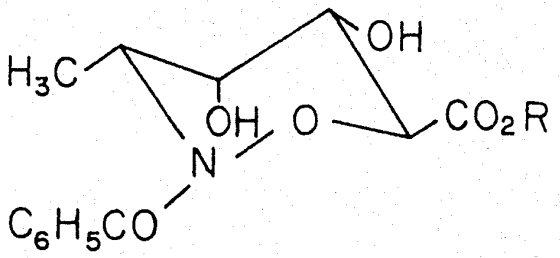


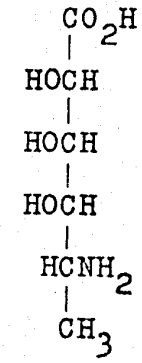
Fig. 4. The NMR spectrum of cis-diacetate of (XLVII) measured in benzene.



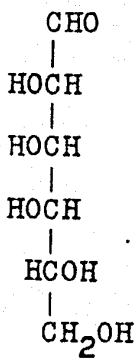
(XLVI, R=H)
(XLVII, R=CH_3)



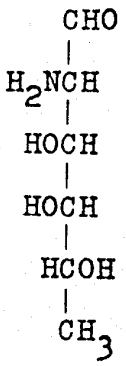
(XLVIII)



(XLIX)



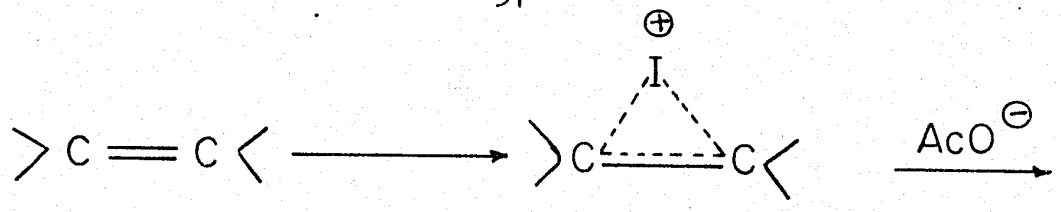
D-talose
(L)



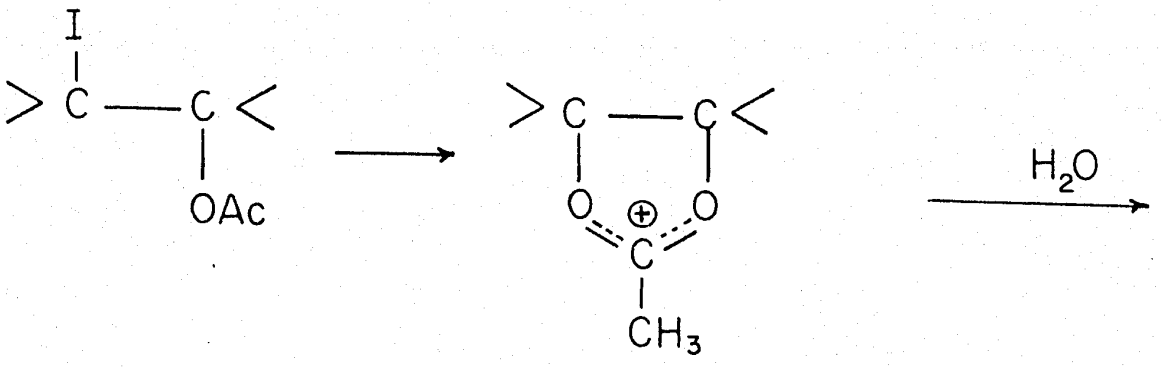
(LI)

configuration in the adduct (XL) (vide infra), a total of four racemates in the 5,6-dideoxy-5-aminohexonic acid series should be theoretically obtainable by synthesis. It has been shown in the steroid series that hydroxylation of olefins with the iodine-silver acetate-wet acetic acid reagent produces cis-glycols of configuration opposite to that obtained with osmium tetroxide.[27] The course of the reaction is believed to proceed by way of the sequence (LII) → (LIII) → (LIV) → (LV) → (LVI) and the opposite stereochemical outcome can be attributed to an initial attack by iodine from the same side of the plane of the olefin as with osmium tetroxide. The subsequent inversion of configuration is self-explanatory and should this method be applied to the benzoyl adduct (XLI), it would be expected that the alternative cis-stereoisomer (LVII) would result. Unfortunately, several attempts to apply this procedure were of no avail, the starting material being refractory to the reagents. An alternative approach designed to circumvent this difficulty is described below.

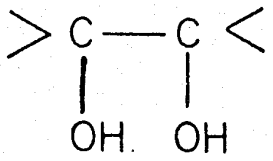
In order to gain entry into the 4,5-trans-series of stereoisomers of (XLVII), the epoxidation of (XLI) was next studied. It was initially observed that the double bond of (XLI) failed to consume perbenzoic acid over a period of three weeks. This lack of reactivity of the olefinic bond in (XLI) can only be attributed to the presence of strongly electronegative substituents on the carbons α- to the double



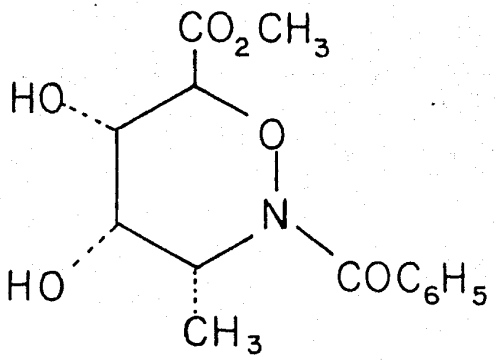
(LII) (LIII)



(LIV) (LV)



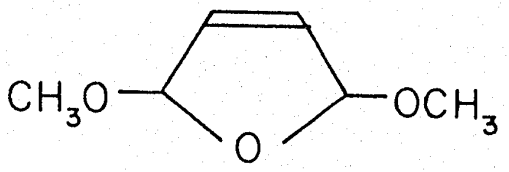
(LVI)



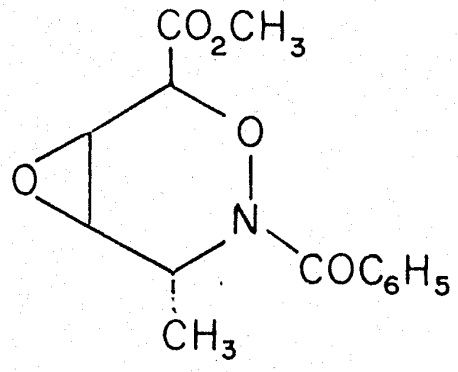
(LVII)

bond. This is reminiscent of the lack of reactivity of 2,5-dimethoxy-2,5-dihydrofuran (LVIII) towards the same reagent.[27a] The use of a more powerful reagent was therefore indicated, and indeed when trifluoroperacetic acid was substituted for perbenzoic acid, rapid oxidation ensued and led to the isolation in high yield of a mixture of the two epoxides (LIX) and (LX). The NMR spectrum (Fig. 5) of this crystalline mixture showed that the isomer ratio was 1:1. Separation of the components could readily be achieved in good yields by simple crystallization of the mixture from methanol. The homogeneity of each isomer was ascertained by NMR spectroscopy (Fig. 6 and Fig. 7) which however could not be relied upon for configurational determinations. The complete lack of stereospecifity in the epoxidation reaction is easily rationalized only if the 3,6-substituents assume the <u>trans</u>-configuration in the adduct (XL) and its benzoate (XLI) (see Discussion section).

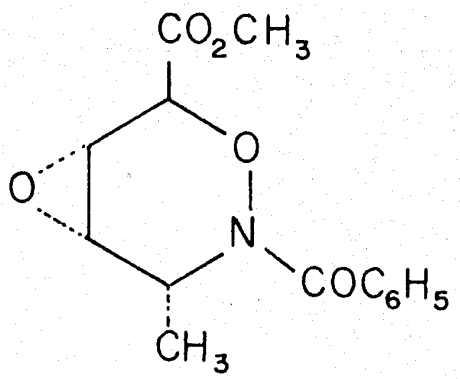
Reaction of both epoxides with formic acid afforded mixtures of isomeric glycol formates. It is probable that the major constituents have the structures (LXI) and (LXII) respectively (vide infra). Acid catalyzed methanolysis of either glycol formates afforded the same mixture of 4,5-diols isolated as the crystalline oxazine-hydrochlorides, which were assigned constitutions (LXIIIa) and (LXIIIb). It should



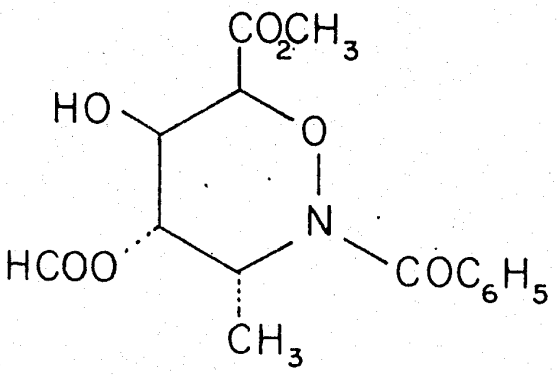
(LVIII)



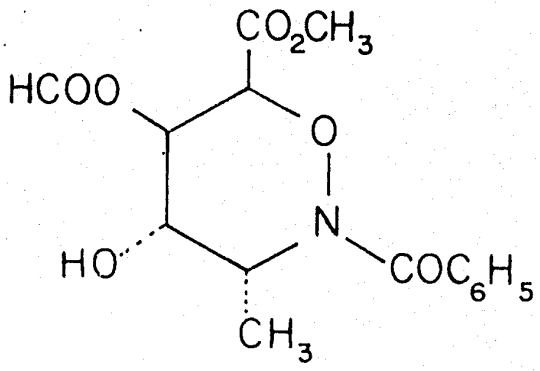
(LIX)



(LX)



(LXI)



(LXII)

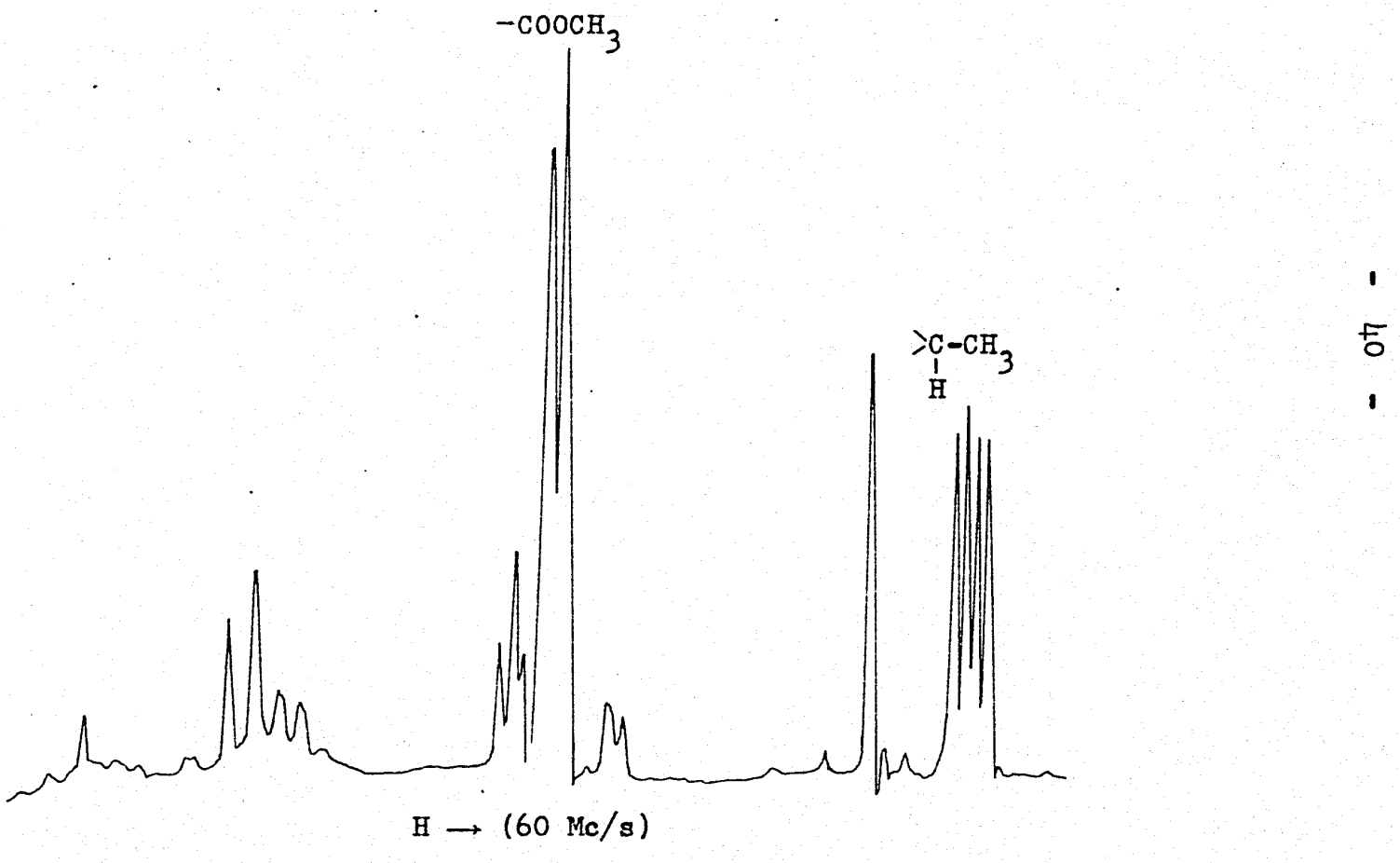


Fig. 5. The NMR spectrum of epimeric epoxide (LIX) and (LX) measured in pyridine.

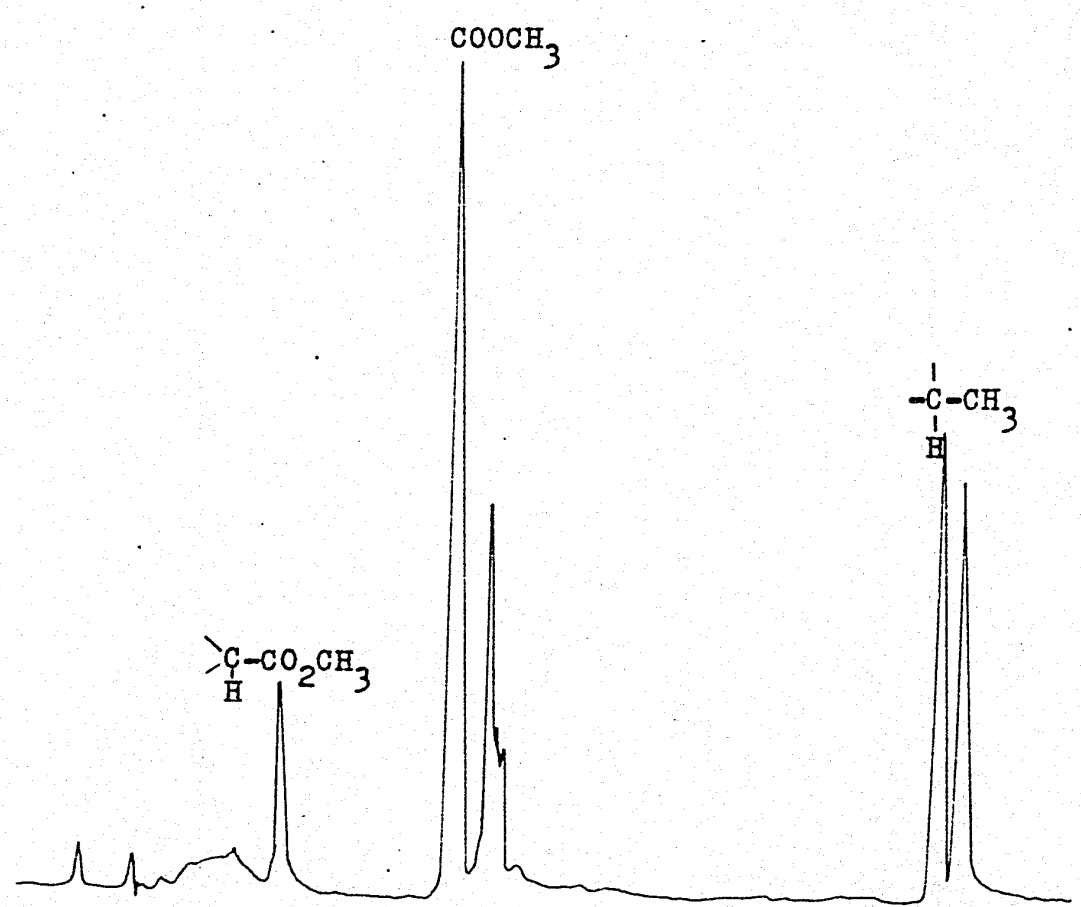


Fig. 6. The NMR spectrum of epoxide (LIX) measured in $CHCl_3$.

