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ALKYLATION REACTIONS OF NITRO ALCOHOLS and SYNTHESIS OF MISEROTOXIN

by

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A thesis submitted in partial fulfillment
of the requirements of the degree of
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Research Supervisor

Douglas C. Shields
Candidate

To Elizabeth

PREFACE

This thesis consists of two independent parts. Part I, which is the major part, was undertaken in order to explore a new synthetic approach to nitro cyclitols, (in particular, the isomeric 2-nitrocyclohexane-1,3-diols) and to investigate certain reactions of these nitro alcohols. Many nitro alcohols and their derivatives have been found to give biological activity in the areas of pest control and others have found use as pharmacologically active substances. In the Introduction, a brief survey of some of the biologically active nitro alcohols is followed by an outline of the general methods available for their chemical synthesis. This is followed by a discussion of some aspects of the chemistry of nitro alcohols. The research work presented here led to the isolation of several nitro olefins and to a possible route for the synthesis of antibiotics containing nitrogenous moieties.

Part II of this thesis describes the synthesis of miserotoxin, the most recently discovered naturally occurring nitro compound. Miserotoxin is the β-D-glucopyranoside of 3-nitro-1-propanol and occurs in nature in certain species of milkvetch.

ACKNOWLEDGMENTS

I wish to express my sincere thanks to my research supervisor, Prof. Hans H. Baer, for his guidance, moral support, and patience during the course of this research work and preparation of this thesis.

I am very much obliged to my fellow workers for the many helpful discussions we have had and for their much appreciated advice. Valuable help received from Prof. R. R. Fraser in discussing some of the n.m.r. spectra is gratefully acknowledged.

I am indebted to my parents whose encouragement prompted me to continue my studies.

The help of my wife, Elizabeth, in typing this thesis is greatly appreciated. Her love and patience have inspired me throughout the course of this work.

This work was made possible by financial support from the research grants of Prof. Hans H. Baer.

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1(e),3(e)-Dimethoxy-2(e)-nitrocyclohexane (IV) and 3(e)-methoxy-2(e)-nitrocyclohexan-1(e)-ol (V) were prepared from 2(e)-nitrocyclohexane-1(e),3(e)-diol (II) by reaction with diazomethane in the presence of boron trifluoride. The dimethyl ether (IV) was also prepared by reaction of 2(e)-nitrocyclohexane-1(e),3(e)-diol diacetate (III) with sodium methoxide. An analogous elimination-addition reaction with sodium benzoxide yielded the dibenzyl ether (VII). Reaction of the diacetate (III) with sodium isopropoxide did not yield the diisopropyl ether and the only product isolated from this reaction was 3-acetoxy-2-nitrocyclohexene (IX). The Schmidt-Rutz dehydroacetylation of the diacetate (III) also furnished the olefin IX. 3-Methoxy-2-nitrocyclohexene (X) was prepared by the Schmidt-Rutz reaction of 3(e)-methoxy-2(e)-nitrocyclohexan-1(e)-ol acetate (VI). This olefin X was also prepared by dehydration of the monomethyl ether V with basic aluminum oxide and by reaction of the acetoxy olefin IX with refluxing methanol. 3-Ethoxy-2-nitrocyclohexene (XI) was similarly prepared by refluxing IX in ethanol.

Part II

3-Nitropropyl 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranoside (VI) was prepared by Koenigs-Knorr reaction of tetra-O-acetyl-α-D-glucopyranosyl bromide (V) with 3-nitro-1-propanol (IV) in the presence of silver oxide. Deacetylation of VI with sodium methoxide furnished 3-nitropropyl β-D-glucopyranoside (miserotoxin) (II).

PART I

ALKYLATION REACTIONS OF NITRO ALCOHOLS

INTRODUCTION

In recent years, aliphatic and cyclic nitro alcohols and some of their derivatives have attained great importance as biologically active compounds and have found wide usage as fungicides, insecticides, pesticides and as pharmacologically active substances. In addition to their biological significance, compounds of this class are of interest to the chemist because they may serve as precursors of unsaturated nitro compounds whose importance in polymer chemistry and in organic syntheses generally is considerable. Cycloaliphatic nitro alcohols and their derivatives are also of special interest in the field of conformational analysis. For these reasons they are attractive as subjects of further study.

A Biologically Active Nitro Alcohols

The biochemistry and pharmacology of compounds possessing the nitro group are active areas of current research, but it does not appear possible yet to attempt a treatment of the interdependence of chemical structure and biological activity. However, by considering a few

of the more important examples, an opportunity is provided for outlining some aspects of the pharmacology and toxicology of this class of compounds.

1. Synthetic Nitro Alcohols

Extensive synthetic work has been performed in the past two decades in the search for biologically active nitro compounds. To give a detailed discussion of these various syntheses would exceed the scope of this thesis. However, a number of compounds have been selected to serve as examples which are listed, together with their biological activities, in Table I.

2. Naturally Occurring Nitro Alcohols

The first aliphatic nitro compound found in nature was isolated from the root of the Javanese tree Hiptaga madablota by Gorter (11) in 1920 and was identified by Carter (12) as β-nitro propionic acid (I).

$$NO_2CH_2CH_2COOH$$

I

In this plant, the compound exists in the form of the glycoside hiptagin; however, it is found in many other plants as the free acid. It has been recognized to

TABLE I

Biologically Active Synthetic Nitro Compounds

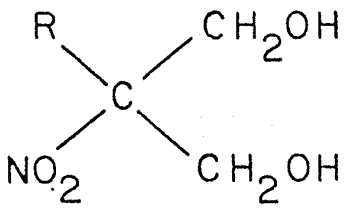
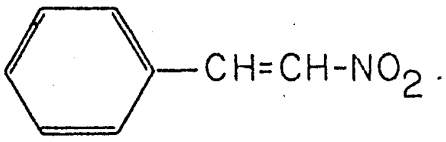
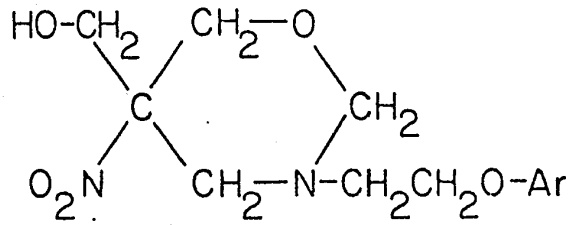
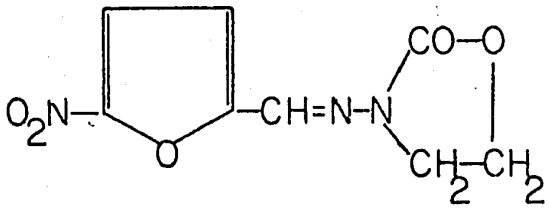
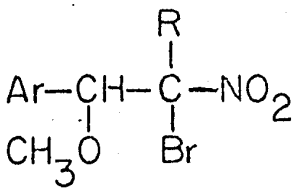
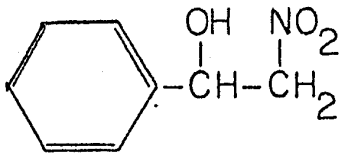
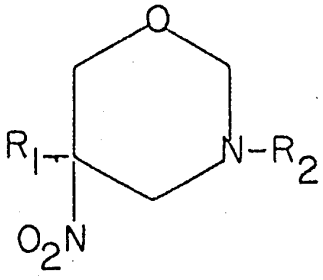
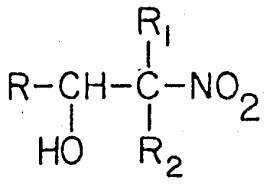
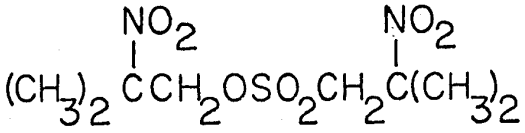
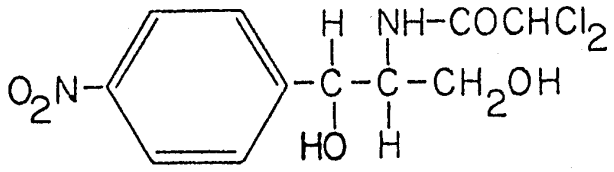
Structure	Activity	References
 R=2,4-Cl_2-C_6H_3	Fungicide	Eckstein et al. (1)
	Insecticide	Byrdy et al. (2)
 Ar=2,5-Cl_2-C_6H_3	Bactericide	Eckstein et al. (3)
	Bactericide	Gever et et al. (79)

Table I (cont'd)

	Fungicide	Hodge et al. (4,5,6)
	Antimicrobial agent	Koremura et al. (7)
	Tuberculo-stat	Urbanski (8)
	Sedative and anticonvul-sant	(9)
	Antiviral and antitumor agent	Leonard & Anderson (10)

show antibiotic activity against certain Bacillus species (13) and, in fact, has been marketed as a weak tuberculostat under the brand name "Bovicidin" (14).

The first naturally occurring aromatic nitro compound to be discovered was chloramphenicol, and it is the most important from a practical point of view. This compound was isolated in crystalline form from cultures of Streptomyces venezuelae (15) and the chemical structure was established by Rebstock and co-workers (16) to be D-(1)-threo-1-p-nitrophenyl-2-dichloroacetamido-1,3-propanediol (II).



II

Chloramphenicol is a potent antibiotic which has found wide clinical use and has proved to be an invaluable tool for research in molecular biology.

Many other antibiotics contain amino sugars and amino cyclitols, and some of these nitrogenous moieties have been synthesized by way of aliphatic nitro

compounds (17,18). The study of syntheses in the field of nitro alcohols and related compounds is, therefore, of potential medicinal interest.

B Some Aspects of the Chemistry of Nitro Alcohols

To provide a background for the work undertaken for this thesis, some aspects of the chemistry of nitro alcohols will be discussed in the following pages.

1. Syntheses

Aldehydes and ketones react with primary and secondary nitro alkanes to produce β-nitro alcohols. These reactions are usually carried out in basic media, but acid catalysts have occasionally been used (19,20). β-Nitro alcohols also arise in the first stage of the reaction between aromatic and heterocyclic aldehydes and nitroalkanes, but generally they spontaneously dehydrate to form unsaturated nitro compounds. Synthesis of β-nitro alcohols from α-epoxides and nitrite salts, first carried out by Japanese workers (21), may find application on an industrial scale. The preparation of β-nitro alcohols from halo alcohols and silver nitrite by Meyer's reaction (22) is of secondary importance. Early work on these reactions has been reviewed by Hass

and Riley (23), and a monograph by Perekalin (24) covers the various preparations of nitro alcohols and includes extensive tables. Lichtenthaler (25) and, more recently, Baer (26) and Baer and Urbas (27) have reviewed recent applications, especially in the field of sugars and cyclitols.

Certainly the most versatile among the synthetic methods just mentioned is the Henry reaction (28), i.e., the base-catalyzed addition of nitroalkanes to aldehydes or ketones. Large numbers of nitro alcohols, including polyhydroxy nitro compounds so obtained, have served as intermediates for the preparation of nitro olefins and other nitro derivatives as well as amino alcohols, oximes, and hydroxycarbonyl compounds.

The primary products of the base-catalyzed reaction are actually aci-nitro salts. Acidification of the salts with weak acids yields a mixture of two epimeric nitro alcohols, while the use of strong acids may lead to nitroalkenes by elimination of water. If an excess of strong mineral acid is used, the Nef reaction (29) usually occurs, resulting in a mixture of epimeric hydroxy aldehydes (Fig. 1).

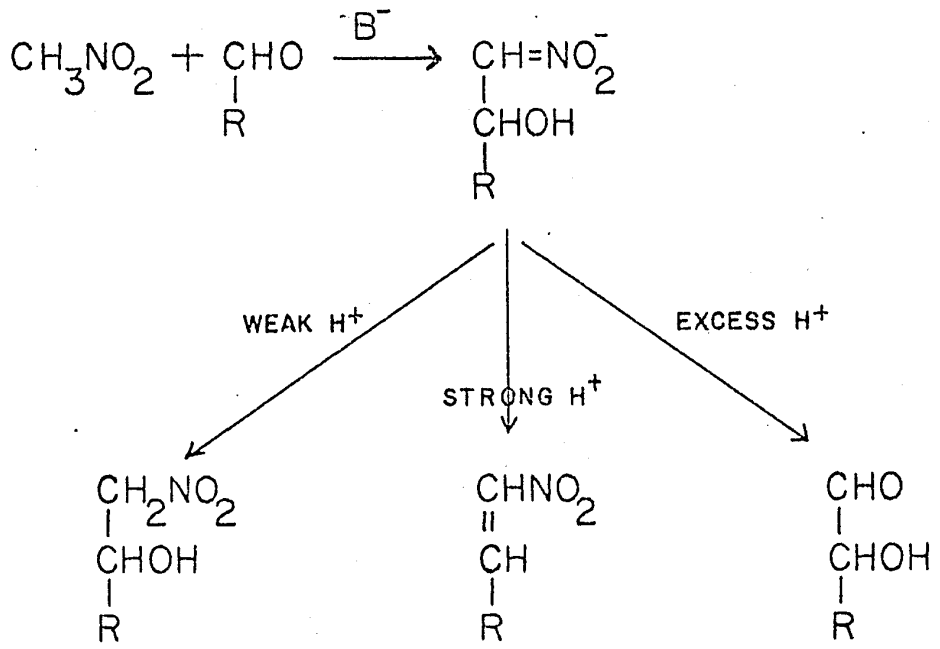
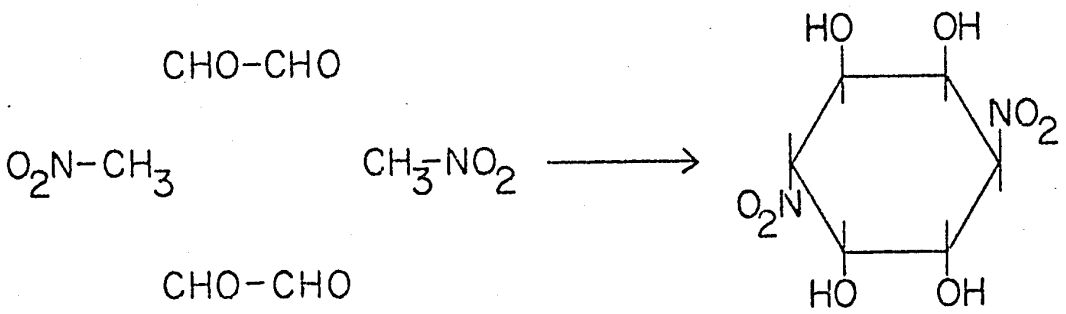


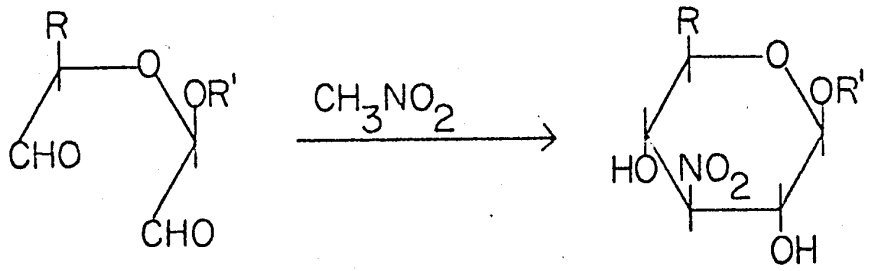
Fig. 1 The Henry Reaction

The Henry and Nef reactions have attained great importance in carbohydrate chemistry where, following initial work by Sowden and Fischer (30), they afforded a facile method of lengthening the carbon chain.

With suitable dialdehydes, a cyclizing nitromethane addition can occur. The reaction of equimolar amounts of nitromethane and glyoxal in aqueous solution with sodium carbonate leads to a mixture of isomeric 1,4-dideoxy-1,4-dinitroinositols. One of the stereoisomers has been isolated and assigned the neo-1,4-configuration (31).

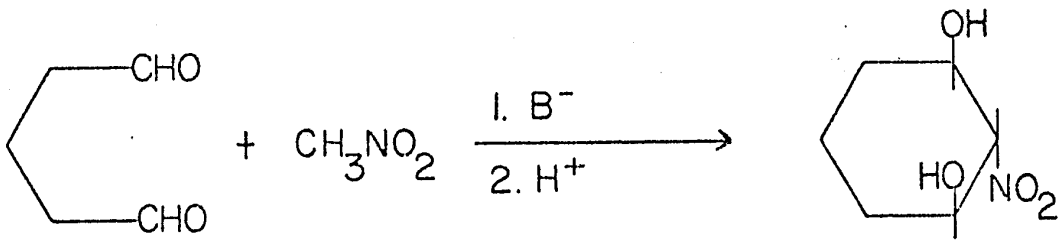


The reaction between "sugar dialdehydes" and nitromethane has served as a useful method for introducing the nitro group into pyranose rings (26,32).



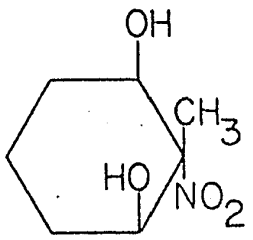
Branched-chain nitro sugars can be obtained when nitroethane is substituted for nitromethane (33).

Glutaric dialdehyde is cyclized with nitromethane in sodium carbonate solution to yield a mixture of isomeric 2-nitrocyclohexane-1,3-diols from which one of the three theoretically possible isomers (III) has been isolated, in 51% yield, and assigned the trans-trans configuration by n.m.r. spectroscopy (34,35).

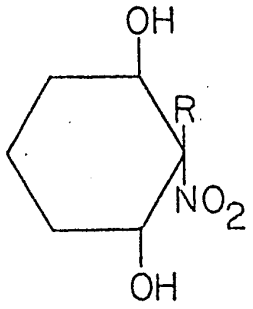


III

It is interesting to note that isomer III, with all substituents equatorially oriented, was formed preferentially over the other two possible isomers. Different results were obtained when other nitroalkanes instead of nitromethane were allowed to react with glutaric dialdehyde. Thus, nitroethane gave the trans-trans compound IV in 43% and 27% yield in the hands of two independent groups of workers (36,37), whereas phenylnitromethane and 1-nitropropane gave the cis-trans compounds V and VI in 20% and 34% yield, respectively (37). Conformational factors playing a role in such systems will be discussed in a subsequent section.



IV



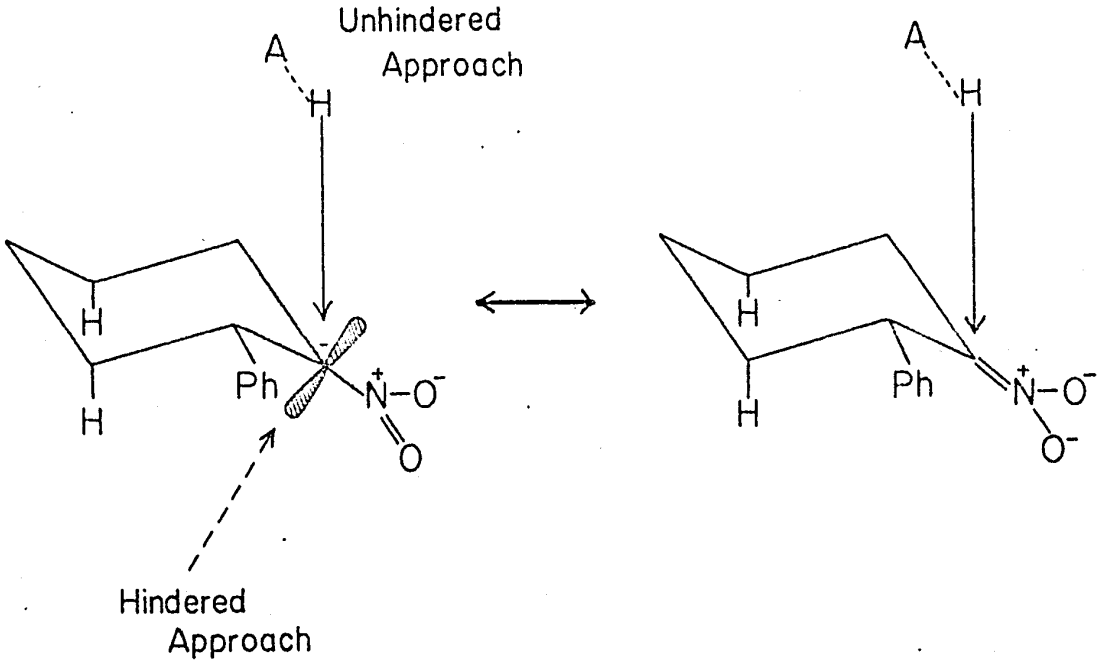
V R = C_6H_5

VI R = C_2H_5

2. Stereochemistry

The stereochemistry of salt formation in nitrocyclohexanes and the reverse process, the protonation of cyclohexanenitronate ions, has been studied by several workers (38,39,40,41,42). Since the main product obtained from the glutaric dialdehyde–nitromethane cyclization was the epimer with an equatorial nitro group, it had been suggested (43) that the protonation of the nitronate ion occurred under thermodynamic control. However, Zimmerman (38) has shown that acidification of the anion of 1-nitro-2-phenylcyclohexane yields only the less stable, cis epimer while the equilibrium mixture contains 99% of the trans derivative. He stated that the transition state for protonation of the aci-nitro salt was essentially sp^2-hybridized (as in VII). The nitro group, therefore, did not exert any sterically

directive influence, leaving the prototopic ease of attack as the controlling factor. Assuming that the phenyl group in the anion occupied an equatorial position, he concluded that the addition of the proton from the axial side was hindered, by the syn-diaxial hydrogen atoms at C-3 and C-5, compared with addition from the equatorial side.

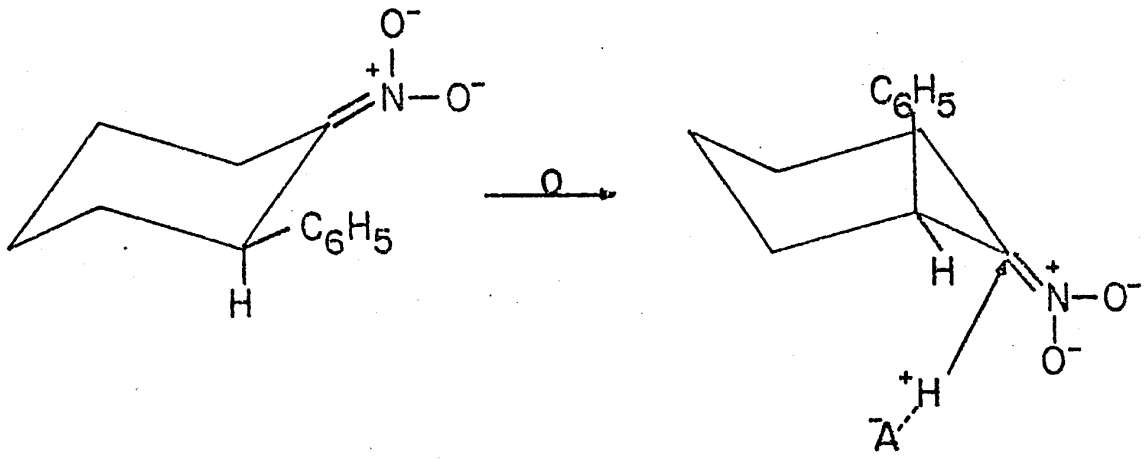


VII

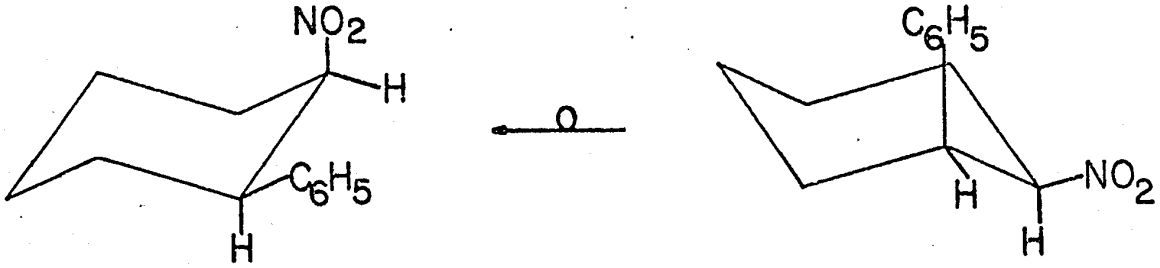
This interpretation of the predominance of cis epimer was questioned by Malhotra and Johnson (39) who proposed that the phenyl group in fact occupies the axial position because of what they called $A^{(1,3)}$ strain (Fig. 2). They defined $A^{(1,3)}$ strain as the strain encountered because of non-bonded interaction between

Fig. 2

$A^{(1,3)}$ Strain



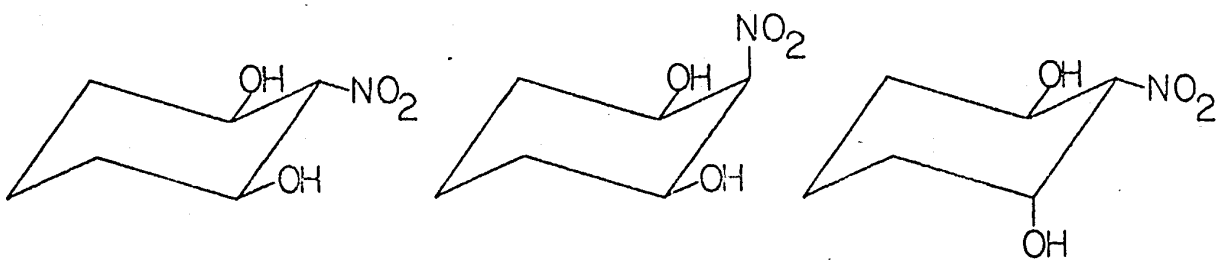
VIII IX



XI X

an equatorial substituent and a group attached at the end of a double bond originating from the adjacent ring carbon atom. Subsequent protonation of this conformer then takes place from the axial side which these authors consider to be less hindered since, in their view, the influence of the syn-diaxial hydrogens at C-3 and C-5 is not so important as that of the axial phenyl group (or of other axial groups vicinal to the nitromethylene carbon). The reaction, therefore, leads to X, which then rearranges to XI. They supported this proposal by citing n.m.r. data which indicated the presence of conformer IX. Trager and co-workers (44), in their work with substituted 2-phenylnitrocyclohexanes, also found that protonation of the nitronate was kinetically controlled and yielded almost exclusively the thermodynamically less stable cis isomer. Bordwell and Vestling (45) confirmed that an axial 2-phenyl group sizeably hinders proton approach from the same side, and they showed that in the protonation of 4-t-butylcyclohexanenitronate (which has no substituent at C-2), there was only a small preference for axial over equatorial approach (3:1). Angyal and Luttrell (40) later demonstrated that, if properly carried out, the protonation of 4-t-butylcyclohexanenitronate gives nearly equal amounts of cis and trans isomers, and they ascribe the threefold preponderance of the trans

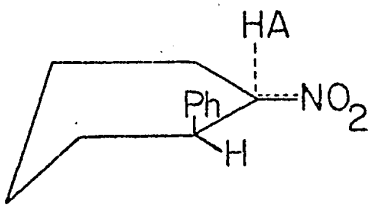
isomers observed by Bordwell to subsequent thermodynamic equilibration. Angyal and Luttrell (40) also investigated the protonation of the nitronate of trans, trans 2-nitrocyclohexane-1,3-diol XII. They obtained a mixture containing mainly the trans-trans isomer XII together with the cis-cis isomer XIII and the cis-trans isomer XIV. The latter arose by β-epimerization, which is known to occur very easily in nitro carbohydrates in the presence of base (26).



