A CONTRIBUTION TO THE PREPARATIVE CHEMISTRY
OF
NITRO COMPOUNDS

by

Shuet-Hing Lee Chiu

A thesis submitted in partial fulfilment
of the requirements of the degree of
Doctor of Philosophy

Department of Chemistry
Faculty of Science and Engineering
University of Ottawa
Ottawa, Canada

December, 1971

S. H. Lee Chiu
Candidate

Prof. Hans H. Baer
Research Supervisor

PREFACE

The goal of the research undertaken for this thesis was to make some contributions to the preparative chemistry of organic nitro compounds. Various independent projects in that area were pursued. Accordingly, the discussions and descriptions of results that follow a general introduction are divided into three parts. Part I deals with the synthesis of nitroalkyl glucosides which are analogs of the natural product, miserotoxin, and with a bioassay of their toxicity. Part II is concerned with the oxidation of amino sugars as a new approach to the synthesis of nitro sugars. Part III describes efforts to synthesize a heterocyclic system by a Dieckmann-type cyclization of nitro esters.

ACKNOWLEDGMENTS

I wish to express my hearty thanks to Professor Hans H. Baer, my research supervisor, for his advices and guidance in the past years during which time this work was undertaken; and for his patience and suggestions in the preparation of the manuscript.

I would like to thank Dr. J. Kovář, with whom I had many stimulating discussions.

I am indebted to my parents, whose never-fading confidence in me has encouraged my continuation in study.

I am thankful to my husband, Chung-Wai. His enthusiasm in research has been a constant source of stimuli which has encouraged and inspired my work.

The assistance of Dr. M. MacConaill of the Pharmacology Department, University of Ottawa, in carrying out the biological test is gratefully acknowledged.

TABLE OF CONTENTS

INTRODUCTION

RESULTS AND DISCUSSION

PART I

THE SYNTHESIS OF MISEROTOXIN ANALOGS

PART II

OXIDATION OF AMINO SUGARS TO NITRO SUGARS

Page

PART II

PART III

LIST OF FIGURES

Figure Page

PART I

PART II

Figure | Page

PART III

ABSTRACTS *

PART I

The synthesis of five nitroalkyl β-D-glucopyranosides is described. These compounds are analogs of the poisonous plant product miserotoxin (3-nitropropyl β-D-glucopyranoside). Koenigs-Knorr condensation between acetobromoglucose (VI) and 2-nitropropanol (I), 1-nitro-2-propanol (II), 2-nitrobutanol (III), 2-nitro-3-pentanol (IV), and 2-methyl-2-nitro-1-propanol (V), respectively, afforded the tetra-_O_-acetyl-β-D-glucopyranosides (VII-XI) of these nitro alcohols. Mixtures of silver carbonate and silver perchlorate were found to be the most satisfactory condensing agent. Evidence was obtained in some cases for the formation of distinguishable stereoisomers due to asymmetry in the aglycon. The glucoside tetraacetates were deacetylated to the free glucosides XIII-XVII. Except for XI, which contains a tertiary nitro group and could be deacetylated under alkaline conditions, the nitroalkyl glucosides proved to be sensitive towards alkali and their tetraacetates had therefore to be deacetylated by carefully controlled acid catalysis. This was achieved by the use of methyl

---

* An independent set of Roman numerals is used in each Part to designate compounds.

p-toluenesulfonate in methanolic solution.

The toxicity of the new glycosides was compared with that of miserotoxin in a chicken bioassay and was found to be similar in XIV and XVI, higher in XIII and XV, and lower in XVII.

PART II

The oxidation of the secondary carbinamine function with m-chloroperbenzoic acid was first studied on trans-2-aminocyclohexanol (I), a model compound for amino sugars. The reaction led to trans-2-nitrocyclohexanol (II) and trans-2-nitrosocyclohexanol trans dimer (III) in yields of 16 and 28%, respectively. The oxidation was then extended to various amino glycosides. These included methyl 3-amino-3,6-dideoxy-2,4-di-O-methyl-α-L-glucopyranoside hydrochloride (IV), methyl 3-amino-3,6-dideoxy-α-D-glucopyranoside (VIII), methyl 3-amino-3-deoxy-β-D-galactopyranoside (XV), methyl 3-amino-3-deoxy-α-D-mannopyranoside (XIX), methyl 3-amino-3-deoxy-β-D-xylopyranoside (XXII), and, in a preliminary way, methyl 2-amino-2,6-dideoxy-α-D-altropyranoside (IX). Compounds VIII, XV, and XIX upon peracid oxidation gave mixtures of the corresponding nitro glycosides (XII, XVI, and XX) and nitroso glycoside dimers (XIII, XVII, and XXI). Compound IV afforded only the nitro derivative (V) while compound XXII furnished only the nitroso derivative (XXIII). In general, good yields were obtained. In some of the examples, variations in the product composition depending on reaction conditions were observed.

The amino sugars VIII and IX were synthesized by action of ammonia upon methyl 2,3-anhydro-4-O-benzoyl-6-deoxy-α-D-allopyranoside (VII) and characterized as N-acetyl derivatives (X and XI, respectively). The mannoside XIX was characterized in crystalline form for the first time.

PART III

2-(2-aci-Nitroethylideneamino)-benzoic acid (IV) and its methyl ester I were synthesized by condensation of methazonic acid with anthranilic acid and methyl anthranilate, respectively. The p-nitrophenyl ester (VI) of IV was obtained by esterification of the components in the presence of dicyclohexylcarbodiimide. The methyl ester I was reduced with sodium borohydride to give methyl 2-(2-nitroethylamino)-benzoate (VII). Cyclising Intramolecular ester condensation of I and VI, which was expected to lead to 4-hydroxy-3-nitroquinoline (III), did not succeed. Cyclization of the saturated ester VII, on the other hand, was successful. However, the product was not the dihydroquinoline derivative which was expected in that case but proved to be III. Evidently an oxidative step was involved in the reaction.

INTRODUCTION

An Outline of Research Projects in the Context of the Present State of Development of the Chemistry of Nitro Compounds

Until 1949, no products containing a nitro group had been known to exist in Nature. In that year, however, the plant glycoside hiptagin was revealed to contain β-nitropropionic acid, which is released upon hydrolysis (1), and at about the same time the important antibiotic, chloramphenicol, was shown to possess an aromatic nitro group (2). Although the number of nitro compounds discovered in Nature has grown in subsequent years (3), they may still be regarded as rare, and each new discovery is therefore received with great interest. Recently it has been reported (4) that the poisonous principle present in certain species of timber milkvetch (*Astragalus miser*), a plant native to the western parts of Canada and the United States, is 3-nitropropyl β-D-glucopyranoside. The compound, which has been named miserotoxin, was presumed to be responsible for livestock losses that have occurred in areas infested with milkvetch (5,6).

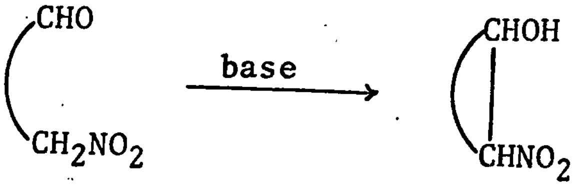
Baer and Shields (7) synthesized 3-nitropropyl β-D-glucopyranoside, and the properties of the synthetic product tended to confirm the structural assignment for miserotoxin which had been based largely on spectroscopic data. In continuation of those studies it was deemed interesting to synthesize various structural analogs of miserotoxin, i.e., glucosides having different nitroalkyl groups as aglycons, and to compare them with respect to toxicity in a bioassay. Research undertaken in this direction forms Part I of this thesis.

For the synthesis of miserotoxin the Koenigs-Knorr glycoside synthesis had been applied sucessfully. It was decided to make use of the same method, if possible, for the preparation of the desired analogs, but it was realized that certain complications might be encountered. The general features of the method and potential sources of difficulties will therefore be outlined later in this Introduction.

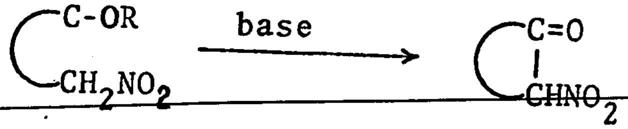
Unlike miserotoxin and previously discovered hiptagin, in which the nitro group is not attached directly to the sugar molecule, recently discovered evernitrose is a real nitro sugar, namely, 4-O-methyl-3-C-methyl-3-nitro-2,3,6-trideoxy-L-*ribo*-hexose (8).

It is a component of an antibiotic, everninomycin, and represents the first nitro sugar to be found in Nature. Undoubtedly this discovery will provide an additional stimulus for research in nitro carbohydrate synthesis, an area which has received much attention during the past decade (9) mainly because of its interconnection with the chemisrty of amino sugars, the latter being of paramount biological significance. There are several methods for introducing a nitro group into a sugar molecule, and these will be enumerated later on. Reduction of nitro sugars readily affords amino sugars. However, the reverse approach, namely, synthesis of nitro sugars by oxidation of amino sugars, has never been attempted. Since it was considered that such a process could be a valuable complement to existing methods, an investigation into this possibility was undertaken, and the results are to be presented in Part II of this thesis.

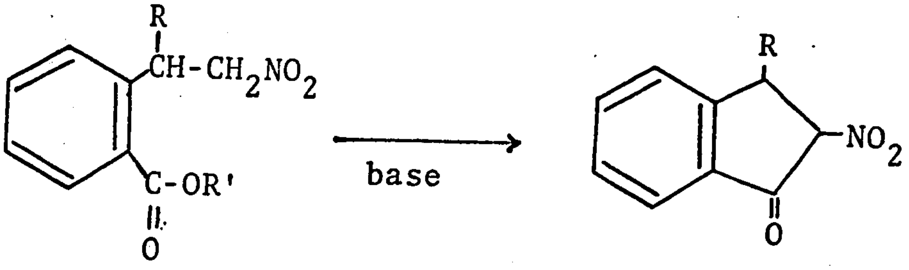
The most widely employed method for the synthesis of nitro alcohols is the Henry reaction, the base-catalyzed, aldol-type addition reaction between a nitroalkane and an aldehyde or ketone (10, 11). The various nitroalkanols required for the glycoside syntheses of Part I were obtained in this way. However, the reaction has also served for the synthesis of polyhydroxy nitro compounds, by use of sugars as carbonyl components, and it was in fact the first, and for a long time the only, avenue to nitro carbohydrates (12, 13). Besides open-chain nitro alcohols one can easily synthesize, by the same principle, cyclic structures such as nitro inositols (14) and nitro pyranosides (15). In that case, cyclization is brought about by intramolecular addition in a nitro carbonyl compound:



Some years ago, when this cyclization based on a Henry-type addition had already found many useful applications, Baer and Naik (16, 17) investigated a similar proposition, namely, a Dieckmann-type cyclizing condensation involving a reactive nitromethylene and an ester function, which should lead to cyclic nitroketones :

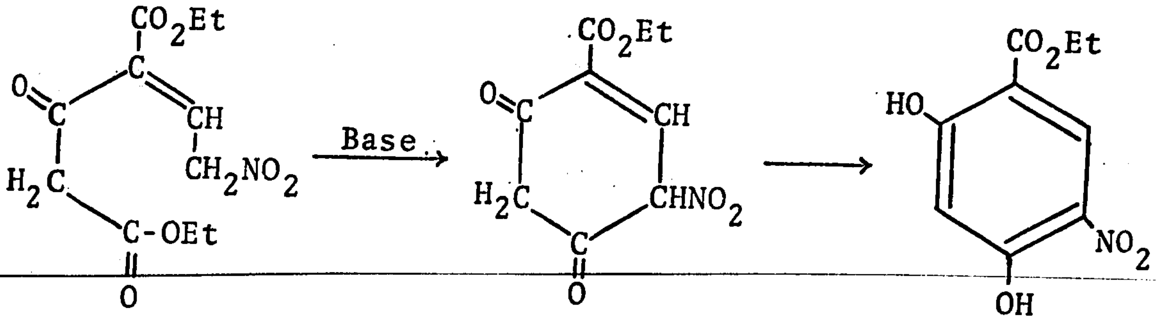


At the outset of their work, Baer and Naik were surprised that this seemingly simple approach to nitroketones had apparently not been described in the literature before. They were able to synthesize 2-nitroindanones by cyclization of 2-(2-nitroethyl)benzoates (16, 17).

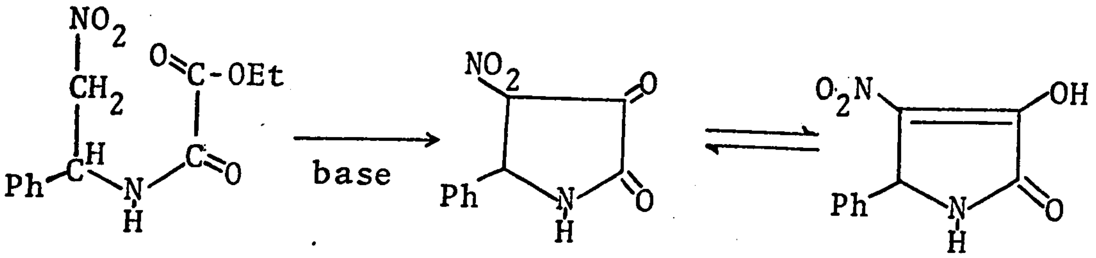


R= H, OCH$_3$, or CH$_2$NO$_2$
R'= CH$_3$, or Ph

In the meantime, two articles describing similar cyclizations were published. The first one dealt with the synthesis of an aromatic product according to the following sequence (18):



The second instance involved the synthesis of a pyrrolinone (19):

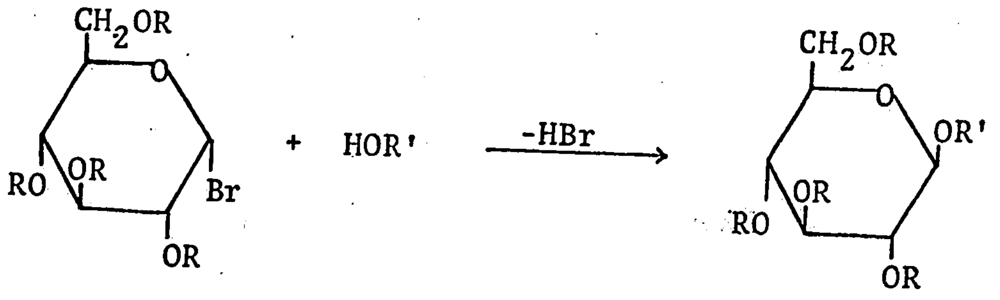


In view of the limited amount of research that seems to have been devoted to this potentially useful variation of the Dieckmann ester condensation, it was decided to attempt a further synthesis along these lines. The work performed in this connection is described in Part III of this thesis.