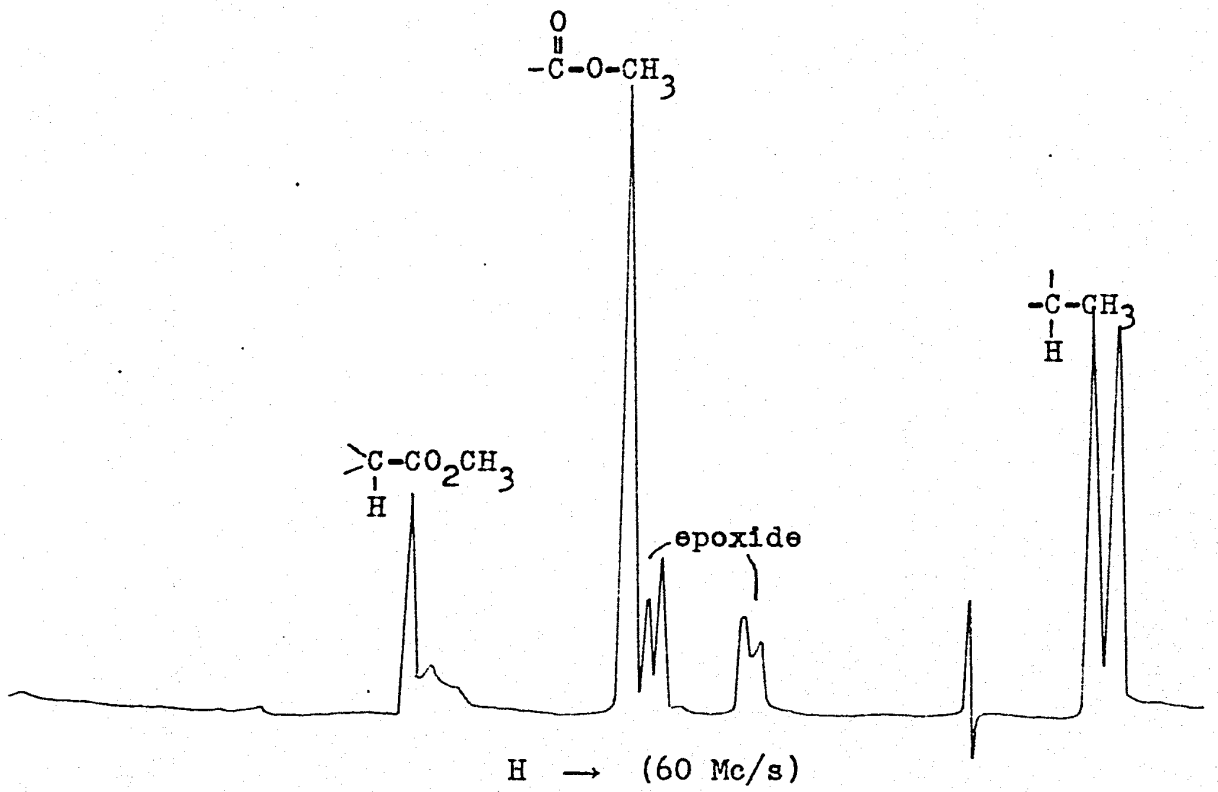
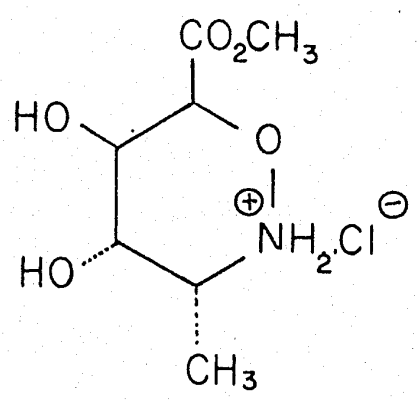


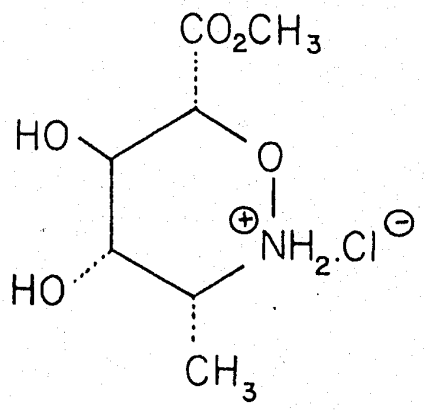
Fig. 7. The NMR spectrum of epoxide (LX) measured in chloroform.

be noted that although the epoxidation reaction is not stereospecific, the overall conversion of the adduct benzoate (XLI) to a mixture of trans-4,5-glycols (LXIIIa) and (LXIIIb) appears to be appreciably stereoselective (one isomer predominating largely). Separation of these isomers could not be achieved effectively as yet. The configurational assignments are tentative and are discussed later. Thus far, we have provided two examples of the stereospecific and stereoselective construction of four contiguous asymmetric centers as present in hexoses.

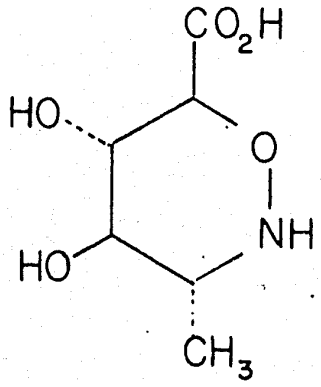
A specific approach to the alternative trans-configuration (LXIV) has not been found. Attention was then directed at the synthesis of the 4,5-cis-diol (LXV) which represents the last possible racemate theoretically obtainable from the trans-adduct (LX). Mention was already made that the benzoate (XLI) proved inert to the iodine-silver acetate-wet acetic acid reagent. If one refers to the mechanism through which this reagent is believed to achieve cis-hydroxylation (LII) ⟶ (LVI), of olefins, it is evident that should the intermediate (LIV) be accessible by another route, the same desired glycol should become available through the application of solvolytic conditions in a wet solvent (LIV) ⟶ (LVI). The ready availability in pure form of the two epoxides (LIX) and (LX) suggested that one of them could perhaps serve as a good source of the corresponding iodohydrin acetate in which the



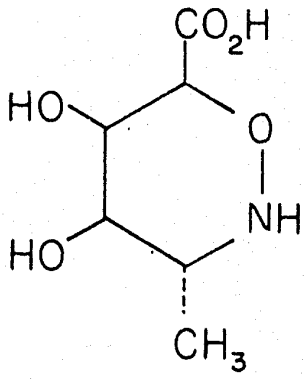
(LXIIIa)



(LXIIIb)



(LXIV)



(LXV)

iodine would assume that configuration eventually conducive to the cis-diol (LXV) rather than the already known diol (LVII). As will become evident, this approach to the synthesis of cis-4,5-diols did not bear fruit but much useful stereochemical information was derived from the study of the epoxides and the corresponding iodohydrins.

It was found that treatment of the epoxides (LIX) and (LX) with aqueous hydriodic acid in the cold led in quantitative yields to the isomeric iodohydrins (LXVI) and (LXVII) respectively. Both proved homogeneous as ascertained by NMR spectroscopy* (Figs. 8 and 9) so that the opening of the oxide rings by hydriodic acid can be deduced to be entirely stereospecific. Structural and configurational assignments (see Discussion section) were made using as a basis the remarkable difference in the reactivity of these isomeric iodohydrins towards acid catalyzed methanolysis. Whereas iodohydrin (LXVI) is left unchanged after treatment with cold methanolic-hydrogen chloride, its isomer (LXVII) is smoothly converted to the corresponding free oxazine hydrochloride (LXVIII) under the same conditions. Accepting structures (LXVI) and (LXVII) as the correct ones for the

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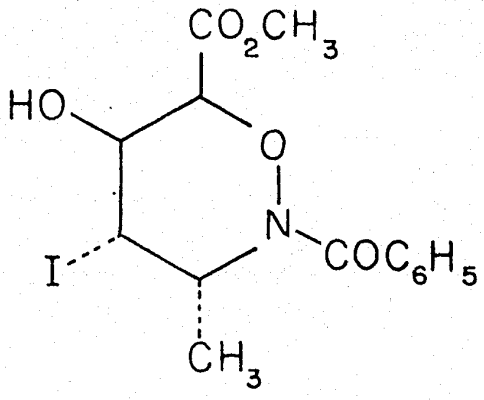
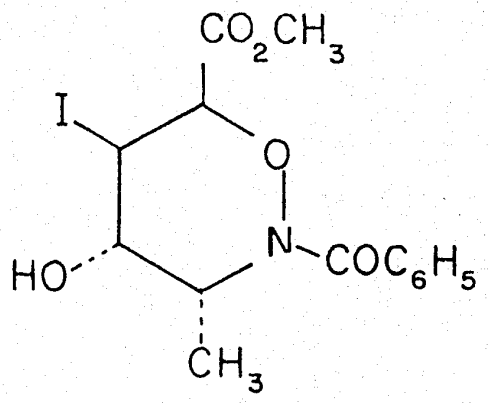
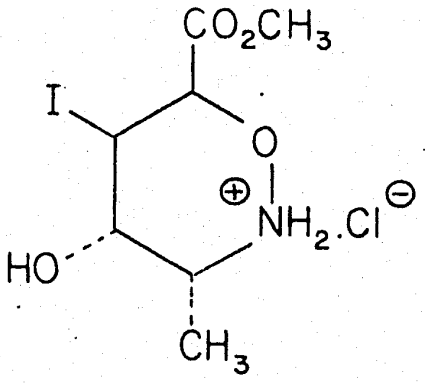
* Performed on the corresponding acetate of (LXVI) and hydrochloride of (LXVII).



(LXVI)



(LXVII)



(LXVIII)

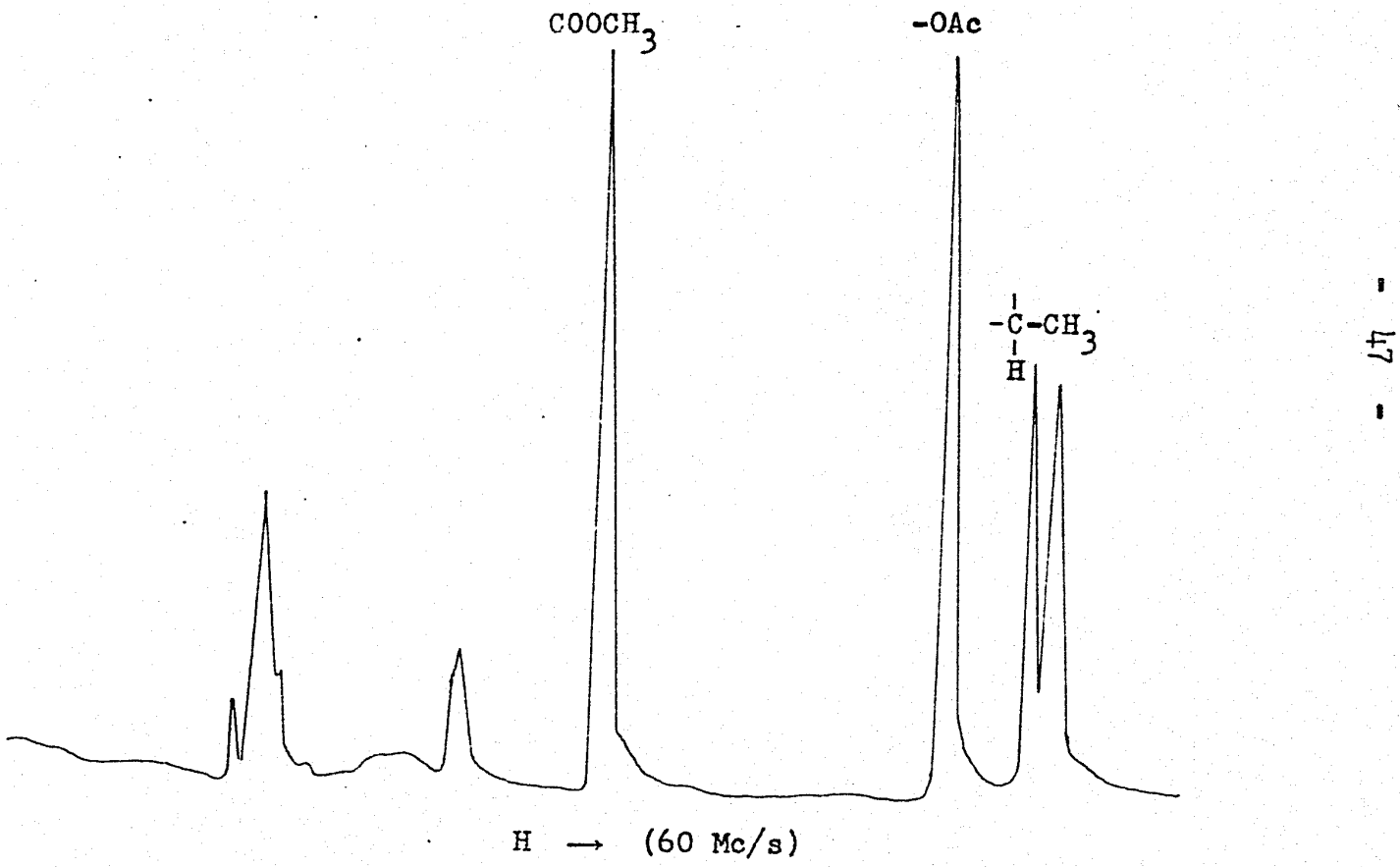


Fig. 8. The NMR spectrum of Iodohydrin (LXVI) acetate measured in chloroform.