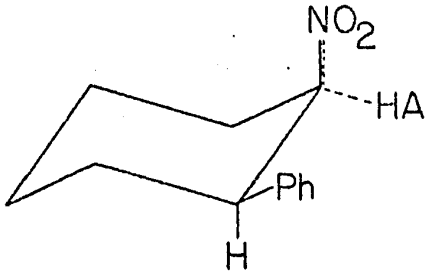
XII XIII XIV

The authors concluded from their work that protonation of nitronates is a kinetically controlled process and that normally there is no preference for addition from the axial or the equatorial side, but that in the case of 2-substituted nitronates, steric hindrance could control the direction of proton approach and give predominantly one epimer. In the case when the nitro group has adjacent hydroxyl groups, kinetic control

is not achievable because thermodynamic equilibration is very rapid, resulting in a mixture containing predominantly the more stable epimer. Very recently, Bordwell and Yee (41,42) have discounted $A^{(1,3)}$ strain as the contributing factor in the stereochemistry of protonation. They pointed out that the interpretation of the n.m.r. spectrum of 2-phenylcyclohexanenitronate to suggest an axial phenyl group has been questioned (46) and that their own recent studies of ultraviolet spectra indicate the group to be, in fact, equatorial. They conclude that the preferred transition state for protonation of 2-phenylcyclohexanenitronate ion will resemble that for deprotonation of cis-2-phenyl-1-nitrocyclohexane XI. In this transition state, the H-C bond has been appreciably formed and the C=N bond appreciably broken. This state can exist without undue strain if protonation occurred from the equatorial side (as in XVI). Proton approach from the axial side (as in XV) would force the NO_2 group into a pseudoequatorial position and the phenyl group into a pseudoaxial position where it would interfere with the approach of the proton donor.



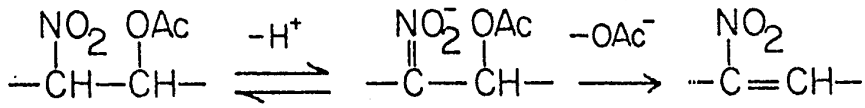
XV



XVI

3 Some Important Reactions of Nitro Alcohols

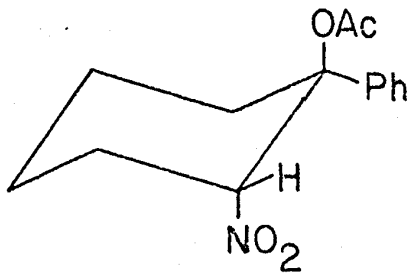
(a) One of the more important reactions in the field of aliphatic nitro compounds is the formation of α-nitroalkenes by base-catalyzed elimination of acetic acid from β-nitroalkanol acetates.



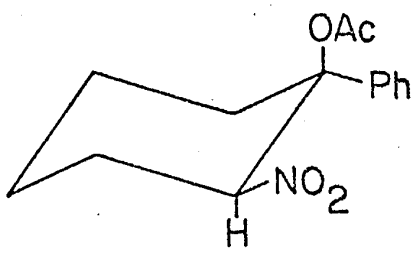
The reaction has been known and widely used for some time (47), but its stereochemistry has received close attention only recently. For the study of this reaction it was of obvious interest to find out whether the first step, i.e., the deprotonation of the nitromethylene carbon, is a decisive factor that depends on stereochemical features of the molecule. Therefore,

Bordwell and Yee (41) at first investigated the rates of deprotonation, by methoxide ion in methanol, in a number of 2-aryl and 4-t-butyl substituted nitrocyclohexanes in which no subsequent β-elimination takes place. They observed that, compared with nitrocyclohexane, the deprotonation rates in the substitution products varied depending on cis-trans isomerism, but the variations were not great. There was, however, one notable exception: whereas cis-2-phenyl-1-nitrocyclohexane reacted 2.6 times faster, the trans isomer reacted 135 times more slowly than nitrocyclohexane. The authors attribute the slight acceleration in the cis isomer to the inductive effect of the phenyl group. For the trans isomer, they invoke a sharp increase in activation energy due to ring deformation. The nitro and phenyl groups bend away from one another, flattening the chair, and causing the phenyl group to come much closer to the acidic hydrogen atom whose abstraction is thereby hindered.

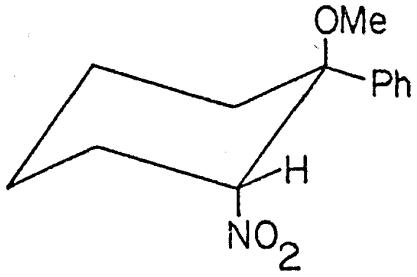
With these results in mind, they undertook a series of experiments to study the mechanism of β-eliminations and to see if a similar effect was present (48). Comparison of the rates of elimination of methanol from the stereoisomeric ethers XIX and XX with the deprotonation rates of the corresponding nitrocyclohexanes XXI and XXII showed that the retarding effect for the



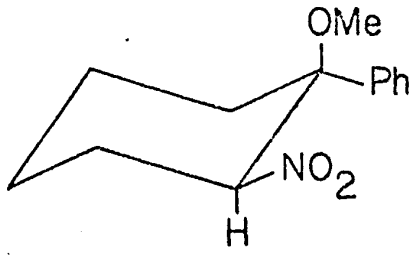
XVII



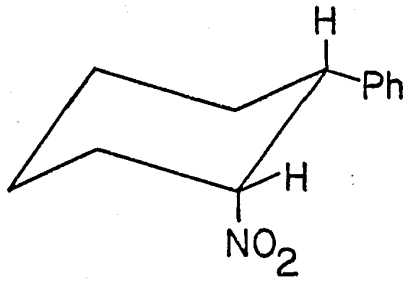
XVIII



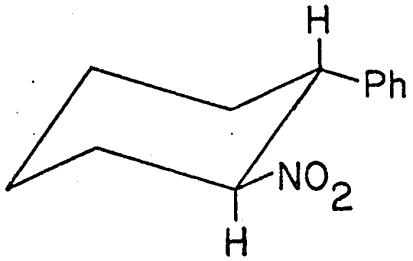
XIX



XX

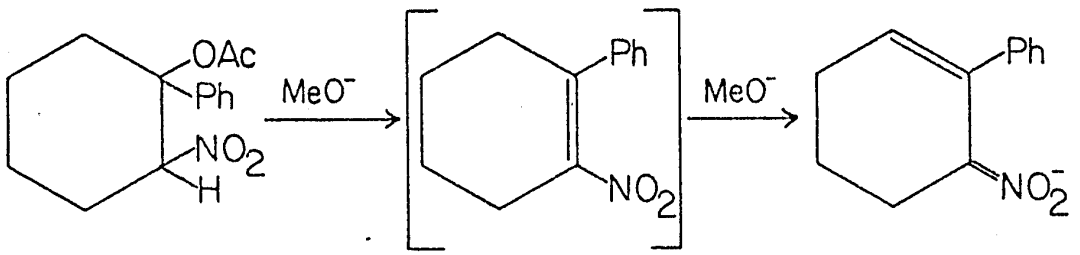


XXI



XXII

trans isomer was not present in this case. Similar studies with the esters XVII and XVIII were complicated by difficulties in observing the rates spectrophotometrically because the elimination product XXIII was unstable and was rapidly converted into the strongly absorbing unsaturated nitronate XXIV.

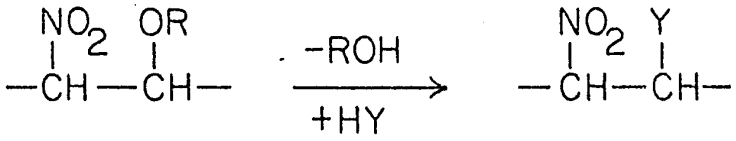


XVII or XVIII XXIII XXIV

However, the authors inferred that no retardation in the deprotonation, and therefore, no ring deformation, is present in the trans isomer.

They proposed as the reason that in the 2-phenyl-2-acetoxy (and 2-methoxy) -1-nitrocyclohexanes, the acetoxy (or methoxy) group prevented such deformation. Thus, moving the nitro group and phenyl group away from each other so as to stabilize the system could well force the nitro and acetoxy (or methoxy) groups closer together, thereby offsetting any gain in stability.

(b) Due to the activating effect of the nitro group, α-nitroalkenes readily undergo nucleophilic addition reactions with a wide variety of nucleophiles, which allows facile introduction of substituents in the β position. For preparative purposes it is frequently unnecessary to prepare the nitro-olefins as starting materials. Rather, nitro alcohols or esters may be employed, and the action of nucleophiles generates α-nitroalkenes <u>in situ</u> and then proceeds to give addition products (24, 27).



R = $COCH_3$; H

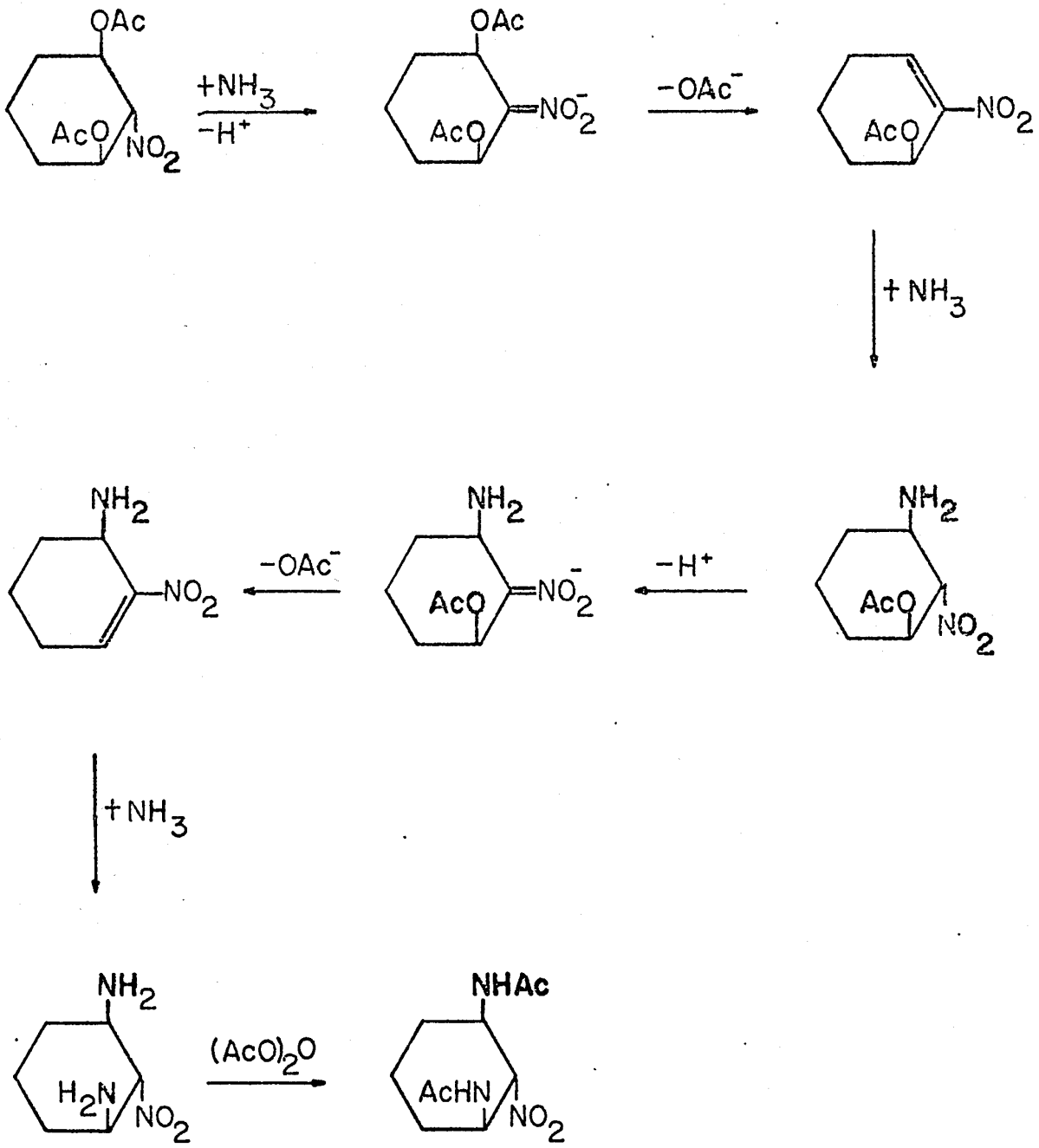
Y = Nucleophile

For example, Baer and Wang (49) successfully used such an elimination-addition sequence in the diamination of <u>trans-trans</u>-2-nitrocyclohexane-1,3-diol diacetate which, when treated with ammonia, afforded <u>trans-trans</u>-1,3-diamino-2-nitrocyclohexane in a single operation. (The product was isolated, after eventual N-acetylation, as the diacetamido derivative.) (Fig. 3).

This reaction principle has found many further applications in carbohydrate chemistry for the syntheses of diamino and triamino sugars, sugar ethers and thioethers, branched-chain sugars, and disaccharides (26).

Fig. 3

Diamination of trans-trans-2-Nitrocyclohexane-1,3-diol Diacetate


OAc
AcO
NO2
+NH3
−H+
OAc
AcO
NO2−
−OAc−
AcO
NO2
+NH3
NH2
AcO
NO2
−H+
NH2
AcO
NO2−
−OAc−
NH2
NO2
+NH3
NH2
H2N
NO2
(AcO)2O
NHAc
AcHN
NO2

THE PURPOSE OF THIS RESEARCH

At the time of inception of this work, synthetic and stereochemical studies on nitro sugars were being pursued in this Laboratory, and it seemed worthwhile to assist in the progress of these investigations by studying certain reactions in the less complicated model system, 2-nitrocyclohexane-1,3-diol. Thus it was to be examined whether improvements or modifications can be made in the nitromethane cyclization of dialdehydes; whether nitro alcohols can be methylated with diazomethane; whether nitro ethers or, eventually, glycosides may be prepared by nucleophilic elimination-addition reactions and if so, what stereochemical course such reactions would take. As an important part especially of the last-mentioned aspect, the preparation and characterization of some substituted nitrocyclohexene derivatives was to be attempted.

RESULTS AND DISCUSSION*

I Attempted Cyclization of Glutaric Dialdehyde-Bisulphite Adduct with Nitromethane

A Glutaric Dialdehyde-Bisulphite Adduct

Sodium bisulphite forms crystalline adducts with aldehydes and ketones, which have frequently been used for purification and separation of these carbonyl compounds. By shaking an aqueous solution of glutaric dialdehyde with an excess of aqueous sodium bisulphite, the adduct (I) was obtained in 51% yield as a fibrous white precipitate. Attempts at precipitating the dialdehyde more completely resulted in mixtures of the addition compound and sodium bisulphite. An infrared spectrum of the initial precipitate showed bonded and non-bonded OH absorptions at 3300 cm^{-1} to 3600 cm^{-1} as expected for the α-hydroxy sulfonate structure of the

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* For convenience, compounds in this chapter are numbered using a new set of Roman numerals.

adduct. The peaks in the fingerprint region were in accord with the structure of I (see Experimental). However, there was also a weak absorption at 1640 cm^{-1}. No definite assignment was made for this peak which might possibly have been due to hydrogen-bonded carbonyl from a small amount of free aldehyde accompanying the addition product.

B Attempted Cyclization

As has been mentioned in the previous section, the base-catalyzed cyclization of dialdehydes with nitroalkanes has been successfully used for the preparation of many ring compounds including nitro sugars and nitro cyclitols. However, one modification of the nitroalkane-aldehyde addition reaction had not yet been applied to dialdehydes for the purpose of ring syntheses. It is the method that was devised by Kamlet (20) and consists of interaction between the aldehyde sodium bisulfite adduct and sodium alkanenitronate (50):

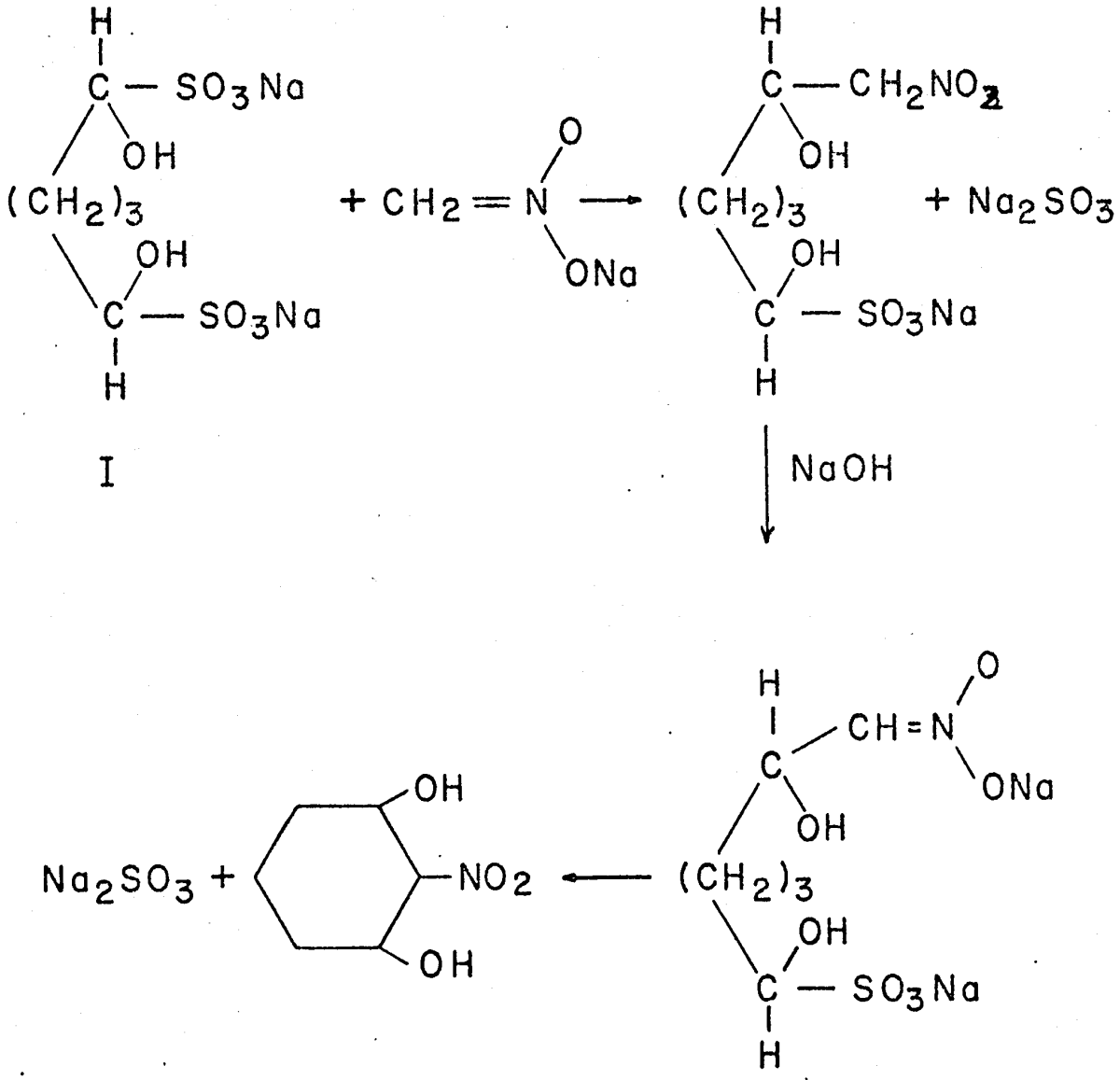
$$R\text{-}CH(OH)SO_3Na + RCH{=}NO_2Na \rightarrow R\text{-}CH(OH)CHRNO_2 + Na_2SO_3$$

It appeared worthwhile, therefore, to try this modification in the preparation of 2-nitro-1,3-cyclohexanediol which was required for this work and which had previously been obtained (35) by sodium carbonate-catalyzed nitromethane cyclization of glutaric dialdehyde in aqueous solution. It was also of some interest to see whether such a modification, if successfully leading to ring closure, would yield the trans-trans diol as does the conventional method, or whether one or both of the possible stereoisomeric diols would arise (Fig. 4).

When a chilled solution of nitromethane in 1 equivalent of aqueous sodium hydroxide was allowed to react with 1 molar equivalent of the glutaric dialdehyde addition compound at 0° for 10 minutes, an oily product was obtained. Comparative t.l.c. with an authentic sample of trans-trans-2-nitro-1,3-cyclohexanediol (II) indicated its presence in the oily mixture, and an infrared spectrum showed an absorption at 1550 cm^{-1} and other absorptions in the fingerprint region which corresponded to absorptions exhibited by the reference diol, thus showing that cyclization had occurred. However, the desired product was not obtained in crystalline condition, and the method did not seem to offer an advantage over that previously employed (35).

Fig. 4

Cyclization of Glutaric Dialdehyde Bisulphite Adduct with Sodium Methanenitronate


H
C — SO3Na
OH
(CH2)3
OH
C — SO3Na
H
I
+ CH2 = N
O
ONa
C — CH2NO2
OH
(CH2)3
OH
C — SO3Na
H
+ Na2SO3
NaOH
CH = N
O
ONa
OH
(CH2)3
OH
C — SO3Na
H
Na2SO3 +
OH
NO2
OH

As another modification, cyclization of glutaric dialdehyde was to be attempted in methanolic (rather than aqueous) solution, and sodium bisulfite was to be used simply as a vehicle of transferring the dialdehyde from its commercial, aqueous solution into a methanolic medium.

Treatment of a suspension of the bisulfite adduct in anhydrous methanol with cation exchange resin produced a methanolic solution of glutaric dialdehyde. (The solution gave a positive carbonyl test when treated with Brady's reagent.) When this solution was then treated with a 1 molar equivalent of nitromethane in methanolic sodium hydroxide at 0°, the reaction mixture became turbid. Stirring was maintained for 2 hours, after which time t.l.c. indicated the presence of several unidentified products. Deionization of the mixture with a cation exchange resin followed by acetylation with acetic anhydride and boron trifluoride gave a material which, according to t.l.c., was a complex mixture of products. A similar reaction using sodium methoxide in place of methanolic sodium hydroxide produced much the same result, and the attempts at improving the preparation of 2-nitro-1,3-cyclohexanediol were abandoned.

II Alkylation Reactions of 2(e)-Nitrocyclohexane-1(e),3(e)-diol

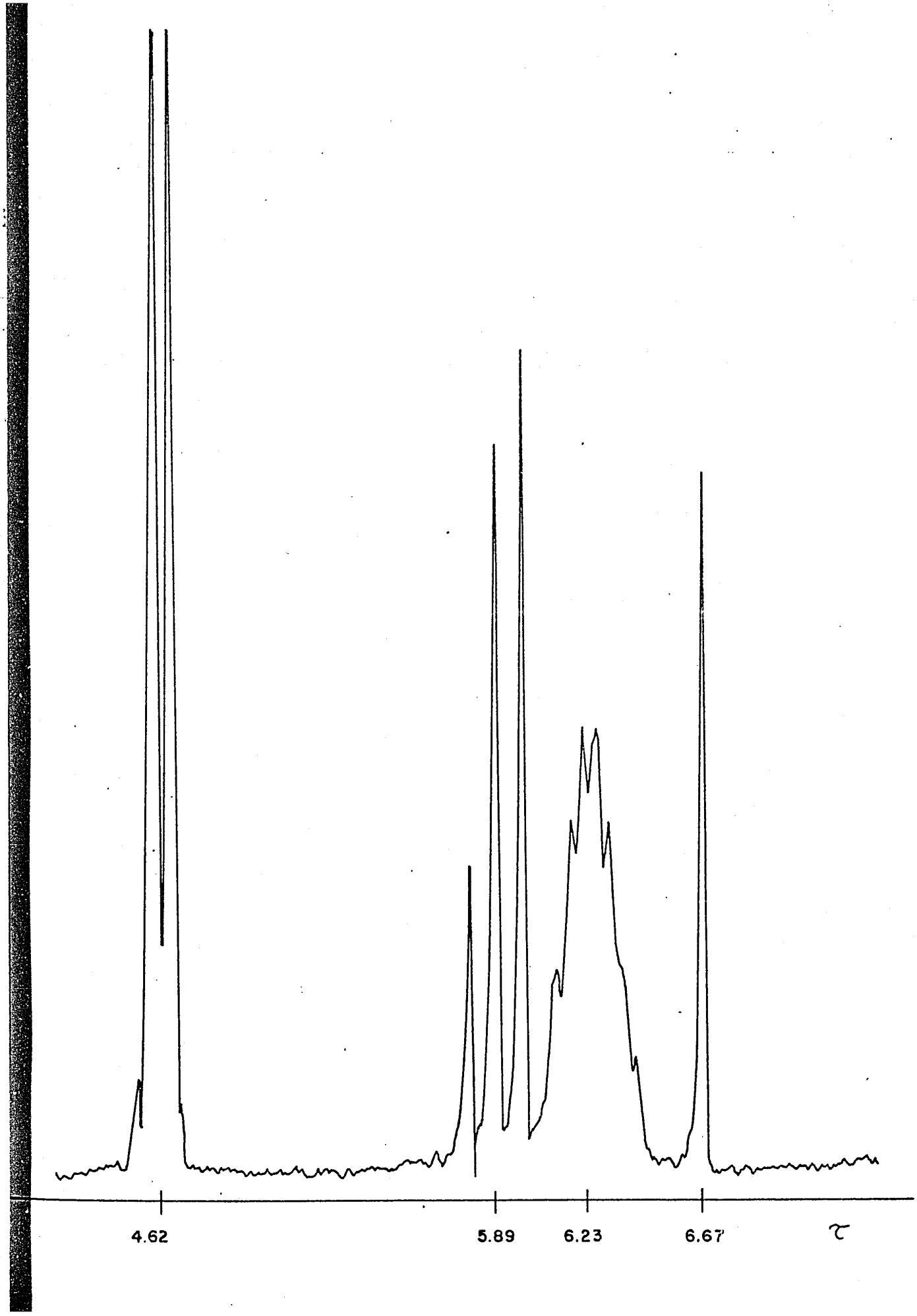
A 2(e)-Nitrocyclohexane-1(e),3(e)-diol

The required trans-trans-nitrocyclohexane diol (II) was prepared in 42% yield by sodium carbonate-catalyzed nitromethane cyclization of glutaric dialdehyde according to Lichtenthaler (35).