Some Aspects of Chemical Synthesis Pertinent to the Projects of this Thesis

I. The Koenigs-Knorr glycoside synthesis.

The Koenigs-Knorr reaction is the most widely used method for the synthesis of glycosides and oligosaccharides (20,21,22,23). In it, a glycosyl halide is condensed, generally in the presence of an acid acceptor, with an alcohol (for alkyl glycosides) or with a hydroxyl group of a second sugar molecule (for oligosaccharides).



R= acetyl, benzoyl or other blocking groups

R'=alkyl, aryl or glycosyl

In order to prevent condensation at unwanted sites, reactive groups in both components must be suitably protected. The glycosyl halide is therefore usually employed as a fully acylated derivative. Chlorides and bromides have been used most often. The latter are preferred by many workers because they are more reactive than the former, which is an advantage that outweighs the disadvantage of instability on storage. Protection of the hydroxyl functions is most frequently provided by acetyl or benzoyl groups, although other means of blocking, e.g., by trichloroacetyl or nitrate ester groups, have been used (24, 25) for special purposes. Perhaps the best-known glycosylating agent is 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide ("acetobromoglucose"), and it will be shown in Part I that this reagent has served satisfactorily for the present task.

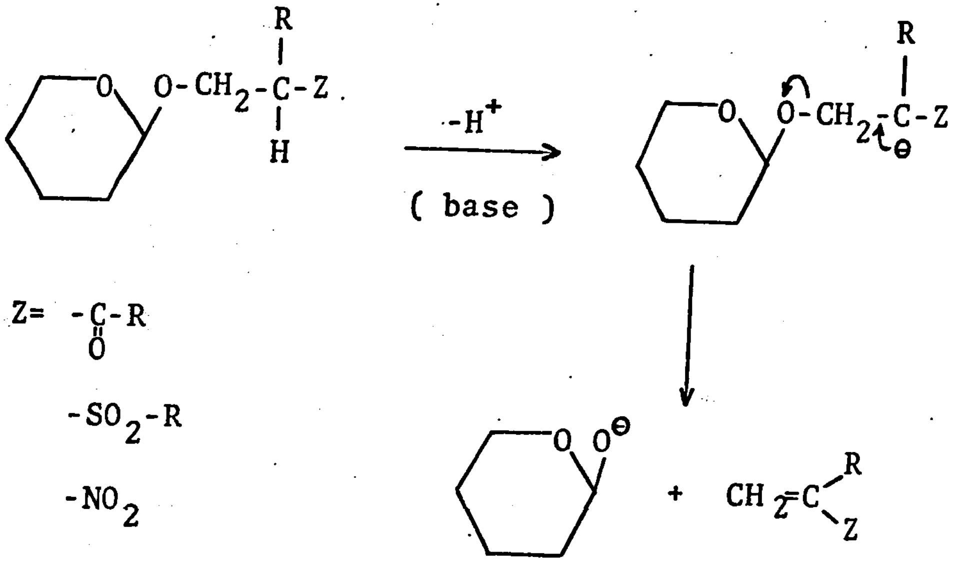
As for the alcoholic component in the condensation, simple alcohols offer few problems. However, bulky molecules may give rise to steric hindrance, in which case yields in the Koenigs-Knorr reaction can be quite low. Possible difficulties in this respect would have come as no surprise with the secondary alcohols to be glycosylated in the present work. Another question which might be asked is whether the presence of a nitro group in the alcoholic component would be compatible with the desired condensation reaction. In view of the successful uses of 3-nitro-1-propanol in the synthesis of miserotoxin (7), and of a partially blocked nitro sugar in a recent disaccharide synthesis (26), no complications were anticipated in that regard.

The classical condensing agents in the Koenigs-Knorr reaction are silver oxide and carbonate (20). Since the reaction system is heterogeneous, the surface condition of these agents influences the yield, and the use of reactive preparations, freshly made by precipitation, is recommended (27). One unavoidable drawback is the formation of water resulting from the neutralizing action of the silver compounds, and this leads to varying amounts of hydrolysis of glycosyl halide concurrent with the glycoside synthesis. Hence 2,3,4,6-tetra-_O_-acetylglucose is invariably a by-product in syntheses with acetobromoglucose; moreover, unreacted bromo compound may combine with the hydrolysis product to give a disaccharide. These side reactions may be minimized though not wholly suppressed by adding an internal desiccant to the medium, e.g. anhydrous calcium sulfate (28). Other condensing agents such as mercuric cyanide, mercuric acetate, lutidine or quinoline have been favored more recently, but various side reactions have also been observed in these cases (29,30,31). One promising procedure appeared to be the use of a combination of silver perchlorate and silver carbonate (25,32). Accelerated rates and doubled yields have been observed. It has been suggested that the soluble silver perchlorate reacts with the glycosyl halide, causing its dissociation, and the perchloric acid produced in the condensation step then is neutralized by the silver carbonate, whereby silver perchlorate is regenerated.

The stereochemistry of the Koenigs-Knorr reaction also requires comment. A tetra-O-acyl-α-D-glucopyranosyl halide (which has the C-1 and C-2 substituents in cis relation) generally reacts in a straightforward manner with inversion at C-1 to give a β-D-glucoside, especially when silver catalysts are used.

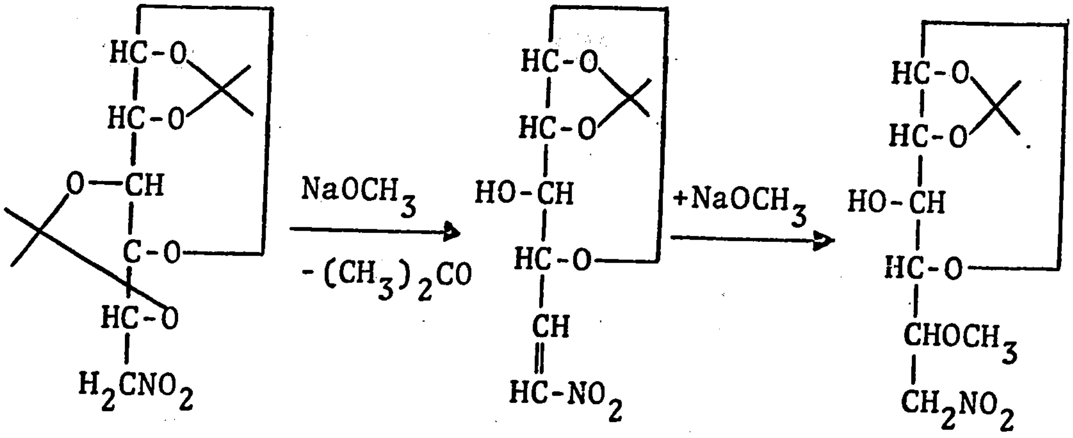
Only very small amounts of the anomeric α-D-glucoside arise, but these may increase when some of the other catalysts are employed (29). The situation in poly-O-acyl-glycopyranosyl halides with a 1,2-trans substituent relationship (e.g., with the β-D-glucopyranosyl or the α-D-mannopyranosyl configuration) is more involved; both glycoside anomers may be obtained and, in addition, 1,2-orthoester structures may result. Neighboring group participation comes into play in these cases (33). Fortunately, the present project required the synthesis of β-D-glucosides, and these could be anticipated to be obtainable by use of α-acetobromoglucose without serious complications regarding stereoselectivity. The stereochemically more complex aspects of the reaction, pertaining to the synthesis of α-D-glucosides and to the behaviour of 1,2-trans halides, were therefore of no special relevance in this context.

Certain difficulties, however, had to be expected in another connection, namely, in the deblocking of the sugar moiety after the condensation. With ordinary glycosides this is no problem, as de-O-acetylation can be routinely performed by methoxide-catalyzed alcoholysis (Zemplén method)(34) or by ammonolysis (35,36,37), which are procedures that do not affect the alkali-stable glycosidic bond. However, most of the nitroalkyl glycosides to be synthesized would belong to a category of alkali-sensitive glycosides (38). If the structure of the aglycon is such that a hydrogen in β-position to the glycosidic oxygen link is activated by an adjacent carbonyl, sulfonyl, or other electron-withdrawing group, the glycosidic bond is prone to alkaline cleavage by β-elimination (39,40,41):

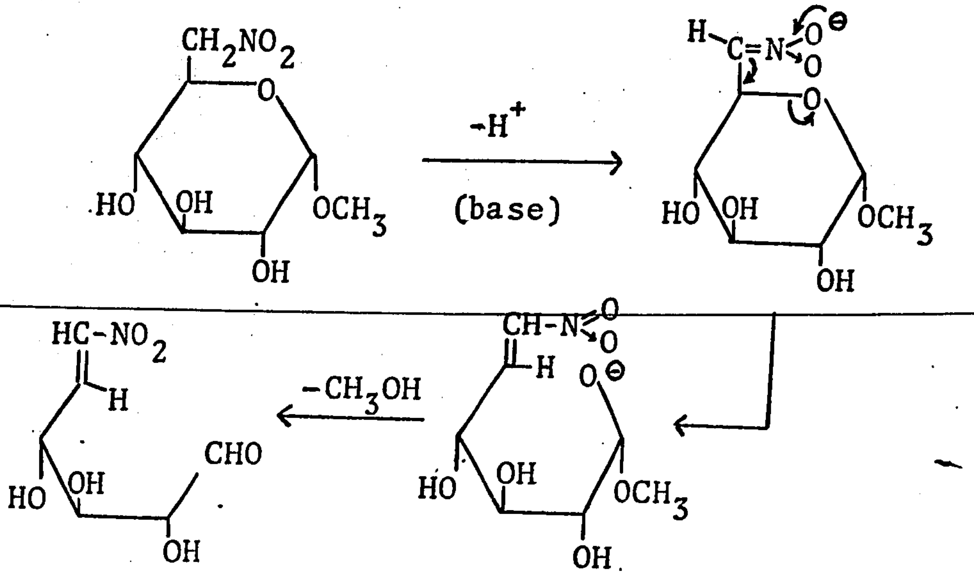


Only one example is described in the literature for Z = NO_2. Helferich and Hase (42) observed complete glycoside cleavage when they attempted to deacetylate by base catalysis the tetraacetate of 2-nitroethyl β-D-glucopyranoside. Miserotoxin, which is the only other nitroalkyl glycoside known, does not belong into this group since its nitro substituent is in position 3, not

2, of the aglycon, and alkaline deacylation of its tetraacetate met with no difficulties (7). However there is much evidence for alkali lability of β-nitro substituted acetal linkages in structurally similar circumstances. For example, 1,2:3,5-di-O-isopropylidene-6-deoxy-6-nitro-α-D-glucofuranose readily loses its 3,5-isopropylidene group by the action of base under very mild conditions (43):



More recently it was found that methyl 6-deoxy-6-nitro-α-D-glucopyranoside is also cleaved by alkali (44):

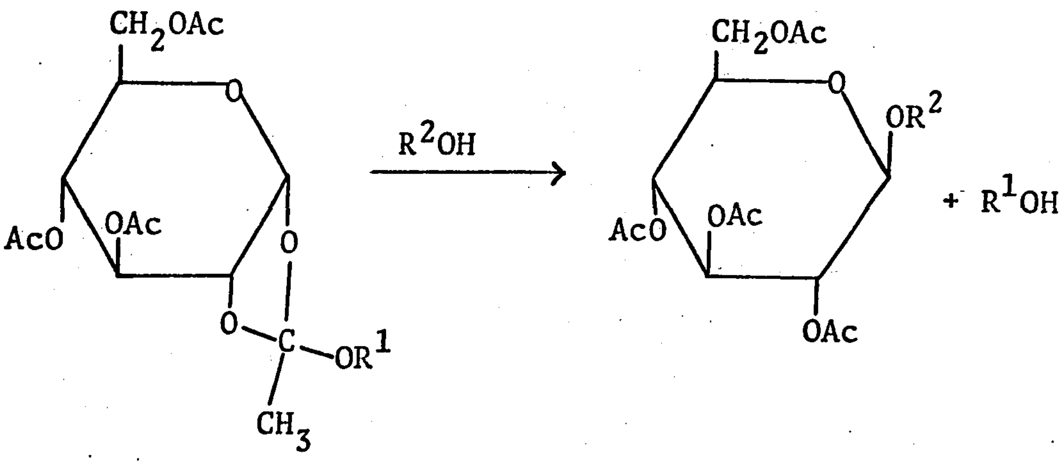


For this reason, a different way of deacylation had to be developed when the glucoside just mentioned was to be prepared from its triacetate. Removal of the acetyl groups by straight acid hydrolysis was not practicable because the glycosidic bond, too, would suffer hydrolysis even though it has been reported (45,46) to be more stable in nitro sugars than in ordinary sugars. Baer and Furić (47) solved the problem by employing methanolysis in the presence of methyl p-toluenesulfonate, which produced the aforementioned 6-nitro glucoside from its triacetate in over 80% yield. The process presumably amounts to a controlled acid catalysis due to a gradual generation of p-toluenesulfonic acid:

$$\text{P-TsOCH}_3 + \text{HOCH}_3 \longrightarrow \text{p-TsOH} + \text{CH}_3\text{OCH}_3$$

As will be shown in Part I, the method also proved useful in the present work.