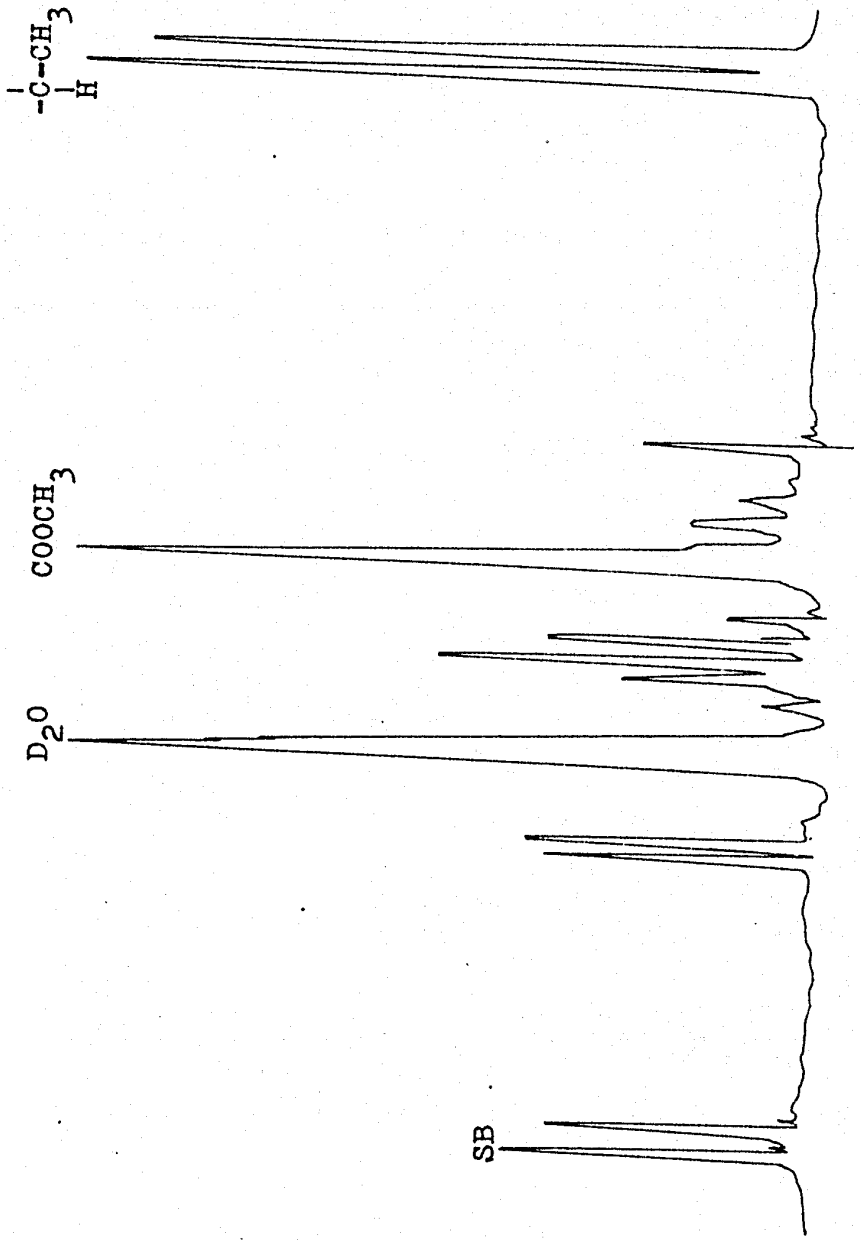
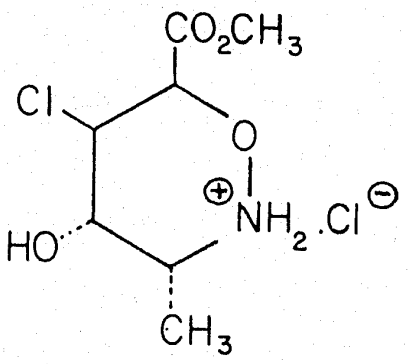
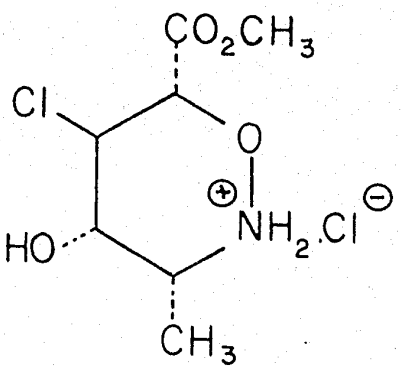


Fig. 9. The NMR spectrum of iodohydrin hydrochloride (LXVIII) measured in D_2O.

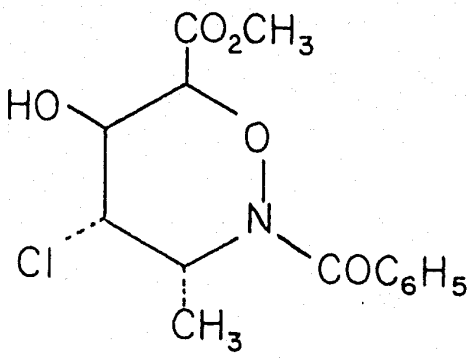
iodohydrins, it becomes obvious that the former should serve as a source of the cis-diol (LXV) and the latter as a potential precursor of the alternative cis-diol (LVII) described earlier. The acetate corresponding to (LXVI) was therefore prepared and obtained in high yield. Although it appeared to liberate iodide ion readily when digested in wet acetic acid containing silver acetate no characteristic product could as yet be isolated from the reaction mixture. For purposes of comparison, it was of interest to attempt converting the isomeric iodohydrin (LXVII) to the above described diol (LVII) but curiously enough, this failed at the earlier stage of acetylation, the original epoxide (LX) being regenerated under conditions conducive to high yields of the isomeric iodohydrin (LXVI) acetate. This contrasted behavior of (LXVII)towards acetylating conditions cannot be easily explained.

The reaction of the two epoxides with hydrogen chloride was also examined somewhat superficially. It was found necessary for reasons of solubility to use methanolic hydrogen chloride and under these conditions, the chlorohydrin which is formed from epoxide (LX) is directly converted to a mixture of stereoisomers of the free oxazine hydrochloride (LXIX). Of remarkable interest again, the epimeric oxide (LIX) did not suffer appreciable loss of its benzoyl group during the process of chlorohydrin formation (LXX). The possible significance of

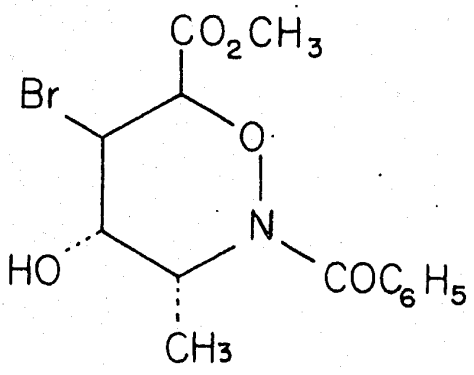




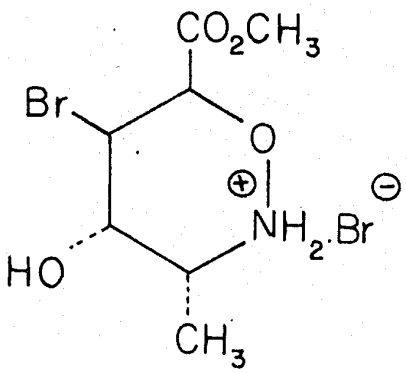
(LXIX)



(LXX)



(LXXI)



(LXXII)

these contrasting results is discussed later (see Discussion).

Finally, the reaction of epoxide (LX) with aqueous hydrobromic acid was examined and presumably because the intermediate bromohydrin benzoate (LXXI) is soluble in the medium, the reaction ultimately affords in high yield the free oxazine-acid hydrobromide (LXXII) as the only recognizable product. It is worthwhile mentioning that the various above described halohydrins should serve as potential precursors of 3- and 4-deoxy analogs in our series of novel carbohydrate-related structures.

EXPERIMENTAL*

Preparation of 3-Methyl-6-carbomethoxy-3,6-dihydro-1,2-oxazine hydrochloride (XI). (28)

To 41 g. (0.28 mole) of cold 1-chloro-1-nitroso cyclohexane (29) in a mixture of 105 ml. diethyl ether and 41 ml. ethyl alcohol, was added 105.8 g (0.84 mole) of freshly distilled methyl sorbate; the mixture was allowed to stand at 0° C for 3 days, after which time 23.1 g. of a colorless crystalline product (42% yield) had separated; m.p. 151-2°. After two weeks, another crop weighing 13.2 g. was obtained. The total yield was 67%. Its IR spectrum (Nujol Mull) showed strong absorption at 1730 cm^{-1}, and 1580 cm^{-1}. The NMR spectrum is shown in Fig. 1.

Anal. calcd. for $C_7H_{12}NO_3Cl$: C = 43.4%, H = 6.2%, Cl = 18%.

Found: C = 43.7%, H = 6.9%, Cl = 18%.

The experiment was repeated in monodeuterated ethanol (C_2H_5OD) instead of in ethyl alcohol; NMR analysis of the product showed it to be identical with that obtained in the absence of deuterated solvent.

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* All m.p. were determined microscopically on a hot stage and are uncorrected. The expression "Worked up in the usual manner" refers to extraction with an immiscible organic solvent ether or chloroform) followed by washing with either water, aqueous 5% sodium hydroxide or 5% hydrochloric acid as the case may be. The solvent is then dried over sodium sulfate and evaporated in vacuo.

(a) N-benzoyl Derivative (XLI)

Ten g. (0.052 mole) of the adduct was dissolved in 100 ml. of cold water containing cracked ice, and the flask kept immersed in an ice-water bath; then 8.8 g. (0.104 mole) of sodium bicarbonate was added slowly with stirring. After all the sodium bicarbonate had dissolved, 7.3 g. (6 ml.) of benzoyl chloride was added in three portions with vigorous stirring. The mixture was allowed to stand, with occasional stirring, for 30 minutes. The crystals which formed were removed by filtration, and washed thoroughly with cold water. The product could be purified by recrystallization from ether-pentane. (If the product would not crystallize out from the reaction mixture, the latter was worked up in the usual manner and the residual oil induced to crystallize from ether-pentane); m.p. 43-44°. The yield was 13 g, or 84%. The IR spectrum (chloroform) had strong bands at 1640 cm^{-1} and 1750 cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C = 64.36%, H = 5.74%.

Found: C = 64.27%, H = 5.17%.

The procedure above was repeated in D_2O, and the NMR spectrum of the product showed that no epimerization had occurred during the benzoylation reaction.

(b) N-carbobenzoxy Derivative (XLII)

Six g. (0.03 mole) of the adduct was dissolved in

50 ml. of cold water, and 1.6 g. (0.015 mole) of sodium carbonate slowly added with good stirring while cooling in an ice-water bath; then, 5.1 g. of benzyl chloroformate (30) (10% excess) was added dropwise from a separating funnel and simultaneously another 1.6 g. of sodium carbonate was added in portions. The mixture was stirred for 20 minutes, after which time the solution was worked up in the usual manner. A yellow liquid weighing 8.5 g. (96% yield) was obtained. The IR spectrum (liquid film) had strong bands at 1770 cm^{-1} and 1750 cm^{-1}.

(c) N-acetyl Derivative

To 1 g. of the adduct in 9 ml. of cold water containing cracked ice was added slowly 0.88 g. of sodium bicarbonate. After the addition, 0.53 g. (0.5 ml.) of acetic anhydride was added in portions and the temperature kept at about 0° C. The mixture was allowed to stand for 30 minutes with occasional shaking, extracted with ether, and the ether evaporated *in vacuo* to yield 0.6 g. of a colorless liquid. The IR spectrum (liquid film) had strong bands at 1680 cm^{-1} and 1760 cm^{-1}.

Synthesis of 2-hydroxy-5-amino caproic acid (XLIII)

A solution of 6 g. (0.03 mole) of the adduct in 250 ml. acetic acid was hydrogenated over 0.8 g. of platinum oxide at a pressure of 50 p.s.i. After 30 minutes, about 2 equivalent moles of hydrogen were taken up; no further uptake of hydrogen was observed after 3 hours. The reaction mixture

was filtered and freed from acetic acid in vacuo, then 15 ml. of conc. HCl was added, and the mixture allowed to stand overnight. It was then diluted with distilled water before evaporating in vacuo at 45°. A light, yellow, viscous liquid was obtained.

A solution of 3 g. of this liquid in 15 ml. of water was shaken with 50 g. of Dowex 50 W-X8 (200-400 mesh) in H^+ form for 30 minutes. The adsorbed amino acid was eluted with two 125 ml. portions of 2 N triethylamine in 20% (vol/vol) methanol/water. (31). The combined eluates were evaporated to dryness in vacuo, and the residue was crystallized by adding isopropyl alcohol; two fractions (a) and (b) were obtained: (a) 0.2 g. of the first crop was recrystallized from a large volume of hot methanol to give colorless prisms, m.p. 178-180° (decomp.). This material gave a negative ninhydrin test. A 0.5% solution of it in water gave a pH of 3.72. Its NMR spectrum (Fig. 3) showed it to be 3-methyl-2,4,5,6-tetrahydro-1,2-oxazine-6-carboxylic acid (XLV). Its IR spectrum (Nujol Mull) showed bands at 3021 cm^{-1} and 1625 cm^{-1}.

Anal. Calcd. for $C_6H_{11}NO_3$: C = 49.65%, H = 7.58% N = 9.65%.

Found: (1) C = 49.54%, H = 7.89%, N = 9.52%.

(2) C = 49.45%, H = 7.66%, N = 9.33%.

Fraction (b): about 0.125 g. of a second fraction crystallized when the mother liquors were allowed to stand

at room temperature for 3 days; this was recrystallized from water and ethanol to give colorless crystals, m.p. 192°; it gave a positive ninhydrin test (deep blue) sluggishly even at 100°. Descending paper chromatography on Whatman paper No. 1 using solvent I (80 ml. ethanol, 20 ml. water and 4 ml. pyridine) as the mobile phase and ninhydrin as the developer, revealed a single sharp spot with an R_F of 0.638.

Anal. Calcd. for $C_6H_{13}NO_3$: C = 48.97%, H = 8.84%.
Found: C = 48.52%, H = 8.69%.

Phenyl Ureide Derivative of 2-Hydroxy-5-Amino Caproic Acid

A suspension of 0.4 g. of methyl 2-hydroxy-5-amino caproate hydrochloride in 20 ml. chloroform was washed with cold saturated sodium bicarbonate solution. On stripping off the chloroform, 0.47 g. of yellow liquid was obtained. To this residue, 0.36 g. of phenylisocyanate was added whereupon heat was evolved. The mixture was warmed for 10 minutes to 45° C; excess 5% hydrochloric acid was added, and the mixture heated on the steam bath for one hour and then cooled to room temperature. A brown solid separated out, which was recrystallized from dichloromethane-ether to give colorless crystals; m.p. 178°. The IR spectrum (Nujol Mull) showed bands at 3400 cm^{-1}, 1725 cm^{-1}, 1620 cm^{-1} and 1590 cm^{-1} and 1540 cm^{-1}.

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C = 58.64%, H = 6.76%.
Found: (1) C = 58.78%, H = 6.84%.
(2) C = 58.58%, H = 6.47%.

Synthesis of 5,6-Dideoxy-5-Aminotalonic Acid (XLIX)

(a) 2-Benzoyl-3-methyl-6-carboxy-4,5-dihydroxy-3,4,5,6-tetrahydrooxazine (XLVI)

One and two tenths grams of N-benzoyl-3-methyl-6-carbomethoxy-3,6-dihydro-1,2-oxazine, 1 g. of osmium tetroxide and 1 ml. of dry pyridine were mixed in dry ether at room temperature. The mixture deposited almost immediately a mass of brown crystals, which were collected after 12 hours and then washed with ether. The yield was 2.5 g. or 96% (25).