The configuration of the compound was confirmed by the n.m.r. spectrum taken in deuterated dimethyl sulphoxide (Fig. 5). The spectrum showed the expected triplet (J=9.5 c.p.s.) for the proton on the carbon bearing the nitro group, at τ 5.89. The C-1 and C-3 protons appeared as overlapping sextets centred at τ 6.23. The protons on C-4, C-5, and C-6 appeared as multiplets between τ 7.9 and τ 9.0. The doublet (2H, J=6 c.p.s.) centred at τ 4.62 was assigned to the two hydroxy protons. The singlet at τ 6.67 was thought to be caused by water in the sample solution (51).

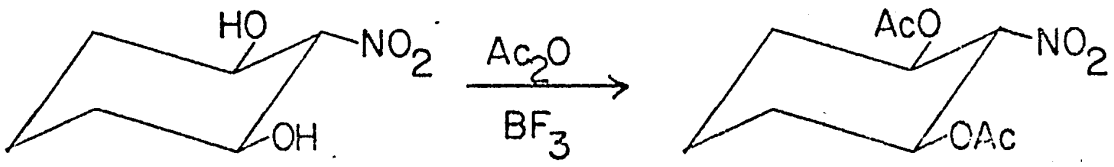
Fig. 5

N.M.R. spectrum of 2(e)-nitrocyclohexane-1(e),3(e)-diol (II) in deuterated dimethyl sulphoxide


4.62
5.89
6.23
6.67
τ

B 2(e)-Nitrocyclohexane-1(e),3(e)-diol Diacetate

The 2(e)-nitrocyclohexane-1(e),3(e)-diol was acetylated using acetic anhydride and boron trifluoride as a catalyst, to give the diacetate (III) in 90% yield. This compound had been prepared earlier (35), in 75% yield, by acetylation using sulfuric acid as a catalyst.

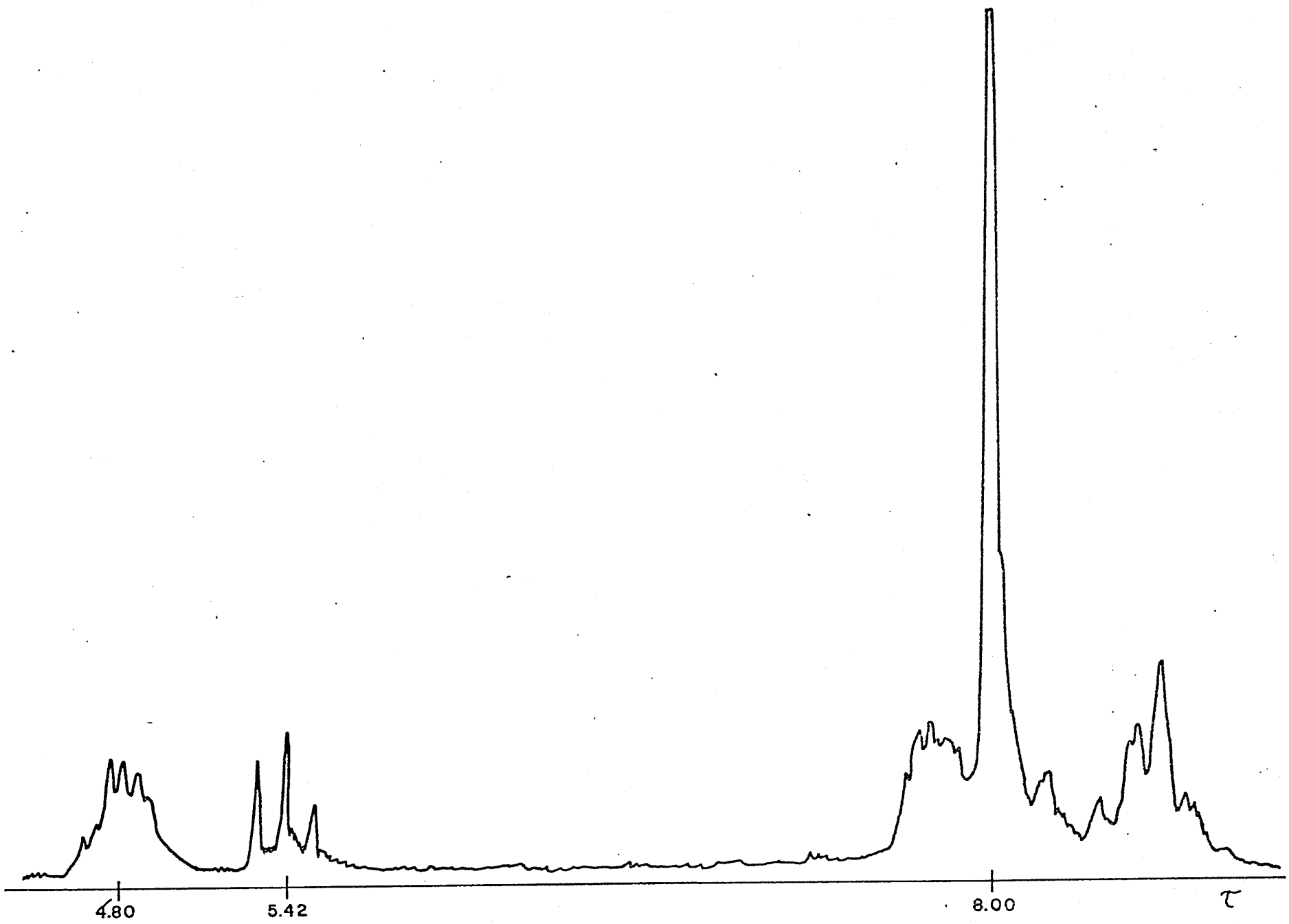


II III

The n.m.r. spectrum in deuterochloroform (Fig. 6) showed the triplet (J=10.2 c.p.s.) for the proton on the carbon bearing the nitro group centred at τ 5.42, and an acetoxy singlet (6H) at τ 8.00. These were in agreement with the previous author's values.

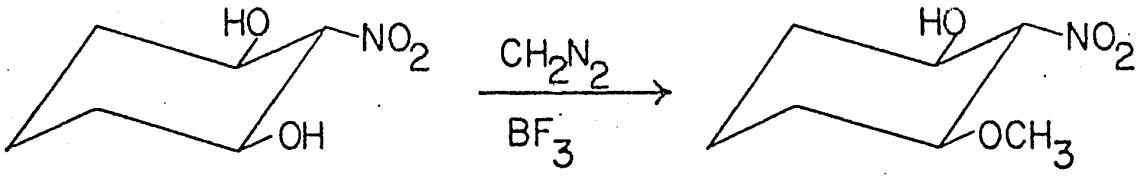
Fig. 6

N.M.R. spectrum of 2(e)-nitrocyclohexane-1(e),3(e)-diol diacetate (III) in deuterochloroform

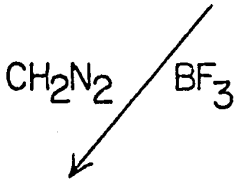

4.80
5.42
8.00
τ

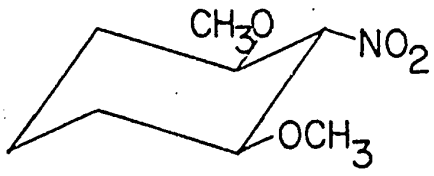
C <u>1(e),3(e)-Dimethoxy-2(e)-nitrocyclohexane</u>

1) An ethereal solution of 2(e)-nitrocyclohexane-1(e),3(e)-diol was methylated using a large excess of diazomethane and boron trifluoride (52,53) at -70°. A colorless crystalline product, m.p. 81°, was obtained in 87% yield after a reaction time of 3 hours. It proved to be the dimethyl ether IV, although the monomethyl ether (V) is formed as an intermediate and can be isolated as will be shown in a subsequent section.



II V

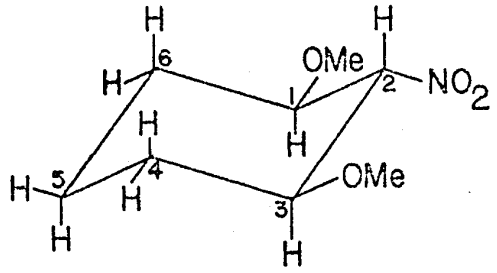




IV

The elemental analysis of IV agreed with the molecular formula $C_8H_{15}NO_4$. The infrared spectrum showed a nitro band at 1555 cm^{-1} and ether bands at 1105 cm^{-1} and 1095 cm^{-1}. The absence of an OH absorption showed that the diol was completely methylated.

The structure of the product was confirmed by the n.m.r. spectrum in deuterochloroform (Fig. 7). The spectrum showed a symmetrical triplet centred at τ 5.71 (1H); a sextet centred at τ 6.38 (2H); a sharp singlet at τ 6.69 (6H); and multiplets at τ 7.8, τ 8.2, and τ 8.8 which integrated to a total of 6 protons. The triplet at τ 5.71 is due to H-2. Its large splitting of 10 c.p.s. shows that H-2 must be axial and equally coupled with axial protons H-1 and H-3 (44,54). The latter protons gave sextets with the same chemical shift (τ 6.38), which indicated that they were in an identical steric environment. The spacing of the sextet given below shows that H-1 and H-3 were each coupled with two vicinal, axial protons and one vicinal, equatorial proton. On a first-order basis, the theoretical splitting pattern would be as shown below.



IV

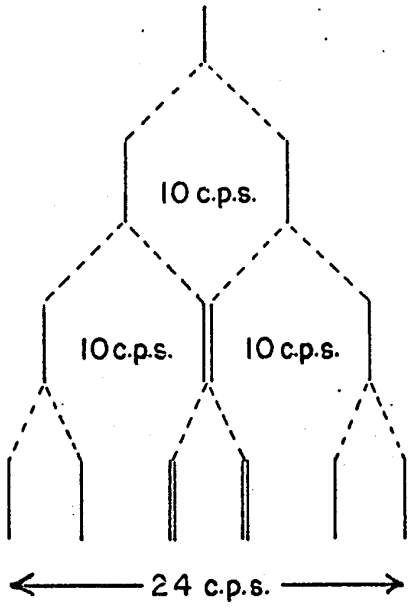
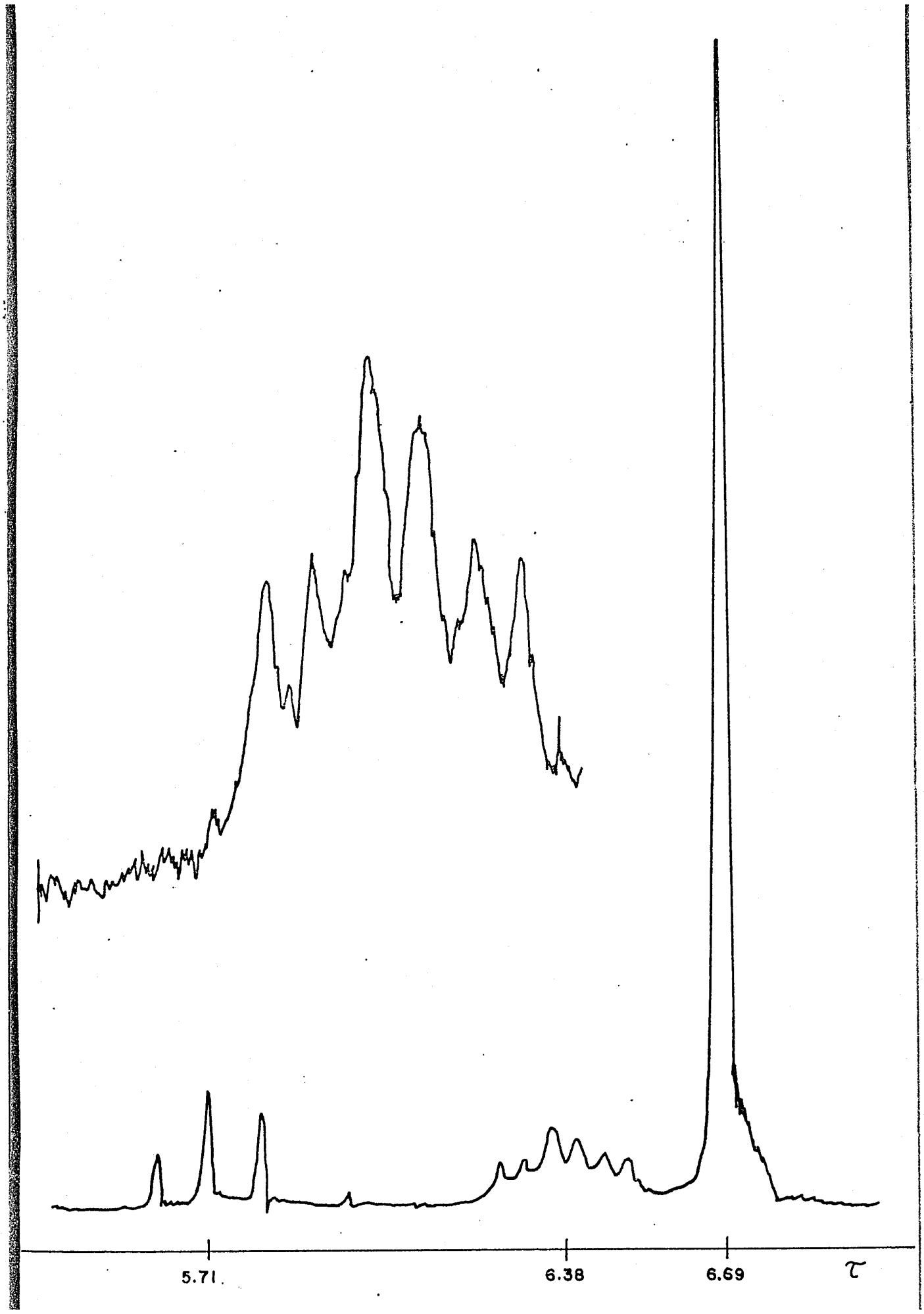


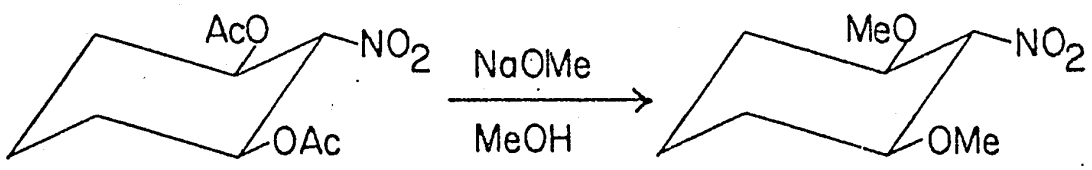
Fig. 7

N.M.R. spectrum of 1(e),3(e)-dimethoxy-2(e)-nitrocyclohexane (IV) in deuterochloroform


5.71
6.38
6.69
τ

It follows that the nitro and methoxy functions must be equatorial, i.e., the configuration must be trans-trans. The sharp singlet at τ 6.69 is attributed to the two O-CH_3 groups, and the fact that these two groups give only one signal supports the structure with both groups having the same configuration. The multiplets at higher field are due to the ring protons on C-4, C-5, and C-6.

2) The dimethyl ether (IV) was also obtained by reaction of the diacetyl ester (III) with methanolic sodium methoxide.

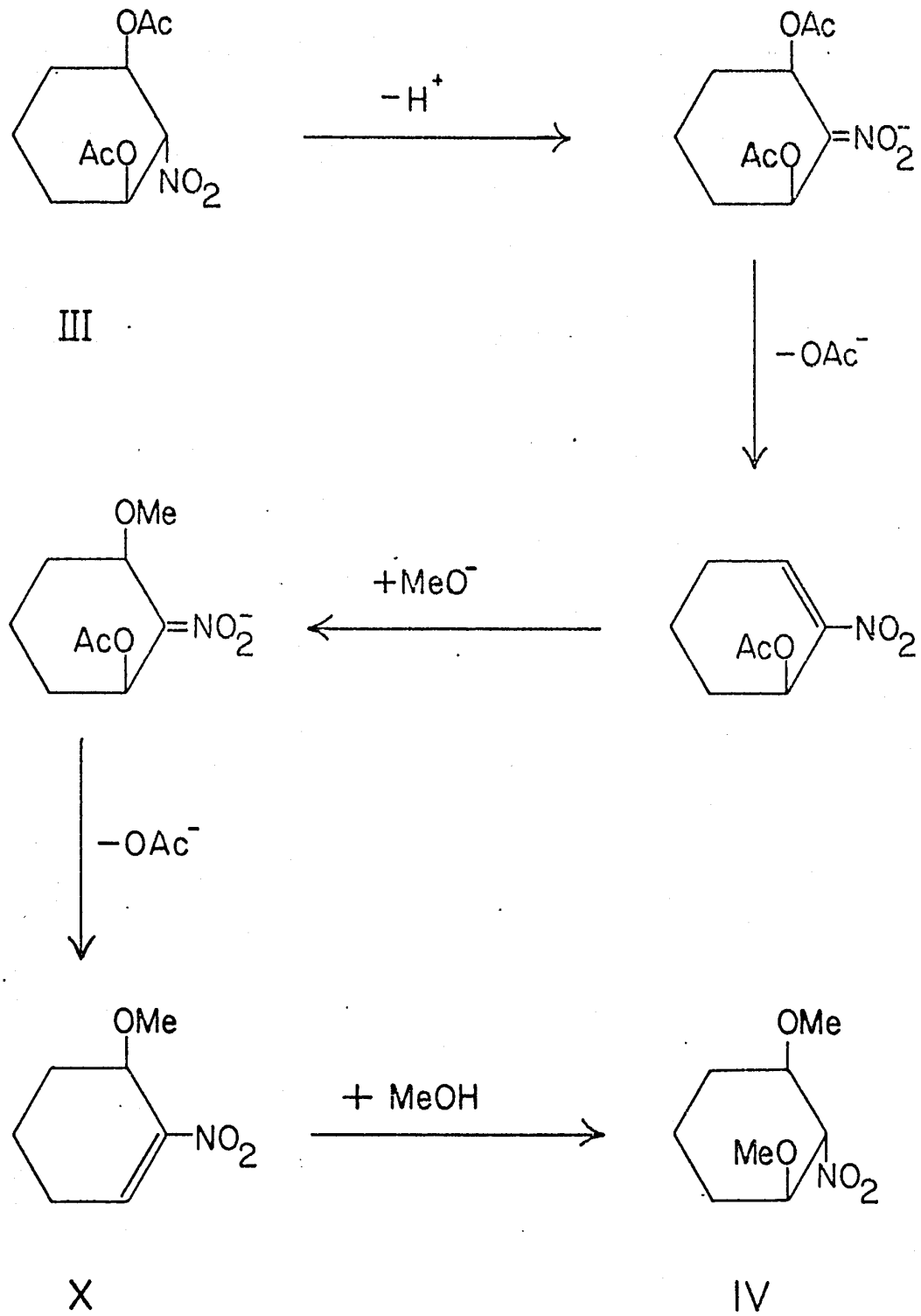


III IV

The product was obtained in 55% yield and gave an infrared spectrum identical to that of the product resulting from methylation, with diazomethane, of the diol. A mixed melting point was undepressed. The proposed mechanism is shown in Fig. 8. It is seen that for this mechanism, the methoxy olefin X is postulated

Fig. 8

Proposed mechanism for the formation of 1(e),3(e)-dimethoxy-2(e)-nitrocyclohexane (IV) from 2(e)-nitrocyclohexane-1(e),3(e)-diol diacetate (III)


OAc
AcO
NO2
−H+
OAc
AcO
=NO2−
III
−OAc−
OMe
AcO
=NO2−
+MeO−
AcO
NO2
−OAc−
OMe
NO2
+ MeOH
OMe
MeO
NO2
X
IV

to be an intermediate. The olefin was synthesized in independent experiments as reported in a later section, and its treatment with methanolic sodium methoxide indeed resulted in formation of IV as indicated by comparative t.l.c. and infrared spectroscopy.

D 3(e)-Methoxy-2(e)-nitrocyclohexan-1(e)-ol

In preliminary experiments, the methylation of the diol II with diazomethane, which furnished the diether IV as described in a preceding paragraph, was monitored by t.l.c. under a variety of reaction conditions. It was found that the reaction mixtures contained, besides fast-moving IV, varying proportions of a more slowly moving material which was presumed to be the monoether V. When the methylation was allowed to proceed at 0° for 3 hours, a relatively large proportion of V was present in the mixture, and this product could be isolated in crystalline form in a yield of 37%. Although its melting point (80-81.5°) was virtually the same as that of IV, it was clearly distinguished by its analysis and spectral data. The elemental analysis was in agreement with the molecular formula $C_7H_{13}NO_4$. The infrared spectrum gave an OH absorption at 3440 cm^{-1} but also gave an ether peak at 1060 cm^{-1}, thus indicating

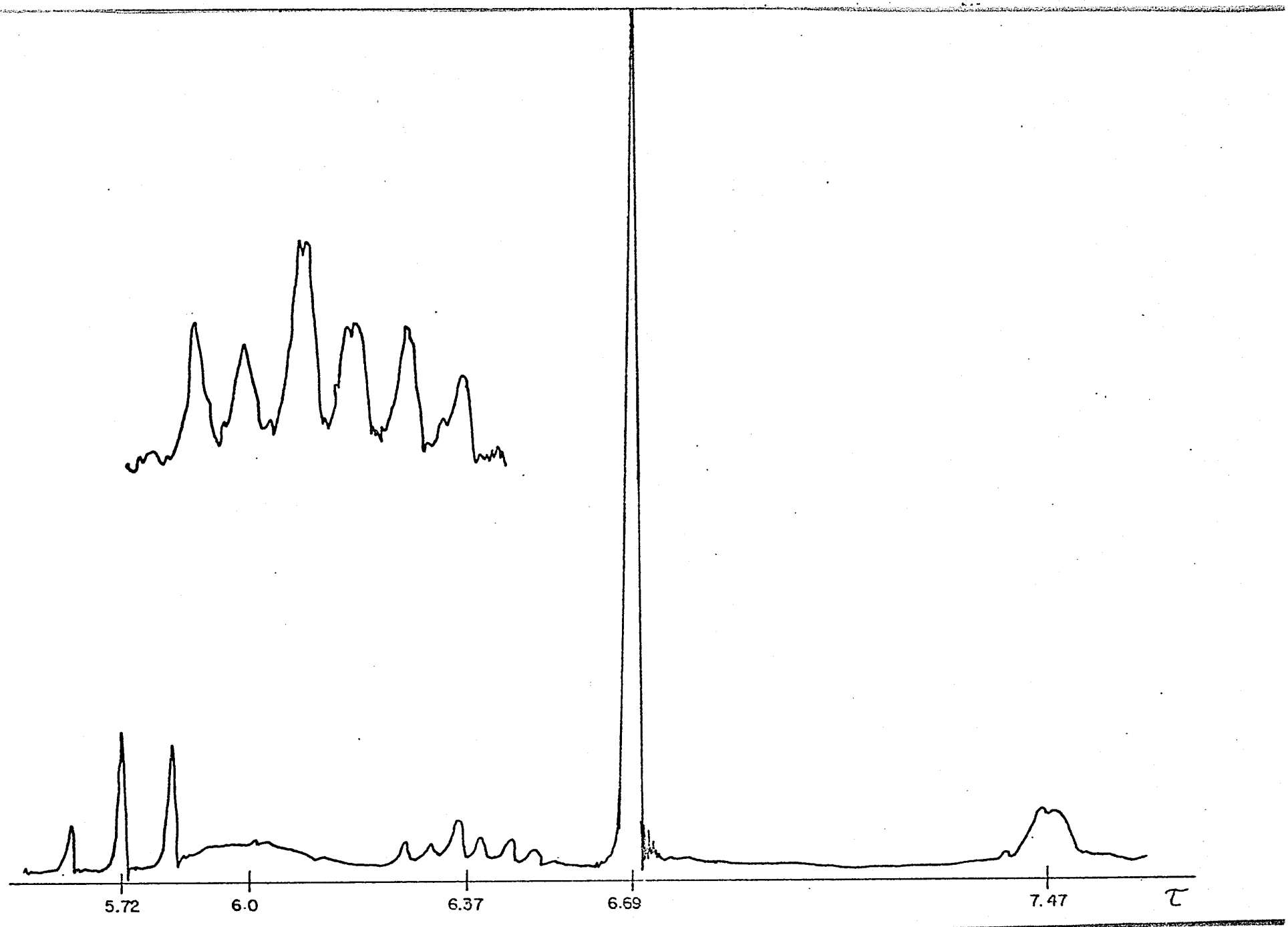
monomethylation.

The n.m.r. spectrum in $CDCl_3$ (Fig. 9) showed a triplet centred at τ 5.72 (1H); a broad peak at τ 6.0 (1H); an irregular sextet centred at τ 6.37 (1H); a sharp singlet at τ 6.69 (3H); and a broad doublet centred at τ 7.47 (1H). The total integration of overlapping multiplets at τ 7.9, τ 8.2,and τ 8.7 corresponded to six protons.