Although the Koenigs-Knorr reaction has served well in the present work, it may be mentioned that, should it have failed, alternative methods of glycoside synthesis might have been tried. One of the most common, and probably the best-investigated, method was originally devised by Emil Fischer and consists of direct interaction between free sugar and alcohol in the presence of acid (48) or a cation exchange resin (49). However, it is usually applied only to simple aliphatic alcohols, and it invariably gives mixtures of α- and β-anomers of both the pyranoside and the furanoside type, with product ratios strongly depending on sugar configuration and reaction conditions. Detailed mechanistic studies have been carried out by Bishop and Cooper (50). Another method of considerable potential has been developed more recently. It involves reaction of alcohols with acetylated sugar orthoesters. Since it especially leads to 1,2-<u>trans</u> glycosides it may rival the Koenigs-Knorr reaction for syntheses of β-D-glucosides (51,52,53,54):

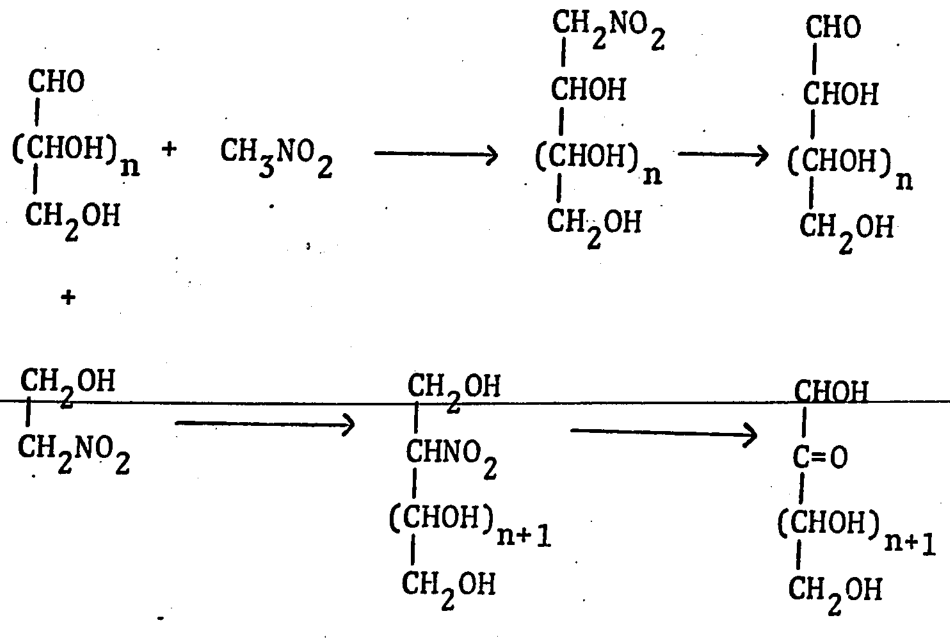


R^1 = ethyl
isopropyl
t-butyl

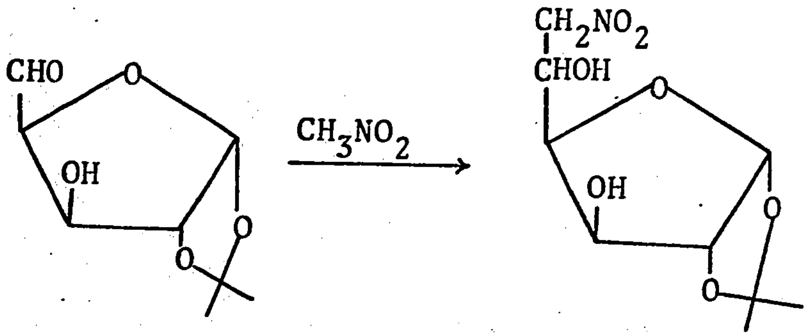
II. Methods for the Synthesis of Nitro Sugars

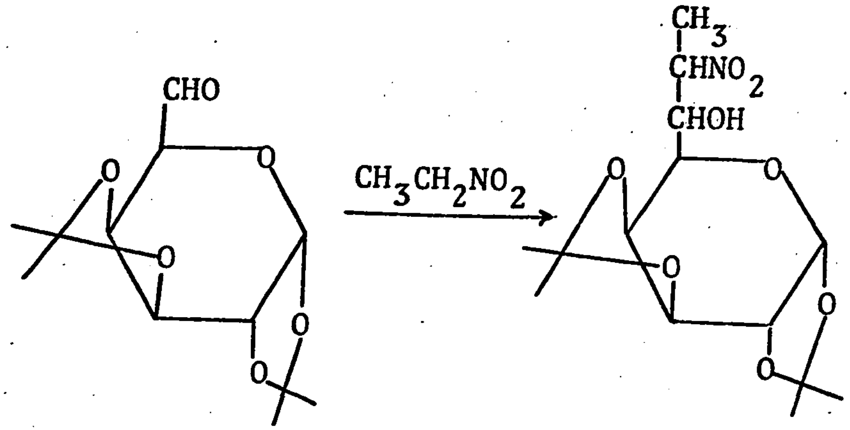
A. Nitroalkane addition

The base-catalyzed addition of nitroalkanes to carbonyl compounds (Henry reaction) has been employed extensively in carbohydrate chemistry, as has been mentioned previously in this Introduction. It is in fact the avenue by which the largest number of nitro sugar derivatives have been obtained. Manifold possibilities of variation exist. Addition of nitromethane to aldoses leads to 1-deoxy-1-nitroalditols having one more carbon, and these can be converted into aldoses so that, over-all, extension of the sugar chain is accomplished. Similarly, addition of nitroethane leads to extension by two carbons and allows the synthesis of higher ketoses from lower aldoses (9,13) :

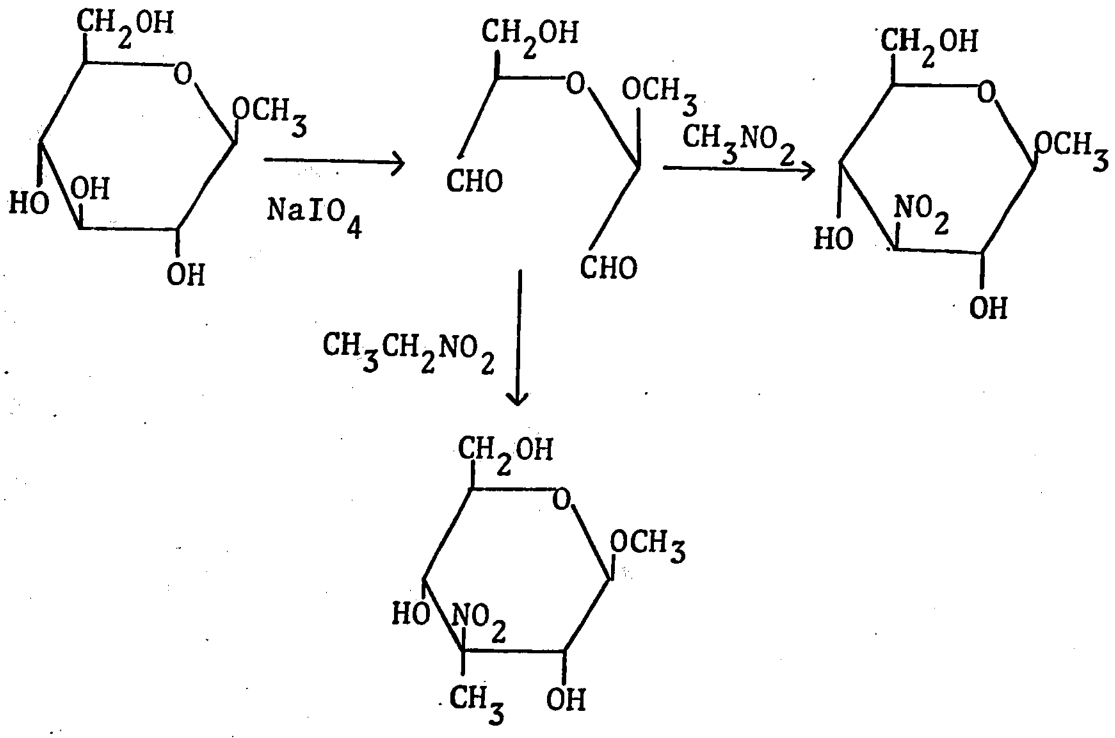


Extensions of the sugar chain at the other end have also been achieved by using suitably blocked terminal *aldo* derivatives (14,55):

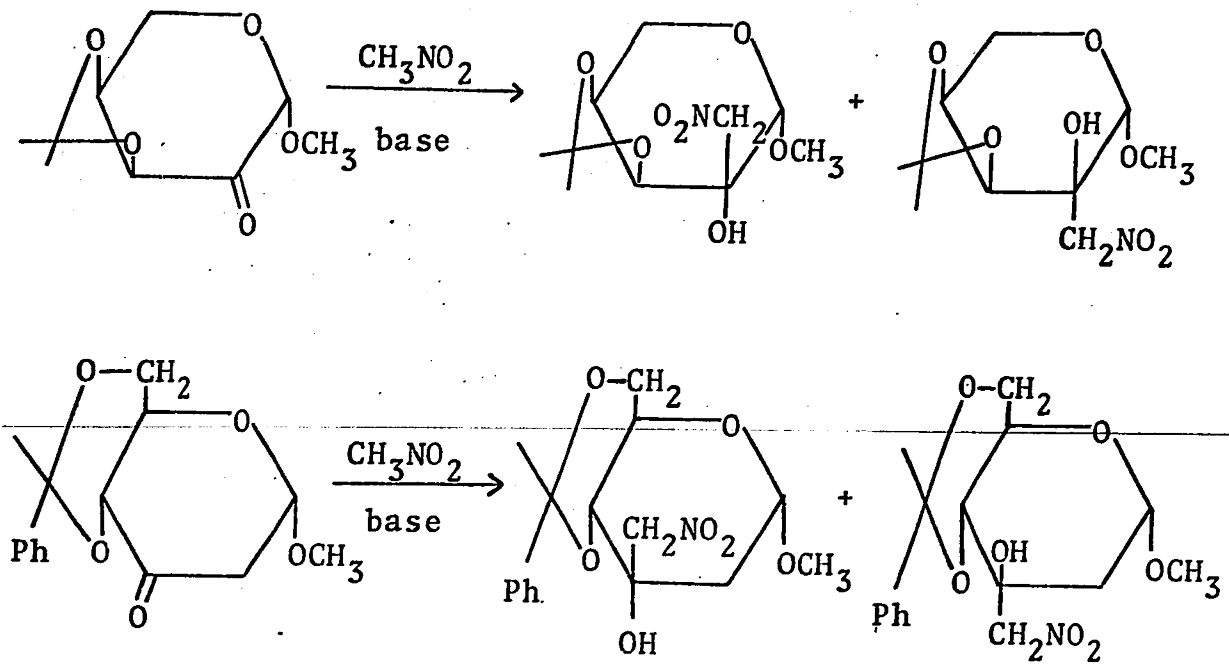




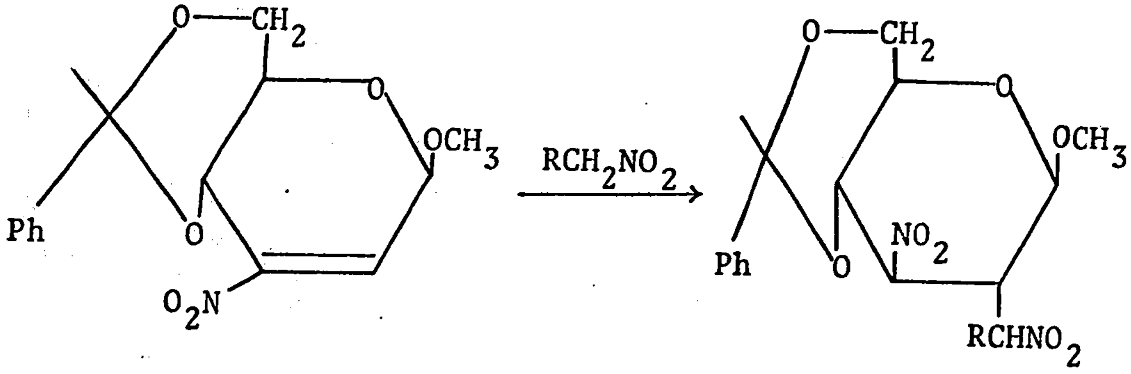
Cyclization of periodate-oxidized glycosides ("Sugar dialdehydes") with nitromethane affords 3-deoxy-3-nitro-pyranosides (9,15), and use of nitroethane gives analogous branched-chain derivatives (56,57):



Branched-chain sugars are also obtained by reaction of nitromethane with oxo glycosides as follows(58,59):