This osmate-pyridine complex was shaken with 2.5 g. of sodium carbonate in aqueous methanol (1:4 by vol.) for 2 days. The solution was filtered and the filtrate evaporated to dryness; the residue was dissolved in water and the solution filtered through celite. The filtrate was made to a volume of 200 ml. with water, and acidified by the addition of 150 ml. of conc. hydrochloric acid. Greyish crystals precipitated out in almost quantitative yield (1 g.). The crystals were purified by dissolving them in 8 N ammonium hydroxide and treating the solution with charcoal. The product was reprecipitated by acidification, m.p. 202-3° (decomp.). The IR spectrum (Nujol mull) displayed bands at 3450 cm^{-1}, 1740 cm^{-1} and 1630 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO_6$: C = 55.5%, H = 5.3%.
Found: C = 54.71%, H = 4.9%.

The isolation procedure for OsO_4-pyridine adduct was repeated in D_2O and Na_2CO_3. The NMR spectrum of the product was identical to that obtained when water was used.

The methyl ester (XLVII) was obtained in quantitative yield by treating a solution of the preceding acid in dimethyl formamide with an excess of ethereal diazomethane. It crystallized from methanol in the form of colorless needles, m.p. 213°.

The IR spectrum (Nujol Mull) showed bands at 3600 cm^{-1}, 3300 cm^{-1}, 1750 cm^{-1} and 1640 cm^{-1}. The NMR spectrum is shown in Fig. 4.

Anal. Calcd. for $C_{14}H_{17}NO_6$: C = 56.94%, H = 5.76%.
Found: C = 56.82%, H = 5.89%.

(a) 5,6-Dideoxy-5-Aminotalonic Acid (XLIX)

Five hundred milligrams of the above diol acid (XLVI) was mixed with 20 ml. of conc. hydrochloric acid and the suspension heated to 100° until a clear solution was obtained. At this point, it is essential that the temperature of the solution be lowered to room temperature as otherwise, extensive decomposition of the product takes place. The solution was allowed to stand at room temperature for 2 days after which time one volume of water was added and the solution extracted with ether. The aqueous phase was evaporated to dryness in vacuo and the syrupy residue

dissolved in a mixture of 25 ml. of ethanol and 5 ml. of conc. hydrochloric acid. After adding 100 mg. of platinum oxide, the solution was shaken under 50 p.s.i. of hydrogen (Parr instrument) for 16 hours. The catalyst was removed and the filtrate taken to dryness in vacuo. The residue was dissolved in water and excess silver carbonate added. After a few minutes, the mixture was filtered through celite which was then washed with hot water. The combined filtrates were saturated with hydrogen sulfide and the solution filtered again through celite. The clear and colorless filtrate was evaporated to dryness in vacuo to yield a syrup which crystallized readily from water-ethanol to give colorless prisms, m.p. 230° (decomp.). The yield was 250 mg. or 78%. It gave a positive ninhydrin test (blue color) sluggishly at 100°. The IR spectrum (Nujol mull) showed bands at 3500 cm^{-1}, 3250 cm^{-1}, 1650 cm^{-1} and 1600 cm^{-1}.

Anal. Calcd. for $C_6H_{13}NO_5$: C = 40.22%, H = 7.26%.
Found: C = 40.10%, H = 7.32%.

Epimeric 4,5-Epoxy-3-methyl-6-carbomethoxy-3,4,5,6-tetrahydro-1,2-oxazines (LIX) and (LX). (32)

To a cooled suspension of 1.5 ml. (0.066 mole) of 90% hydrogen peroxide in 6.1 ml. of ethylene dichloride was added over a fifteen minute period, 9.2 ml. (0.08 mole) of trifluoroacetic anhydride. This solution was then added

dropwise over a 50 minute period to a mixture of 30.6 g. of disodium hydrogen phosphate, 37 ml. ethylene dichloride and 8 g. of the adduct benzoate (XLI) while stirring vigorously. After the period of addition, the solution was stirred for one hour. Then 88 ml. of water was added and the solution stirred again until the salts had dissolved. The organic layer was separated, and the aqueous layer was extracted with several portions of chloroform. The combined organic extracts were washed with 10% sodium bicarbonate solution, dried over sodium sulfate, and freed of chloroform under vacuum. The crude epoxide (6.5 g.) mixture solidified upon addition of a few drops of ether and pentane; it was fractionally recrystallized from methanol. The procedure for separating the two isomers was as follows: (a) The crude epoxide was dissolved in hot methanol, allowed to stand overnight at room temperature to give 3.5 g. of white cubic crystals, m.p. 137° (it may be recrystallized again from methanol). (b) The mother liquor from (a) on standing overnight at 0° C deposited the other isomeric epoxide as colorless needles, which when twice recrystallized from methanol had m.p. 95°. The IR spectra (chloroform) of the two oxides had major bands at 1750 cm^{-1} and 1640 cm^{-1}. The NMR spectra are shown in Fig. 6 and 7.

Anal. Calcd. for $C_{14}H_{15}NO_5$: C = 60.65%, H = 5.41%.

Found: C = 60.40%, H = 5.36% (m.p. 137°)

C = 60.80%, H = 5.70% (m.p. 95°).

Reaction of the Epoxides with Halogen Acids

(A) With Hydriodic acid

(a) A mixture of 1.4 g. of the epoxide m.p. 137° and 1.5 ml. of 50% hydriodic acid was stirred vigorously for 15 minutes, and then allowed to stand for a further 10 minutes. The crystalline product which separated was washed thoroughly with water, and recrystallized from methanol or ethyl acetate; m.p. 180-181°. The yield was 2 g. or 98%. The IR spectrum (Nujol Mull) showed bands at 3350 cm^{-1}, 1750 cm^{-1} and 1630 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}NO_5I$: C = 41.48%, H = 3.95%.
Found: C = 41.80%, H = 4.20%.

(b) The epoxide of m.p. 95° was treated with 50% hydriodic acid as in procedure (a). The product was recrystallized from methanol, m.p. 215°-7°. The yield was 91%. The IR spectrum (Nujol Mull) exhibited strong bands at 3350 cm^{-1}, 1750 cm^{-1} and 1630 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}NO_5I$: C = 41.48%, H = 3.95%.
Found: C = 41.10%, H = 4.33%.

(B) With Hydrobromic Acid

One hundred and seventy milligrams of the epoxide m.p. 137° was mixed with 15 ml. of 40% hydrobromic acid and the solution allowed to stand at room temperature. After

3 days, the benzoic acid which had separated was removed, the filtrate washed twice with ether, diluted with water and evaporated to dryness under vacuum. A solid residue was obtained which was recrystallized from ethanol and ether. The product (LXXII) decomposed partially on further purification.

Anal. Calcd. for $C_6H_{11}NO_4Br_2$: C = 22.4%, H = 3.42%.
Found: C = 21.8%, H = 3.86%.

(C) With Aqueous Hydrochloric Acid

The insolubility of the epoxides in this medium caused the reaction to be extremely sluggish.

(D) With Methanolic Hydrogen Chloride

(a) Hydrogen chloride was passed in a solution of 1.02 g. of the epoxide m.p. 137° in 100 ml. of methanol at 0° C for 10 minutes, and the mixture allowed to stand overnight at room temperature. The methanol was then evaporated in vacuo, and a few ml. of ether added to the residue whereupon 0.6g. (or 68%) of the product (LXIX) crystallized. It could be recrystallized from isopropyl alcohol, m.p. 138-145° (decomp.). As judged from the IR spectrum two ester carbonyls were present (bands at 1770 cm^{-1} and 1750 cm^{-1}). The NMR spectrum shows that the product was a mixture of two isomers in the ratio of 1:3.

Anal. Calcd. for $C_7H_{13}NO_4Cl_2$: C = 34.14%, H = 5.2%.
Found: C = 34.14%, H = 4.67%.

In the ethereal layer, 0.2 g. of N-benzoyl chlorohydrin was obtained. The melting point was 155°. The IR spectrum (Nujol Mull) exhibited strong bands at 3400 cm^{-1}, 1775 cm^{-1} and 1630 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}NO_5Cl$: C = 53.58%, H = 5.10%.
Found: C = 54.32%, H = 5.14%.

(b) 0.8 g. of epoxide m.p. 95° was dissolved in 25 ml. of methanol and the same conditions applied as in procedure (a) above. The product was isolated by crystallization from ether and isopropyl alcohol, and recrystallized from isopropyl alcohol; m.p. 203°. The IR spectrum showed that the benzoyl group had not been removed in this case, as evidenced by the presence of strong bands at 1630 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}NO_5Cl$: C = 53.58%, H = 5.10%.
Found: C = 54.31%, H = 5.20%.

Methanolysis of the Iodohydrin Benzoates (33)

(a) The iodohydrin (LXVII) from epoxide m.p. 137°, (158 mg.) was dissolved in 20 ml. of hot methanol, the solution cooled in an ice-water bath, and hydrogen chloride passed into it for 8 minutes. The mixture was then allowed to stand at room temperature overnight, freed from methanol and hydrogen chloride by evaporation in vacuo; the residue solidified when ether was added. It was recrystallized from isopropyl alcohol to give 0.125 g. colorless needles (96% yield),

m.p. 138-140° (decomp.).

The IR spectrum (Nujol Mull) had major bands at 3600 cm^{-1}, 1750 cm^{-1} and 1565 cm^{-1}. The NMR spectrum (Fig. 9) showed that the compound was homogeneous.

Anal. Calcd. for $C_7H_{13}NO_4ICl$: C = 24.88%, H = 3.85%.
Found: C = 25.05%, H = 3.96%.

(b) The iodohydrin (LXVI) from epoxide m.p. 95° was treated by the same procedure as above but the starting material was recovered unchanged. The experiment was repeated under different conditions: 0.5 g. of the iodohydrin was dissolved in 40 ml. of methanol containing excess dry hydrogen chloride and the solution heated under reflux for 3 hours, after which time, the mixture was allowed to stand overnight and then evaporated <u>in vacuo</u>. An oily residue was obtained which consisted of a complex mixture as ascertained by NMR spectroscopy.

<u>Acetylation of the Isomeric Iodohydrin (LXVI) and (LXVII)</u>

(a) A solution of the iodohydrin (LXVI) was prepared by dissolving 0.59 g. of the material in 20 ml. of hot dry dimethyl formamide; after cooling, six ml. of acetic anhydride and a few drops of dry pyridine were added. The mixture was heated at about 60° for 10 minutes, allowed to stand overnight at room temperature and then concentrated to

two thirds of its volume in vacuo; excess cold water was added whereupon crystallization occurred. The yield was 0.53 g. or 81%; m.p. 177-178°. The IR spectrum (Nujol Mull)showed strong bands at 1775 cm^{-1}, 1750 cm^{-1} and 1650 cm^{-1}. The NMR spectrum (Fig. 8) showed that the compound was homogeneous.

Anal. Calcd. for $C_{16}H_{18}NO_6I$: C = 42.90%, H = 4.02%.
Found: C = 42.89%, H = 4.03%.

(b) The same procedure was applied to the iodohydrin (LXVII), but in this case, the only product that could be isolated was the epoxide m.p. 137° (LX).

Reaction of the Epimeric Epoxides with Formic Acid

(A) With Epoxide m.p. 137° (LX)

(a) A mixture of 1 g. of the epoxide m.p. 137° in 15 ml. of 90% formic acid was heated on the steam-bath for 45 minutes; the excess formic acid was evaporated in vacuo to leave a white crystalline product after trituration with a few drops of ether and isopropyl alcohol. This was recrystallized from isopropyl alcohol to give colorless needles (LXII). The yield was 0.68 g. m.p. 187-189°. The IR spectrum (Nujol Mull) had strong bands at 3300 cm^{-1}, 1770 cm^{-1}, 1725 cm^{-1} and 1640 cm^{-1}.

Anal. Calcd. for $C_{15}H_{17}NO_7$: C = 55.7%, H = 5.2%.
Found: C = 55.6%, H = 5.8%.

(b) 3-Methyl-6-carbomethoxy-4,5-trans-dihydroxy-3,4,5,6-tetrahydro-1,2-oxazine hydrochloride (LXIII)

Methanolysis of the preceding material was accomplished as described above in the case of the iodohydrin (LXVII). The product was crystallized from isopropyl alcohol and ether; m.p. 78-85° (decomp). The IR spectrum showed the major bands at 3300 cm^{-1}, 1750 cm^{-1} and 1570 cm^{-1}. The NMR spectrum showed that the compound was heterogeneous.

(B) With Epoxide m.p. 95° (LIX)

(a) The formate (LXI) was prepared by the same method as (A); 0.15 g. of the product was obtained from 0.28 g. of the starting epoxide. The yield was 46%; m.p. 155-175°. It was recrystallized from isopropyl alcohol, m.p. 179-184°. The IR spectrum (Nujol Mull) had major bands at 3400 cm^{-1}, 1770 cm^{-1}, 1725 cm^{-1} and 1640 cm^{-1}.

Anal. Calcd. for $C_{15}H_{17}NO_7$: C = 55.7%, H = 5.2%.
Found: C = 55.2%, H = 5.0%.

(b) Treatment of this product with methanolic hydrogen chloride as described above in the case (LXII) afforded the same diol hydrochloride (LXIII), m.p. 78-82° (decomp.) in 83% yield. Both the IR and NMR spectra of this material were identical to those of (LXIII) described above.

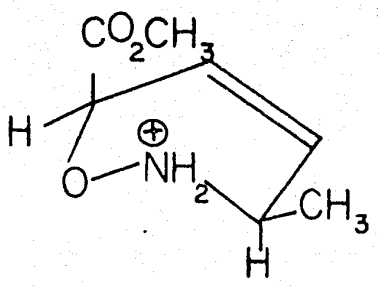
Anal. Calcd. for $C_7H_{14}NO_5Cl$: C = 36.92%, H = 6.15%.
Found: C = 36.97%, H = 6.92%.

Discussion of Results

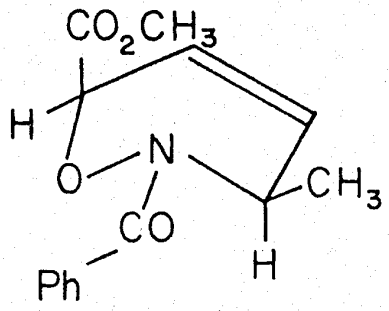
As pointed out earlier, it did not appear possible to predict the direction of the addition of the nitrosoalkane across the diene system of methyl sorbate. Our experiments demonstrate clearly that the addition is entirely unidirectional and the fact that the product of catalytic hydrogenation and hydrogenolysis is not an α-aminoacid supports unambigously the alternative structure (XL) for the adduct. Hence, it is the nitrogen of the nitroso group which must act as the electron donor as shown in complex (XXXVIII), a behavior which finds a parallel in the dimerization of nitrosobenzene to (XXXVII) (34). These observations should be useful in predicting the structure of similar adducts when derived from different dienes.