The triplet at τ 5.72 is due to the C-2 proton. Its coupling constant of 9.5 c.p.s. proves that it must be in an axial configuration and split by two adjacent axial protons (44). This necessitates that the adjacent fuctional groups have an equatorial disposition, i.e., all the substituents are equatorial in the trans-trans configuration. The broad peak at τ 6.0 is due to the proton on the carbon bearing the hydroxy group, as evidenced by its resolution to an irregular sextet after exchange of the hydroxy proton with deuterium. The sextet at τ 6.37 is due to the proton on the carbon bearing the methoxy group and, the splitting suggests coupling with two adjacent axial protons and one adjacent equatorial proton. This reaffirms the equatorial disposition of the methoxy group. The sharp singlet at τ 6.69 is due to the $O-CH_3$ pro-

Fig. 9

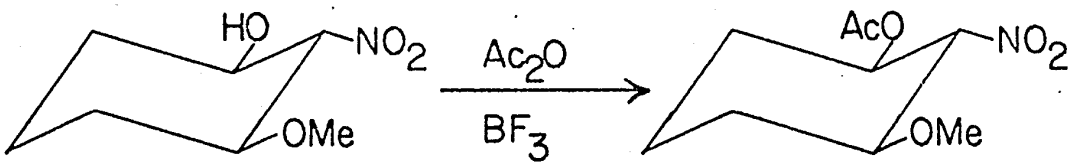
N.M.R. spectrum of 3(e)-methoxy-2(e)-nitrocyclohexan-1(e)-ol (V) in deuterochloroform


5.72
6.0
6.37
6.69
7.47
τ

tons. The broad doublet at τ 7.47 is the signal for the hydroxy proton, and the highfield multiplets are the resonances of the methylene ring protons.

E 3(e)-Methoxy-2(e)-nitrocyclohexan-1(e)-ol Acetate

3(e)-Methoxy-2(e)-nitrocyclohexan-1(e)-ol acetate VI was obtained by the acetylation of the monomethyl ether (V) in acetic anhydride with boron trifluoride as catalyst. The crystalline product was obtained in 90% yield and exhibited m.p. 92-93°.



V VI

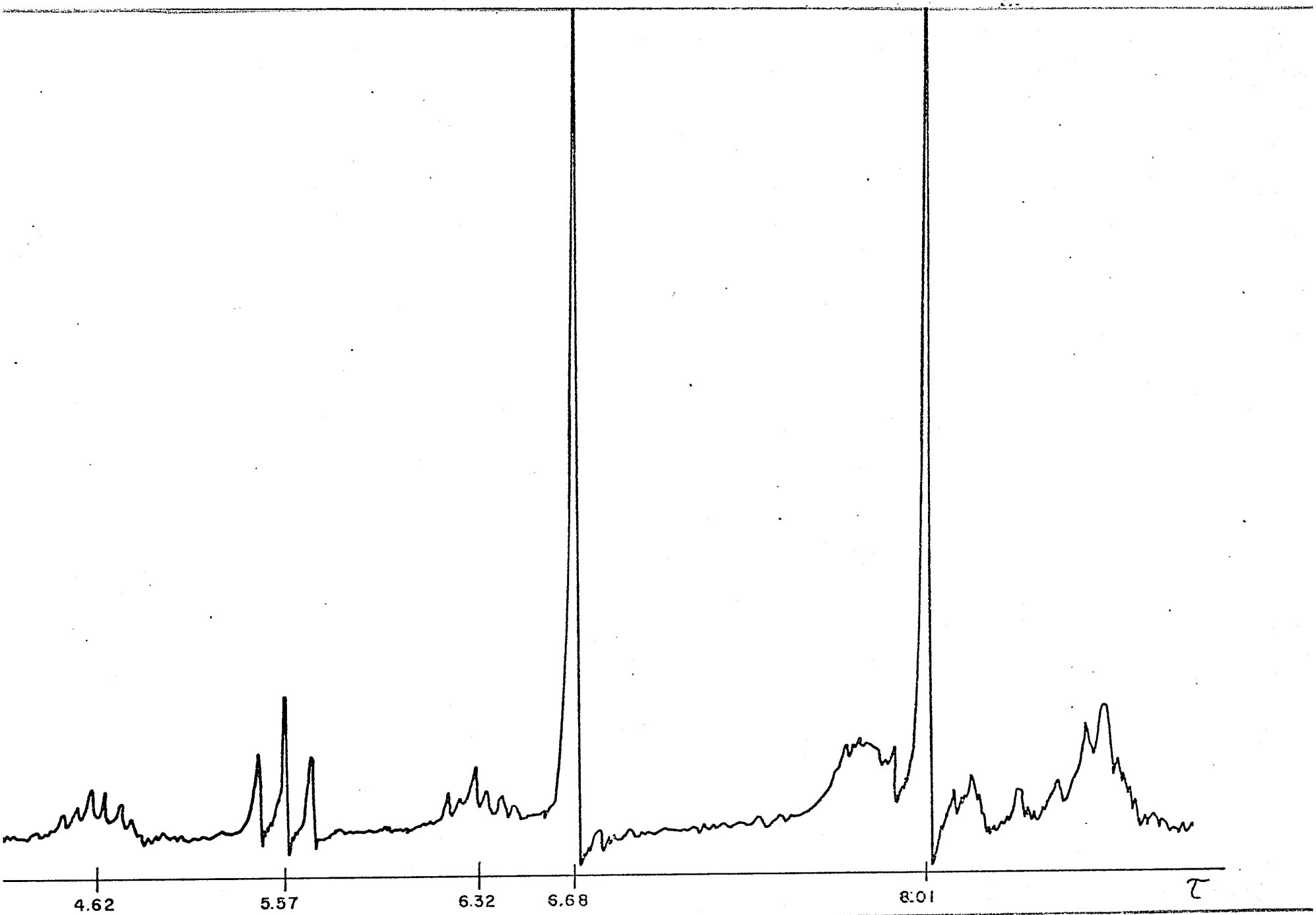
The infrared spectrum did not show any OH absorption but did exhibit a strong carbonyl peak at 1740 cm^{-1}. Elemental analysis confirmed the composition $C_9H_{15}NO_5$.

The configuration was confirmed by the n.m.r. spectrum (Fig. 10) taken in deuterochloroform. The spectrum shows a sextet centred at τ 4.86 (1H); a symmetrical triplet centred at τ 5.57 (1H); a sextet centred at τ 6.32 (1H); a sharp singlet at τ 6.68 (3H); a sharp singlet at τ 8.01, which partially overlapped multiplets at τ 7.8, τ 8.2, and τ 8.7. The sum of the integration of these signals corresponded to nine protons.

The triplet at τ 5.57 is the signal for the proton on the carbon bearing the nitro group. Its coupling constant, J=10.2 c.p.s., shows that it is in an axial configuration and is equally coupled with two adjacent axial protons. The coupling constants of each sextet is the result of coupling of the axial protons on C-1 and C-3 with two adjacent axial protons and an adjacent equatorial proton. This information shows that all the substituents must be in an equatorial disposition, i.e., the trans-trans configuration. The singlet at τ 6.68 is the signal for the methoxy protons and the singlet at τ 8.01 is the signal for the acetoxy methyl protons.

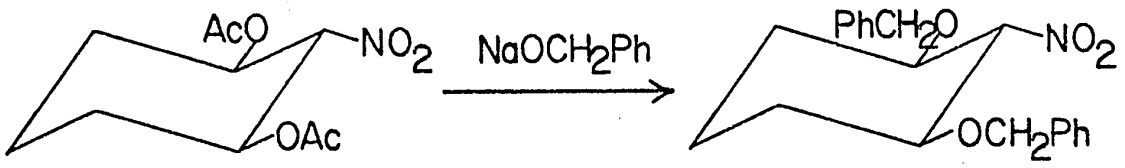
Fig. 10

N.M.R. spectrum of 3(e)-methoxy-2(e)-nitrocyclohexan-1(e)-ol acetate (VI) in deuterochloroform


4.62
5.57
6.32
6.68
8.01
τ

F 1(e),3(e)-Dibenzoxy-2(e)-nitrocyclohexane

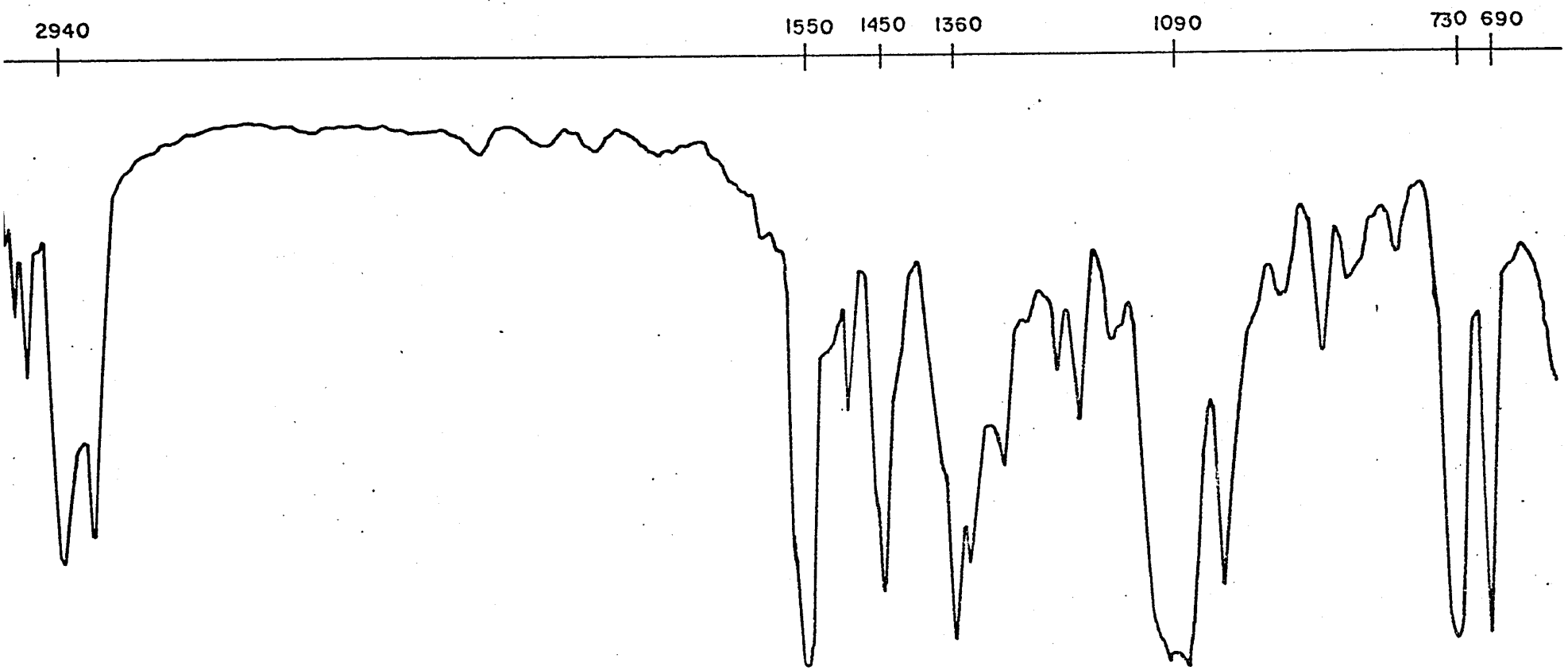
The dibenzoxy compound (VII) was prepared by an elimination-addition reaction analogous to that for the preparation of the dimethyl ether (IV) starting with the diacetate (III). In this case, the diacetate was allowed to react for 8 minutes at 23° with a solution of sodium benzoxide-benzyl alcohol in anhydrous tetrahydrofuran. The oily product obtained in 12% yield after chromatographic purification gave an infrared spectrum (Fig. 11) which showed a strong nitro absorption at 1550 cm^{-1}, a strong ether absorption at 1090 cm^{-1}, and strong aromatic peaks at 730 cm^{-1} and 690 cm^{-1}. It did not show any of the carbonyl absorption of the starting material, nor any peaks attributable to a nitroolefin. However, it was observed in preliminary experiments that if the reaction time was too short, the infrared spectrum showed olefin absorption at 1660 cm^{-1} and a nitro peak at 1515 cm^{-1} characteristic of a nitroalkene.



III VII

Fig. 11

Infrared spectrum (neat) of 1(e),3(e)-dibenzoxy-2(e)-nitrocyclohexane (VII)


2940
1550
1450
1360
1090
730
690

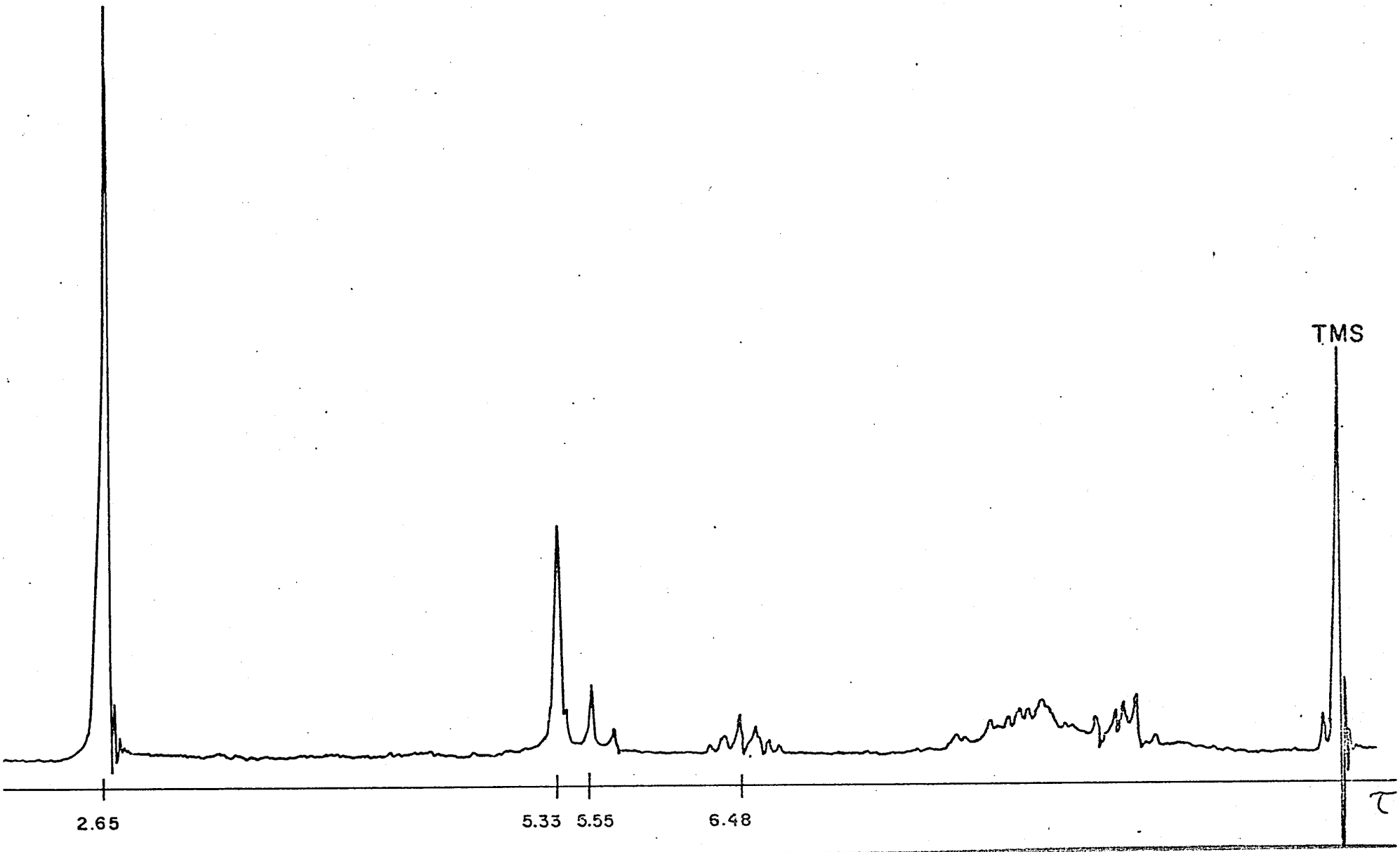
The n.m.r. spectrum taken in deuterochloroform (Fig. 12) showed a sharp singlet at τ 2.65 (10H); a sharp singlet at τ 5.33 (4H); a triplet centred at τ 5.55 (1H); a sextet centred at τ 6.48 (2H); and overlapping multiplets at τ 7.7-8.8 whose total integration equalled six protons. The singlet at τ 2.65 is the signal for the aromatic protons, and the singlet at τ 5.33 is the signal due to the methylene protons of the benzyl substituents. The triplet at τ 5.55 is due to the proton on the carbon bearing the nitro group. Since its coupling constant is large (J=9 c.p.s.), it is concluded that the substituents are all equatorial in the trans-trans configuration. The fact that the two phenyl groups gave one singlet and H-1 and H-3 give one sextet reaffirms this configuration to the extent that it excludes the cis-trans configuration.

G Reaction of 2(e)-Nitrocyclohexane-1(e),3(e)-diol Diacetate with Sodium Isopropoxide

When the diacetate (III) was allowed to react with sodium isopropoxide in benzene at room temperature, the diisopropyl ether was not obtained. Instead, the product isolated proved to be 3-acetoxy-2-nitrocyclo-

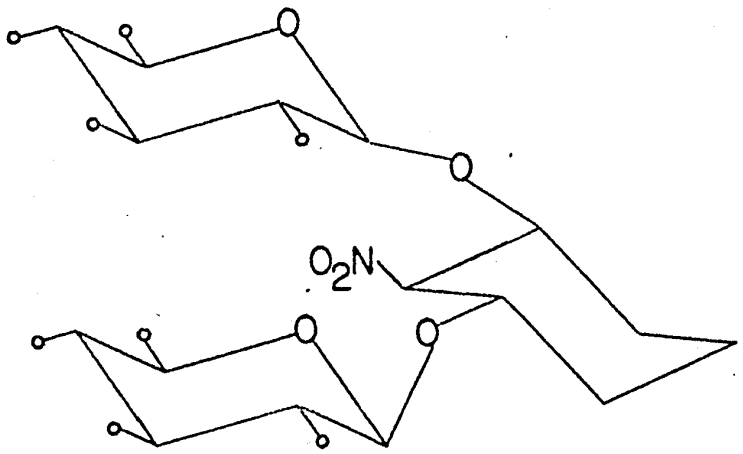
Fig. 12

N.M.R. spectrum (60 MHz) of 1(e),3(e)-dibenzoxy-2(e)-nitrocyclohexane (VII) in deuterochloroform

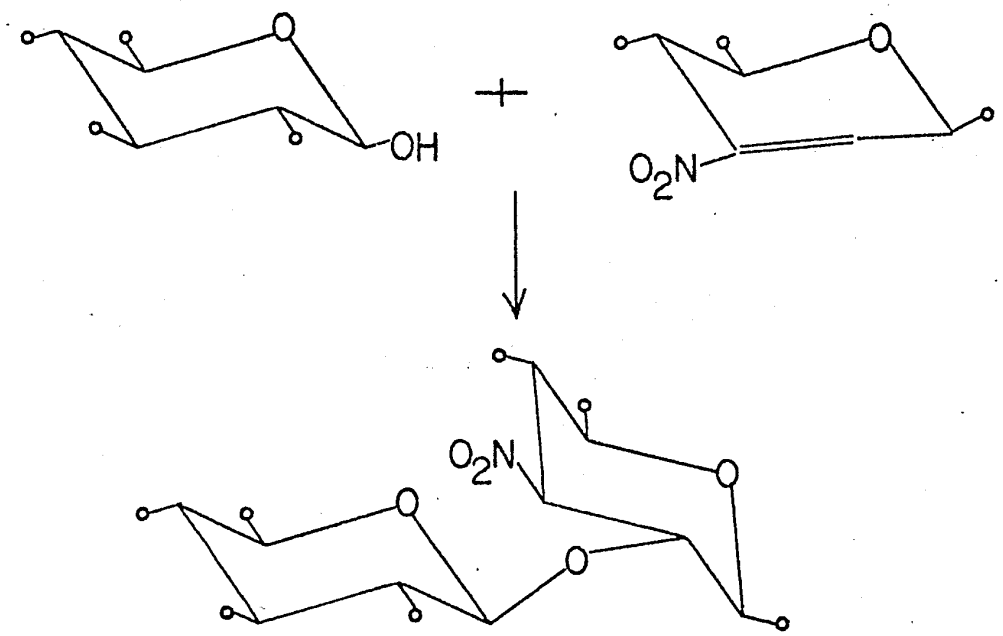

TMS
2.65
5.33
5.55
6.48
τ

hexene (IX) (identified by comparison of the infrared and n.m.r. spectra with those of an authentic sample). Reaction at elevated temperatures did not yield the desired ether and destroyed the starting material. Inspection of molecular models of the trans-trans diisopropyl ether and the trans-trans dibenzyl ether will show that the isopropyl groups are much more sterically hindered than are the benzyl groups. It would seem likely, therfore, that the energy required for formation of the diisopropyl ether would be much greater than that required for formation of the dibenzyl ether, and on these grounds, the failure of the trans-trans diisopropyl ether to arise might be explicable. The models suggest, however, that when the nitro group is in the axial configuration, its interference with the isopropyl groups should be decreased. Several workers have shown that protonation of 2-arylcyclohexanenitronates (where aryl is usually phenyl) leads preferentially to the cis product, i.e., an axial nitro group (38-42, 44-46). However, neither the trans-trans nor the cis-cis product could be isolated from these reactions although t.l.c. did show, in addition to the olefin, trace amounts of other products.

It should be interesting to try analogous elimination-addition reactions using, as alcoholic components, appropriately blocked sugar derivatives. If successful, such reactions would open a new avenue to sturctures related to antibiotics of the neomycin type:



In fact, the reactions described above were undertaken, as model reactions, with that goal in mind. The failure of introducing isopropyl groups, apparently due to steric hindrance, was, of course, discouraging in this regard. On the other hand, the synthesis of certain nitro disaccharides, which was a similar proposition, has recently been accomplished (55) (see scheme), and it would therefore seem worthwhile to pursue the synthesis of nitrocyclohexanediol glycosides along the same lines.



III Synthesis of Olefin Intermediates

A 3-Acetoxy-2-nitrocyclohexene

By refluxing 2(e)-nitrocyclohexane-1(e), 3(e)-diol diacetate (III) with anhydrous sodium bicarbonate in dry 1,4-dioxane the acetoxy olefin (IX) was obtained in 46% yield. The crystalline material exhibited m.p. 65-66° and its elemental analysis was in accord with the formula $C_8H_{11}NO_4$. The acetoxy group gave infrared bands at 1730 cm^{-1} (C=O) and 1225 cm^{-1}

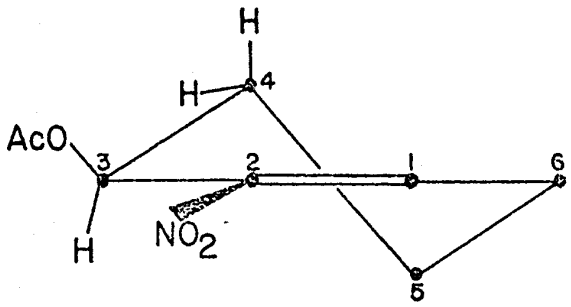
(C-O-C). Nitro absorptions at 1515 cm^{-1} and 1340 cm^{-1} and a sharp peak at 1660 cm^{-1} were indicative of a nitroalkene.

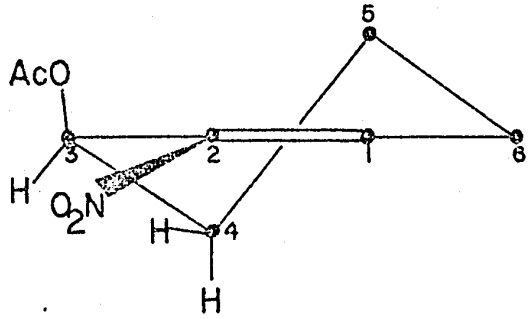
The n.m.r. spectrum (Fig. 14) taken in deuterochloroform showed a quartet centred at τ 2.42 (1H); an unresolved triplet centred at τ 3.97 (1H); and a sharp singlet at τ 8.00 which overlapped a multiplet. There were other multiplets at τ 7.6 and τ 8.3. The sum of the integration of these overlapping signals corresponded to nine protons.

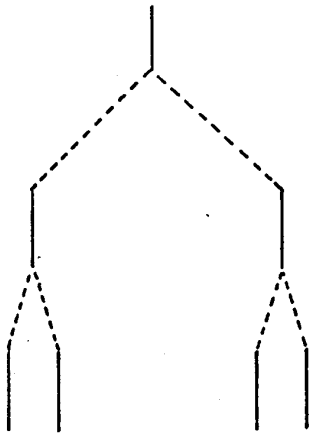
A study of molecular models indicates that the preferred conformation for this system is a half-chair. There are two possible arrangements for the half-chair: HC_5^4, with C-4 above the plane formed by C-6, C-1, C-2, C-3, and with C-5 below this plane; and HC_4^5, with C-5 above the plane and C-4 below it. Both possible conformers are shown in Fig. 13. In the case of the HC_5^4 form, the pseudoaxial C-3 proton is coupled with the axial and equatorial C-4 protons. The theoretical signal in the n.m.r. spectrum for H-3 in this arrangement would be as shown in Fig. 13, i.e., a quartet of approximately 12 c.p.s. width. For the second arrangement, the pseudoequatorial C-3 proton is coupled with the axial and equatorial C-4 protons, and the dihedral angle between the C-3 proton and each of the

Fig. 13

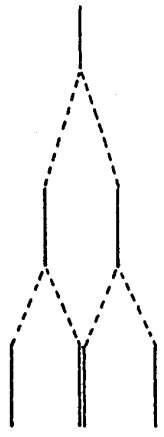
Conformational arrangements possible for 3-acetoxy-2-nitrocyclohexene (IX)







HC_5^4



HC_4^5

C-4 protons is approximately the same. The theoretical signal in the n.m.r. spectrum for the C-3 proton would be as shown in Fig. 13 with the coupling constant equal to approximately 3 c.p.s. When the dihedral angles are equal, the signal would appear as a triplet with the height of the centre peak and the flanking peaks in the ratio 2:1.