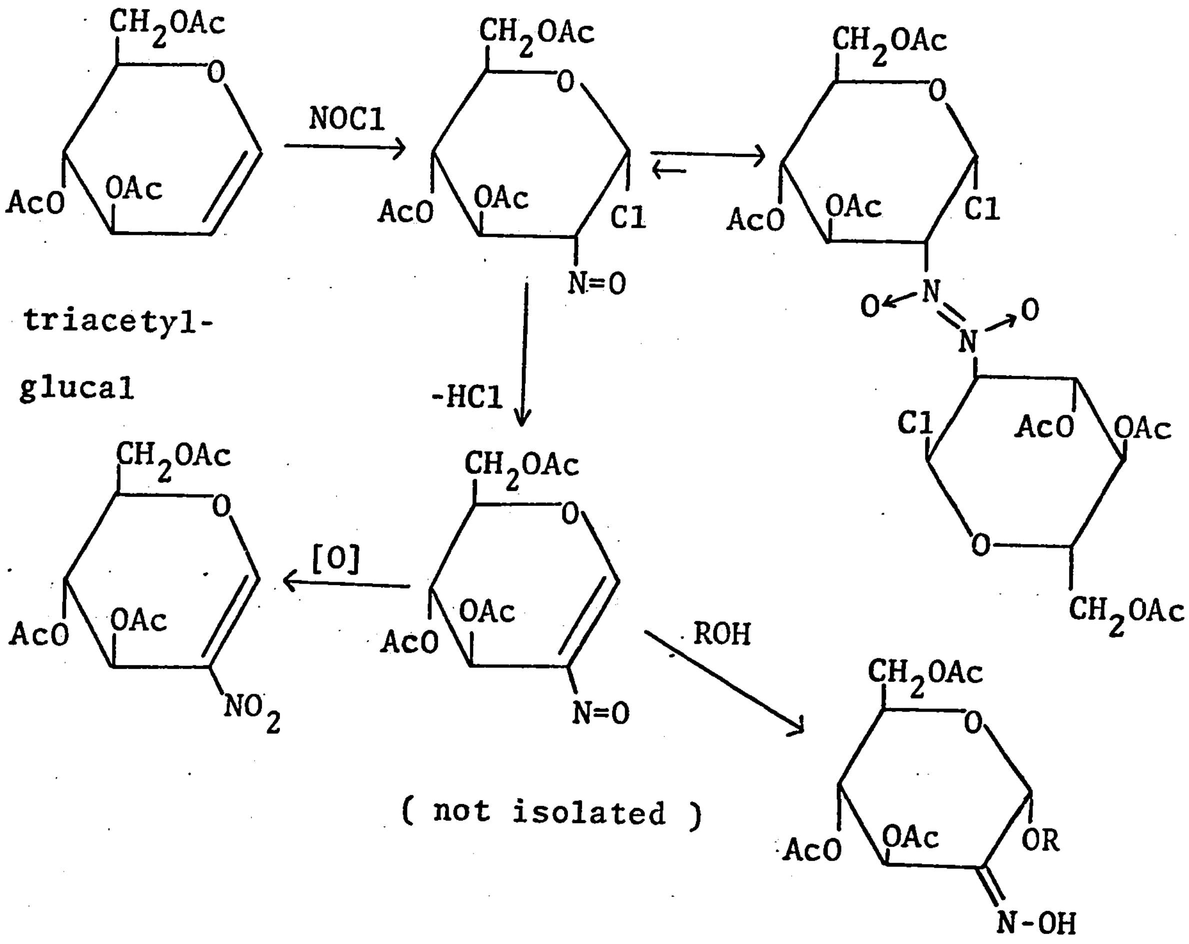
Branched-chain dinitro sugars can be made by Michael addition of nitroalkanes to nitroolefinic sugars (60):



In all the addition reactions mentioned above are generated one, two, or three asymmetric centers, and accordingly the formation of stereoisomers is expected. A large part of the research performed on these reactions revolves around the separation and characterization of stereoisomers and is concerned with the factors which influence isomer ratios (9,61,62,63).

B. Nitrosyl chloride and dinitrogen tetroxide additions

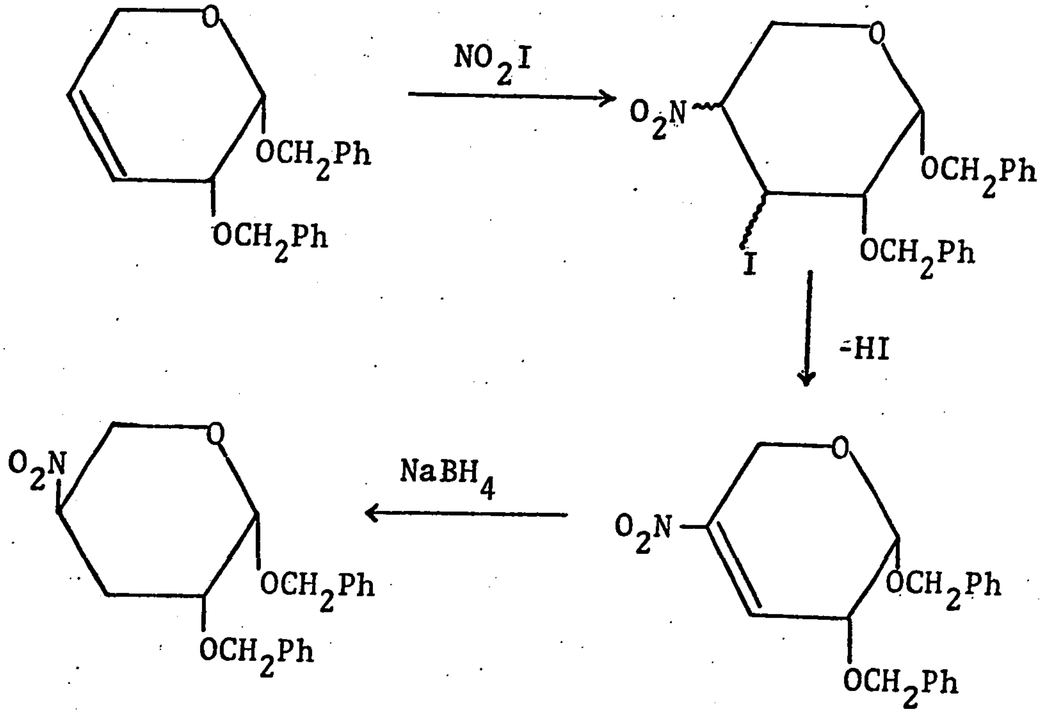
Addition of nitrosyl chloride to triacetyl glucal affords (64,65) a 2-nitroso glucosyl chloride which is isolated as a dimer. The compound readily undergoes dehydrochlorination, and the resulting nitroso glucal is oxidized to the corresponding nitro compound, or it can be trapped by addition reaction of alcohol which gives an oximino glucoside.



Addition of dinitrogen tetroxide to the glucal gives in similar fashion the corresponding 2-nitroso glucosyl nitrate which can also be isolated as a dimer or converted into 2-nitro glucal or oximino glucosides (66, 67).

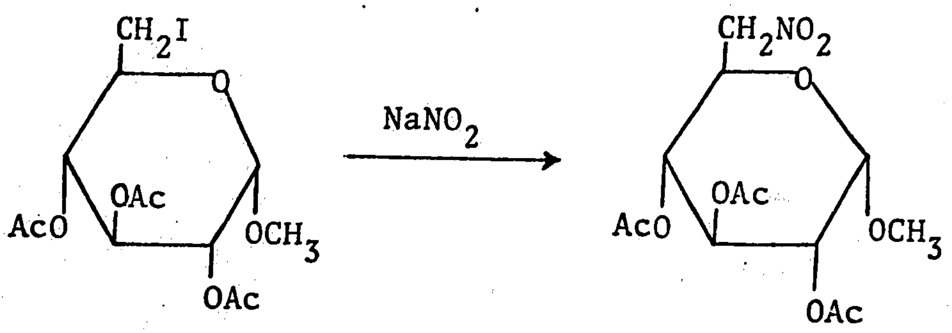
C. Addition of nitryl iodide

Nitryl iodide, NO_2I, has been found to add across the double bond of an unsaturated sugar. The adduct readily underwent dehydroiodination to give a nitroolefin which was subsequently reduced with sodium borohydride to give a saturated nitro sugar (68):



D. Nucleophilic displacement by sodium nitrite

Displacement by sodium nitrite of the iodine in methyl 3,4,6-tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside afforded the corresponding 6-nitro glycoside (45,47, 69).

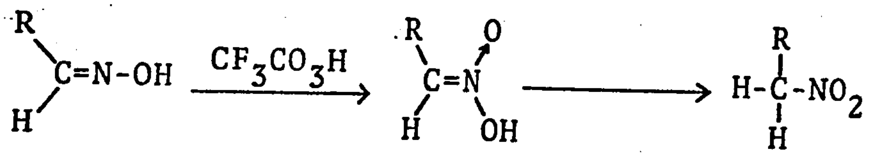


In similar manner was synthesized 1,6-dinitro-2,3:4,5-di-O-benzylidene mannitol from the corresponding diiodo derivative (69).

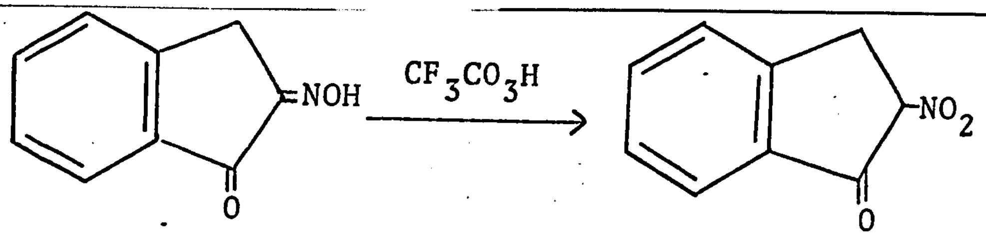
These syntheses were applications of the well-known Victor Meyer reaction (70) which for a long period of time had been the only available access to aliphatic nitro compounds (71). The original procedure using silver nitrite in ether suspension was later improved by Kornblum (72) who recommended sodium nitrite in dimethyl sulfoxide or dimethylformamide. With the improved procedure, secondary iodides are said to react more readily, and the amount of isomeric nitrite ester accompanying the nitro product is diminished. Moreover, tosyl groups can be displaced instead of halogen. Nevertheless, the method has been used little in sugar chemistry.

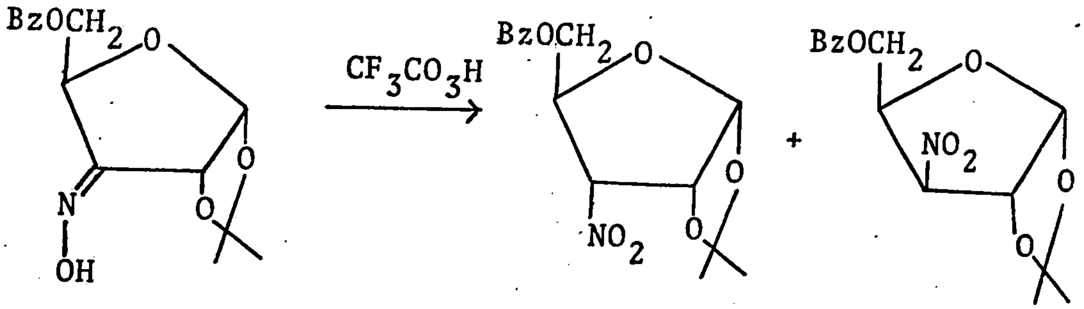
E. Oxidation of oximino and amino derivatives

At the outset of these studies, no nitro sugars had been prepared from sugar derivatives containing nitrogen in a lower state of oxidation although, in other areas of chemistry, oximes and amines had been successfully oxidized to nitro compounds. The use of potassium permanganate is limited to oxidation of amino groups situated on tertiary carbon atoms (73), which prevents it from becoming a generally applicable method in carbohydrate chemistry. More promising appears to be the use of peroxy acids as oxidants. Emmons and Pagano (74)found that trifluoroperacetic acid furnished good yields of nitro compounds from aldoximes and also from ketoximes which are not sterically hindered.



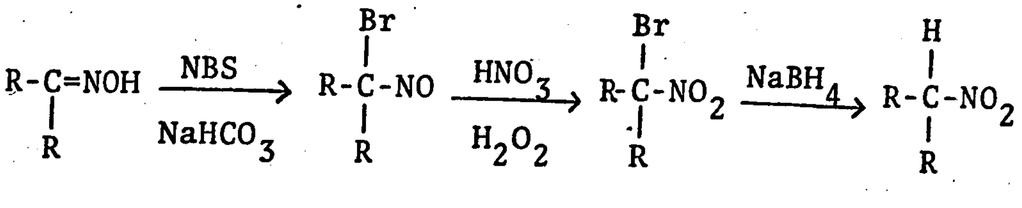
A recent application was the oxidation of indanedione monoxime to 2-nitroindanone (17), and the first and only example in carbohydrate chemistry was reported in 1971 (75) :





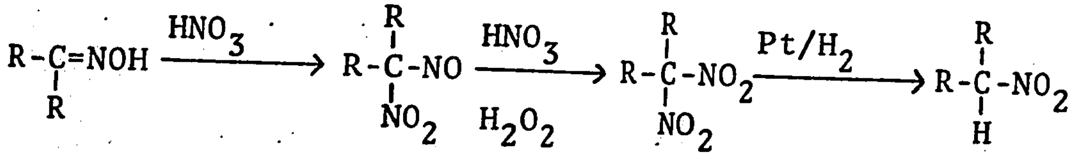
Disadvantages of the trifluoroperacetic acid method are the side reactions that may occur when unsaturated groups or ester functions are present, and also certain hazards in the preparation of the reagent (76,77, 78).

Two indirect ways of converting oximes into nitro compounds are worth mentioning. According to Iffland and Yen (79), nitroalkanes are obtainable by bromination of oximes with N-bromosuccinimide followed by oxidation of the resulting bromonitroso compound with hydrogen peroxide and nitric acid, and subsequent reductive removal of the bromine:



$$R-\underset{R}{\underset{|}{C}}=NOH \xrightarrow[NaHCO_3]{NBS} R-\overset{Br}{\overset{|}{\underset{R}{\underset{|}{C}}}}-NO \xrightarrow[H_2O_2]{HNO_3} R-\overset{Br}{\overset{|}{\underset{R}{\underset{|}{C}}}}-NO_2 \xrightarrow{NaBH_4} R-\overset{H}{\overset{|}{\underset{R}{\underset{|}{C}}}}-NO_2$$

The method is compatible with the presence of both olefinic and ester functions as has been demonstrated in steroid chemistry (80). The other indirect method involves nitration of the oxime to give a nitroso-nitro derivative which is then oxidized to a gem-dinitro product. The latter can be converted into the mononitro compound by selective reduction (81):

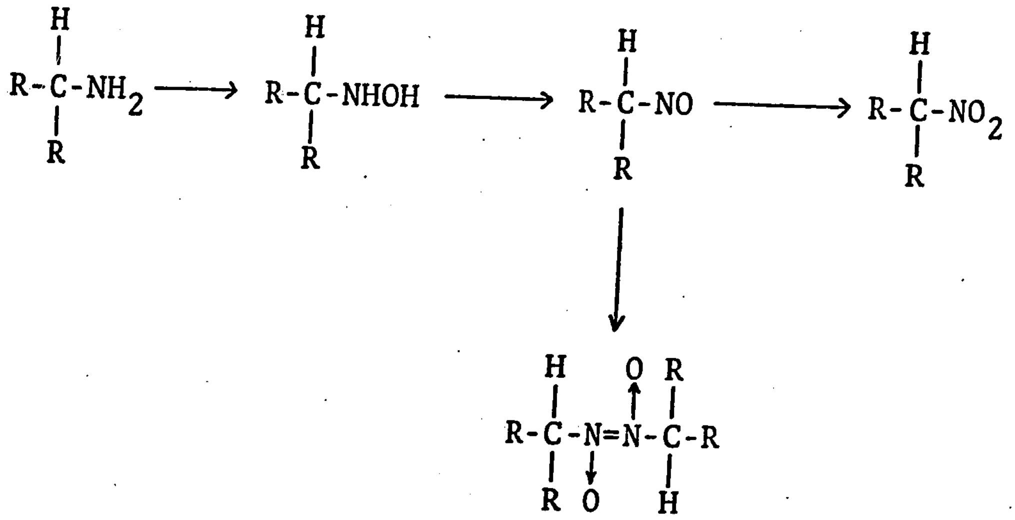


$$\underset{R}{R\text{-}C}\text{=NOH} \xrightarrow{HNO_3} \underset{NO_2}{\overset{R}{R\text{-}C}}\text{-NO} \xrightarrow[H_2O_2]{HNO_3} \underset{NO_2}{\overset{R}{R\text{-}C}}\text{-}NO_2 \xrightarrow{Pt/H_2} \underset{H}{\overset{R}{R\text{-}C}}\text{-}NO_2$$

Neither one of the indirect methods has been tried in carbohydrate chemistry.