The configuration of the 3,6-substituents in the adduct poses a problem of considerable interest especially in view of the remarkable rigidity of the stereochemical rules that can be applied in the prediction of configurations in Diels-Alder products. As shown earlier, the adduct should be assigned the cis-configuration (XXXIX) since trans-trans-methyl sorbate was used as the diene component. Furthermore, the preferred conformation (LXXIII) would be expected for a cis-adduct since it is now known that in the cyclohexane series, the methyl group is bulkier than the carbomethoxyl (the energies of non-bonded interactions differing by approximately 0.6 kcal

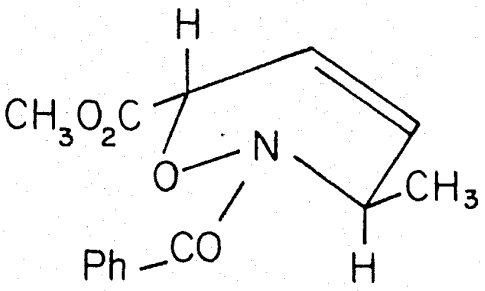
in favor of the methyl group) (35). Although we were ready to accept a priori the cis-configuration for the adduct, a number of subsequent observations could not be reconciled with this assignment, and although we cannot supply as yet a rigorous proof, there is strong presumptive evidence favoring a trans-configuration in the adduct (XXXIX). For instance, as the N-benzoyl derivative (LXXIV), the cis-configuration readily allows the prediction that approach of an epoxidizing reagent to the top side of the double bond should be considerably hindered by the axial carbomethoxyl group and also to a lesser degree by the equatorial methyl group. As an example, it has been shown that 3-methoxy cyclohexene (LXXVI) is attacked by perbenzoic acid to give a predominating proportion of the oxide (LXXVII) even though in this case, the hindrance effect is produced by an equatorial group rather[35a] than an axially oriented one. Reasoning by analogy, epoxidation of (LXXIV) should be still more stereoselective. However, additional directional influences must be considered. In contrast to (LXXVI), cyclohexene-3-ol (LXXVIII) gives mostly the cis-oxide and this is interpreted as resulting from an orienting effect of hydrogen bonding as shown (36,37). That this may be the case was demonstrated when acetylation of the hydroxyl group (LXXIX) was observed to abolish the stereo-directional influence of the latter. On that basis, it would



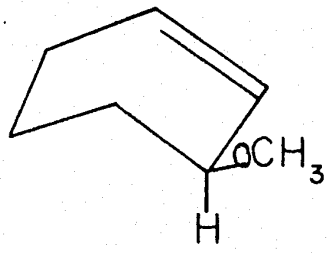
(LXXIII)



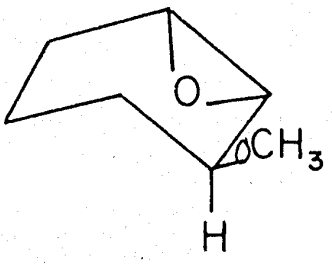
(LXXIV)



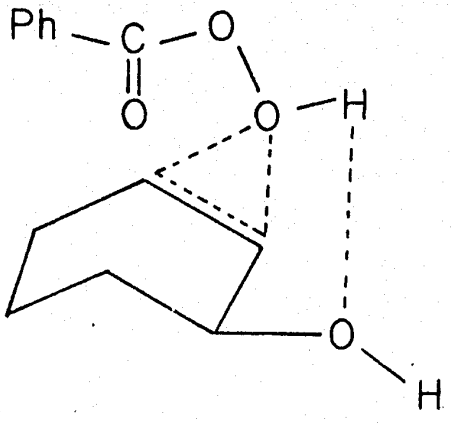
(LXXV)



(LXXVI)



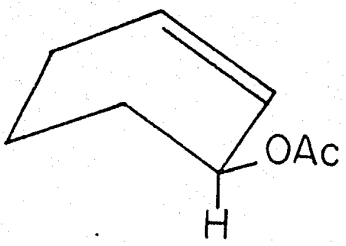
(LXXVII)



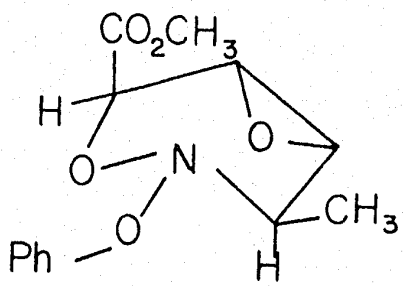
(LXXVIII)

appear unlikely that the axial carbomethoxyl in (LXXIV) could outweigh, though hydrogen bonding, the unfavorable steric hindrance to approach from the top side of the molecule. Simple logic can then be seen to allow the prediction that epoxidation should take place mostly on the bottom side of the molecule to give a large proportion of the oxide (LXXX). However, this is not borne out by experiment; epoxidation of the benzoyl adduct leads to a 1:1 mixture of both possible epoxides. This complete lack of selectivity could perhaps reflect the operation of a fine balance between a variety of directional factors, but it is certainly justifiable in view of the proceeding discussion to conclude that there appears to be little difference in the steric restrictions between the two sides of the double bond. It is obvious that only the trans-configuration (LXXV) can fulfill this requirement and provided the oxidizing agent is relatively small, stereo-directional effects should be negligible and a 1:1 mixture of the two epoxides (LXXXI) and (LXXXII) should result as is the case. However, we are fully aware that more rigorous evidence would be desirable but as will be seen, only the present interpretation can in addition account satisfactorily for the chemistry of the epoxides.

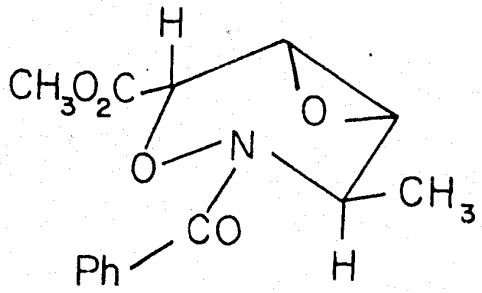
The oxazine-carboxylic acid (XLV) derived from the benzoyl adduct by hydrogenation should then be assigned configuration (LXXXIII). The NMR spectrum of the latter is shown in Fig. 3. It should be emphasized that although the



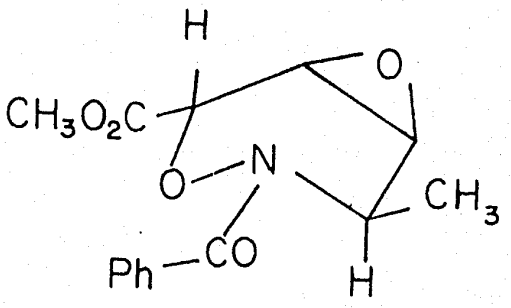
(LXXIX)



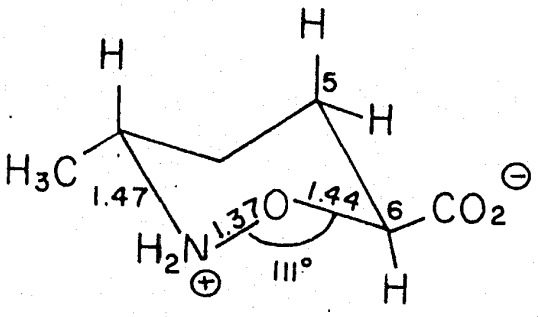
(LXXX)



(LXXXI)



(LXXXII)

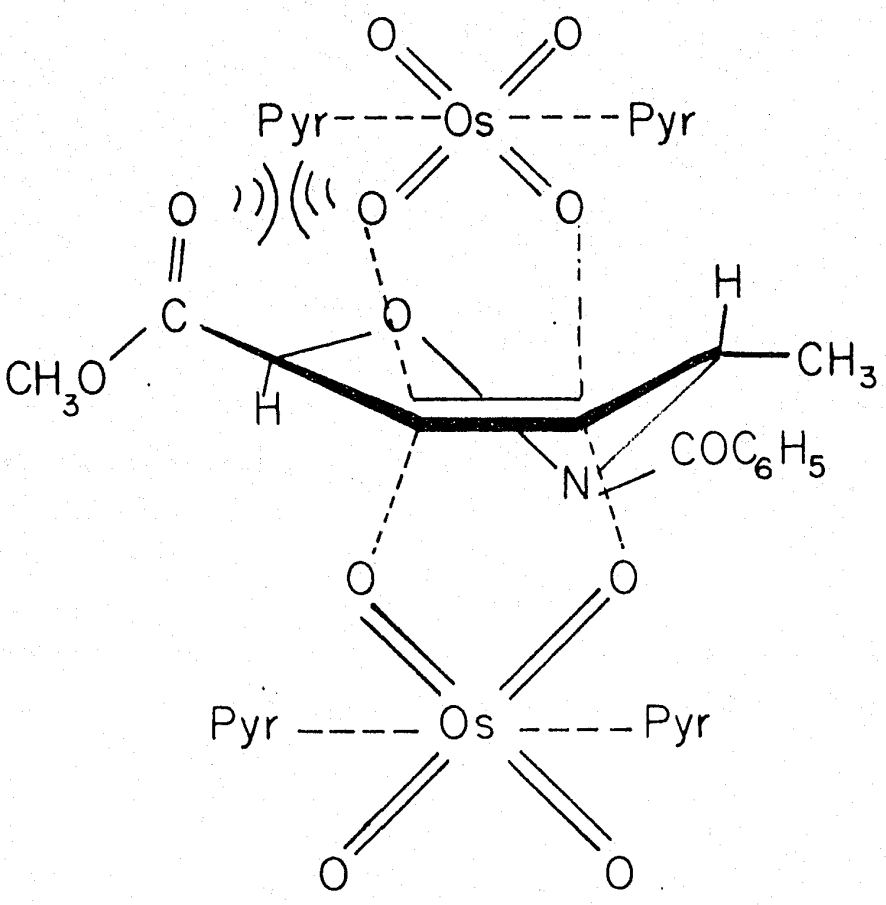


(LXXXIII)

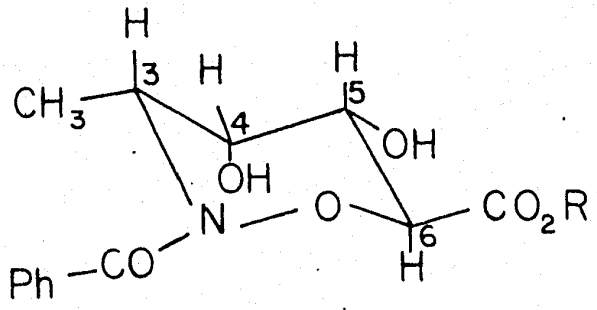
tetrahydro-1,2-oxazine ring no doubt has cyclohexane-like geometry, there certainly exist differences with the latter especially in the bond angle relationships. Because the C-N, the N-O and O-C bonds are all shorter than the normal C-C bond and since the C-N-O as well as the N-O-C bonds have different bond angles than the C-C-C bond in cyclohexane, it can be expected (and confirmed by the study of Courtauld molecular models) that the relative geometry of the ring hydrogens will differ from that of the cyclohexane counterpart. This results for instance in that the C_6-hydrogen of (LXXXIII) has reduced axial character, a situation which can serve to explain its NMR spectral characteristics (triplet centered at 13.78 c/s with smaller splitting than normal). Taking this to mean that the carboxyl group of (LXXXIII) is equatorially oriented, it follows that the methyl group must also be equatorial since in the alternative cis-configuration, it would be expected that the carboxyl group would be the one axially oriented rather than the methyl group (see above in connection with the relative bulks of methyl and carboxyl groups). Attempts to apply equilibrating conditions to (LXXXIII) were unsuccessful, the product suffering extensive degradation in strong acid or alkali. The use of the corresponding methyl ester led to similar results.

The high degree of stereospecificity achieved in the hydroxylation of the benzoyl adduct with the osmium

tetroxide-pyridine complex might appear surprising in view of the course of the epoxidation reaction. However, the results are entirely expectable if due regard is paid to the fact that the osmium tetroxide-pyridine complex has very high steric requirements being of considerable bulk; therefore the course of the reaction should be much more sensitive to stereo-directional factors which are too small to influence the stereochemical consequences of an attack by a less demanding reagent. Accordingly, in the postulated trans-configuration for the N-benzoyl adduct (LXXV), the prediction is permissible that attack from above the plane (LXXXIV) will be repelled by strong dipole-dipole interactions between the oxygens of the carbomethoxyl and those of the reagent. Approach from the bottom of the molecule should be favored, the repulsive forces induced by the methyl group being of a smaller order of magnitude. Although the methyl group is bulkier (vide supra), the magnitude of the dipole-dipole interactions should be such as to constitute the major stereo-directional factor in the hydroxylation reaction and hence, the configuration of the resulting cis-diol should be represented by formula (LXXXV, R = H). An attempt was made to confirm this configurational assignment by NMR spectroscopy. The corresponding methyl ester (LXXXVI, R = CH_3) was found suitable (as the diacetate)for this purpose (see Fig. 4) and if one ascribes the diffuse doublet centered



(LXXXIV)

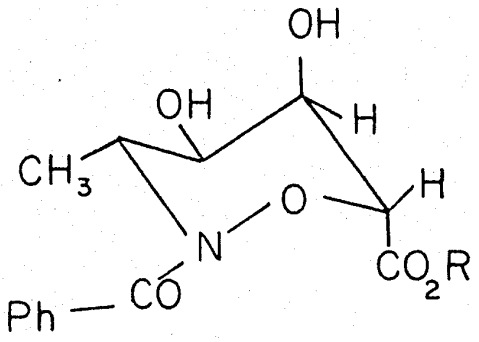


(LXXXV, R=H)

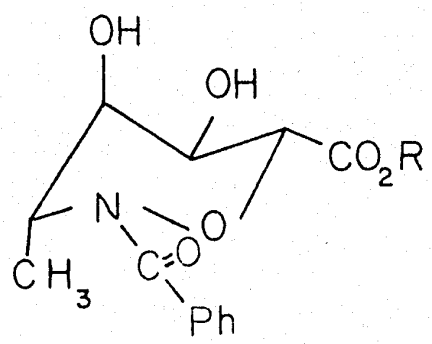
(LXXXVI, R=CH_3)

at 136.69 c/s to the C_6-hydrogen, then there is no doubt, as judged from the spacing (10.2 c.p.s.) that the C_5- and C_6-hydrogens are both axially oriented. The presence of two strongly electronegative substituents on carbon-6 should account for the appearance of that doublet at such a low field whereas its diffuse appearance may be due to the two consecutive lone pairs of electrons on the N-O substituent. On that basis, the configurational assignment for (LXXXV) becomes quite acceptable. Moreover, the carboxyl group at C_6 being equatorial, it should follow that the methyl group is also equatorial, since the greater bulk of the latter would favor conformation (LXXXVII) over (LXXXVIII) in the alternative cis-configuration for the C_3 and C_5 substituents. In (LXXXVII), the C_6-hydrogen is no longer axial and hence the spacing of the doublet at 10.2 c/s would have other well-known characteristics. Since we have established already that no epimerization of the carboxyl group has occurred during the isolation procedure, the above arguments also support a trans-configuration in the initial Diels-Alder adduct.