Examination of the n.m.r. spectrum shows the C-3 proton to be a triplet with J=3 c.p.s. Furthermore, the ratio of the peak heights is approximately 2:1. These data show that the molecule exists in the HC_4^5 conformation, i.e., with the acetoxy group pseudoaxially oriented. The preference of this conformation is to be expected by virtue of the $A^{(1,2)}$ effect, the nonbonded interaction between the nitro oxygen and the equatorial, neighboring acetoxy group in the alternative, HC_5^4 conformer (56). A case of precedence for this conformational effect has recently been reported by Lemieux (57) in the unsaturated nitro sugar derivative shown below.

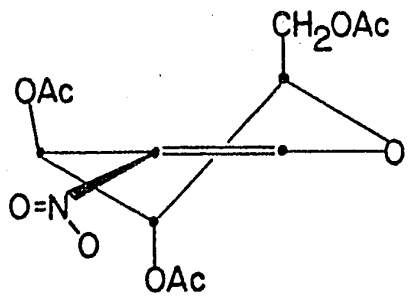
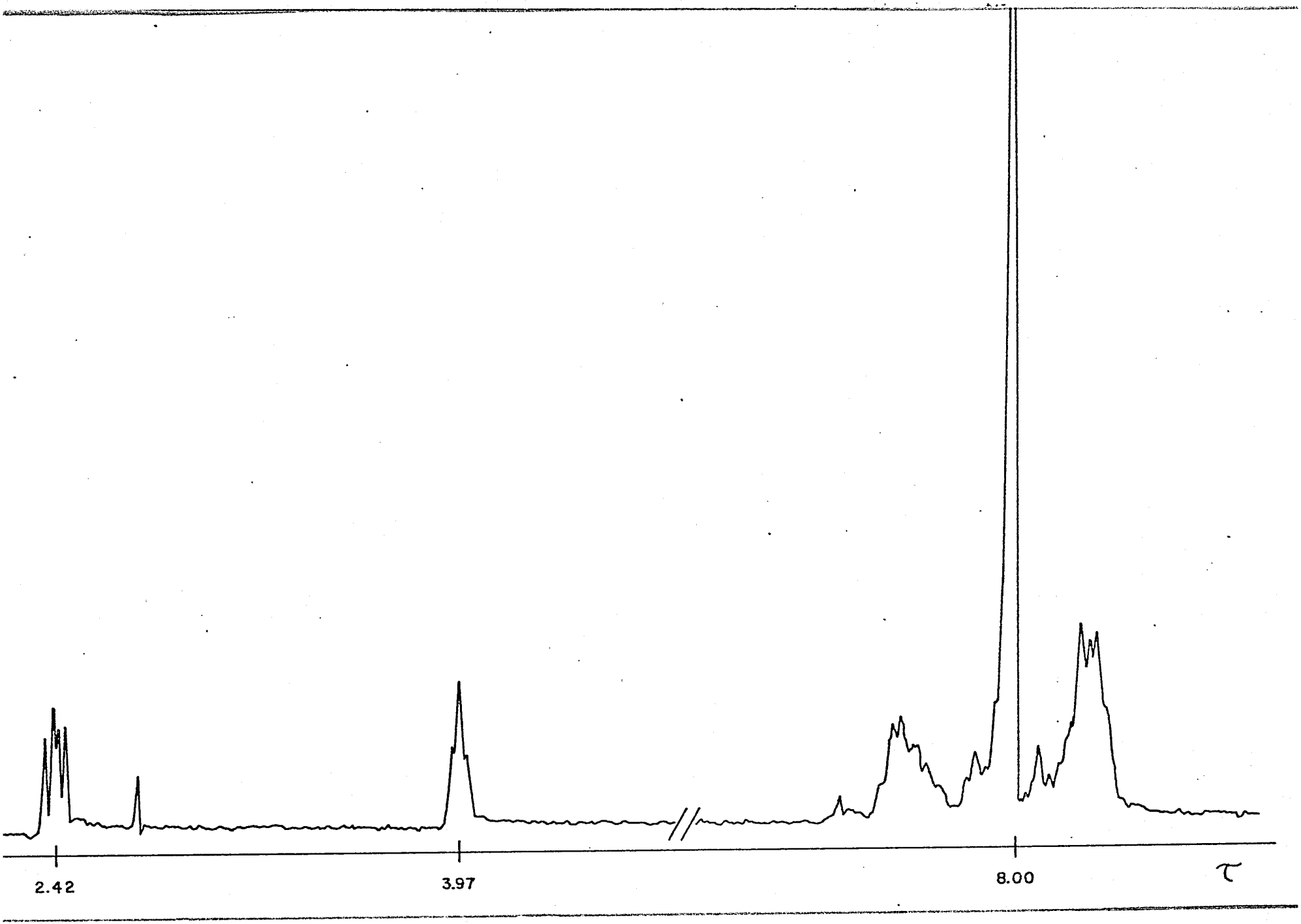


Fig. 14

N.M.R. spectrum of 3-acetoxy-2-nitrocyclohexene (IX)
in deuterochloroform


2.42
3.97
8.00
τ

B 3-Methoxy-2-nitrocyclohexene

1) The methoxy olefin X was prepared in 22% yield by refluxing 3(e)-methoxy-2(e)-nitrocyclohexane-1(e)-ol acetate with anhydrous sodium bicarbonate in dry benzene. Elemental analysis of the oily product corresponded to the formula $C_7H_{11}NO_3$. The infrared spectrum of the neat oil showed an olefin absorption at 1670 cm^{-1} and nitroalkene peaks at 1515 cm^{-1} and 1340 cm^{-1}. The ether peaks at 1090 cm^{-1} and 1070 cm^{-1} and lack of a carbonyl absorption ensured that the acetoxy group had been eliminated.

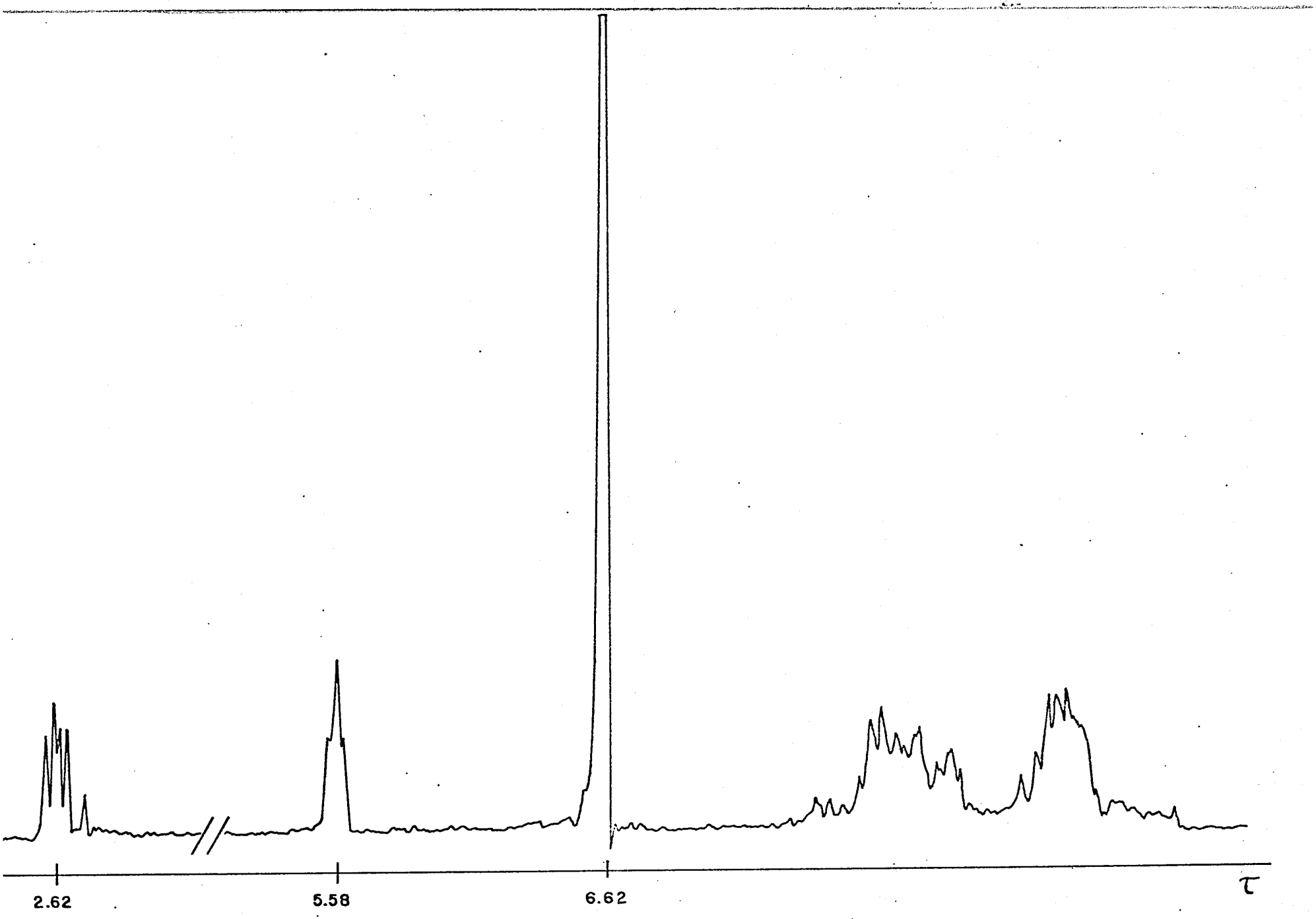
The n.m.r. spectrum (Fig. 15) in deuterochloroform showed a quartet centred at τ 2.62 (1H); an unresolved triplet centred at τ 5.58 (1H); a singlet at τ 6.60 (3H); and multiplets between τ 7.5 and 8.7 whose total integration corresponded to six protons. As in the case of the 3-acetoxy-2-nitrocyclohexene, the conformation was shown to be HC_4^5.

2) The methoxy olefin was also prepared (in quantitative yield) by refluxing the acetoxy olefin IX in methanol for 10 hours. During reflux, only one product was seen on t.l.c. In view of the stability of 3(e)-methoxy-2(e)-nitrocyclohexane-1(e)-ol acetate

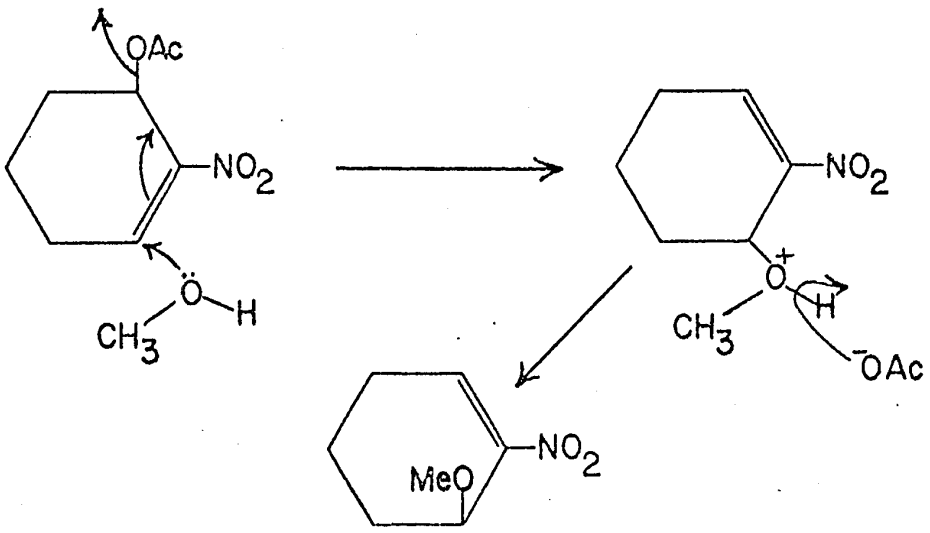
Fig. 15

N.M.R. spectrum of 3-methoxy-2-nitrocyclohexene (X) in

in deuterochloroform


2.62
5.58
6.62
τ

towards mild base and because of the absence of another product during reflux, it would seem reasonable that the reaction goes by a concerted mechanism rather than an addition-elimination mechanism:



C 3-Ethoxy-2-nitrocyclohexene

The ethoxy olefin XI was prepared in quantitative yield by refluxing the acetoxy olefin IX in ethanol for 15 hours.

The elemental analysis corresponded to the formula $C_7H_{11}NO_3$. The infrared spectrum of the neat oil showed an olefin absorption at 1665 cm^{-1} and nitroalkene peaks at 1510 cm^{-1} and 1340 cm^{-1}. The absence

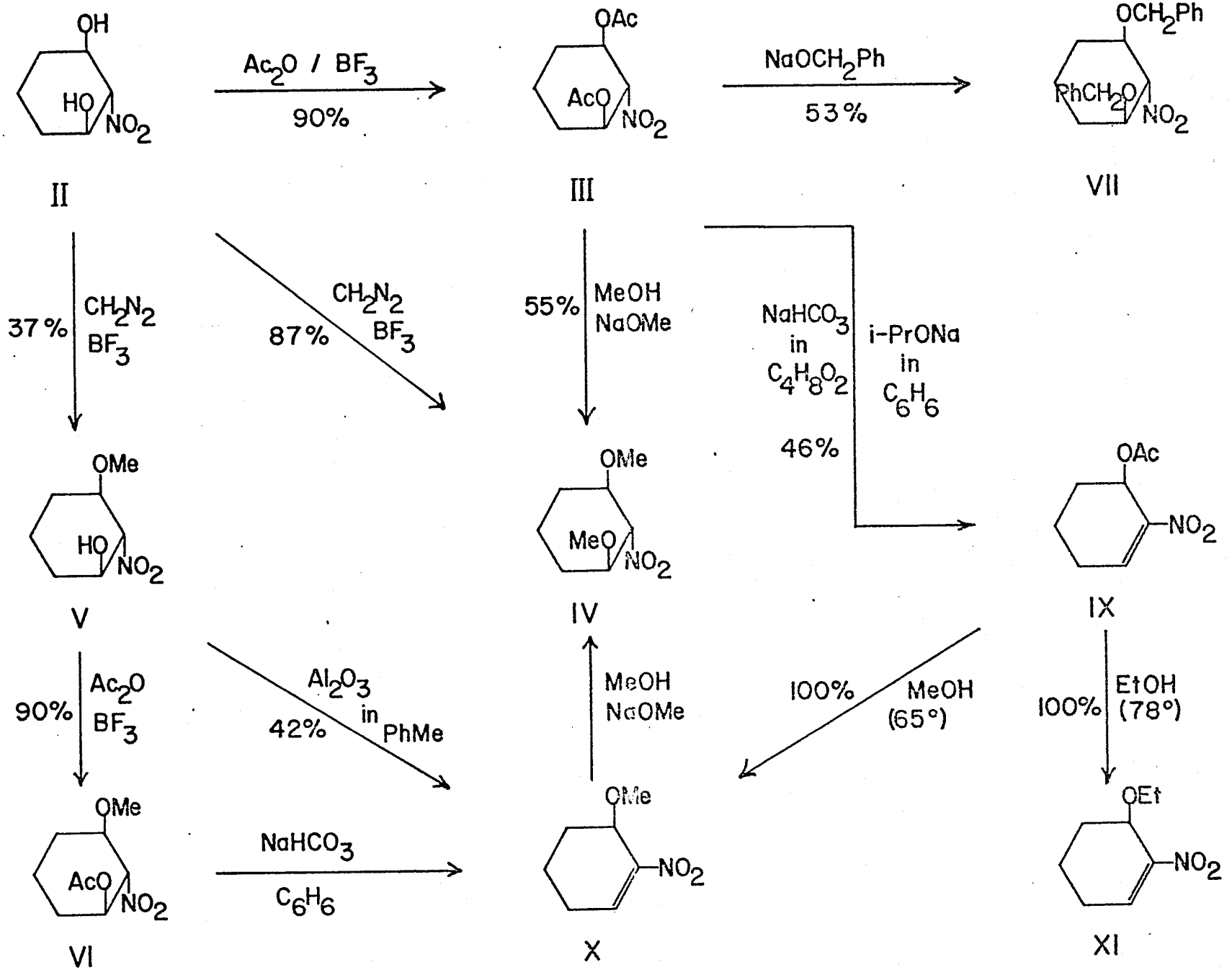
of a carbonyl absorption showed that the acetoxy group had been eliminated and peaks at 1090 cm^{-1} and 1070 cm^{-1} indicated an ether linkage.

The n.m.r. spectrum in deuterochloroform showed a quartet centred at τ 2.63 (1H); an unresolved triplet centred at τ 5.47 (1H); a quartet centred at τ 6.36 (2H); a triplet centred at τ 8.84 (3H); and multiplets between τ 7.4 and τ 8.6 whose total integration corresponded to six protons. As in the case of the 3-acetoxy-2-nitrocyclohexene, the conformation was shown to be HC_4^5.

IV Summary

Attempts at improving the synthesis of trans-trans-2-nitrocyclohexane-1,3-diol (II) or of obtaining the cis-trans or cis-cis epimers, by modifying the nitromethane cyclization of glutaric dialdehyde did not lead to useful results. The yield in the preparation of the diacetate (III) of II could be improved by the use of boron trifluoride as catalyst for the acetylation. It was found that the dimethyl ether (IV) as well as the monomethyl ether (V) of II can be prepared by methylation with diazomethane in the presence of boron trifluoride. Acetylation of V furnished its acetate VI. Action of methoxide upon the diacetate III gave, by an elimination-addition process, the same dimethyl ether (IV) that had been obtained from II with diazomethane. A similar reaction with sodium benzoxide afforded the corresponding dibenzyl ether (VII), whereas sodium isopropoxide did not furnish the desired diisopropyl ether, presumably because of steric hindrance. The only product isolated in the latter reaction was 3-acetoxy-2-nitrocyclohexene (IX) which resulted from dehydroacetylation and which apparently failed to add isopropyl alcohol. The same olefin IX was also obtained by Schmidt-Rutz reaction starting from the diacetate III,

i.e., by dehydroacetylation with sodium bicarbonate in nonhydroxylic solvents. Schmidt-Rutz reaction of the monomethyl ether monoacetate VI led to 3-methoxy-2-nitrocyclohexene (X), as did dehydration of the monomethyl ether V with aluminum oxide and treatment of the acetoxy olefin IX with refluxing methanol. In the presence of methoxide, X added methanol to give the dimethoxy compound IV. 3-Ethoxy-2-nitrocyclohexene (XI) was obtained by refluxing IX in ethanol. The reactions are summarized in the scheme given on p. 63.


OH
HO
NO2
II
Ac2O / BF3
90%
OAc
AcO
NO2
III
NaOCH2Ph
53%
OCH2Ph
PhCH2O
NO2
VII
37%
CH2N2
BF3
V
87%
CH2N2
BF3
55%
MeOH
NaOMe
OMe
MeO
NO2
IV
NaHCO3
in
C4H8O2
46%
i-PrONa
in
C6H6
OAc
NO2
IX
90%
Ac2O
BF3
OMe
AcO
NO2
VI
42%
Al2O3
in
PhMe
NaHCO3
C6H6
MeOH
NaOMe
OMe
NO2
X
100%
MeOH
(65°)
100%
EtOH
(78°)
OEt
NO2
XI

EXPERIMENTAL

GENERAL REMARKS

Melting points were determined in capillaries using a Gallenkamp Melting Point Apparatus equipped with a calibrated thermometer, and are uncorrected.

Thin layer chromatography was performed using silica gel G (according to Stahl) on 7.5-cm plates (microscope slides) unless otherwise mentioned. The solvent systems used for irrigation were: benzene-diethyl ether, 3:1 (solvent A); benzene-ethanol, 3:1 (solvent B); carbon tetrachloride-ethyl acetate, 2:1 (solvent C); carbon tetrachloride-ethyl acetate, 4:1 (solvent D); carbon tetrachloride-ethyl acetate, 6:1 (solvent E); ethyl acetate-methanol, 5:1 (solvent F). The spots were developed by spraying the plates with a solution of 1% ceric sulfate in 10% sulfuric acid and heating for 2-3 minutes on a hot plate. All silica gel columns were packed with MERCK 7734 Silica Gel, 0.05-0.20 mm (70-325 mesh ASTM).

All n.m.r. spectra were obtained on a Varian HA-100 spectrometer. Unless otherwise speci-

fied, infrared spectra were recorded using Nujol mulls on a Beckman IR-20 spectrophotometer.

Optical rotations were measured using a Perkin-Elmer 141 polarimeter.

All references to cation exchange resin are to AMBERLITE IR-120 (H^+) Ion Exchange Resin[1].

References to ether are to diethyl ether.

Petroleum ether refers to the fraction boiling at 30-60°.

All evaporations were done in vacuo with bath temperature $< 40°$, unless otherwise indicated.

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1. Mallinckrodt Chemical Works, Montreal

Glutaric Dialdehyde-Bisulphite Adduct (I)

Glutaric dialdehyde[1] (25% aqueous solution, 100 ml) was added to 200 ml of sodium bisulfite reagent[2] and the solution was shaken vigorously for 6 hours. Since no precipitate was evident, a further 200 ml of sodium bisulfite reagent was added to the reaction mixture and shaking was continued for 2 hours at which time a white, fibrous precipitate appeared. The reaction mixture was left to stand at room temperature overnight, then filtered by suction, and the precipitate washed with cold ethanol (2x50 ml), ether (2x50 ml), and dried over calcium chloride in the desiccator. Yield: 40.3 g (52.5%).

Infrared frequencies (cm^{-1})[3,4]: 3565s (OH); 3500s (OH); 3315s,bd (OH); 1220s,bd (S=O); 1175s,bd (S=O); 1050s,sh (C-O); 1035s (C-O); 630s,bd (S=O);

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1. Aldrich Chemical Company, Milwaukee, Wisconsin.
2. A. I. Vogel, Practical Organic Chemistry, 3rd Ed., Longmans, Green, and Co. Ltd., London, p. 331,1962.
3. Beckman IR-8 Spectrophotometer
4. Designations are: s(strong), ms(medium strong), m(medium), w(weak), bd(broad), sh(shoulder), ^{b}(several bands).

1640w; 1335m; 1255m,sh; 1110m; 1085w; 980m; 850w; 730m.

Attempted Cyclization of Glutaric Dialdehyde Bisulphite Adduct (I) with Nitromethane

a) In the Presence of Aqueous Sodium Hydroxide

To a chilled solution of glutaric dialdehyde bisulphite adduct I (2.0 g) in 10 ml of water was added slowly, with stirring, a chilled solution of nitromethane (0.35 ml; 1 molar equivalent) in aqueous sodium hydroxide (0.26 g in 5 ml of water; 1 molar equivalent) and the solution stirred for 10 minutes at 0°, during which time it turned yellow. The reaction mixture was then extracted with ether (3x20 ml), the pooled extracts were dried over anhydrous magnesium sulphate (10 g), filtered, and evaporated giving 127 mg of brown oil. The aqueous layer was acidified with 0.1N hydrochloric acid and extracted as above to yield 340 mg of brown oil. Comparative t.l.c. of these extracts with a sample of compound II, using solvent A, gave two major spots and at least four minor ones. One of the major spots corresponded to the reference diol and the infrared spectrum (cm^{-1}) of the crude product showed a broad nitro peak at 1550 and other

peaks at 1340, 1150, 1050, 1030, 960, and 750, which corresponded to peaks in the spectrum of the reference diol. No crystalline material could be isolated and no attempt was made to separate the components.

In a similar experiment, at room temperature and with a prolonged reaction time of 30 minutes, the reaction pattern was more or less the same.

When an aqueous methanolic solution (1:1) of nitromethane and sodium hydroxide (1 molar equivalents) was added dropwise at 0° to a stirred, aqueous methanolic solution (3:1) of compound I, allowed to react for 7 hours at room temperature, then acidified with 0.1N acetic acid, a dark brown solution resulted. Comparative t.l.c. using solvent A showed the crude product to be a complex mixture.

b) In the Presence of Methanolic Sodium Hydroxide

Glutaric dialdehyde bisulphite adduct I (6.2 g) was suspended in anhydrous methanol[1] (200 ml), stirred for 15 hours at room temperature with 40 ml of cation exchange resin, then filtered. The filtrate

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1. A. I. Vogel, Practical Organic Chemistry, 3rd Ed., Longmans, Green, and Co. Ltd., London, p.169, 1962.

was cooled in an ice-bath, and a chilled solution of nitromethane (1.08 ml; 1 molar equivalent) in methanolic sodium hydroxide (0.80 g in 20 ml methanol; 1 molar equivalent) was added with stirring in the course of 5 minutes. The reaction mixture became turbid. The reaction was monitored by t.l.c.[1] and stopped after 2 hours when it appeared that all the glutaric dialdehyde had reacted. The reaction mixture was then divided into two equal portions, 'A' and 'B'. Part 'A' was stirred with 10 ml of cation exchange resin until clear, filtered, and evaporated. The resulting light brown syrup was treated immediately with acetic anhydride (10 ml) and boron trifluoride etherate[2] (10 drops), left to stand overnight, and the excess acetic anhydride hydrolyzed with 100 ml of water. This solution was then extracted with ether (5x100 ml), and the

---

1. Samples (0.5 ml) of the reaction mixture were withdrawn every half hour, treated with AMBERLITE IR-120 (3 ml), and the chromatographic plates were irrigated with solvent B.

2. Forty-seven per cent boron trifluoride in anhydrous ether, distilled and stored under nitrogen.

combined ether extracts were dried over anhydrous magnesium sulphate, filtered and evaporated yielding a dark brown oil. Comparative t.l.c. (solvent B) with glutaric dialdehyde showed a complex mixture of at least five spots, one of which corresponded to the dialdehyde. No pure product was obtained. Part 'B' was stored at 5° overnight, during which time the suspension settled. The supernatant liquid was decanted, treated with 10 ml of ion exchange resin, filtered and evaporated leaving a pale yellow residue which turned dark brown at 0° over 2 weeks. Comparative t.l.c. (solvent B) of this residue with glutaric dialdehyde and compound II showed at least four distinct spots and heavy streaking near the origin. One minor spot corresponded to the dialdehyde. No crystalline product could be isolated. The residue from part 'B' was suspended in 100 ml of methanol and stirred with 10 ml of cation exchange resin until the solution became clear, filtered and evaporated leaving a brown liquid. Comparative t.l.c. (solvent B) showed much the same as above.