Amines have also been successfully oxidized to nitro compounds by trifluoroperacetic acid (82). More recently, perbenzoic acid (83) and m-chloroperbenzoic acid (84) have found use for the same purpose. Especially the last-mentioned oxidant seems attractive as its action is relatively mild and it is a stable, commercially available reagent.

It has been suggested that the course of amine oxidation by peracids proceeds via hydroxylamino and nitroso intermediates. The isolation of nitroso dimers in such oxidations was considered to support the proposed mechanism (84,85). It will be shown in Part II of this thesis that such dimers also arise, in varying proportions, in oxidations of amino sugars with m-chloroperbenzoic acid.



PART I

THE SYNTHESIS OF MISEROTOXIN ANALOGS

RESULTS AND DISCUSSION*

This Part of the thesis is divided into three sections. In Section A is described the synthesis of five nitroalkyl β-D-glucopyranoside tetraacetates by the Koenigs-Knorr reaction. Section B deals with the preparation of the free glucosides from their tetraacetates, and Section C reports on a bioassay of the toxicity of these glucosides in comparison with miserotoxin.

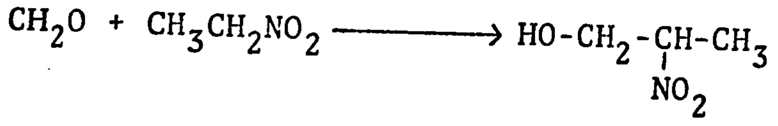
A. Nitroalkyl β-D-Glucopyranoside Tetraacetates

It was considered desirable to synthesize analogs of miserotoxin (3-nitropropyl β-D-glucopyranoside) that would differ from the natural product in their aglycons in various ways while retaining a general similarity. It was decided to use nitro alcohols having three, four, or five carbon atoms. The alcoholic functions were to be primary or secondary; and primary, secondary, and tertiary nitro groups were to be represented. The following nitro alcohols were prepared by Henry addition according to the equations given :

---

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

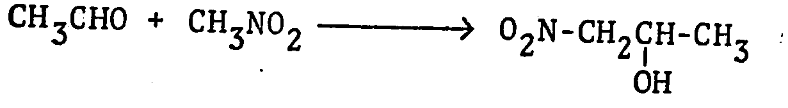
a. 2-nitro-1-propanol (I)



$$CH_2O + CH_3CH_2NO_2 \longrightarrow HO\text{-}CH_2\text{-}\underset{\substack{|\\ NO_2}}{CH}\text{-}CH_3$$

(I)

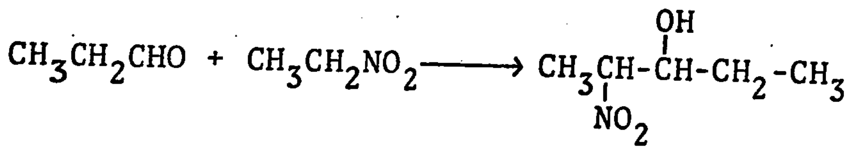
b. 1-nitro-2-propanol (II)



$$CH_3CHO + CH_3NO_2 \longrightarrow O_2N\text{-}CH_2\underset{\substack{|\\ OH}}{CH}\text{-}CH_3$$

(II)

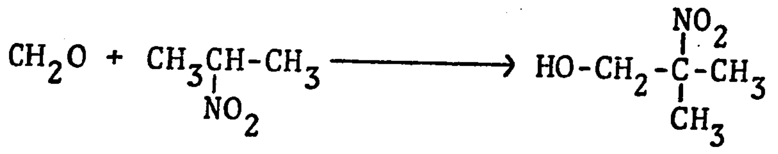
c. 2-nitro-3-pentanol (IV)



$$CH_3CH_2CHO + CH_3CH_2NO_2 \longrightarrow CH_3\underset{\substack{|\\ NO_2}}{CH}\text{-}\overset{\substack{OH\\ |}}{CH}\text{-}CH_2\text{-}CH_3$$

(IV)

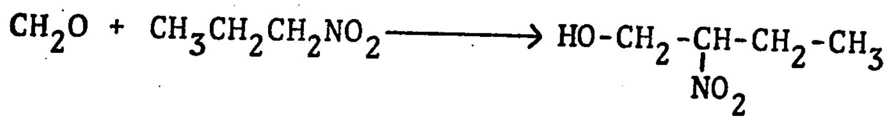
d. 2-methyl-2-nitro-1-propanol (V)



$$CH_2O + CH_3\underset{\substack{|\\ NO_2}}{CH}\text{-}CH_3 \longrightarrow HO\text{-}CH_2\text{-}\overset{\substack{NO_2\\ |}}{\underset{\substack{|\\ CH_3}}{C}}\text{-}CH_3$$

(V)

An additional compound, 2-nitro-1-butanol (III), was obtained commercially. It may be made in analogous fashion:

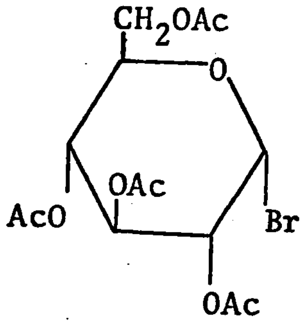


$$CH_2O + CH_3CH_2CH_2NO_2 \longrightarrow HO\text{-}CH_2\text{-}\underset{\substack{|\\ NO_2}}{CH}\text{-}CH_2\text{-}CH_3$$

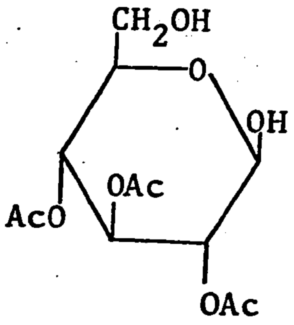
(III)

Compounds I-V had been previously synthesized by Astle and Abbott (86), and essentially the procedure of these authors was followed. The reactions were carried out at room temperature with a basic ion exchange resin (Amberlite IRA-401, hydroxyl form) as catalyst, and the yields obtained (61, 46, 60 and 25% for I, II, IV and V, respectively) generally exceeded those reported. Only compound V is a crystalline solid, the other nitro alcohols are high-boiling liquids. It is difficult to ascertain identity of products by comparing boiling temperatures, in vacuum distillation, with literature values since it is usually not practicable to conduct the distillation at precisely the pressure stated. However, the products prepared showed reasonable agreement with the literature in their refractive indices, and they exhibited the expected infrared bands. The hydroxyl groups gave absorptions in the 3400 cm^{-1} region, and the primary and secondary nitro groups in I, II and IV produced sharp peaks at 1550 cm^{-1}, whereas the tertiary nitro group in V absorbed at 1535 cm^{-1} (87). Moreover, NMR data were in accord with expectations. The physical and spectral data are given in the Experimental Section.

Glycosylation of the nitro alcohols was performed with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (VI, "acetobromoglucose") which was prepared according to directions given by Lemieux (88). For reasons stated in the Introduction it was expected that the glycosides to be synthesized would be sensitive toward base (with the exception of that of the tertiary nitro compound V), and it was therefore deemed inadvisable to use the good, but strongly basic, condensing agent silver oxide. Silver carbonate would appear to be less damaging, but due to its lower reactivity the condensation would require more time and the advantage of a lower basicity might thus be offset, the product being exposed to it for a prolonged period. In fact, exploratory experiments with both of these agents were unsatisfactory. However it was found that Wolfrom's procedure (25), in which silver carbonate is used together with silver perchlorate, gives good results when an excess rather than a catalytic amount of perchlorate is employed. The solvent used in most experiments was dry, ethanol-free chloroform, and anhydrous calcium sulfate (Drierite) was added as an internal desiccant. Different condensation conditions were tried where so indicated. All reactions were carried out in the dark in order to prevent photodecomposition of silver salts, and the reaction mixtures were inspected from time to time by thin layer chromatography (t.l.c.). Invariably, 2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (XII), the hydrolysis product of acetobromoglucose, was found among the products. It owed its formation to the generation of water in the condensation, and evidently the bromo sugar can successfully compete for water even with an effective desiccant such as Drierite. In order to make up for the hydrolytic loss of bromo sugar and to assure glycosylation of the nitro alcohol as far as possible, an excess of the former was employed.



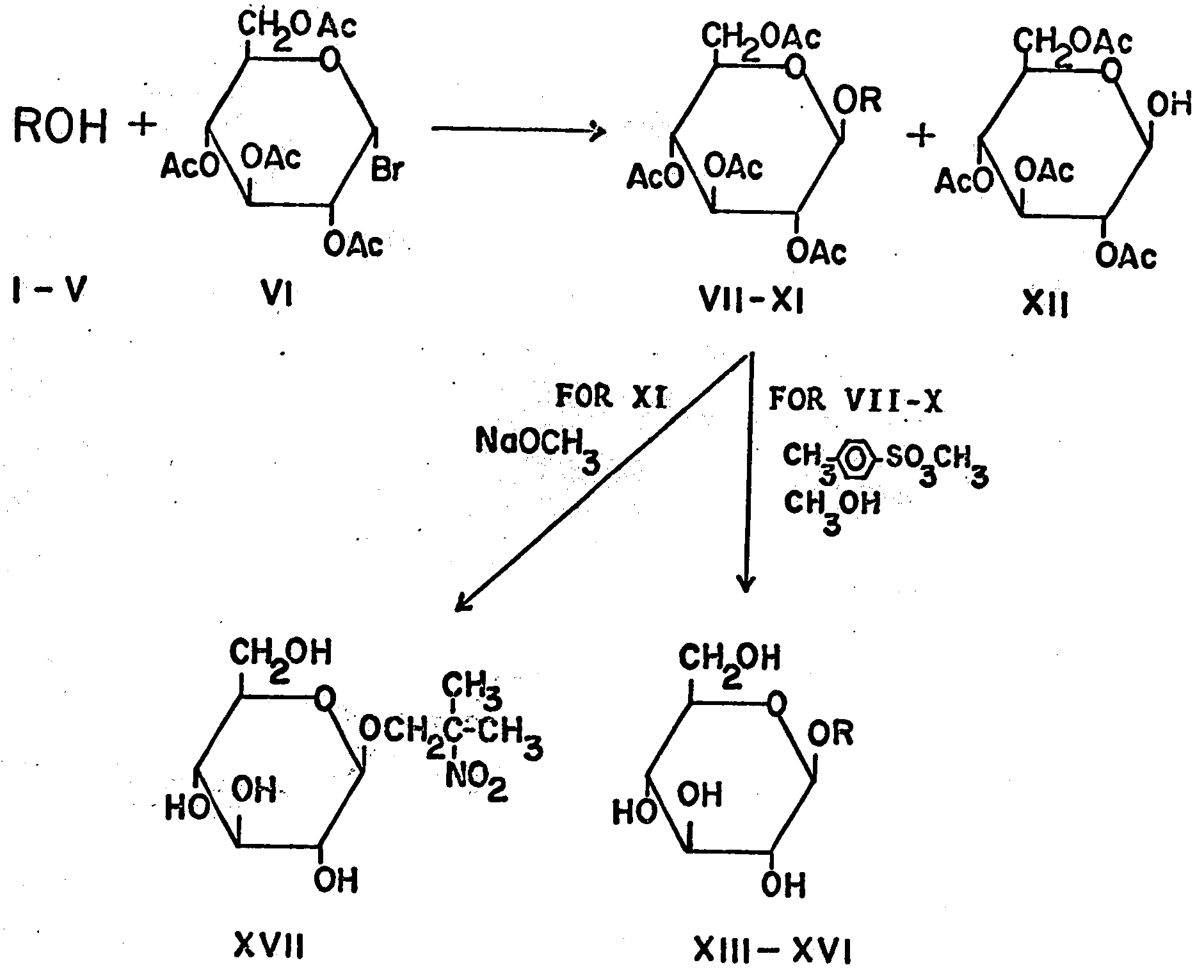
VI



XII

2-Nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (VII)

2-Nitro-1-propanol (I) and acetobromoglucose (VI) in a molar ratio of 1:1.6 were allowed to react for two hours in the presence of silver carbonate and silver perchlorate in a chloroform medium. Thin layer chromatography indicated formation of two products in about equal proportions. These could be separated satisfactorily on



COMPOUND	R GROUP
I, VII, XIII	$CH_2\underset{NO_2}{CH}-CH_3$
II, VIII, XIV	$HC{<}^{CH_2NO_2}_{CH_3}$
III, IX, XV	$CH_2\underset{NO_2}{CH}CH_2CH_3$
IV, X, XVI	$HC{<}^{CH_2CH_3}_{CH(NO_2)CH_3}$
V, XI	$CH_2-\underset{NO_2}{C}(CH_3)_2$

a silica gel column, and the desired nitro glucoside VII was isolated in crystalline form in a yield of 43%. The second product was the glucose tetraacetate XII.