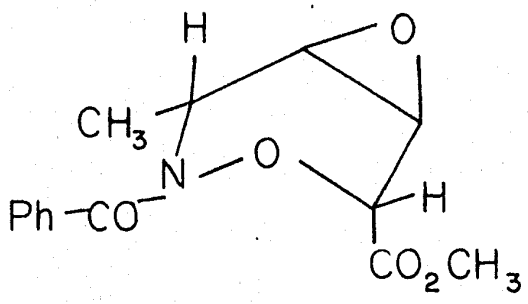
An examination of the behavior of the epimeric epoxides towards hydriodic acid as well as the properties of the derived iodohydrins offers several points of interest. If one assumes at first that the 3,6-substituents are cis-oriented in the epoxides as shown in (LXXXIX) and (XC), one could hardly



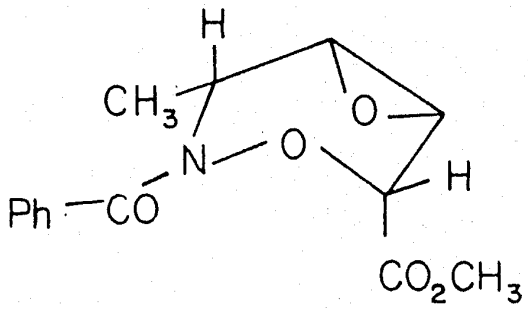
(LXXXVII)



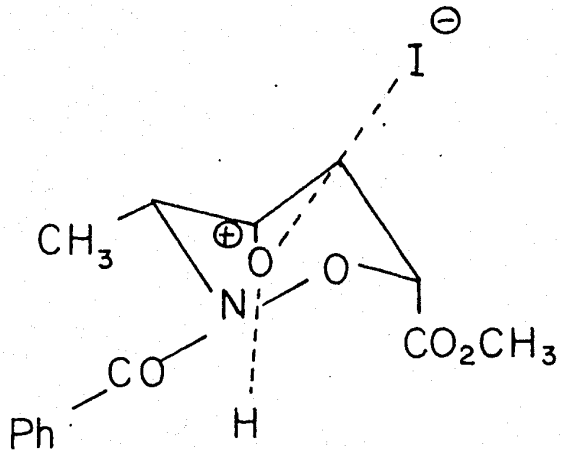
(LXXXVIII)



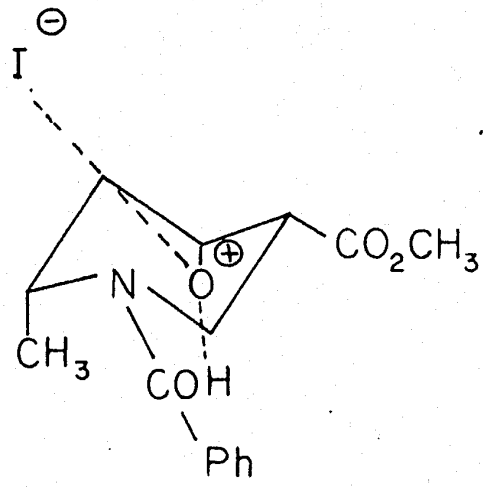
(LXXXIX)



(XC)



(XCI)

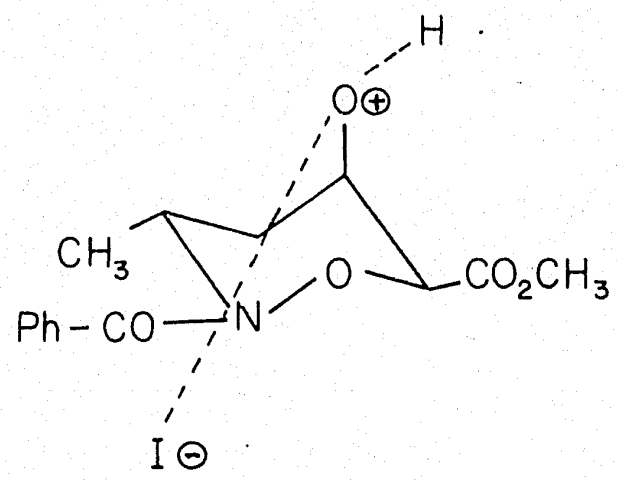


(XCII)

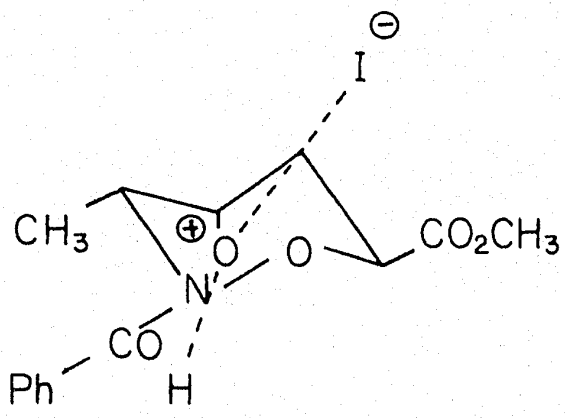
expect appreciable stereospecificity in the opening of the oxide ring by hydriodic acid because the difference in free energy between the two possible transition state conformations as produced for instance from epoxide (XC) is too small (approximately 0.6 kcal) to favor the existance of only one of them (i.e. the one of lowest energy XCI). Of course, this kind of argument is valid only as long as unforseeable interactions do not occur in the hypothetical transition state structure and also only if the rule of trans-diaxial opening is always fully operative. Since there is no apparent reason why the epoxides would represent special or exceptional cases, the above expectations are well within reason. It can be roughly estimated on the basis of a 0.6 kcal difference in the free energies of (XCI) and (XCII) that the latter should be present to the extent of approximately 30% in the mixture. Assuming all other factors to be equal, a mixture of iodohydrin in the ratio of about 1:2 should result. The same kind of reasoning applies to the epimeric epoxide (LXXXIX) and it is of some significance that these expectations were not borne out in either case by experiment. Each epoxide afforded in virtually quantitative yield a homogeneous iodohydrin and this again appears inconsistent with a cis-configuration for the 3,6-substituents. However, a trans-configuration readily accounts for these results, the rule of trans-diaxial opening allowing the unambiguous prediction of a unidirectional fission of the

oxide ring in either compound. In both transition states (XCIII) and (XCIV) the 3,6-substituents assume the diequatorial orientation conducive to the iodohydrins (XCV) and (XCVI) respectively. To obtain the alternative mode of opening by hydriodic acid, the 3,6-substituents would have to adopt the diaxial orientation in the transition state and this is obviously highly unfavorable. As can be seen again, a trans-configuration in the adduct and the derived epoxides accounts best for the stereochemical outcome of the above reactions and there remains to determine which structure, (XCV) or (XCVI) belongs to which iodohydrin.

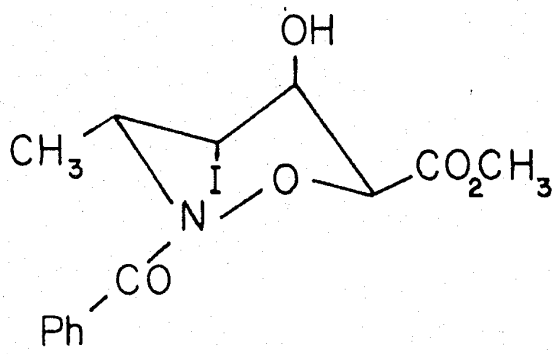
An examination of the relative behavior of each iodohydrin toward acid catalyzed methanolysis provides a basis for structural assignments to the iodohydrins. The remarkable observation was made that whereas the iodohydrin m.p. 180-181° undergoes smooth methanolysis to the corresponding de-benzoylated derivative, the isomeric iodohydrin m.p. 215-217° is refractory towards the same conditions. This is taken as evidence that the reactive iodohydrin of m.p. 180-181° has the structure (XCVI) whereas the unreactive one of m.p. 215-217° has the constitution (XCV). The reasons allowing this decision are as follows: it is well-known that N-acyl-1,2-aminoalcohols undergo ready N $\longrightarrow$ O acyl migration when treated with alcoholic hydrogen chloride; (38) alcoholysis of the resulting ester



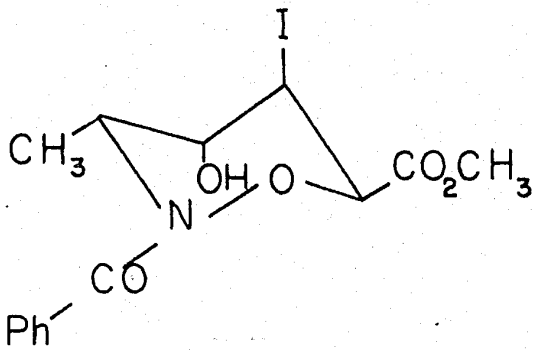
(XCIII)



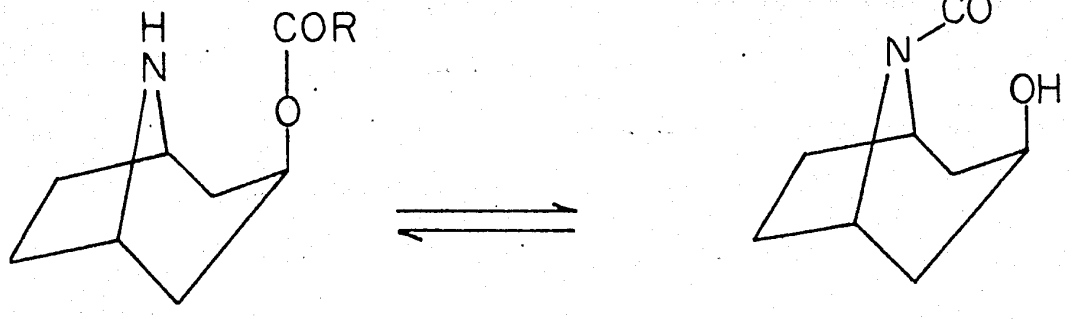
(XCIV)



(XCV)

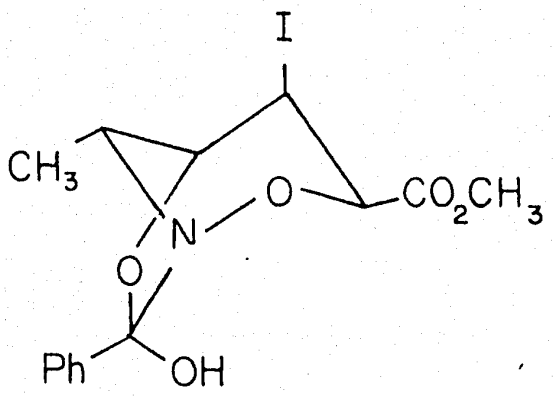


(XCVI)

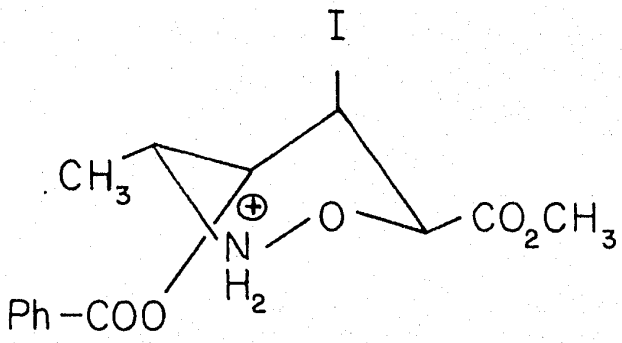


(XCVII) (XCVIII)

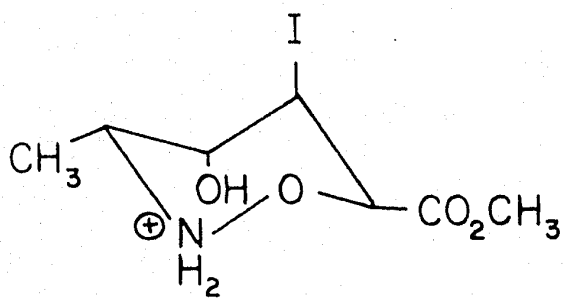
can sometimes occur rapidly enough so that the rate-determining step for the production of the free amino-alcohol is the migration of the acyl group. In the absence of such a neighboring group effect, amides are known to undergo alcoholysis sluggishly. In cases where the geometry is favorable, N-acyl-1,3-aminoalcohols have also been shown to rearrange in a similar fashion. This has been exemplified in the nortropane series, (XCVII ⇌ XCVIII) (39) and the stereochemical requirements for such migrations have been shown to be quite rigid. Examination of structure (XCVI) reveals that ready N → O acyl migration is sterically highly favorable and should it occur, rapid formation of the O-benzoyl derivative (C) by way of the intermediate (XCIX) should obtain. Subsequent methanolysis of (C) in a non-rate-determining step would lead to (CI) as is the case. In contrast, the isomeric structure (XCV) does not provide for ready N → O migration of the benzoyl group, the only conformation theoretically allowing rearrangement being (CII) in which the ring is forced to adopt the boat geometry and the methyl group the axial orientation. Clearly, a high energy barrier opposes rearrangementin the case of (XCV) resulting in a reluctance to suffer methanolysis. On that basis, the structure (XCV) can clearly be assigned to the iodohydrin of m.p. 215-217°, whereas the isomeric iodohydrin of m.p. 180-181° must have structure (XCVI). It follows that



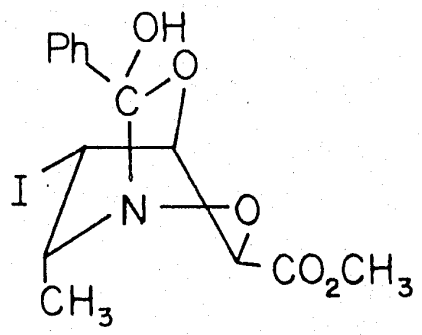
(XCIX)



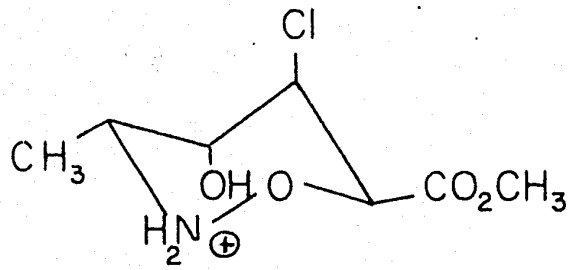
(C)



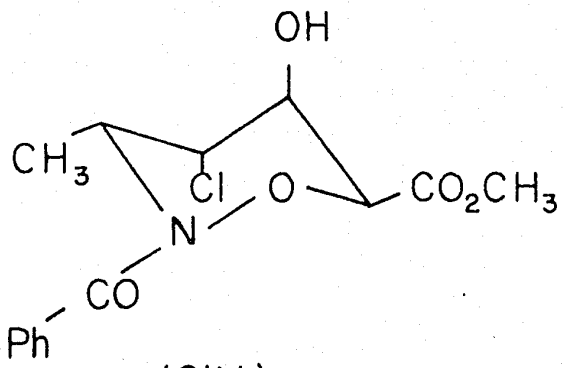
(CI)



(CII)



(CIII)



(CIV)

the epoxide of m.p. 137° must be represented by formula (LX) and that of m.p. 95° by structure (LIX). For convenience, epoxide (LIX) will be referred to as the cis-oxide (oxide oxygen cis to the carbomethoxyl) and the epimeric epoxide (LX) as the trans-oxide.