For a similar experiment in which the reaction temperature was raised to room temperature for 2 hours after stirring at 0° for 2 hours, the yellow oil obtained from the resin-treated supernatant liquid

showed only three spots on t.l.c. using solvent B. However, when a sample of this material was run on a 20-cm chromatographic plate irrigated with benzene-ethyl acetate (3:1), it proved to be a complex mixture of at least six spots. The resin-treated residue of the reaction mixture turned dark brown upon evaporation, indicating decomposition, and comparative t.l.c. was similar to that of the previous experiment.

c) In the Presence of Sodium Methoxide

Treatment of 6.2 g of the bisulphite adduct I with cation exchange resin as described above, followed by reaction with a solution of nitromethane (1.08 ml; 1 molar equivalent) in 50 ml of sodium methoxide solution (1.1 molar equivalents) for 2 hours at 0°, and subsequent similar work-up, yielded a pale yellow oil for both the supernatant liquid and the residue. However, comparative t.l.c. using a 20-cm plate irrigated with benzene-ethyl acetate (3:1) showed both products to be complex mixtures of at least six components. Separation was not attempted.

2(e)-Nitrocyclohexane-1(e),3(e)-diol (II)

Glutaraldehyde (25% aqueous solution, 12.5 ml), nitromethane (5 ml), methanol (12.5 ml), and water (12.5 ml) were mixed, cooled to 0°, and a solution of anhydrous sodium carbonate (9 g) in 32 ml of water was added slowly. The reaction mixture was allowed to stand at room temperature for 5 hours. This solution was then acidified carefully with glacial acetic acid,and the resulting brown solution evaporated. The remaining brown syrup was dissolved in ethanol, and concentrated hydrochloric acid added carefully to produce a white precipitate (sodium chloride). The mixture was then treated with activated charcoal, warmed on the steam-bath for 5 minutes, filtered, and evaporated leaving a yellow viscous mass. This viscous material was extracted with ether in a Soxhlet-Extractor for 20 hours,and the ether changed three times. The combined ether extracts were concentrated to approximately 15 ml, and the resulting pale yellow precipitate filtered by suction giving 2.12 g (42%) of essentially pure compound II. The precipitate showed one main spot and a trace of slightly faster moving material on t.l.c. irrigated with solvent C. The mother liquor gave the same main spot and the

same slightly faster moving material (although more intense in this case) and, in addition, some very slow-moving material, but did not yield any more crystals.

The slightly faster moving compound, although not isolated, was thought to be the isomeric 2(e)-nitrocyclohexane-1(e),3(a)-diol[1].

Recrystallization of the precipitate from benzene-ethanol (4:1) gave 1.98 g of fine, colorless needles, m.p. 165-166.5°, reported, m.p. 159-161° (35). The n.m.r. spectrum is shown in Fig. 5.

Infrared frequencies (cm^{-1}): 3300s,bd (OH); 1550s (asymmetric NO_2); 1340ms (OH); 950ms; 900-700m[b].

2(e)-Nitrocyclohexane-1(e),3(e)-diol Diacetate (III)

To a solution of compound II (1.61 g) in 25 ml of acetic anhydride was added 10 drops of boron trifluoride etherate solution and the reaction mixture stirred at room temperature for 40 minutes. This mixture was then poured slowly into 1.5 litres of ice

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1. Further work done on the reaction by Dr. G. Dawson in this laboratory proved this to be correct.

water, with vigorous stirring, giving a white precipitate. The aqueous solution and the precipitate were extracted with ether (4x200 ml), the combined extracts dried over anhydrous magnesium sulfate (20 g) for 2 hours, and filtered. The solvent was evaporated leaving a yellow-green liquid. Excess acetic acid was removed by successive evaporations with toluene, which gave a yellow crystalline mass (2.34 g). The crude product was then taken up in excess ethanol and heated on a steam-bath with activated charcoal. Evaporation of the filtered solution gave a colorless oil which crystallized upon cooling.

Recrystallization of this product from carbon tetrachloride afforded 1.82 g of III as colorless needles, m.p. 91-92°, reported, m.p. 89-90° (35). Subsequent addition of petroleum ether to the mother liquor yielded another 0.400 g of III (total yield, 90.5%).

Infrared frequencies (cm^{-1}): 1745s (C=O); 1555s (asymmetric NO_2); 1230s,bd (C-O); 1200ms; 1150m; 1060m,sh; 1030s; 950m; 900m; 850m; 730ms.

The n.m.r. spectrum is shown in Fig. 6.

1(e),3(e)-Dimethoxy-2(e)-nitrocyclohexane (IV)

a) The diol II (2.0 g) was dissolved in a small amount of anhydrous ether, Drierite (3 g)[1,2] was added, and the mixture was stirred in a dry ice bath. Now, an ethereal solution of diazomethane (generated from 50 g of N-nitrosomethyl urea (58)) and boron trifluoride etherate (a total of about 5 ml) were added dropwise in alternating sequence in the course of 3 hours. The rate of addition was such that an excess of diazomethane was always present, as evidenced by the pale yellow color of the reaction mixture. During the reaction, a white flocculent precipitate[3] was formed. After 3 hours, t.l.c. (solvent C) showed one major product and a trace of a slow-moving material that corresponded to the monomethyl ether[4]. The reaction mixture was then warmed briefly with activated char-

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1. Powdered and dried in the oven at 150° for 1 day.
2. It was found in previous experiments that Drierite prevented the hydrolysis of boron trifluoride, thereby reducing the amount required.
3. Polymethylene
4. Obtained from previous small-scale experiments.

coal, and evaporation of the solvent furnished a colorless oil which crystallized upon cooling. Recrystallization from benzene-petroleum ether afforded two crops of IV (2.03 g, 87%) as colorless plates, m.p. 79-80°. A second recrystallization from the same solvents raised the melting point to 81°.

Anal. Calcd. for $C_8H_{15}NO_4$ (189.2): C, 50.78; H, 7.99; N, 7.40. Found: C, 50.98; H, 7.83; N, 7.25.

Infrared frequencies (cm^{-1}): 1555s (asymmetric NO_2); 1385s (symmetric NO_2); 1105s (C-O); 1095s (C-O); 1345m; 1295m; 1240w; 1205m; 1190m; 1155w; 1080m, sh; 1020m; 955w; 860m; 730s.

The n.m.r. spectrum is shown in Fig. 7.

b) To a chilled solution (0°) of the diacetate III (40 mg) in 4 ml of anhydrous methanol was added, with stirring, 1 ml of a 0.037 N solution of sodium methoxide (0.23 molar equivalents), and stirring was continued for 7 minutes[1]. Carbon dioxide was then passed through the solution for half an hour. The reaction mixture was taken up in 10 ml of ethyl acetate, treated with activated charcoal, filtered, and evapor-

1. In previous small-scale experiments, the optimum reaction time was found to be 5-10 minutes.

ated to yield a pale yellow oil. Comparative t.l.c., using solvent C, showed a trace of starting material plus two new spots. The major and fast-moving spot corresponded to the diether IV, and the minor and slow-moving one corresponded to the monoether V. The crude material was dissolved in a minimum of benzene-ether (4:1), applied to a 4-g silica gel column, and eluted with benzene-ether (4:1). Fractions of 2-ml size were collected and inspected by t.l.c. The fractions containing compound IV were pooled, treated with activated charcoal, and yielded upon evaporation a nearly colorless oil. Crystallization from benzene-petroleum ether gave a product (17 mg, 55%) which melted at 79-80° and had an infrared spectrum identical to that of IV described under (a).

The minor product that was presumed to be the monoether V could not be isolated in pure form. The column yielded 5 mg of a yellow oil which, on t.l.c.,showed several spots, although the major one corresponded to V.

In two previous, similar experiments using 2 molar equivalents of sodium methoxide and reaction times of 1 hour, and 15 minutes, and in another experiment using 0.5 molar equivalents of sodium methoxide and a reaction time of 20 minutes, it was observed,

from t.l.c. and from the amount of crude material isolated, that an increase in reaction time and/or an increase in the amount of sodium methoxide favored the formation of by-products and consequently decreased the yield of the desired product.

Also, when compound III was refluxed in anhydrous methanol for various periods of time and with varying amounts of anhydrous sodium acetate, it was observed, by t.l.c., that extended reaction times produced complex mixtures of products. No pure product was isolated from these reactions.

c) The olefin X (45 mg, crude) was dissolved in anhydrous methanol (3 ml), 0.5 ml of a 0.1N solution of sodium methoxide added, and the solution stirred for 25 minutes at which time t.l.c. (solvent D) showed that all the olefin had reacted. The yellow reaction mixture was then neutralized with cation exchange resin, heated with activated charcoal, filtered, and evaporated to yield a yellow oil (43 mg). Comparative t.l.c. using a 20-cm chromatographic plate irrigated with solvent D produced four distinct spots, one of which corresponded to compound IV. Separation was not attempted, but peaks at 1555 cm^{-1}, 1385 cm^{-1}, and a broad peak at 1100 cm^{-1} in the infrared spectrum

of the crude material reaffirmed the presence of compound IV.

3(e)-Methoxy-2(e)-nitrocyclohexan-1(e)-ol (V)

a) A solution of the diol II (4.00 g) in anhydrous ether was treated with boron trifluoride etherate and an ethereal solution of the diazomethane produced from 50 g of N-nitrosomethyl urea as previously recorded, except the reaction vessel was cooled in an ice bath. After addition of the diazomethane solution, the reaction mixture was filtered, and the solvent was evaporated leaving a pale yellow oil which t.l.c. (solvent C) showed to be approximately a 5:5:1 mixture of compound II, compound V, and compound IV, respectively. Trituration of this oil with 200 ml of chloroform precipitated the unreacted, insoluble diol which was recovered as a white solid (1.50 g). The filtrate was evaporated and the operation repeated, giving another 40 mg of the diol. This filtrate was then evaporated, and the resulting, pale yellow oil (2.58 g) was taken up in a minimum of carbon tetrachloride-ethyl acetate (2:1) and applied

to a 260-g silica gel column. The column was eluted with solvent C, the fractions (15 ml) were monitored by t.l.c., and the appropriate fractions were pooled and evaporated. There was obtained 1.62 g of the desired monomethoxy compound V, 420 mg of the dimethoxy compound IV, and 190 mg of the starting diol II. The yield was 37% of the theoretical, and 65% if the recovered starting material is taken into account. Crystallization of V from carbon tetrachloride afforded colorless plates, m.p. 80-81.5°.

Anal. Calcd. for $C_7H_{13}NO_4$ (175.3): C, 47.99; H, 7.48; N, 8.00. Found: C, 47.83; H, 7.59; N, 7.86.

Infrared frequencies (cm^{-1}): 3440s (OH); 1550s (asymmetric NO_2); 1385ms,sh (symmetric NO_2); 1060s (C-O); 1345m; 1300-1100w[b]; 1090m,sh; 1080ms,sh; 1000-800m[b]; 735ms.

The n.m.r. spectrum is shown in Fig. 9.

b) In the previously described reaction of compound III with sodium methoxide, it was observed by t.l.c. that the minor product was compound V. Separation of the products by column chromatography gave approximately a 10% yield of this compound as an oil.

3(e)-Methoxy-2(e)-nitrocyclohexan-1(e)-ol Acetate (VI)

Compound V (350 mg) was dissolved in 6 ml of acetic anhydride, 8 drops of boron trifluoride etherate were added, and the solution was stirred at room temperature for 40 minutes. The reaction mixture was poured slowly into 350 ml of ice-water, with vigorous stirring. The resulting white precipitate and the aqueous solution were then extracted with ether (4x100 ml), and the combined extracts were dried over anhydrous magnesium sulphate. Removal of the solvent gave a pale green liquid from which three portions of added toluene were evaporated. The liquid was then taken up in ethanol and treated with activated charcoal. Evaporation of the filtered ethanolic solution yielded a colorless oil which crystallized on cooling. Recrystallization from carbon tetrachloride-petroleum ether afforded 390 mg (90%) of white plates exhibiting m.p. 92-93°.

Anal. Calcd. for $C_9H_{15}NO_5$ (217.4): C, 49.76; H, 6.96; N, 6.45. Found: C, 49.73; H, 7.04; N, 6.47.

Infrared frequencies (cm^{-1}): 2860s (C-H); 1740s (C=O); 1550s (asymmetric NO_2); 1235s (C-O); 1040s (C-O); 1350ms,sh; 1290w; 1200ms; 1150w; 1100ms; 1000-800w[b]; 755ms.

The n.m.r. spectrum is shown in Fig. 10.

1(e),3(e)-Dibenzoxy-2(e)-nitrocyclohexane (VII)

A solution of compound III (70 mg) in 5 ml of anhydrous tetrahydrofuran was stirred at room temperature, and 0.60 ml of a 2N solution of sodium benzoxide in benzyl alcohol (4 molar equivalents) was added drop by drop. A white precipitate was produced immediately. Stirring was continued for 8 minutes after which time carbon dioxide was passed through the reaction mixture for half an hour. The gelatinous reaction mixture was then taken up in 20 ml of ethyl acetate, the solution was treated with activated charcoal, and the solvent was evaporated yielding 500 mg of a pale yellow oil that smelled of benzyl alcohol. Comparative t.l.c. using solvent A showed two major spots (of which the slower one corresponded to benzyl alcohol), and two more slowly moving, minor spots. No starting material remained. The crude product was then taken up in a minimum of benzene and applied to a 50-g silica gel column which was eluted with benzene-ether (4:1), 10-ml fractions being collected. All fractions were examined by t.l.c. A single fraction showing only the fast spot of VII was obtained and yielded, on treatment and evaporation, 12 mg (12%) of VII as a colorless oil. The remaining

fractions containing chiefly VII yielded 40 mg (41%) of slightly impure product. Crystallization could not be achieved.

Infrared frequencies (cm^{-1}) of pure VII (neat): 3100-3000w[b] (C-H); 2940ms (C-H); 2860ms (C-H); 2000-1650w[b] (benzene ring summation bands); 1600w (C=C); 1550s (asymmetric NO_2); 1490w (C=C); 1450m (C=C); 1360s (symmetric NO_2); 1090s,bd (2xC-O); 730s (C-H); 690s (C-H); 1515w,sh; 1340ms,sh; 1300w; 1230w; 1200m; 1165w; 1025ms; 1000-800w[b]. The infrared spectrum is shown in Fig. 11.

The n.m.r. spectrum in deuterated chloroform with TMS as lock signal is shown in Fig. 12.

Crude products obtained in preliminary experiments using tetrahydrofuran as the reaction medium, reaction times of 5 to 30 minutes, and 0.66-2.00 molar equivalents of sodium benzoxide gave infrared spectra which suggested that the predominant products were the acetoxy olefin IX and the benzoxy olefin. It therefore appears that an excess of benzoxide is required to drive the reaction to completion.

In two subsequent experiments using 1,4-dioxan as the reaction medium, reaction times of 7 and 30 minutes, and 1.6 and 2.0 molar equivalents of the sodium salt respectively, the olefins were also the predominant products.

Attempted Synthesis of 1(e), 3(e)-Diisopropoxy-2(e)-nitrocyclohexane (VIII)

To a solution of compound III (245 mg) in 50 ml of benzene[1] was added dropwise, with stirring at room temperature, a suspension of sodium isopropoxide (164 mg; 2 molar equivalents) in 20 ml of benzene, and stirring continued for 1 hour, during which time a flocculent white precipitate was formed. The reaction mixture was then treated with 5 ml of cation exchange resin, and the solvent was evaporated leaving a pale yellow oil which t.l.c. (solvent C) showed to be a mixture of components: two major ones, of which [1] corresponded to the starting material, and some slightly faster moving minor ones. Column chromatography using carbon tetrachloride-ethyl acetate (3:1) as eluent gave 42 mg of the major component which had infrared and n.m.r. spectra identical to those of the olefin IX. No other pure product was isolated.

Two similar experiments were performed using tetrahydrofuran as the solvent and reaction times of 2 and 24 hours. The major product in the first case was the olefin, and in the latter, a mixture of unidenti-

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1. Dried over and distilled from sodium wire.

fiable products was obtained.

Use of isopropyl alcohol as the reaction medium, and 4 molar equivalents of sodium resulted in degradation of the starting material in the course of 3 hours, giving a trace of the acetoxy olefin, but no VIII could be detected.

3-Acetoxy-2-nitrocyclohexene (IX)

Compound III (1.01 g) and anhydrous sodium bicarbonate[1] (6.8 g; 20 molar equivalents) were refluxed with magnetic stirring in 40 ml of 1,4-dioxane[2] for 2½ hours. The reaction mixture, which turned pale yellow, was then cooled to room temperature and filtered. The filtered residue was washed with dioxane and evaporation of the filtrate gave a yellow oil which t.l.c. (solvent E) showed to be a mixture of two major components (of which one was starting material) and several faster moving minor ones. The crude product was taken up in a minimum of carbon tetrachloride and applied to a 70-g silica gel column which was eluted with

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1. Oven-dried at 120° for 1 day.

2. Refluxed over and fractionally distilled from sodium wire.

solvent E. The fractions (10 ml) were monitored by t.l.c. and appropriately pooled to give 350 mg of oily compound IX and 300 mg of unreacted starting material. The yield was 46% of the theoretical, or 65% taking into account the recovered starting material. Crystallization of IX from benzene-petroleum ether afforded buff colored crystals, m.p. 65-66°.

Anal. Calcd. for $C_8H_{11}NO_4$ (185.2): C, 51.88; H, 5.99; N, 7.56. Found: C, 52.03; H, 5.79; N, 7.50.

Infrared frequencies (cm^{-1}) recorded with the neat oil: 3000-2800w[b] (C-H); 1730s (C=O); 1660m (C=C); 1515s (asymmetric NO_2); 1340s (symmetric NO_2); 1225s (C-O); 820m (C-H); 1430w; 1410w; 1365ms,sh; 1155m; 1005m; 1000-900m[b].

The n.m.r. spectrum is shown in Fig. 13.

3-Methoxy-2-nitrocyclohexene (X)

a) Olefin IX (47 mg) was dissolved in 4 ml of anhydrous methanol and refluxed for 12 hours, at which time t.l.c. using solvent D showed only one spot, slightly faster moving than the starting olefin. The solvent was then evaporated giving in quantitative

yield compound X as a colorless oil. Crystals, obtained when the oil was cooled to -10°, melted at room temperature.

Anal. Calcd. for $C_7H_{11}NO_3$ (157.3): C, 53.49; H, 7.05; N, 8.91. Found: C, 53.64; H, 7.23; N, 8.71.

Infrared frequencies (cm^{-1}) (neat oil): 2940s (C-H); 2825ms (C-H); 1670m (C=C); 1515s (asymmetric NO_2); 1450m (C-H); 1340s (symmetric NO_2); 1090s (C-O); 1070s (C-O); 830m (C-H); 1420w,sh; 1190m; 950ms; 930m; 740m; 730m.

The n.m.r. spectrum is shown in Fig. 15.

b) In an experiment similar to that for the preparation of IX, compound VI (217 mg) and anhydrous sodium bicarbonate (3.34 g; 40 molar equivalents) were refluxed with magnetic stirring in 15 ml of dry benzene[1] for 10 hours, at which time the reaction mixture was yellow. The cooled and filtered solution was evaporated yielding a yellow oil. Crystallization from carbon tetrachloride-petroleum ether returned 110 mg of starting material. Comparative t.l.c. of the mother liquor showed two major spots, one of which corresponded to

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1. Dried over and distilled from sodium wire.

the starting material. The mother liquor was then applied to a 10-g silica gel column which was eluted with carbon tetrachloride-ethyl acetate (6:1), 2-3-ml fractions being taken. The appropriate fractions were bulked giving 35 mg of compound X and returning another 20 mg of starting material. Based on recovered starting material, the yield was 56%.

c) Compound V (183 mg) and basic anhydrous aluminum oxide[1] (365 mg, 3.4 molar equivalents) were stirred in 15 ml of sodium-dried toluene at 70-75° for 1½ hours[2]. The pale yellow reaction mixture was then treated with activated charcoal, filtered, and evaporated to give 115 mg of a brown oil which, according to t.l.c. using solvent E, contained the methoxy olefin as the major component. This material was applied to a 15-g silica gel column and eluted with solvent E taking 2-ml fractions. Appropriate fractions were pooled and evaporated yielding 69 mg (42%) of a pale yellow oil which gave

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1. Shawinigan Chemicals

2. Preliminary small-scale experiments had shown this to be the optimum reaction time. Extended times degraded the olefin and produced a complex mixture of products.

an infrared spectrum identical to that of compound X as described under (a).

3-Ethoxy-2-nitrocyclohexene (XI)

Olefin IX (90 mg) was dissolved in 5 ml of 99% ethanol and refluxed for 15 hours, at which time t.l.c. (solvent D) showed essentially one spot. Evaporation of the solvent gave compound XI as a very pale yellow oil in quantitative yield.

Anal. Calcd. for $C_8H_{13}NO_3$ (171.2): C, 56.12; H, 7.65; N, 8.18. Found: C, 56.06; H, 7.57: N, 8.32.

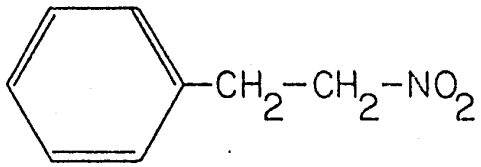
Infrared frequencies (cm^{-1}) (neat oil): 3000-2800ms[b] (C-H); 1665m (C=C); 1510s (asymmetric NO_2); 1440m (C-H); 1340s (symmetric NO_2); 1090s (C-O); 1070s (C-O); 825m (C-H); 1415w; 1165m; 995m; 960m; 930m; 740m; 730m.

PART II

SYNTHESIS OF MISEROTOXIN

INTRODUCTION*

The number of aliphatic nitro compounds presently known to occur in nature is small. One of the first to be discovered was phenylnitroethane,



which was isolated from the wood and bark of the Brazilian plants Aniba canellita and Ocotea pretiosa (59). A second, naturally occurring aliphatic nitro compound was identified as β-nitropropionic acid by Carter in 1949 (12). He isolated it by hydrolysis of the compounds hiptagin (11,60) and karakin (61) which are glucose esters of this acid.

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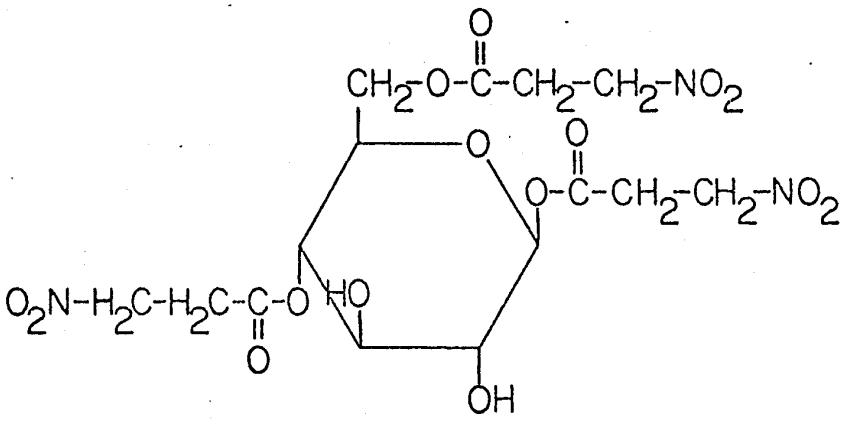
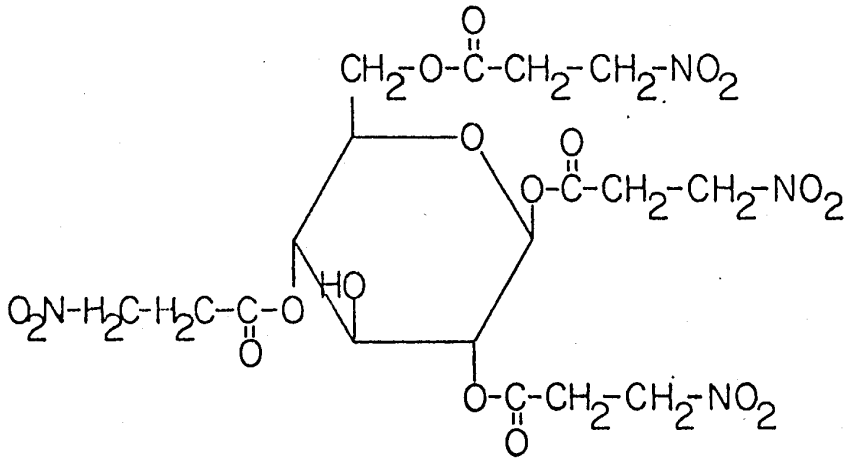
* For convenience, a new set of Roman numerals is used in the following sections.



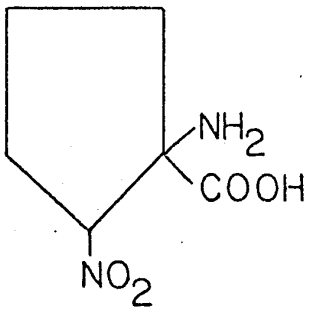
Karakin



Hiptagin

In their work on the toxic extract of Indigofera endecaphylla, a tropical legume which produces acute toxic symtoms in cattle and other animals, Finnegan and Mueller (62,63) have isolated 3-nitropropanoic acid, ethyl 3-nitropropanoate and a series of nine 3-nitropropanoate esters of glucose. Six of these endecaphyllins they have proposed to be isomeric triesters and three, diesters. Another compound isolated from the crude ex-

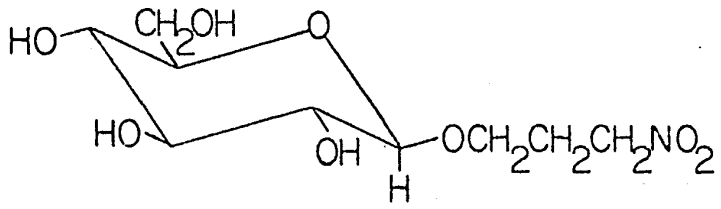
tract is said to be a glucose tetra-3-nitropropanoate. In that same year, Burrows et al. (64) reported the isolation of 1-amino-2-nitrocyclopentanecarboxylic acid (I), a metabolite of Aspergillus wentii.