Elemental analysis of the nitro glucoside agreed with the expected composition $C_{17}H_{25}NO_{12}$, and its levorotation ($[\alpha]_D$ -18.4°) was in accord with a β-D-glucosidic linkage. The crystals melted at 126-127°, but the melt was not transparent; it became clear only upon raising the temperature by another 10°. Possibly this behaviour was due to the presence of diastereoisomers. The alcohol I has an asymmetric center and was employed in its racemic form. Consequently its combination with an optically active sugar should give two diastereomeric β-glucosides which are epimers with respect to the asymmetric nitromethylene carbon atom (Theoretically, two epimeric α-glycosides could arise for the same reason).

The NMR spectrum of VII showed that the product indeed contained two epimers. Thus, the signal assignable to the methyl group of the aglycon consisted of two doublets, at 1.46 and 1.60δ, each having a spacing of 7 Hz. They were approximately equal in intensity. The low field signal attributable to the anomeric proton also was a pair of doublets which were centered at

4.48 and 4.53δ . Each had a spacing of 7.5 Hz, indicating 1,2-diaxial proton arrangements (89) and thereby revealing the β-configuration for both components. The nitromethylene protons (H-2') gave a complicated multiplet around 4.7δ; it consisted of 12 lines, in three groups of four lines. Further details of the spectrum are given in the Experimental Section.

1-Methyl-2-nitroethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (VIII)

Condensation between acetobromoglucose and 1-nitro-2-propanol (II) in the presence of silver carbonate and silver perchlorate in chloroform furnished the desired nitro glucoside in a yield of 35% after column chromatography. Again, a substantial amount of the hydrolysis product XII arose. The nitro glucoside which was obtained in this reaction was, like VII, a mixture of epimers in approximately equal proportions. This mixture (m.p. 128-129°, $[\alpha]_D$ -14.6°) is referred to as VIII A.

When the condensation was performed in a medium of nitromethane and in the presence of silver perchlorate but without silver carbonate, a different mixture of epimers (m.p. 139-143°, $[\alpha]_D$ -17.2°) was produced, in a lower yield of 26%. In this mixture (VIII B) one of the epimers preponderated, their ratio being about 5:1. A large amount of unreacted nitro alcohol (54%) was recovered in this experiment.

The two products VIII A and VIII B gave analytical and spectral data that agreed with the structure. In the NMR spectrum of VIII B (Fig.2) a high-field doublet (1.33δ) with a spacing of 6 Hz was seen, which was assigned to the aglycon methyl group of the preponderant epimer. The doublet partially overlapped that of the minor epimer which was centered at 1.26δ. Integration in an expanded spectrum allowed the estimate (5:1) of the epimer ratio. In VIII A the corresponding signals appeared as a nearly symmetrical triplet (Fig. 1), from which it was concluded that the epimers are present in the ratio 1:1. The signals attributable to the anomeric protons in VIII A were a pair of overlapping doublets near 4.6δ , each showing about the same intensity and a splitting of 7.5 Hz. The product VIII B exhibited only one doublet in that region, albeit with broadened peaks. The remainders of the spectra of VIII A and VIII B were very similar in character as can be seen from the Figures. The magnitude of splitting observed in the anomeric proton signals confirmed that both compounds of the products are β-gluco-

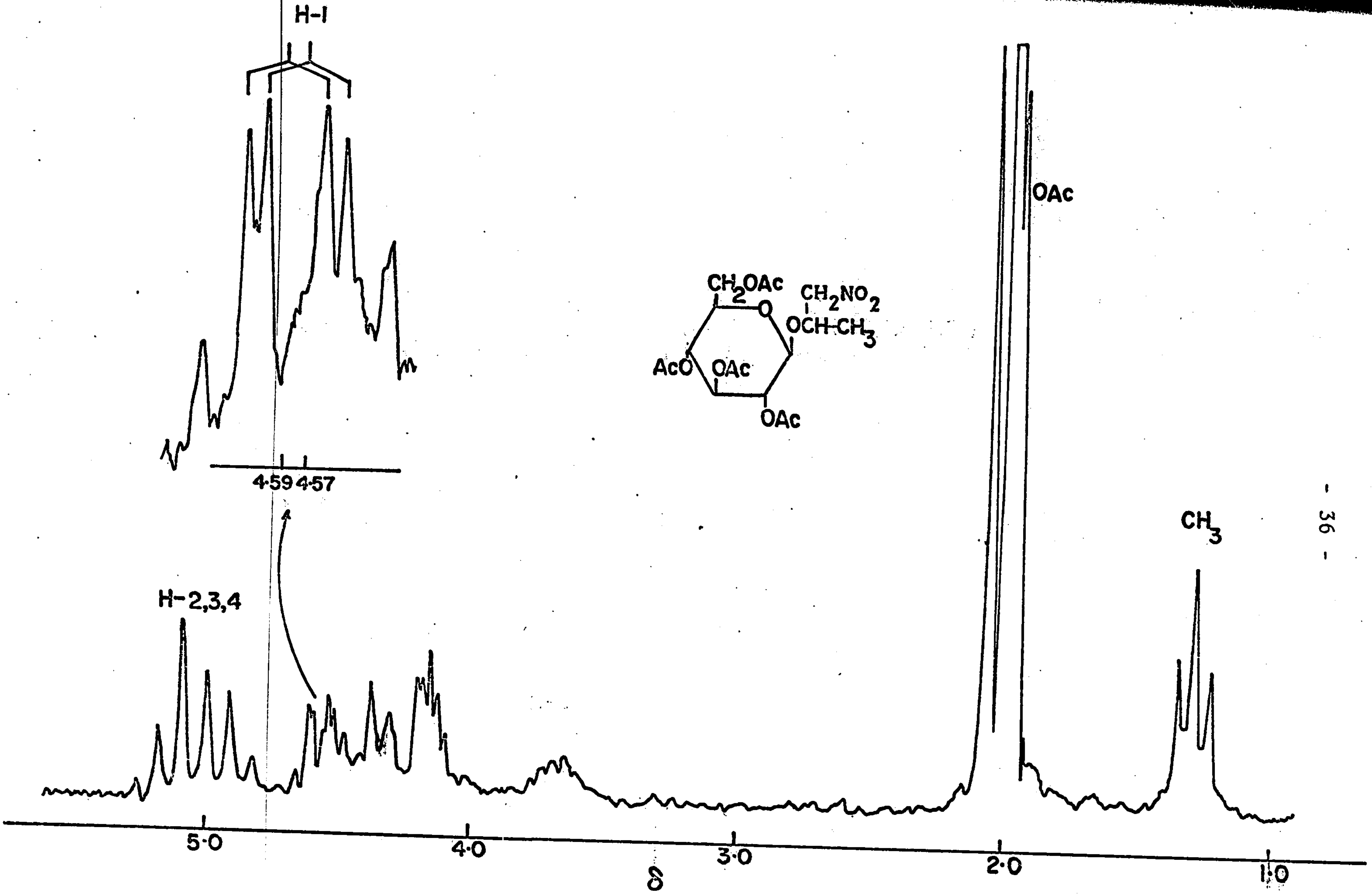


Fig. 1 NMR Spectrum of VIII A (100 MHz) in CDCl$_3$

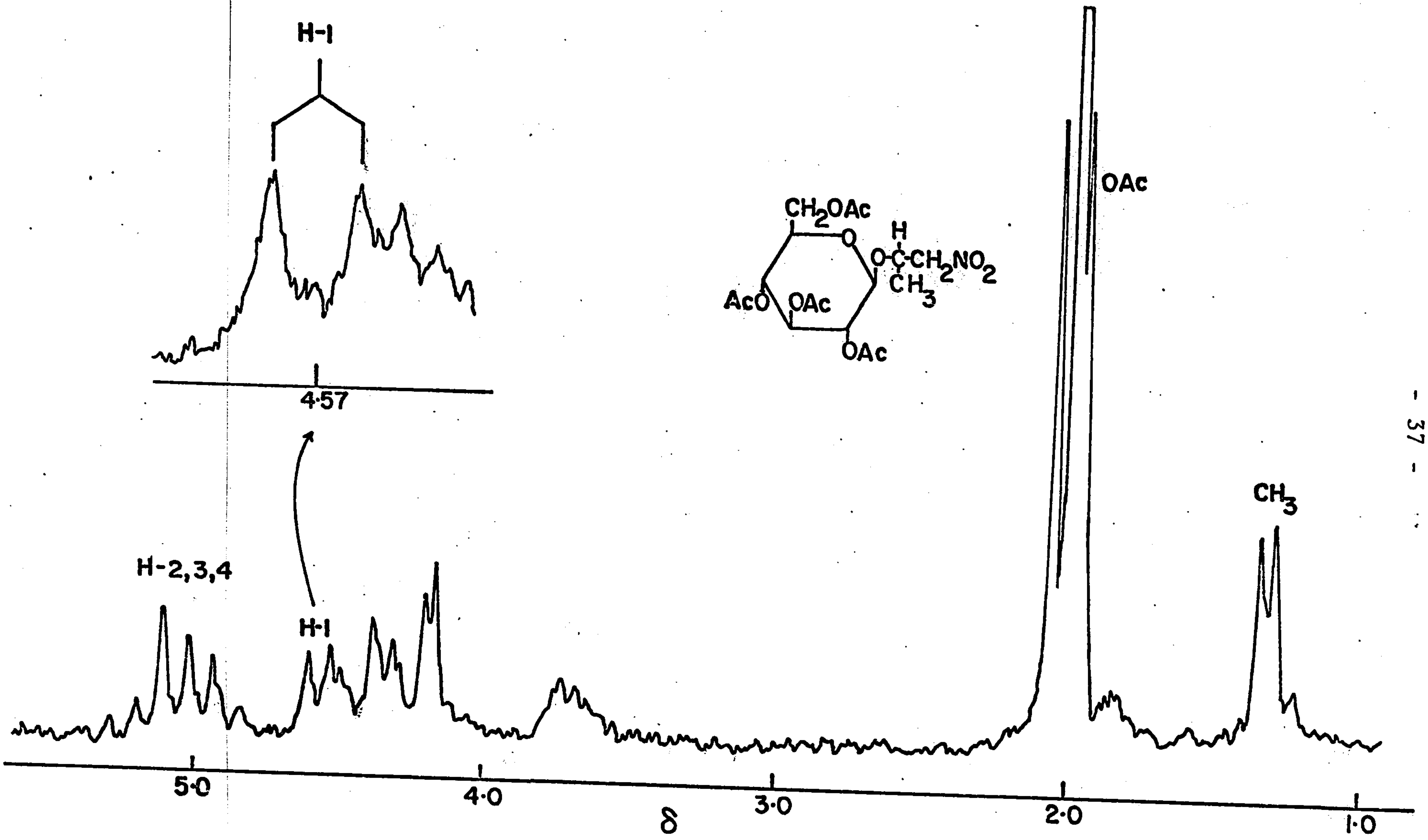


Fig. 2

NMR Spectrum of VIII B (100 MHz) in $CDCl_3$

sides. It follows that they must be epimeric in their aglycons. It appeared reasonable that this epimerism is reflected in small chemical shift differences for the nearby anomeric proton and the methyl group but is of no noticeable influence on the other sugar ring protons and the acetyl substituents.

2-Nitrobutyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (IX)

Prior to the successful synthesis of the 2-nitro-1-butyl glucoside IX by the silver carbonate-silver perchlorate method, a number of other methods were tried but proved unsatisfactory. Thus, attempted condensation of acetobromoglucose and 2-nitro-1-butanol in the presence of silver oxide led to a reaction mixture that contained at least five products according to t.l.c., and tedious column chromatography afforded IX in a yield of less than 5% besides starting alcohol and unidentified products. Silver oxide had been effective in the Koenigs-Knorr reaction of 3-nitro-1-propanol (synthesis of miserotoxin) (7), but in the present case it seems that the strong basicity of the reagent was detrimental because of the base-sensitive structure of the glycoside to be formed

(See the discussion on this subject on p.11).

Another attempt to synthesize IX was made by allowing to react the nitro alcohol III with β-D-glucopyranose pentaacetate in the presence of stannic chloride at 40° (90). The experiments were hampered by the practical difficulty that no suitable t.l.c. solvent system could be found which permitted differentiation between the starting sugar and the glucoside IX. Work-up after a reaction time of five hours gave only a small amount (4%) of IX besides a large amount of unreacted starting material together with some tetraacetate XII. This avenue was therefore abandoned also.

A third trial that failed was reaction of III with α-D-glucopyranose pentaacetate in refluxing benzene in the presence of a catalytic amount of p-toluenesulfonic acid. This is Helferich's method for the synthesis of phenolic glycosides (91), and it was reasoned that it might work with nitro alcohols as they are somewhat more acidic than ordinary alcohols. However, unchanged reactants and tetraacetate XII were all that could be isolated after a reaction time of six hours.

Eventually the silver salt-catalyzed condensation, performed as for the previously described nitro glucosides, was adopted and furnished the 2-nitro-1-butyl derivative

IX in a yield of 42%. The analytical sample, which melted at 86-88° and had $[\alpha]_D$ -18.8°, showed no NMR spectroscopic evidence for being a mixture of epimers, although epimerism due to asymmetry of the nitromethylene carbon should be possible. The terminal methyl group of the aglycon gave one symmetrical triplet at 0.96δ, with a spacing of 7 Hz, and the anomeric proton gave a doublet at 4.53δ having a spacing of 7.5 Hz, in line with the β-glucosidic linkage. However, samples varying somewhat in melting point were obtained in different runs, and in one instance (which could not be reproduced), a crop melting at 99-103° was isolated. This might be an indication that IX, too, may arise in epimers. Perhaps in the analytical sample referred to above a single epimer had crystallized fortuitously, or else the sample contained epimers which were not differentiated spectroscopically.