Reaction of the epoxides with hydrogen chloride was also briefly examined but only under conditions normally conducive to methanolysis because of the insolubility of the oxides in aqueous hydrochloric acid. In this case too were sharp differences in reactivity noticeable between the two isomers. In agreement with the preceding rationalizations, the trans-oxide suffered de-benzoylation readily following chlorohydrin formation (CIII) whereas the cis-oxide gave mostly the chlorohydrin benzoate (CIV) under the same conditions. Of interest is the observation that the expectable product (CIII) from the trans-oxide proved to be heterogeneous as ascertained by NMR spectroscopy (Fig. 10). The relative intensities of the doublets characteristic of the ring methyl group indicate the presence of a second component to the extent of 25%. However, the empirical analysis fully agrees with formula (CIII). Since the IR spectrum showed two distinct carbonyl absorption bands at 1770 cm^{-1} and 1750 cm^{-1}, it was deduced that this new substance must be an epimer of (CIII). It is probable that the carbomethoxyl group of the

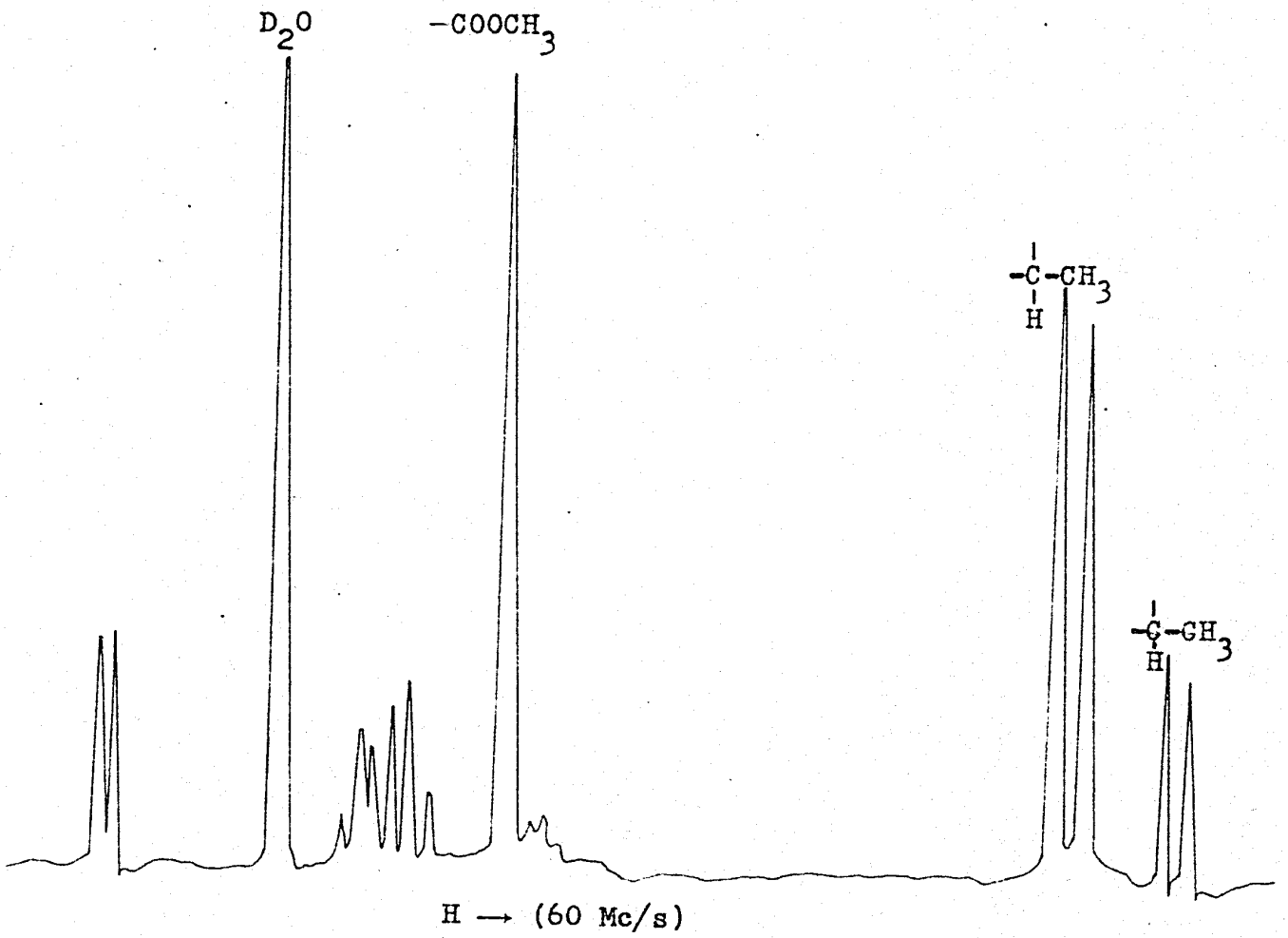
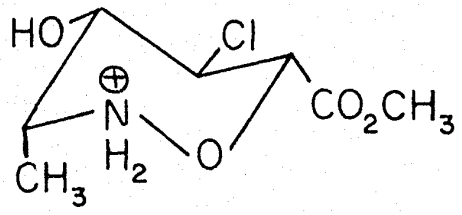
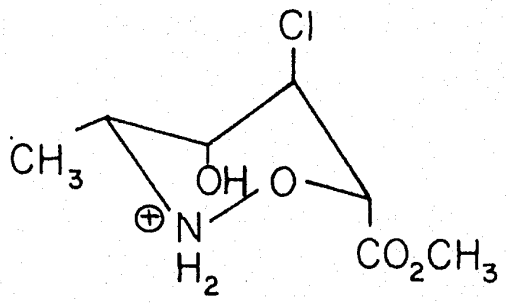


Fig. 10. The NMR spectrum of chlorohydrin hydrochloride (CIII) mixture measured in D_2O.

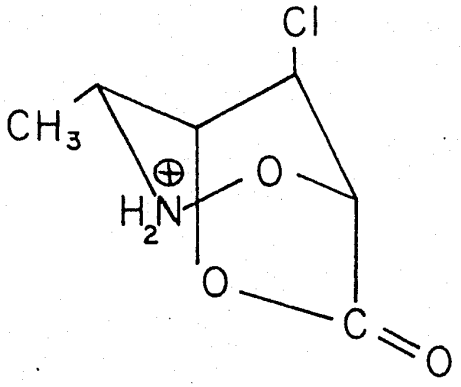
latter could suffer epimerization under the strongly acidic conditions used. This would lead to structure (CV) for this epimer. If this were true, one would expect in addition to the appearance of two carbonyl bands in the IR and two kinds of ring methyls in the NMR, that the relative intensities of the C-methyl bands and the C(=O)-O-methyl peak in the NMR spectrum should correspond to a ratio of 1 to 1. This is not the case however, the intensity of the O-methyl peak being about 25% lower than the theoretical value. This rules out structure (CV) for the epimer and leaves the lactones structure (CVII) as the only acceptable alternative. Obviously, the formation of the latter requires the intermediacy of (CV) but in the alternative conformation (CVI). Attempts to isolate the lactone (CVII) in a pure form are being made. Epimerizations of the type postulated in the conversion of (CIII) to (CV) have previously been noted in the cyclohexane series under similar conditions.[40] It seems improbable that lactone formation would take place as readily if the methyl group would be forced to adopt the axial orientation in (CVII). On that basis, the configuration of the lactone would appear to be well established and confirms unambiguously the direction of the opening of the trans-oxide with hydrogen halides as well as the axial configuration of the resulting hydroxyl group. It is noteworthy that the empirical composition of lactone (CVII)



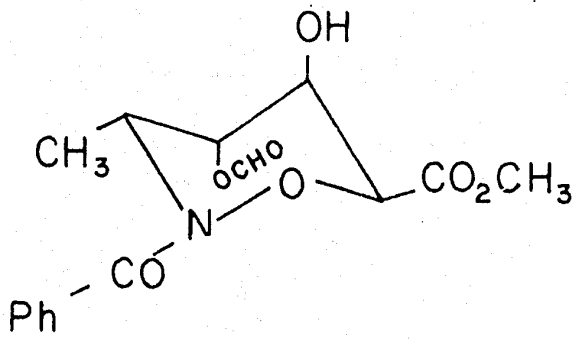
(CV)



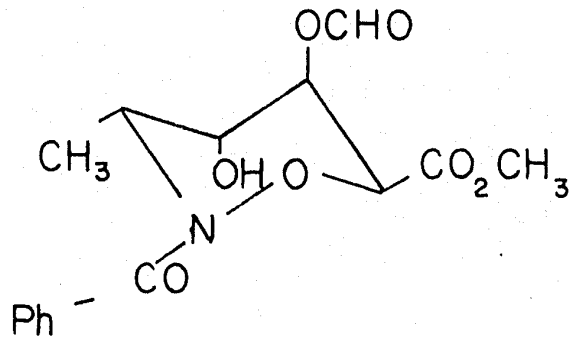
(CVI)



(CVII)



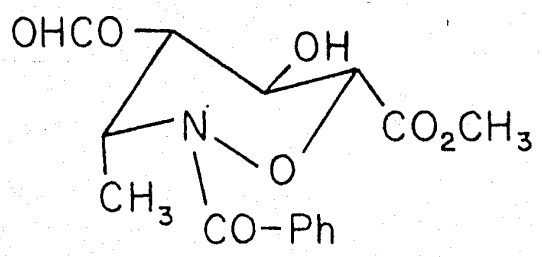
(CVIII)



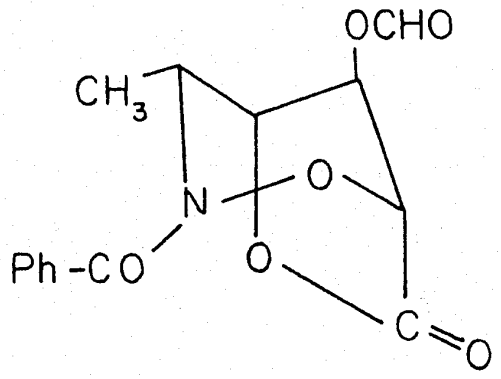
(CIX)

does not differ significantly from that of the ester (CIII).

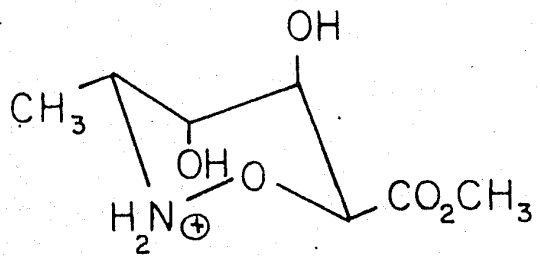
The behavior of the epoxides towards formic acid deserves commenting upon. Using as a basis the above deductions concerning the stereochemistry of the epoxides and their derived halohydrins, it can be expected that reaction of the epimeric oxides with formic acid should yield the glycol monoformates (CVIII, CX) and (CIX, CXI) as primary products. Although the empirical composition fully agreed with these structures, the NMR spectra of the compounds showed that they consist of mixtures inseparable by crystallization. This can perhaps be attributed in part to the presence in the reagent of 10% water which could conceivably cause partial hydrolysis of some of the ester functions in the products. More probably, formic acid may be a sufficiently strong acid to induce epimerization of the carbomethoxyl groups in (CVIII) and (CIX) and in this way lead to the appearance of the epimers (CX) and (CXI), the latter in the form of a lactone. Treatment of either mixture with methanolic hydrogen chloride gave in high yield crystalline products which were identical. It follows that the relative configuration of the substituents in the isomeric glycol monoformates is the same for both as would be expected on the basis of a unidirectional trans-diaxial opening of either epoxide. The NMR spectrum of the methanolysis product showed however that it consisted



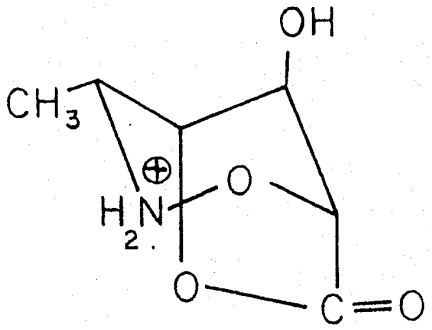
(CX)



(CXI)



(CXII)



(CXIII)

of a mixture of two components in the ratio of 1:3 (Fig. 11), (relative intensities of the methyl doublets). The empirical composition agreed with formula (CXII) but again as in the case of the chlorohydrin (CIII), the ratio of the intensities of the C-methyl bands to that of the O-methyl peak, clearly indicated that the major constituent cannot be a simple epimer of (CXII) but either a lactone (CXIII) or a hydrolysis product. In fact, the intensity of the O-methyl band reaches only about 25% of the expectable value, thus establishing that no more than 25% of (CXII) can be present in the mixture. Since the lactone (CXIII) has an empirical composition close to that of the methyl ester (112) (or its non-lactonized epimer), it would appear logical to conclude that the methyl ester has suffered extensive hydrolysis in the aqueous solvent used for NMR spectroscopy or has extensively lactonized during the course of methanolysis. A careful examination of the IR spectrum of the mixture under high resolution confirmed the presence of two carbonyl bands at 1750.4 cm^{-1} and 1746.4 cm^{-1}. Separation of the presumed lactone from the mixture has been undertaken. It should be noted that if this lactone (CXIII) is indeed formed to the extent of 75%, it provides a facile unexpected entry into the 3,6-<u>cis</u>-series theoretically conducive to four additional racemates in the hexose field.