I

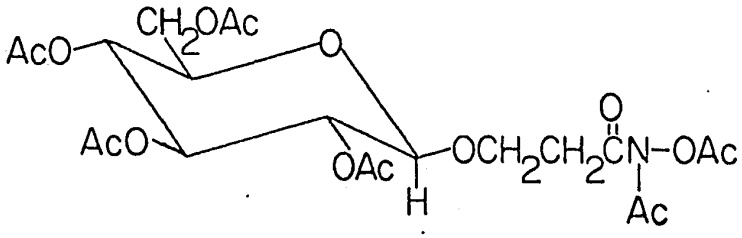
The next aliphatic nitro compound to be reported was isolated from the above-ground parts of a species of timber milkvetch (Astragalus miser) by Stermitz and co-workers (65) in 1968. This poisonous plant occurs throughout the Rocky Mountains and northern states and has been responsible for moderate to severe livestock losses. However, the toxicity has been confined to the extreme northern and southern range of the species while other growths of milkvetch seem to be harmless (66). The fatal dose of this plant has been tested and found to be as low as 1×10^{-3} pounds per pound of body weight in cattle and 3×10^{-4} grams per gram of body weight in chickens (67). Stermitz has characterized the poisonous ingredient of these plants to be the β-D-glucopyranoside

of 3-nitro-1-propanol (II) which he named miserotoxin (68).



II

He reported that pure miserotoxin was an extremely hygroscopic pale yellow glass. The structure was based upon data obtained by n.m.r., infrared, and high resolution mass spectrometry. It was also reported that treatment of miserotoxin with acetic anhydride and sodium acetate produced in high yield a hexaacetyl derivative, rather than the expected tetraacetate, and the structure III was assigned to this derivative.



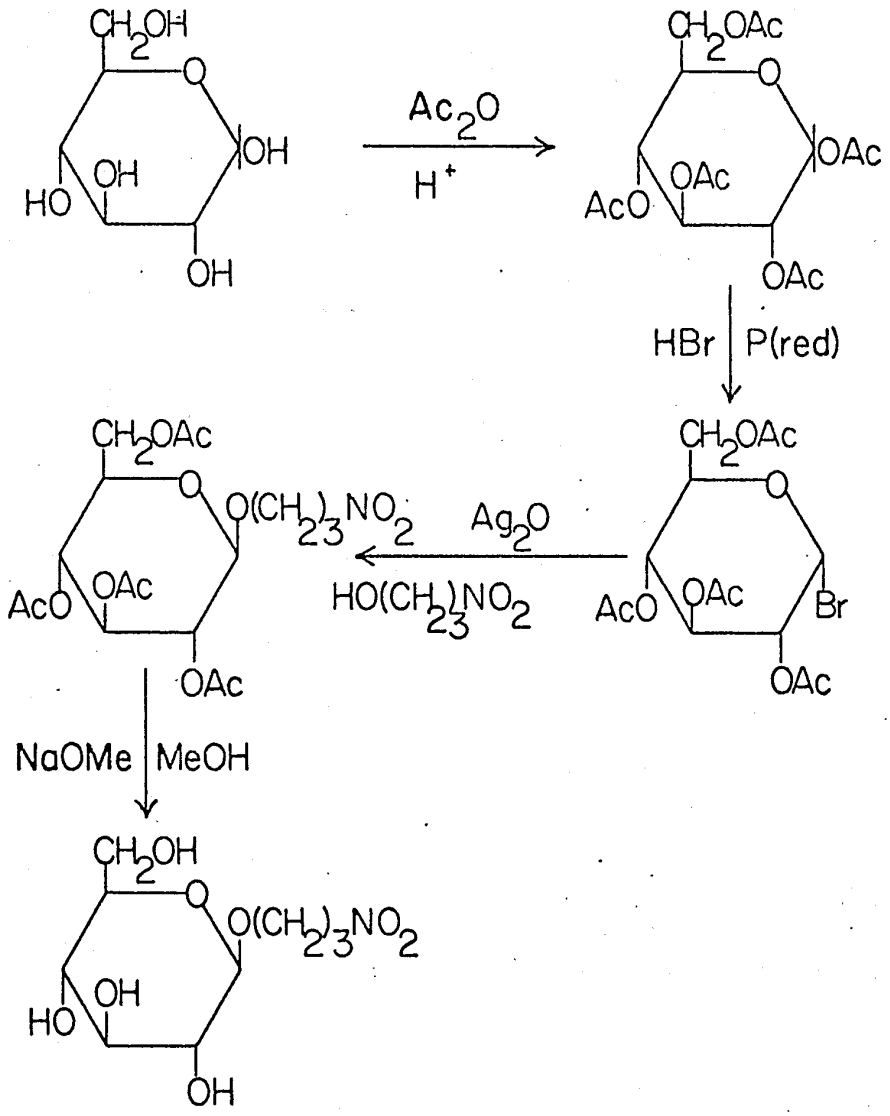
III

The synthesis of miserotoxin was undertaken as part of this thesis. The compound was obtained by a Koenigs-Knorr condensation between 3-nitro-1-propanol

and tetra-O-acetyl-α-D-glucopyranosyl bromide, followed by deacetylation of the condensation product.

RESULTS AND DISCUSSION

The sequence of reactions employed for the synthesis of miserotoxin is shown below.



A 3-Nitro-1-Propanol (IV)

3-Nitro-1-propanol was prepared by the Victor Meyer reaction from 3-bromo-1-propanol with silver nitrite in anhydrous ether at room temperature (69). The infrared spectrum of the pure product, b.p. 135-145° (18 mm), showed an OH absorption at 3300 cm^{-1} and nitro absorptions at 1545 cm^{-1} and 1380 cm^{-1}. The n.m.r. spectrum taken in deuterochloroform with TMS as reference is shown in Fig. 16.

B 3-Nitropropyl 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranoside (VI)

Tetra-O-acetyl-α-D-glucopyranosyl bromide V was prepared in 84% yield by the method described by Lemieux (70), which involves acetylation of glucose and treatment of the product with bromine and red phosphorus. The n.m.r. spectrum taken in deuterochloroform is shown in Fig. 17. The low field doublet centred at τ 3.40 was assigned to the anomeric proton. Generally, the anomeric proton is at lower field than other ring-hydrogen atoms since it is deshielded by the ring oxygen and, in many cases, by another electron withdrawing substituent on C-1 (71,72). The coupling constant of J=4 c.p.s. shows

that the anomeric proton is in an equatorial disposition. This value agrees with the value given by Lemieux (J=4 c.p.s.) for the anomeric proton in tetra-O-acetyl α-D-glucopyranosyl chloride (73). The conformation of the acetoxy substituents is confirmed by their chemical shift: τ 7.91 (6H); 7.96 (3H); 7.98 (3H). These values lie in the range expected for equatorial acetoxy groups (72).

The condensation of the bromo sugar with 3-nitro-1-propanol (Koenigs-Knorr reaction (74,75)), to give 3-nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside, was performed by stirring the reactants with freshly prepared silver oxide (76) in dry, ethanol-free chloroform at room temperature for 3 hours. The desired product was obtained in 46% yield. The crystalline product exhibited m.p. 116°, and elemental analysis verified the molecular formula as $C_{17}H_{25}NO_{12}$ (M.W. 435). The infrared spectrum showed carbonyl absorption at 1750 cm^{-1} and nitro absorption at 1550 cm^{-1}. The β-configuration of the glycosidic bond was anticipated from the well-established fact that the Koenigs-Knorr reaction proceeds with inversion of configuration (77). The low specific rotation of the product ($[\alpha]_D$-4.8° (c 0.5, chloroform)) confirmed this, and additional support was derived from the n.m.r. spectrum.

The n.m.r. spectrum taken in deuterochloroform with TMS as lock signal is shown in Fig. 18a,b . At lowest field (τ 4.6-5.1), there is a group of overlapping signals corresponding to three protons, which are assigned to H-2, H-3, and H-4. Because of the presence of acetoxy substituents in these positions, these ring protons resonate at low field. The signal for the anomeric proton, expected to be a doublet in the τ 5-region (72), is not clearly resolved but is overlapped by the signal due to the nitromethylene moiety of the aglycon. The nitromethylene protons produce a symmetrical triplet centred at τ 5.54 (J =6.5 c.p.s.), and the anomeric proton gives a doublet (τ 5.51) the lowfield peak of which coincides with the lowfield peak of that triplet (thus increasing its intensity), and the other peak is seen as a shoulder (or as a separate peak in the expanded spectrum) slightly upfield to the centre peak of the triplet. The coupling constant of the anomeric proton (J=7.9 c.p.s.) is indicative of 1,2-trans diaxial proton arrangement as required for a β -D-glucopyranoside (72). The group of signals from τ 5.65-5.97 corresponding to two protons is assigned to the C-6 methylene group, and the one-proton quintet following upfield is attributed to H-5 (centred at τ 6.02).

Fig. 16

N.M.R. spectrum of 3-nitro-1-propanol (IV) in deutero-chloroform

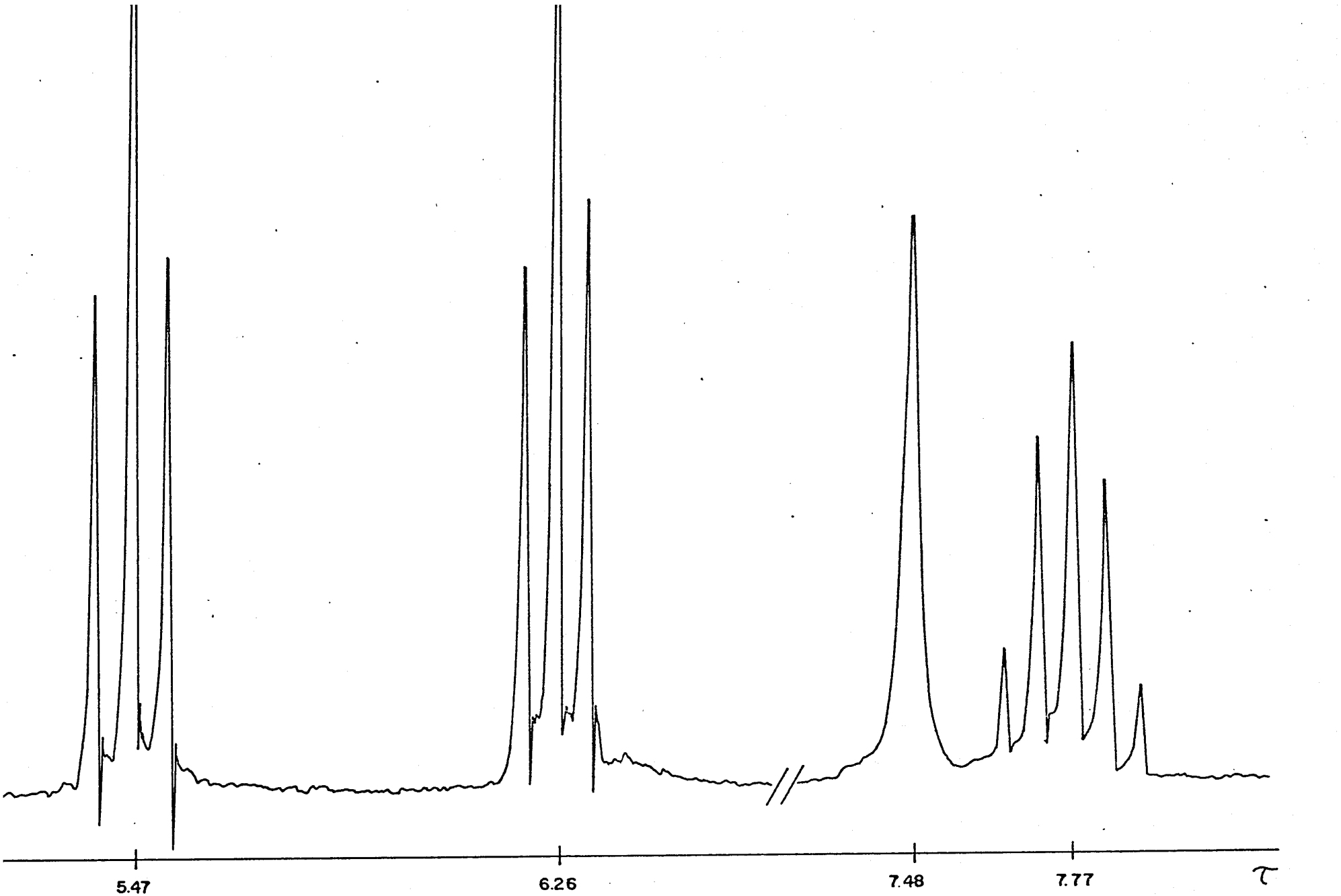

5.47
6.26
7.48
7.77
τ

Fig. 17

N.M.R. spectrum of tetra-O-acetyl-α-D-glucopyranosyl bromide (V) in deuterochloroform

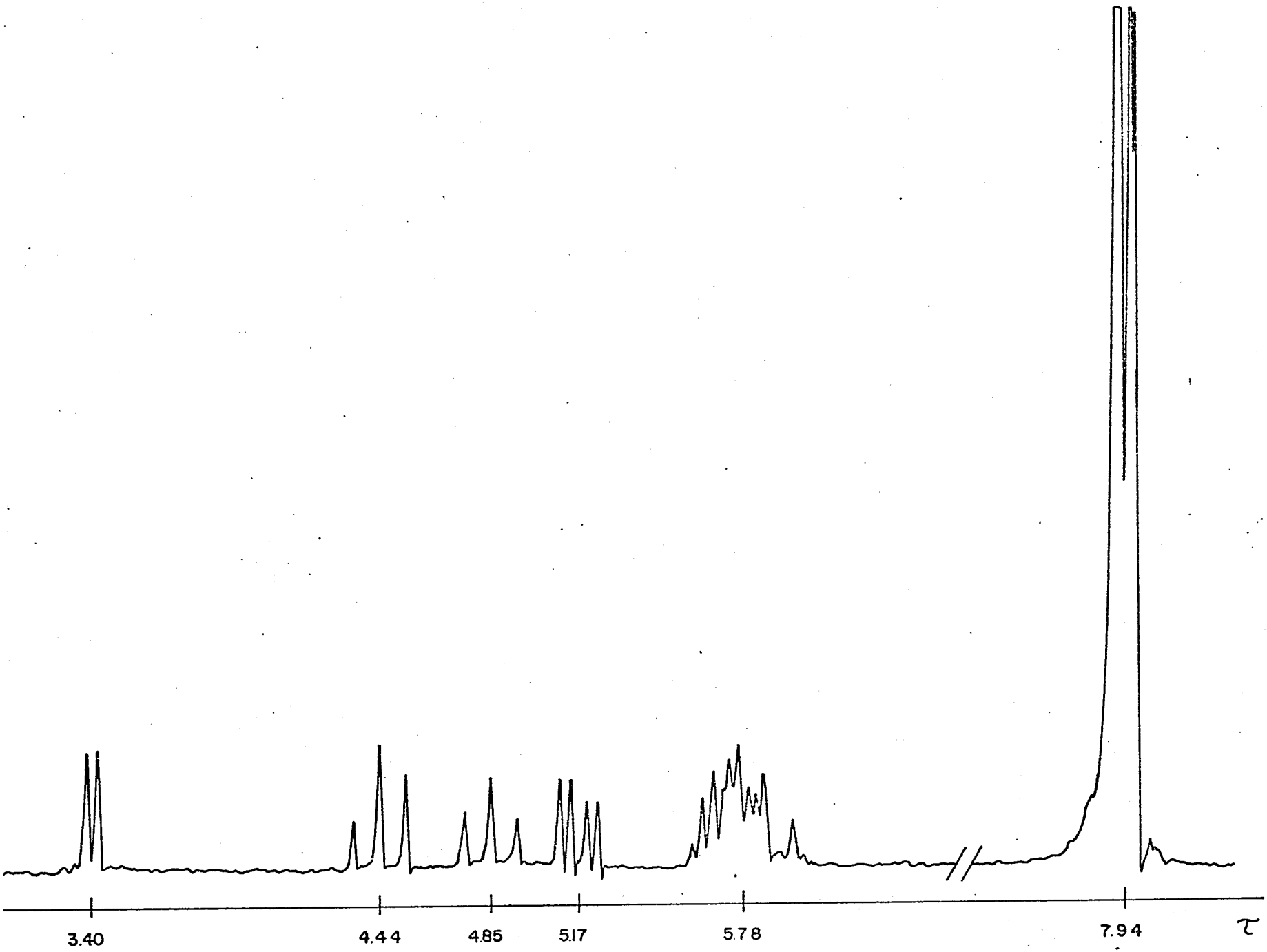
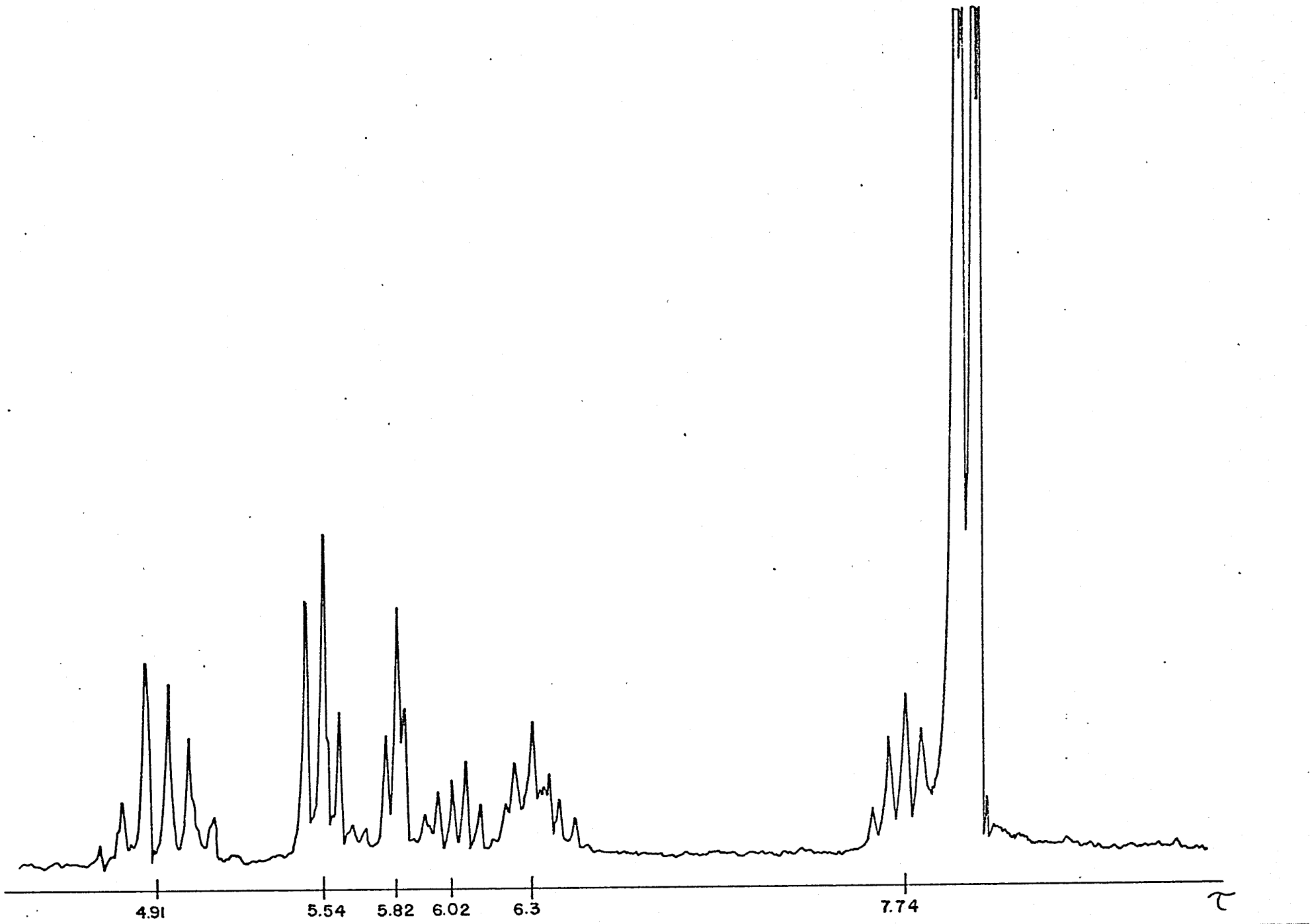
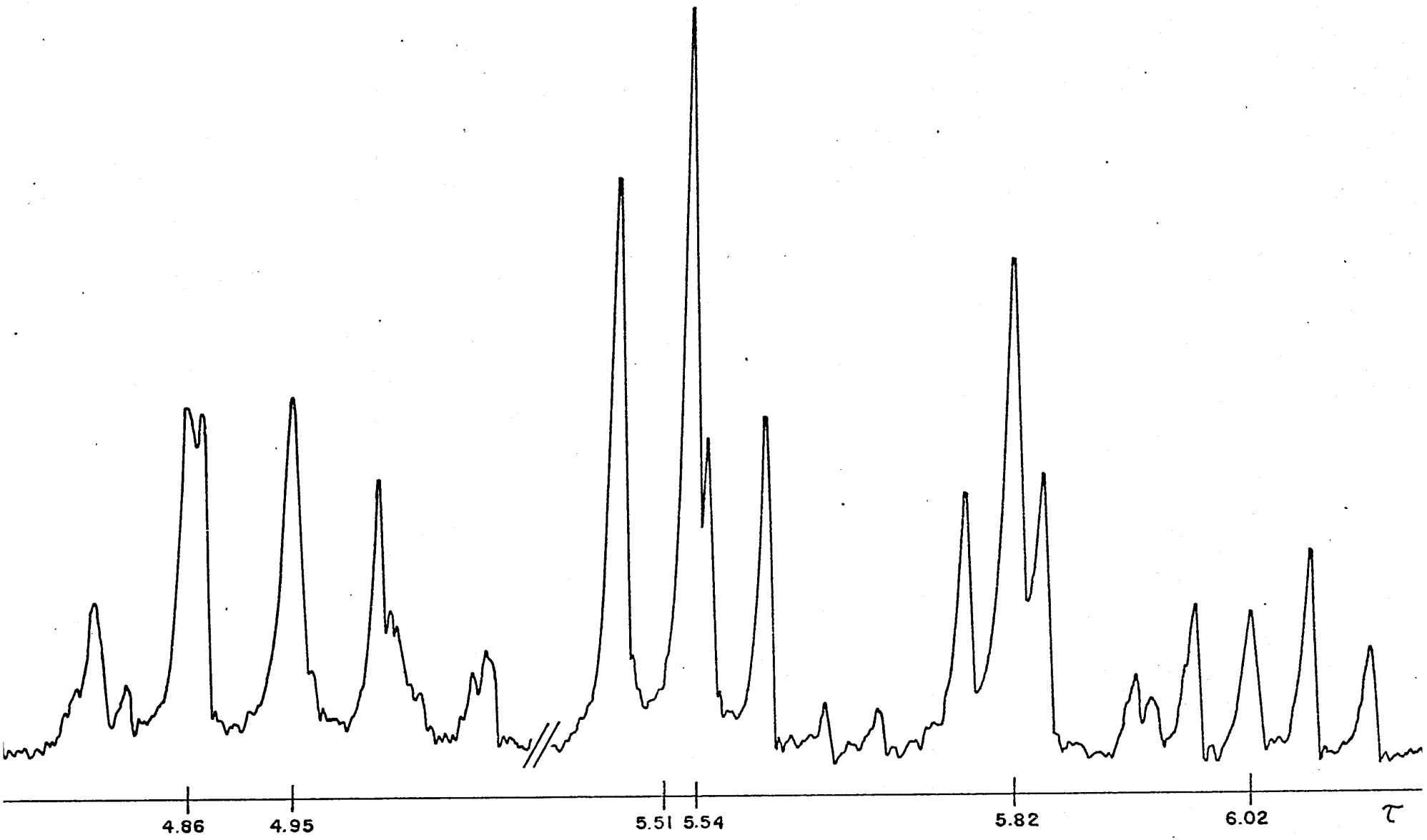

3.40
4.44
4.85
5.17
5.78
7.94
τ

Fig. 18

a. N.M.R. spectrum of 3-nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (VI) in deuterochloroform

b. Expanded spectrum of VI


4.91
5.54
5.82
6.02
6.3
7.74
τ


4.86
4.95
5.51
5.54
5.82
6.02
τ

Further upfield, there are two multiplets, each corresponding in intensity to two protons, which belong to the nitropropyl group. The one at τ 6.3 is due to the methylene group adjacent to the glycosidic oxygen, and the one at τ 7.74 (partly overlapped by acetoxy signals) represents the central methylene group. The acetoxy signals at 7.92 (3H), 7.94 (3H), 7.99 (3H), and 8.01 (3H) are indicative of equatorially oriented acetoxy groups (72). Thus, the spectrum is in good agreement with the structure expected to arise in the Koenigs-Knorr condensation described.

C 3-Nitropropyl β-D-Glucopyranoside (Miserotoxin)

3-Nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside was deacetylated by stirring in a methanolic solution of sodium methoxide for 5 hours. The pale yellow gel obtained after chromatographic purification gave an elemental analysis which corresponded to the formula $C_9H_{17}NO_8$ (M.W. 267). The optical rotation was $[\alpha]_D$ -24.0° (c 2.0, water). The infrared spectrum showed a broad OH absorption centred at 3350 cm^{-1} and typical nitroalkane absorptions at 1545 cm^{-1} and 1380 cm^{-1}. Stermitz and co-workers (68)

listed an optical rotation of $[\alpha]_D$-22.0° (c 2.0, water) for their natural product, and recorded infrared absorptions of 1380 cm^{-1} and 1520 cm^{-1} for the nitro group. Presumably, the latter value was in error as it is too low for a nitroalkane vibration (78).