1-Ethyl-2-nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (X)

For the synthesis of the glucoside X of 2-nitro-3-pentanol (IV), several methods of condensation were examined. Silver oxide was first tried as an acid acceptor but, like in the synthesis of IX, it proved to be inappropriate. In addition to the hydrolysis product XII, the reaction mixture contained several products according to t.l.c. It appeared that the desired glucoside X was formed in small yield. However, it could not be isolated but was present as a minor component (about 10%) in a fraction of recovered 2-nitro-3-pentanol, as judged from the NMR spectrum of that fraction.

In another experiment, acetobromoglucose and the alcohol IV were allowed to react for 25 hours in nitromethane solution in the presence of mercuric cyanide as acid acceptor. Condensation did occur and some β-glucoside X could be isolated by chromatography in crystalline form, but a substantial proportion (estimated at 35% by NMR spectroscopy) of the α-anomeric glucoside was also produced. The latter was contained in mixed fractions that failed to crystallize, and its presence was revealed by a low-field (5.87δ) anomeric proton doublet with a coupling constant of 4 Hz. More successful was the condensation with mercuric cyanide when 1,2 dichloroethane was used as a solvent. In that case, pure β-glucoside was obtained in a yield of 46% although the reaction mixture did contain another (unidentified) product in addition to the apparently inevitable tetraacetate XII. The glucoside isolated in this experiment melted at 136-

139° and showed $[\alpha]_D$ -21.7°. It is subsequently referred to as X A.

Condensation performed with silver carbonate-silver perchlorate resulted in isolation of crystalline β-glucoside in a yield of 52%. However, the product melted at 124-125° and exhibited $[\alpha]_D$ -19.6°. It is referred to as X B and it differed spectroscopically from X A.

The stereochemistry of structure X is more complicated than that of the preceding glucosides inasmuch as the aglycon contains two asymmetric centers. Four stereoisomers differing in aglycon configuration are therefore possible. The NMR spectra of the two products X A and X B (Fig. 3,4) were difficult to analyze, especially because the -O-CH and $-CH(NO_2)$ moieties of the aglycon were expected to give one-proton multiplets in the region of 4-5δ where the anomeric proton as well as the C-6 and C-5 protons of the sugar moieties resonate also. However, the general appearance of the spectra, and particularly the fact that the signals assignable to the methyl protons of the aglycon ethyl moiety (0.9δ region) had the character of double triplets, tended to indicate epimeric mixtures. Similarly, the anomeric proton signal in X A (4.47δ , $J_{1,2}$ = 7.5 Hz in

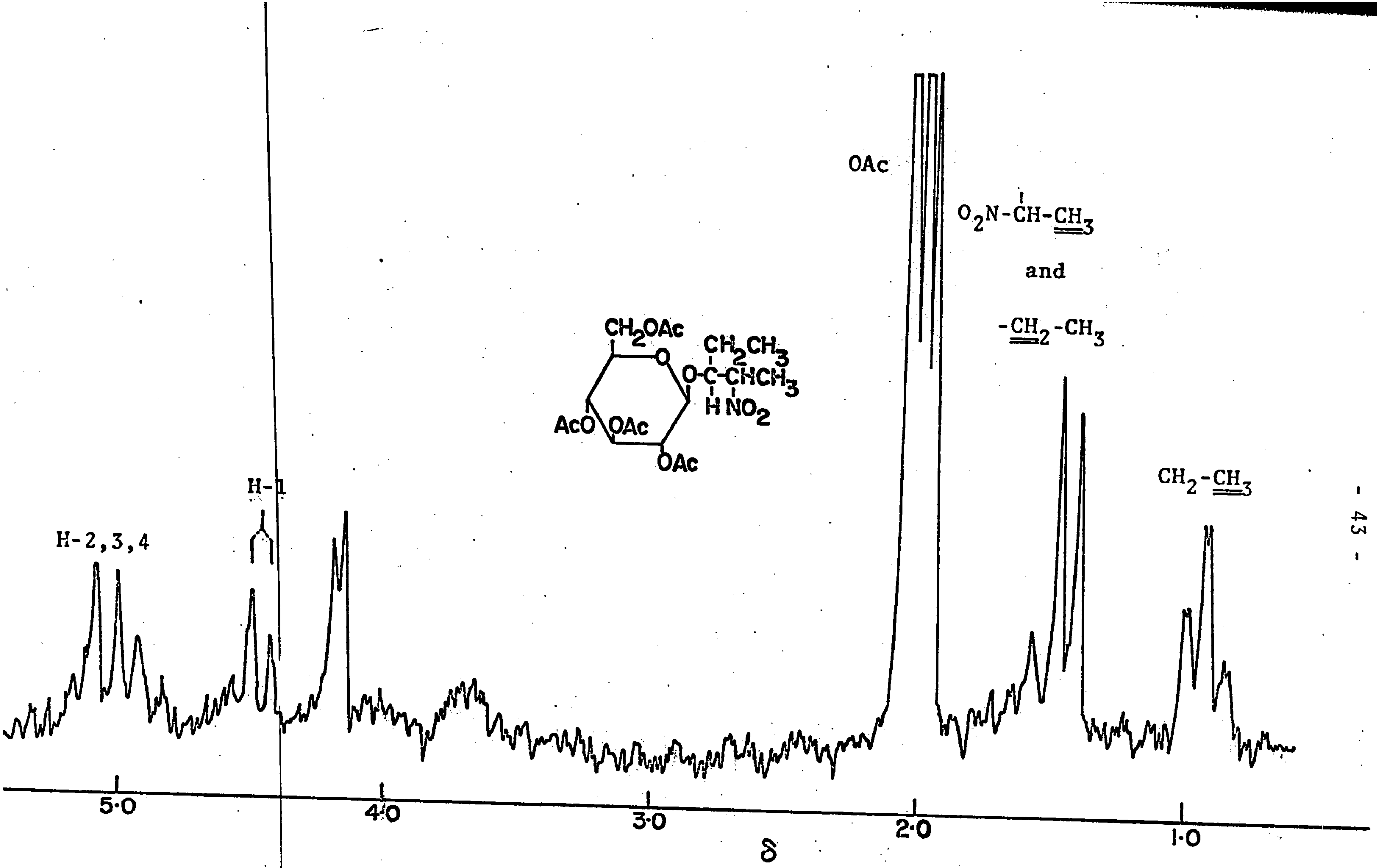


Fig. 3 NMR Spectrum (100 MHz) of X A in $CDCl_3$

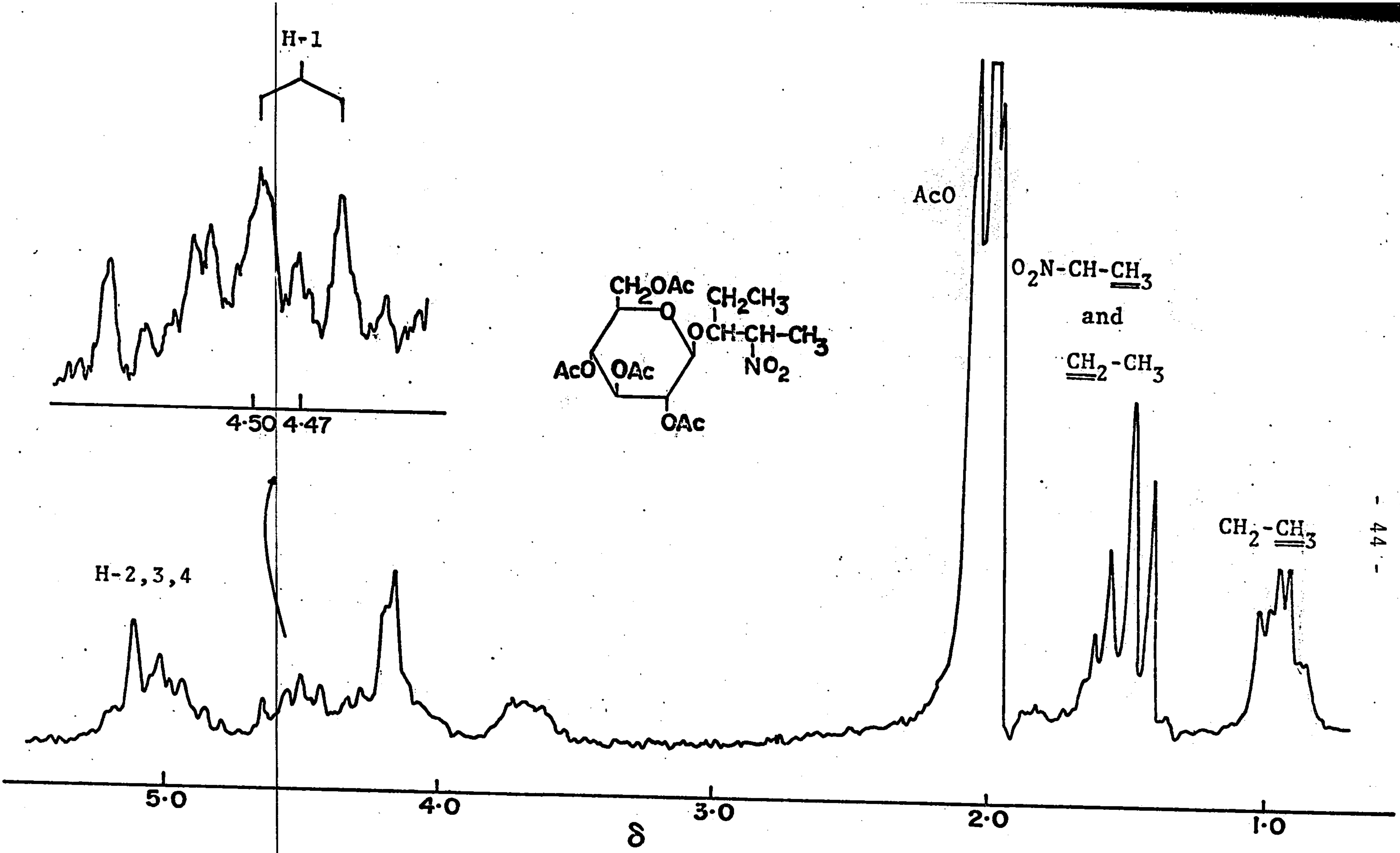


Fig. 4 NMR Spectrum (100 MHz) of X B in $CDCl_3$

accord with β-glucosidic linkage) actually seemed to consist of two nearly coinciding doublets. The number of lines present in the corresponding region of X B also suggested a mixture of closely related diastereoisomers.

2-Methyl-2-nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (XI)

Condensation between acetobromoglucose and the nitro alcohol V offered the least complications. Performed with excess silver carbonate and only a catalytic amount of silver perchlorate it afforded the β-glucoside XI in crystalline form in a yield of 42%. As usual, the tetraacetate XII was a by-product. In the case of XI, no complications due to aglycon epimerism were to be expected, and the product gave a readily interpretable NMR spectrum (Fig. 5). The two aglycon methyl groups (which are magnetically nonequivalent) gave singlets with slightly differing chemical shifts (1.50 and 1.56δ). Interestingly, the two methylene protons of the aglycon had identical chemical shift (3.98δ) and therefore appeared as a sharp, two-proton singlet without exhibiting geminal

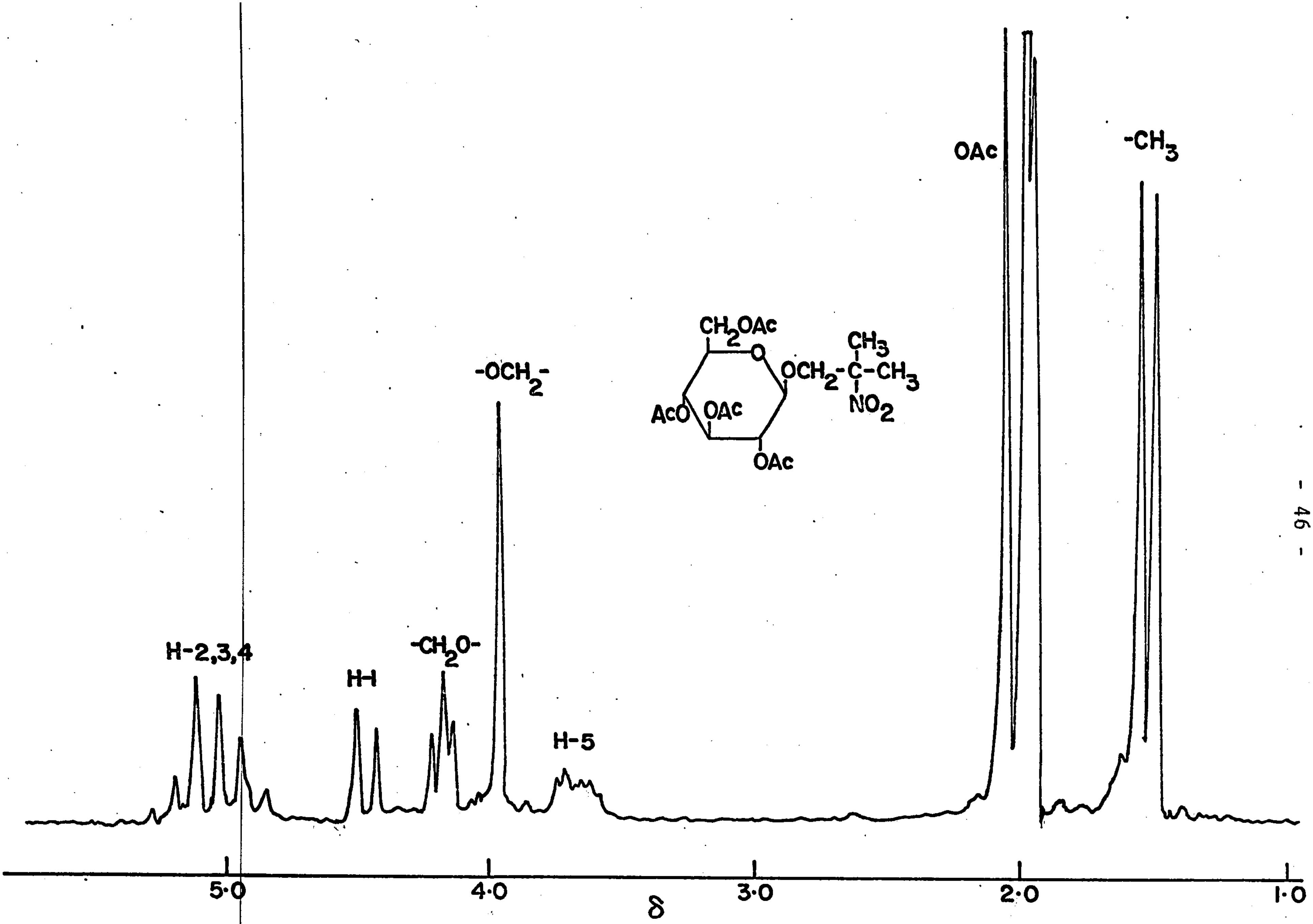


Fig. 5 NMR Spectrum (100 MHz) of XI in $CDCl_3$

coupling. The anomeric proton produced a clear doublet (4.48δ) with a coupling constant of 7.5 Hz indicative of a β-glucosidic bond. The optical rotation of XI, $[\alpha]_D$ -20.1°, also agreed with this type of bond.