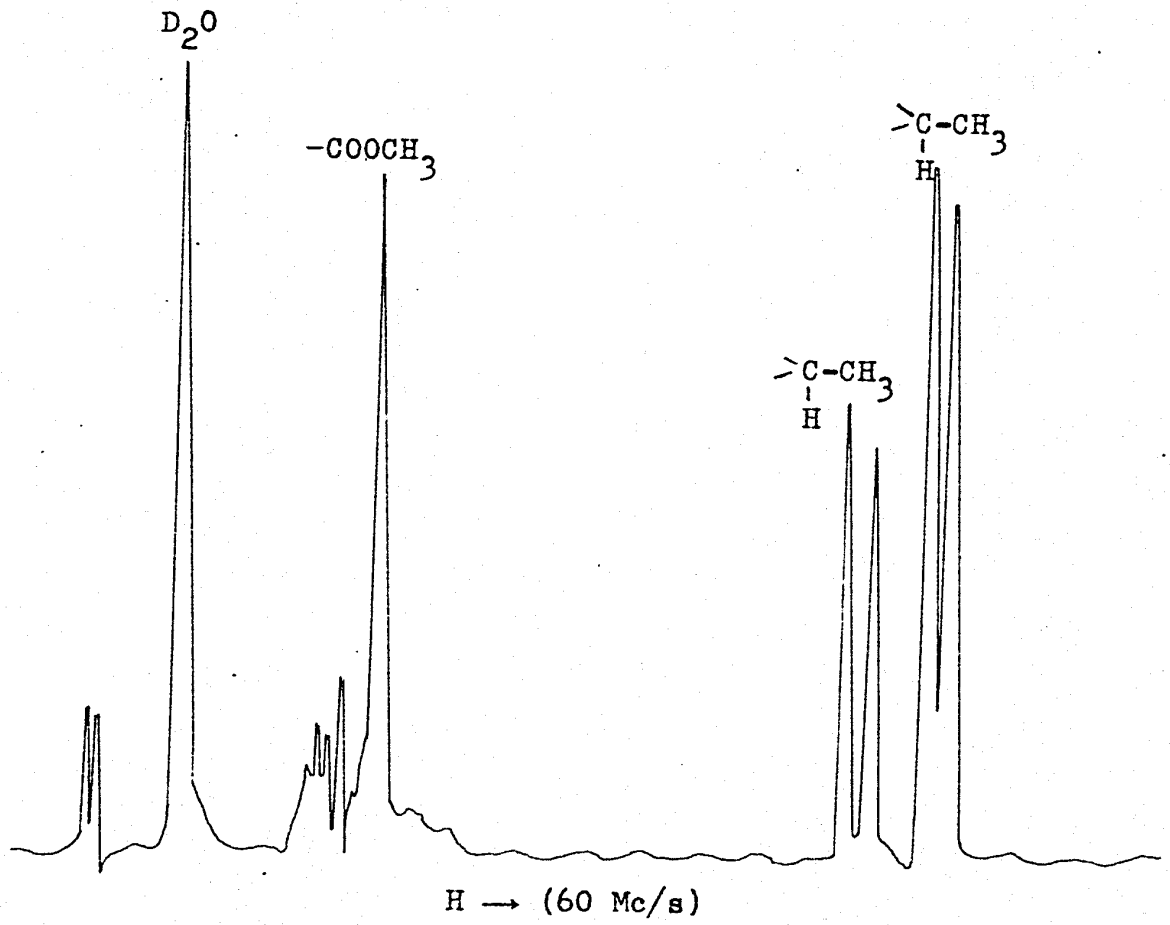
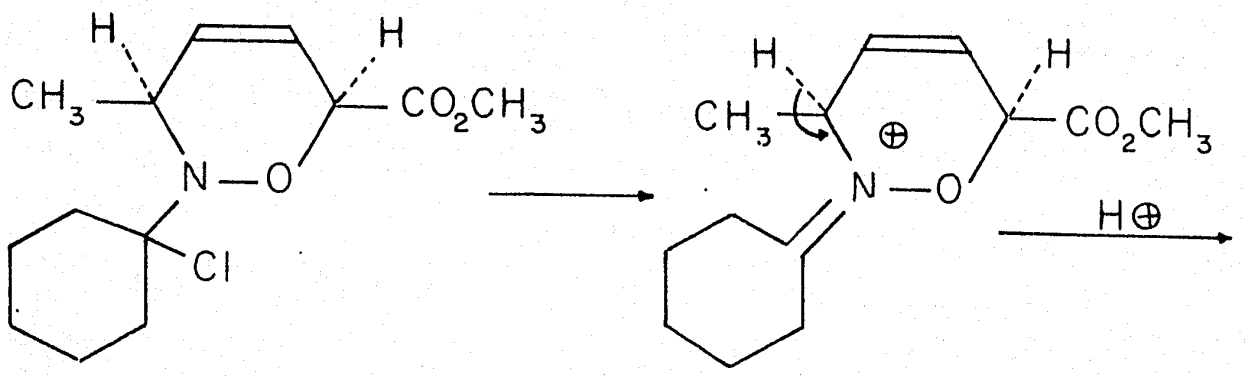
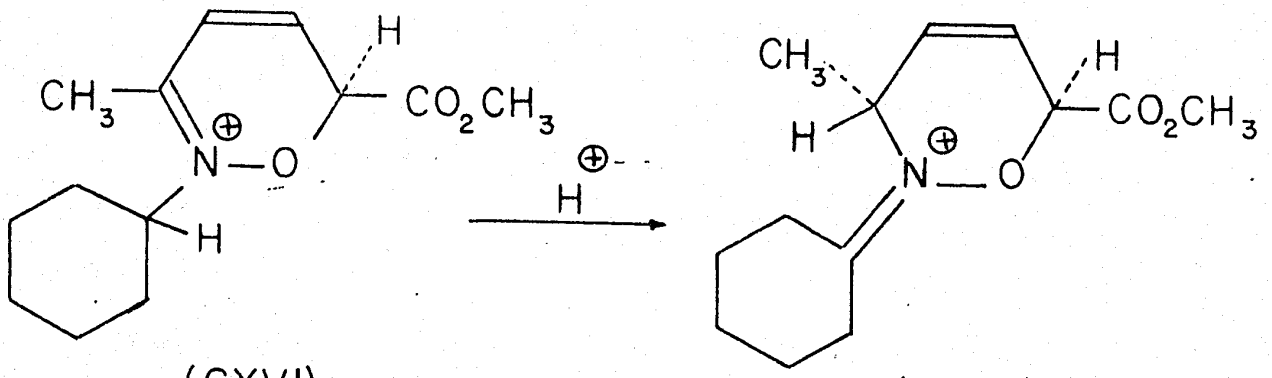


Figure 11. The NMR spectrum of trans-diol hydrochloride (LXIII) mixture measured in D_2O.

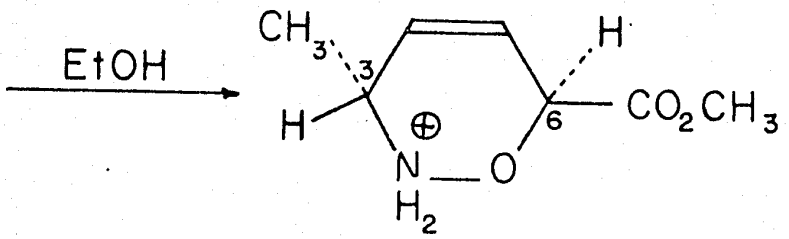
Finally, the mechanism of the Diels-Alder reaction with nitroso-alkanes must be re-examined in view of the evidence presented above in connection with the configuration of the initial adduct. Since the trans-configuration of the 3,6-substituents in the latter accommodates best the stereochemistry of several derived products, one must consider the possibility that it may be the consequence of a chemical artifact since no precedent is available for such an unexpected stereochemical outcome in a Diels-Alder reaction. It is entirely possible that the initial adduct between 1-chloro-1-nitrosocyclohexane and methyl sorbate has the cis-configuration (CXIV) but that inversion of the methyl group by way of intermediates (CXV) $\longrightarrow$ (CXVI) $\longrightarrow$ (CXVII) $\longrightarrow$ (CXVIII) could take place through a simple tautomerization mechanism. If this were true, substituting deuterated ethanol (C_2H_5OD) for normal ethanol in the reaction mixture should lead to the incorporation of deuterium on carbon 3 in the adduct (CXVIII). This should be reflected in the replacement of the methyl doublet of the adduct in the NMR spectrum by a singlet of higher intensity. This was not borne out by experiment (the NMR spectrum being identical) so that this inversion mechanism must be discarded as a possible chemical artifact conducive to the trans-configuration. Since all subsequent chemical transformations involved the use of the N-benzoyl derivative of the adduct (CXVIII), it was



(CXIV) (CXV)

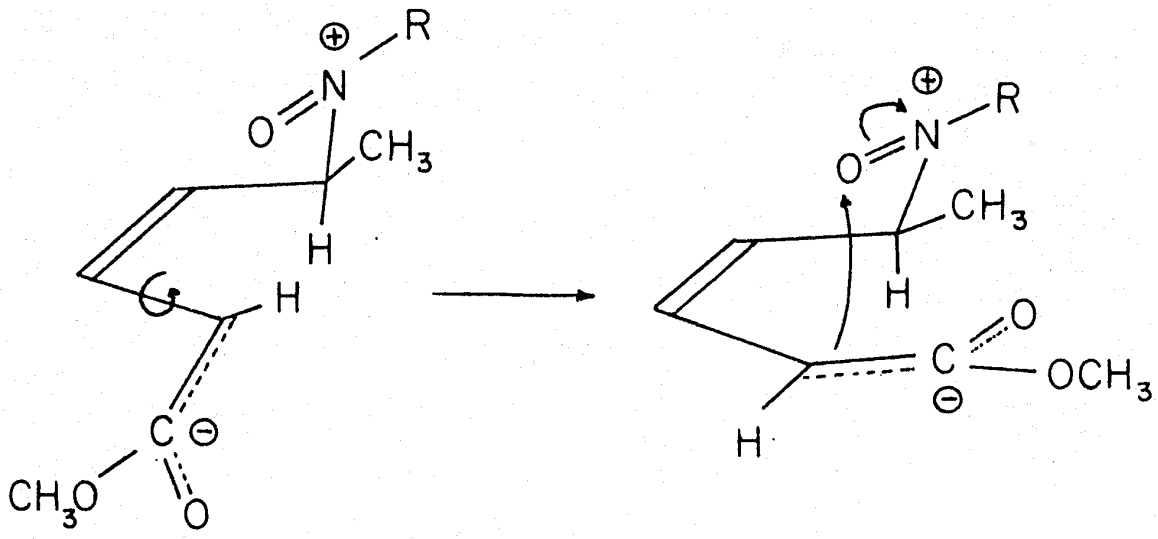


(CXVI) (CXVII)



(CXVIII)

essential to exclude the possibility that inversion about the 3 or 6-substituent had occurred during the course of the benzoylation. By conducting the reaction in deuterium oxide, it would be expected that deuterium would appear in the corresponding N-benzoyl derivative since inversion at either C_3 or C_6 could only occur by way of carbanion intermediates or double bond tautomers. Again, this was not borne out as evidenced by NMR spectroscopy. One is forced to conclude therefore that the addition of the nitrosoalkane across the diene leads directly to the trans-adduct and it follows that the reaction must involve an intermediate of sufficiently long life to allow thermodynamic control of the stereochemistry. In other words, the life of the intermediate must be longer than the time for rotation about the bond carrying the carbomethoxyl group. This is illustrated in structures (CXIX) and (CXX), the origin of which are implicit. This constitutes the only reasonable mechanism that we have been able to derive in order to explain the presumed stereochemical outcome of the Diels-Alder reaction. These results are of considerable theoretical interest as this would constitute the first example of an extreme case of Woodward's and Katz' two stage mechanism for the Diels-Alder reaction. Final confirmation of this novel two-step mechanism is being sought through the use of cis-trans-methyl sorbate as the diene component.



(CXIX) (CXX)

Claims of Original Research

1. A new extension of the Diels-Alder reaction to the synthesis of substituted 1,2-oxazine-6-carboxylic acids and derivatives.
2. A stereospecific synthesis in two basic steps of 2-hydroxy-5-amino-hexanoic acid, a novel amino acid.
3. A stereospecific total synthesis of 5,6-dideoxy-5-amino-talonic acid, a novel type of amino-carbohydrate derivative.
4. The synthesis and structure elucidation of several 3,4,5,6-substituted-1,2-oxazines of potential use as precursors of novel amino sugar like structures.
5. The probable discovery of an authentic case of a two-step mechanism in a Diels-Alder reaction.
6. New applications of some chemical methods for the determination of relative stereochemistry.

REFERENCES

(1) Organic Chemistry, An Advanced Treatise. Gilman, Vol. II. 1613.

(2) G. Ledderhose, Z. Physiol. Chem., 2, 213 (1878); 4, 139 (1880).

(3) C.S. Hudson and J.K. Dale, J. Am. Chem. Soc., 38, 1434 (1916).

(4) W.N. Haworth, W.H.G. Lake and S. Peat, J. Chem. Soc., 271 (1939); cf. J. Chem. Soc., 782 (1939).

(5) Sybils P. James; F. Smith, M. Stacey and L.F. Wiggins, J. Chem. Soc., 625 (1946).

(6) P.A. Levene, J. Biol. Chem., 26, 147 (1916).

(7) E. Fischer and H. Leuchs, Ber., 36, 24 (1903).

(8) R. Kuhn and W. Kirschenlohr; Angew. Chem., 67, 786 (1955).

(9) R. Kuhn and Kirschenlohr; Ann., 600, 115 (1956).

(10) H. Ohle and L. von Vargha, Ber., 61, 1203 (1928); 69, 1022, 1636, 2311 (1936).

(11) H.H. Baer and H.O.L. Fischer, Proc. Nat; Acad, Sci. U.S., 44, 991 (1958).

(12) E. Fischer and J. Tafel, Ber., 20, 1088, 2566 (1887).

(13) H.O.L. Fischer and E. Baer, Helv. Chim. Acta, 19, 519 (1936).

(14) H.S. Isbell, J. Research Nat. Bur. Standards, 20, 97 (1938).

(15) Elderfield, Heterocyclic Compound V 6, 496-563 (1957).

(16) Richter, Organic Chemistry, P. Blakiston Son. and Co. Philadelphia, VIII, 259-268 (1923).

(17) W. Dilthey, J. Prakt. Chem. (N.F.) 156, 27 (1940).

(18) Yu. A. Arbuzov. Izvest. Akad. Nauk. S.S.S.R. Otdel. Khim. Nauk., (1952), 344-52.

(19) G. Kresge and G. Schulz, Tetrahedron, 12, 7 (1961).

(20) O. Wichterle, Collection Czech, Chem. Communs, 16, 33-41 (1951).

(21) O. Wichterle, Chem. Listy, 51, 605-15 (1957).

(21a) Edward E. Smissman, J. Am. Chem. Soc., 81, 2909 (1959).

(22) R.B. Woodward and Thomas J. Katz, Tetrahedron Vol. 5, 70-89 (1959).

(23) John D. Roberts, J. Am. Chem. Soc., 83, 2198 (1961).

(24) P. Yates and P. Eaton, Tetrahedron Letters, No. 11, 5 (1960).

(25) R.C. Cookson, J. Hudec and R.O. Williams, Tetrahedron Letters, No. 22, 29 (1960).

(26) Criegee, R., B. Marchand, and H. Wannowins, Ann., 550, 99 (1942).

(26a) S.A. Barker, Nature 189, No. 4761, pp. 303 (1961).

(27) R.B. Woodward and F.V. Brutcher, J. Am. Chem. Soc., 80, 209 (1958).

(27a) John C. Sheehan and Barry M. Bloom, J. Am. Chem. Soc., 74, 3825 (1952).

(28) Yu. A. Arbuzov and A. Markovskaya, Izvest. Akad. Nauk, S.S.S.R., Otdel. Khim. Nauk (1952) 363-66.

(29) O. Wichterle and M. Hudlicky, Collection Czechoslov. Chem. Communs. 12, 661-71 (1947).

(30) Org. Synthesis, Vo. 23, 13 (1943).

(31) C.K. Harris, E. Tigane and C.S. Hanes, Can. J. Biochem., and Phys., V39, 439-450 (1961).

(32) W.D. Emmons and A.S. Paguno, J. Am. Chem. Soc., 77, 89 (1955).

(33) Max Frankel, Y. Knobler and G. Zrilichowsky, Tetrahedron Letters, 18, 28 (1960).

(34) Lütte, Habilitationsschrift, Freiburg, i. Br., 1956.

(35) E.L. Eliel, H. Haubenstock and R.V. Acharya, J. Am. Chem. Soc., 83, 2351 (1961).

(35a) G. Kavadias' thesis "The Effect of 3-substituents on the Properties of 1,2-disubstituted Cyclohexanes" p. 146.

(36) Henbest, H.B. and B. Nicholls, J. Chem. Soc., 4608 (1957).

(37) Henbest, H.B. and R.A.L. Wilson, J. Chem. Soc., 1958 (1957).

(38) Fodor, G. and J. Kiss, Nature 163, 287 (1949).
Fodor, G. and J. Kiss J. Am. Chem. Soc., 72, 3495 (1950).

(39) Fodor, G. and K. Nador, J. Chem. Soc., 721 (1953);
A. Nicken and W.F. Fieser, J. Am. Chem. Soc., 74, 5566 (1952).

(40) H. Van Bekkum, A.A.B. Kleis and A.A. Massier, Recueil, 80, 595 (1961).