The n.m.r. spectrum taken in deuterated acetone with TMS as internal standard (Fig. 19) showed, at lowest field, a two-proton triplet (J=6.9 c.p.s. at τ 5.35) which was assigned to the nitromethylene group, and at highfield, a two-proton quintet centred at τ 7.73, which was assigned to the central methylene group, in the aglycon. The anomeric proton signal expected at τ 5.5-5.6 was buried by other signals, presumably those for hydroxyl protons. There were other signals between τ 5.9 and τ 7.7 which could not be resolved but whose integration approximately equalled ten protons.

After the addition of deuterium oxide, the lowfield triplet appeared at τ 5.32 (2H). The anomeric doublet (1H, J=7.6 c.p.s.) appeared, partially overlapped by the HDO signal, at τ 5.60 (Fig. 20). (When the HDO peak was displaced by the addition of DCl, the anomeric doublet (J=7.5 c.p.s.) appeared at τ 5.56). The highfield quintet appeared at τ 7.68.

Fig. 19

N.M.R. spectrum of 3-nitropropyl β-D-glucopyranoside (miserotoxin) (II) in deuterated acetone

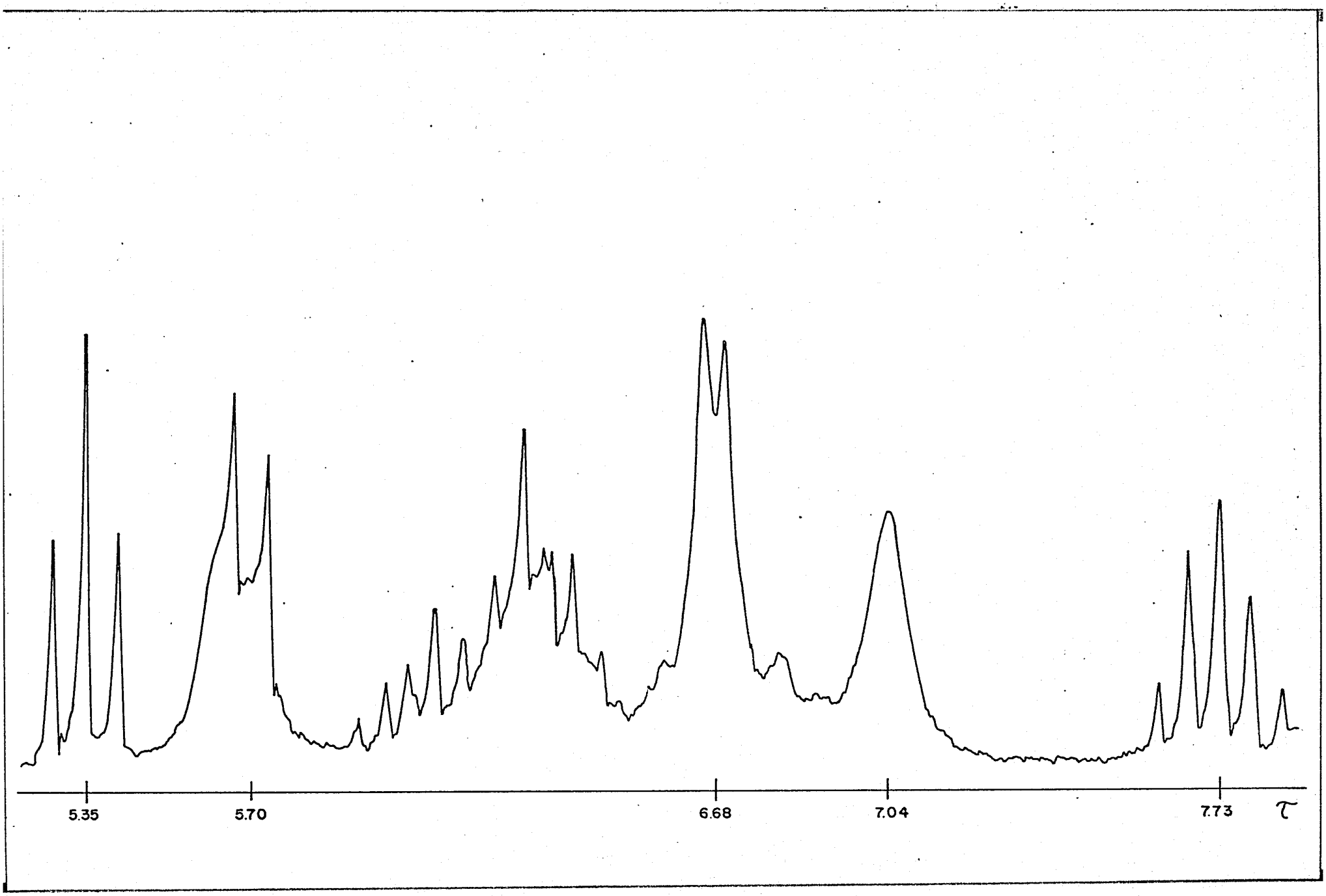
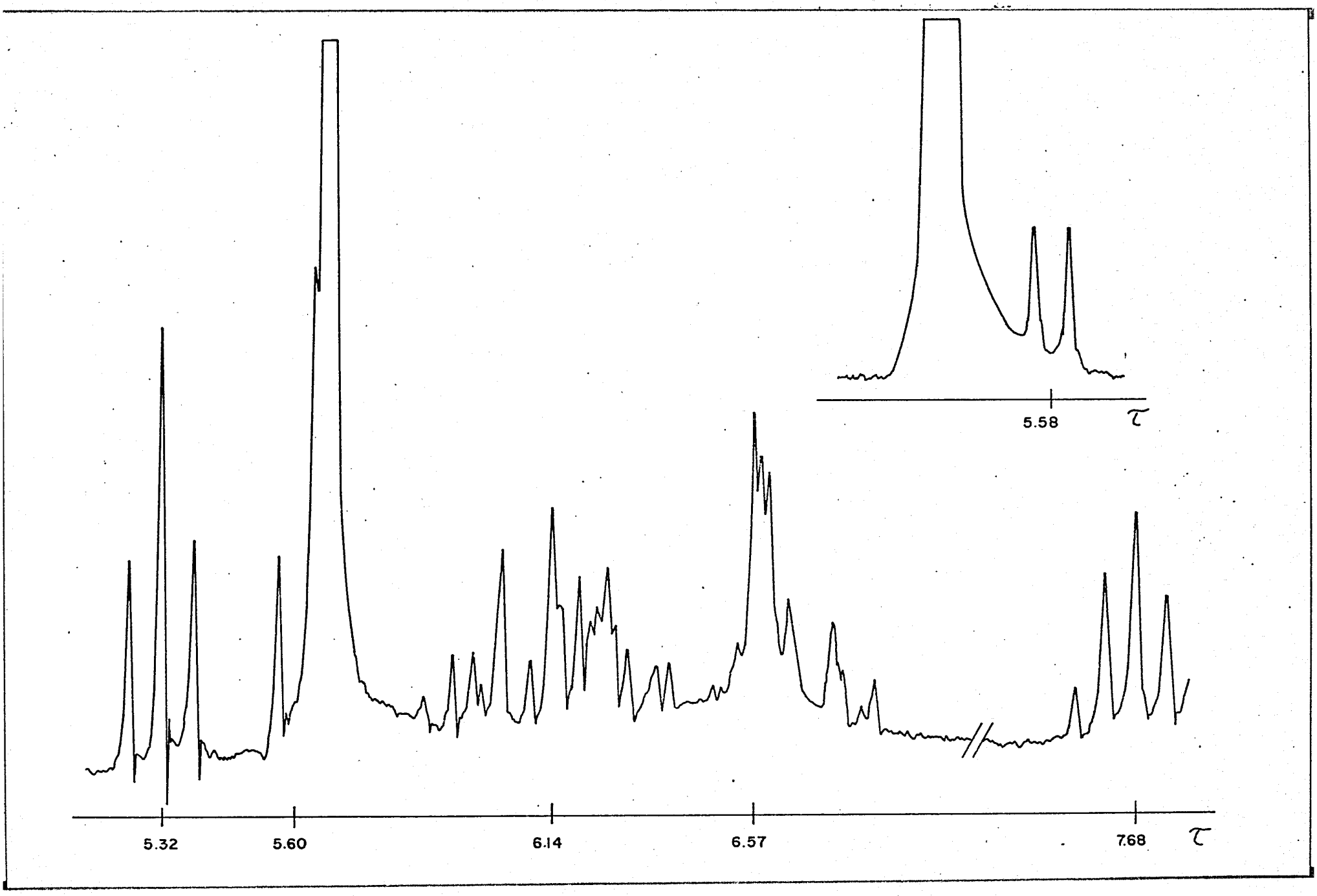
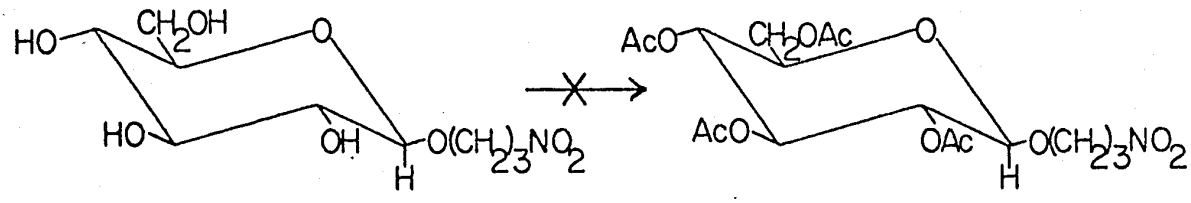

5.35
5.70
6.68
7.04
7.73
τ

Fig. 20

N.M.R. spectrum of miserotoxin (II) in deuterated acetone with deuterium oxide added. (Insert shows the signal for the anomeric proton after addition of DCl.)

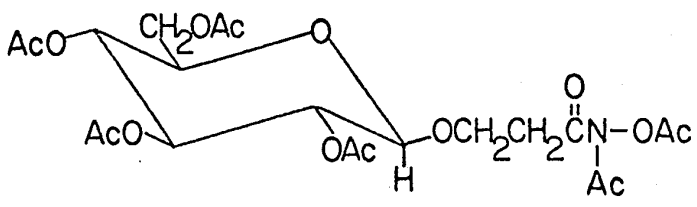

5.58
τ
5.32
5.60
6.14
6.57
7.68
τ

The only other absorptions were in the τ 5.8-6.9 range and these were not successfully analyzed. Stermitz reported that the 60-MHz n.m.r. spectrum (in D_2O with added DCl to displace the HDO peak) of the natural product showed: a triplet (2H, J=6 c.p.s.) assigned to the nitromethylene group, at τ 5.32; the anomeric doublet (1H, J=7.5 c.p.s.) at τ 5.49; and a highfield quintet (2H, J=6 c.p.s.), centred at τ 7.66. He reported other unresolved signals in the τ 5.8-7.0 range. In order to characterize their natural product, Stermitz and co-workers attempted to prepare the tetraacetate by treatment with acetic anhydride and sodium acetate but obtained, instead, a hexaacetyl derivative for which they suggested formula III.



II

VI



III

No specific reaction conditions were given for this acetylation, and when it was tried with synthetic miserotoxin by heating the mixture on a steam bath, the desired product was not obtained.

A sample (1 g) of synthetic 3-nitropropyl β-D-glucopyranoside was submitted to the Department of Agriculture for toxicity testing[1]. The testing was done on one-week-old chickens, using four birds for testing and four birds as a control. Aqueous doses corresponding to approximately 5 mg of miserotoxin per gram of body weight were administered. This dosage produced the symtoms associated with miserotoxin poisoning (lethargy, incoordination, and rapid heartbeat), and the birds died within ten hours. The control birds, which were given pure water, remained normal. Toxicity tests (done in duplicate) using the plant extract were performed by Williams and Norris (66) who found that dosages corresponding to 100 mg of plant material per gram of body weight were fatal to one-week-old chickens. The plants contained 3.2% miserotoxin.

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1. This work was done by Dr. K. R. Pastro of the Animal Research Institute, Ottawa.

In view of the microanalysis, the physical data, and the results of the toxicity tests, it is proposed that the synthetic 3-nitropropyl β-D-glucopyranoside corresponds to the naturally occurring compound.

EXPERIMENTAL

3-Nitro-1-Propanol (IV)

3-Bromo-1-propanol[1] (10.0 g) and 2.0 g of powdered, freshly activated Drierite were stirred in 30 ml of anhydrous ether at room temperature for half an hour. The reaction vessel was then wrapped in aluminum foil to exclude light, 15.0 g of silver nitrite was added in small portions over half an hour, and stirring was continued for 12 hours. The reaction mixture was then filtered through sintered glass, the residue washed with ether, and the combined filtrate and washings were evaporated giving 8.5 g of a pale yellow liquid. This material was then fractionally distilled at 18 mm on the water aspirator, and the desired product distilled over between 135° and 145° (Lit. (69) b.p. 60-63° (0.8 mm)). The total yield of colorless oil (IV) was 5.4 g (71%).

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1. Distilled from the commericial product supplied by Eastman Kodak.

Infrared frequencies (cm^{-1}): 3300s,bd (OH); 2800-3000ms[b] (C-H); 1545s (asymmetric NO_2); 1430ms (C-H); 1380s (symmetric NO_2); 1050s (C-O); 950w.

The n.m.r. spectrum is shown in Fig. 16.

3-Nitropropyl 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranoside (VI)

Anhydrous D-glucose (50 g) was reacted with acetic anhydride, hydrogen bromide and red phosphorus according to the method described by Lemieux (70), giving 96 g (84%) of tetra-O-acetyl-α-D-glucopyranosyl bromide (V). Recrystallization from diethyl ether afforded colorless needles, m.p. 88-89°, $[\alpha]_D$+198° (c 2, chloroform).

The nitro propanol IV (1.65 g), Drierite[1] (8.3 g), and freshly prepared silver oxide (7.00 g) (76) were stirred in 50 ml of pure, ethanol-free chloroform[2] for half an hour under nitrogen in a three-

1. Powdered and dried in the oven at 120° for 1 day.

2. A. I. Vogel, Practical Organic Chemistry, 3rd Ed., Longmans, Green, and Co. Ltd., London, p 176, 1962.

necked flask equipped with a condenser and separatory funnel, and protected from light. A solution of acetobromoglucose (V) (5.84 g) in 30 ml of pure chloroform was then added dropwise over 2 hours to the stirred reaction mixture and stirring continued for another hour until all of compound V had reacted. The reaction mixture was filtered through sintered glass, the residue and reaction vessel were washed with chloroform, washings and filtrate combined, and the solvent was evaporated to yield 7.10 g of a pale yellow oil. Comparative t.l.c. with solvent C showed two major spots of which the slower moving corresponded to that of an authentic sample of 2,3,4,6-tetra-O-acetyl-β-D-glucose, i.e., the hydrolysis product of acetobromoglucose. Several minor spots were also evident. The oil was applied to a 500-g silica gel column and eluted with carbon tetrachloride-ethyl acetate (7:4), 18-ml fractions being taken. The appropriate fractions were combined and gave, on evaporation, 2.86 g (46%) of virtually pure compound VI as a colorless gel. Crystallization from ethanol afforded beautiful colorless leaflets, m.p. 116°, $[\alpha]_D$-4.8° (c 0.5, chloroform).

Anal. Calcd. for $C_{17}H_{25}NO_{12}$ (435.1): C, 46.89; H, 5.79; N, 3.22. Found: C, 46.77; H, 5.93; N, 3.12.

Infrared frequencies (cm^{-1}): 2865s (C-H); 1750s,bd (C=O); 1550s (asymmetric NO_2); 1450s,sh (C-H); 1225s,bd (C-O); 1060s,bd (C-O); 1035s,bd (C-O); 1160w; 1095w,sh; 1000-600w[b].

The n.m.r. spectrum is shown in Figs. 18a,b.

3-Nitropropyl β-D-Glucopyranoside (Miserotoxin)(II)

To a stirred solution of 1.63 g of compound VI in 25 ml of anhydrous methanol was added 10 ml of a 0.1N solution of sodium methoxide (0.28 molar equivalents) and stirring continued at room temperature for 5 hours. The reaction mixture was then treated with cation exchange resin until the solution was slightly acidic to pH paper. Filtration and evaporation gave a pale yellow gel (1.10 g). Comparative t.l.c. with solvent F showed one major spot and a more slowly moving minor one. Separation of the components on a 100-g silica gel column using solvent F as eluent gave 900 mg (90%) of a very pale yellow gel. Crystallization of this gel could not be achieved.

$[\alpha]_D$-24.0° (c 2.0, water).

Anal. Calcd. for $C_9H_{17}NO_8$ (267.2): C, 40.45; H, 6.41; N, 5.24. Found: C, 40.50; H, 6.47; N, 5.25.

Infrared frequencies (cm^{-1}) (neat gel): 3350s,bd (OH); 2880ms,bd (C-H); 1545s (asymmetric NO_2); 1380s (symmetric NO_2); 1350s,sh (O-H); 1160ms (C-O); 1050s,bd (C-O); 1425ms; 890w.

The n.m.r. spectrum is shown in Figs. 19 and 20.

REFERENCES

1. Z. Eckstein, E. Grochowski, R. Kowalik, and T. Urbański, Bull. Acad. Polon. Sci., Ser. sci. chim., 11, 687 (1963).
2. S. Byrdy, Z. Eckstein, and J. Plenkiewicz, Bull. Acad. Polon. Sci., Ser. sci. chim., 9, 627 (1961).
3. Z. Eckstein, T. Urbański, and J. Mikulski, Roczniki Chem., 33, 519 (1959).
4. E. B. Hodge, J. R. Dawkins, and E. Kropp, J. Amer. Pharmaceut. Assoc., Sci. Ed., 43, 501 (1954).
5. F. C. Bocobo, A. C. Curtis, W. D. Block, E. W. Harrell, E. E. Evans, and R. F. Haines, Antibiotics and Chemotherapy, 6, 385 (1956).
6. Z. Eckstein, Österreichische Chemiker-Zeitung, 66, 111 (1965).
7. M. Koremurea, H. Oku, T. Shono, and T. Nakanishi, Takamine Kenkyusho Nempo, 13, 198 (1961); C. A. 57, 16450 c.
8. T. Urbański, Nature (London), 168, 562 (1951).
9. Brit. Pat. 835671; Chem. Zbl., 1708 (1962).
10. F. Leonard and F. E. Anderson, J. Amer. Chem. Soc., 77, 4425 (1955).
11. K. Gorter, Bull. Jard. bot. Buitenzorg., 2, 187 (1920).

12. C. L. Carter and W. J. McChesney, Nature (London), 164, 575 (1949).

13. S. Nakamura and C. Shimoda, J. Agric. Chem. Soc. Japan, 28, 909 (1954); C. A. 50, 15723 (1956).

14. K. Anzai and S. Suzuki, J. Antibiotics (Tokyo), A 13, 133 (1960).

15. J. Ehrlich, Q. R. Bartz, R. M. Smith, D. A. Joslyn, and P. B. Burkholder, Science (New York), 106, 417 (1947).

16. M. C. Rebstock, H. M. Crooks, J. Controulis, and Q. R. Borte, J. Amer. Chem. Soc., 71 2458 (1949).

17. R. U. Lemieux and R. J. Cushley, Can. J. Chem., 41, 858 (1963).

18. M. Nakajima, A. Hasegawa, and M. Kurihara, Tetrahedron Letters, 17, 967 (1964).

19. Z. Eckstein, J. Plenkiewicz, and S. Byrdy, Bull. Acad. Polon, Sci., Ser. sci. chim., 8, 623 (1960).

20. J. Kamlet, U. S. Pat. 2,151,517 (1939); C. A. 33, 5003 (1939).

21. Joshioka, C. A., 44, 2008 (1950).

22. R. Demuth and V. Meyer, Ber., 21, 3529 (1888).

23. H. B. Hass and E. F. Riley, Chem. Rev., 32, 373 (1943).

24. V. V. Perekalin, Nepredel'nye nitrosoedineniya, Goskhimizdat, Leningrad, 1961; English translation by L. Mandel, Unsaturated nitro compounds, Israel Program for Scientific Translations Ltd., Jerusalem, 1964. - Second revised edition by V. V. Perekalin and A. S. Sopova, Moscow and Leningrad, 1966.

25. F. W. Lichtenthaler, Angew. Chem. internat. Edit., 3, 211 (1964).

26. H. H. Baer, Advan. Carbohydrate Chem., 24, 67 (1969).

27. H. H. Baer and L. Urbas, in The Chemistry of the Nitro and Nitroso Groups Part 2, Ed. H. Feuer, p. 75, Interscience Publishers, N.Y. 1970.

28. L. Henry, Compt. Rend., 120, 1265 (1895).

29. W. E. Noland, Chem. Reviews, 55, 137 (1955).

30. J. C. Sowden and H. O. L. Fischer, J. Amer. Chem. Soc., 67, 1713 (1945).

31. F. W. Lichtenthaler and H. O. L. Fischer, J. Amer. Chem. Soc., 83, 2005 (1961).

32. H. H. Baer, in Nitro Compounds, Ed. T. Urbanski, p. 263, The MacMillan Co., N. Y. (1964).

33. a) H. H. Baer and G. V. Rao, Ann., 686, 210 (1965). b) S. W. Gunner, W. G. Overend, and N. R. William, Chem. and Ind., 1523 (1964). c) F. W. Lichtenthaler, Angew. Chem., 78, 744 (1966).

34. F. W. Lichtenthaler, Angew. Chem., 73, 654 (1961).

35. F. W. Lichtenthaler, Chem. Ber., 96, 845 (1963).

36. K. Sakai, S. Oida, and E. Ohki, Chem. Pharm. Bull. (Tokyo), 16(6), 1048 (1968).

37. F. W. Lichtenthaler, H. Leinert, and H. K. Yahya, Z. Naturforsch., 21b, 1004 (1966).

38. H. E. Zimmerman and T. E. Nevins, J. Amer. Chem. Soc., 79, 6559 (1957).

39. S. K. Malhotra and F. Johnson, J. Amer. Chem. Soc., 87, 5493 (1965).

40. S. J. Angyal and B. M. Luttrell, Aust. J. Chem., 23, 1485 (1970).

41. F. G. Bordwell and K. C. Yee, J. Amer. Chem. Soc., 92, 5933 (1970).

42. F. G. Bordwell and K. C. Yee, J. Amer. Chem. Soc., 92, 5939 (1970).

43. F. W. Lichtenthaler, H. Leinert, and U. Scheidegger, Chem. Ber., 101, 1819 (1968).

44. W. T. Trager, F. F. Vincenzi, and A. C. Huitric, J. Org. Chem., 27, 3006 (1962).

45. F. G. Bordwell and Martha M. Vestling, J. Amer. Chem. Soc., 89, 3906 (1967).

46. H. E. Zimmerman and P. S. Mariano, J. Amer. Chem. Soc., 90, 6091 (1968).

47. E. Schmidt and G. Rutz, Chem. Ber., 61, 2142 (1928).

48. F. G. Bordwell, M. M. Vestling, and K. C. Yee, J. Amer. Chem. Soc., 92, 5950 (1970).

49. H. H. Baer and Margaret C. T. Wang, Can. J. Chem., 46, 2793 (1968).

50. J. F. Bourland and H. B. Hass, J. Org. Chem., 12, 704 (1947).

51. R. R. Fraser, Private Communication, 1970.

52. M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, Tetrahedron, 6, 36 (1959).

53. H. Meerwein and G. Hinz, Liebigs Ann., 484, 1 (1930).

54. T. Suami and S. Ogawa, Bull. Chem. Soc., Japan, 37(2), 194 (1964).

55. H. H. Baer and F. Kienzle, Can. J. Chem., 47(15), 2819 (1969).

56. F. Johnson and S. K. Malhotra, J. Amer. Chem. Soc., 87, 5492 (1965).

57. R. U. Lemieux, T. L. Nagabhushhan, and I. K. O'Neill, Can. J. Chem., 46, 413 (1968).

58. E. A. Werner, J. Chem. Soc., 115, 1095 (1919).

59. O. R. Gottlieb and M. T. Magalhaes, J. Org. Chem., 24, 2070 (1959).

60. R. A. Finnegan and R. A. Stephani, J. Pharm. Sci., 57, 353 (1968).

61. M. S. Carrie, J. Soc. Chem. Ind., 53, 288 (1934); C. A. 29, 173 (1935).

62. R. A. Finnegan, W. H. Mueller, and M. P. Morris, Proceedings Chem. Soc., 182 1963.

63. R. A. Finnegan and W. H. Mueller, J. Pharm. Sci., 54, 1136 (1965).

64. B. F. Burrows, S. D. Mills, and W. H. Turner, Chem. Comm., 75 1965.

65. F. R. Stermitz, F. A. Norris, and M. C. Williams, Proc. Midwest Reg. Amer. Chem. Soc., 45 1968 (Abstr.).

66. M. C. Williams and F. A. Norris, Weed Sci., 17, 236 (1969).

67. M. C. Williams and W. Binns, Weeds, 15, 359 (1967).

68. F. R. Stermitz, F. A. Norris, and M. C. Williams, J. Amer. Chem. Soc., 91, 4599 (1969).

69. W. F. Baitinger, P. von R. Schleyer, T. S. S. R. Murty, and L. Robinson, Tetrahedron, 20(7), 1635 (1964).

70. R. U. Lemieux, Methods in Carbohyd. Chem., Vol. II, 221 (1963).

71. Rodd's Chemistry of Carbon Compounds, Vol. I, Part F, 2nd Ed., Edited by S. Coffey, Elsevier Publishing Co., London 1967.

72. L. D. Hall, Advan. Carbohyd. Chem., 19, 51 (1964).

73. R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, J. Amer. Chem. Soc., 80, 6098 (1958).

74. W. Koenigs and E. Knorr, Ber., 34, 957 (1901).

75. W. L. Evans, D. D. Reynolds, and E. A. Talley, Advan. Carbohyd. Chem., 6, 27 (1951).

76. B. Helferich and W. Klein, Ann., 450, 219 (1926).

77. J. Conchie, G. A. Levvy, and C. A. Marsh, Advan. Carbohyd. Chem., 12, 157 (1957).

78. A. D. Cross, Practicsl Infra-Red Spectroscopy, Butterworths Scientific Publications, London, p.70 1960.

79. G. Gever, C. O'Keefe, G. Drake, F. Ebetino, J. Michels, and K. Hayes, J. Amer. Chem. Soc., 77, 2277 (1955). G. Gever, Can. Pat. 583,646 (1959).