B. Deacetylation of the Glucoside Tetraacetates

2-Nitropropyl β-D-glucopyranoside (XIII)

Deacetylation of the glucoside tetraacetate VII was first attempted by sodium methoxide-catalyzed methanolysis (Zemplén method). It was observed by t.l.c. that within five minutes of the start of the reaction a number of products travelling more slowly than VII were formed. Undoubtedly they were products of partial deacetylation. However, after an additional five minutes the only product present gave an immobile t.l.c. spot resembling that of free D-glucose, and no glycoside was found. Apparently, complete cleavage of the glycosidic bond had occurred, and this reaffirmed the lability of that kind of activated linkage (see the earlier discussion on p.11).

Deacetylation catalyzed by methyl p-toluenesulfonate proved successful. The amount of catalyst usually employed corresponded to 1/13-1/15 (mole per moles) of the sugar acetate to be treated, and the concentration (in anhydrous methanolic solution) was adjusted to 0.005-0.010 mmole/ml. The deacetylation proceeded at a slow rate at reflux temperature and was monitored by t.l.c. Generally, 22-29 hours were required, and the most suitable moment for stopping the reaction was ascertained by t.l.c. which was done at hourly intervals during the last several hours. Besides the desired deacetylation there occurred slowly an undesirable but readily understandable side reaction, namely, transglycosylation to give methyl α-D-glucopyranoside. The methanolysis was quenched when it was judged by t.l.c. that only small amounts of incompletely deacetylated materials were remaining and the amount of methyl glucoside was not too large yet. The same procedure was used for deacetylation of the other nitroalkyl glucosides (see the subsequent sections), with minor variations in the amounts of catalyst and in reaction time as indicated where relevant.

From the glucoside tetraacetate VII was obtained in this way 2-nitropropyl β-D-glucopyranoside (XIII) in yields of 65-75% after chromatography of the reaction mixture on silica gel. An infrared spectrum of the crystalline compound showed strong hydroxyl absorption in the 3500-3300 cm^{-1} region but no ester carbonyl absorption in the 1750 cm^{-1} region, thus confirming total deacetylation.

Levorotation of the product ($[\alpha]_D$ -12.3°) indicated that the glucosidic β-configuration had been retained during the deacetylation. The NMR spectrum was in accord with the structure to the extent that individual signal assignments could be made (see Fig. 6 and Experimental). In particular, a doublet assignable to the anomeric proton showed a splitting of 7.5 Hz indicative of trans-diaxial coupling with H-2 and hence, of the β-glucosidic configuration. The methyl protons of the aglycon gave a clear doublet at highest field (splitting, 7 Hz). The spectrum was free from signals attributable to acetyl groups.

The minor side product, methyl α-D-glucopyranoside, was also isolated by chromatography and identified by comparison of its NMR spectral and optical rotation data with those of a commercial sample.

No evidence, spectral or otherwise, was obtained for XIII to contain aglycon epimers although the precursor VII had been shown to be an epimeric mixture. One may assume either that the spectrum of the deacetylated material did not reveal epimers although they were present,

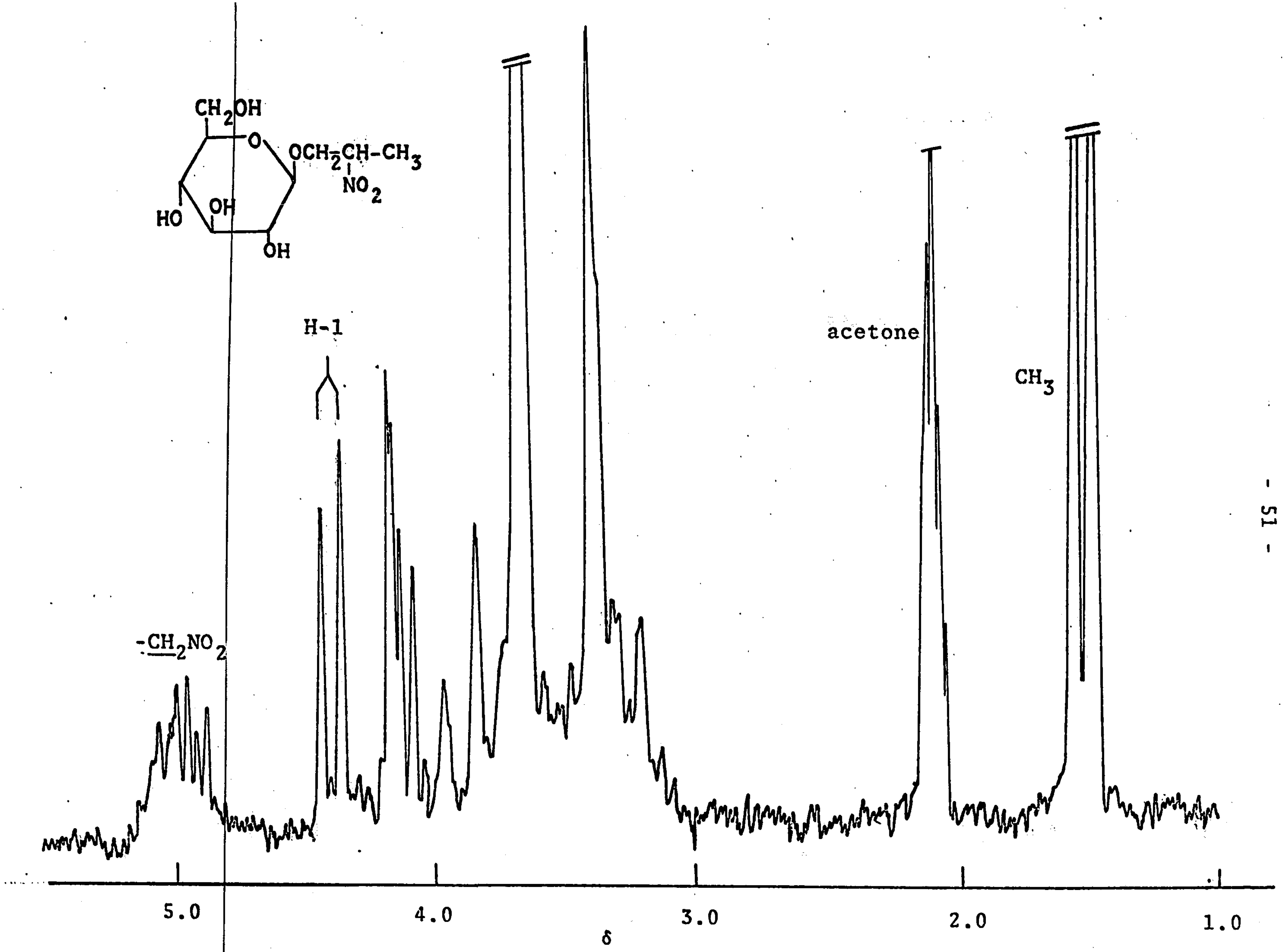


Fig. 6 NMR Spectrum (100 MHz) of XIII in acetone d_6 (+0.05 ml D_2O)

or that in fact a single epimer had crystallized. The latter explanation is perhaps the more valid one since spectroscopic evidence for epimerism was obtained for the isomeric glucoside XIV (see the following section) which was not crystalline but syrupy.

1-Methyl-2-nitroethyl β-D-glucopyranoside (XIV)

Pilot experiments indicated that somewhat less time was appropriate for deacetylation of the glucoside VIII. After a reaction time of 18 hours and following column separation, the 1-methyl-2-nitroethyl β-D-glucopyranoside(XIV) was obtained as a syrup in 56% yield. Two other products detected in the reaction mixture were methyl α-D-glucopyranoside (more slowly moving) and a substance (faster moving) that showed ester carbonyl absorption in the infrared and was therefore presumed to be incompletely deacetylated glucoside. An attempt was made to improve the yield of XIV by repeating the methanolysis on the partially deacetylated material, but this was to no avail. Presumably any gain in product by the second methanolysis was offset by losses occurring due to transglycosylation and/or in repeated column

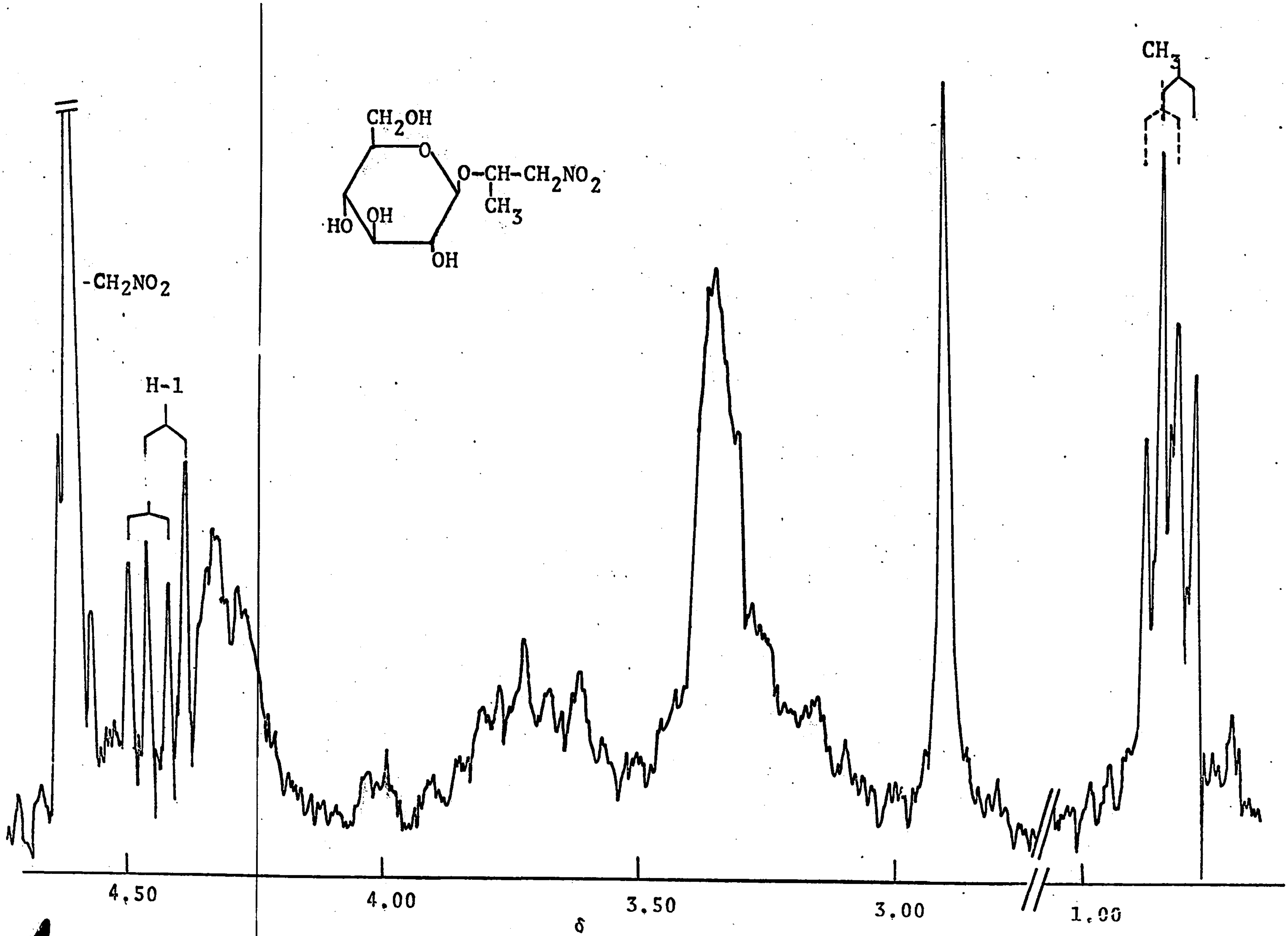


Fig. 7 NMR Spectrum (100 MHz) of XIV in acetone-d_6

chromatography.

Chromatographically pure but syrupy XIV had a specific rotation of $[\alpha]_D$ -18.3°, and its infrared spectrum indicated absence of acetyl groups, The NMR spectrum in acetone-d_6 (Fig. 7) showed a group of high-field peaks centered at 1.30δ, which were due to the aglycon methyl protons (intensity, 3H). If the substance were a single diastereoisomer, one would expect this signal to be a doublet, split by the adjacent proton at C-1'. However, the signal consisted of two overlapping doublets, each with a spacing of 6.5 Hz, and this is regarded as evidence for the presence of two diastereoisomers. Similarly, the signal of one-proton intensity attributable to the anomeric proton was a pair of overlapping doublets at 4.41 and 4.44δ, each having a splitting of 7.6 Hz.

2-Nitrobutyl β-D-glucopyranoside (XV)

Deacetylations of the glucoside tetraacetate IX were carried out using catalyst to sugar ratios ranging from 1/10 to 1/19, and reaction times of 23-26 hours were employed. At the end, the reaction mixtures usually exhibited one major t.l.c. spot for the desired

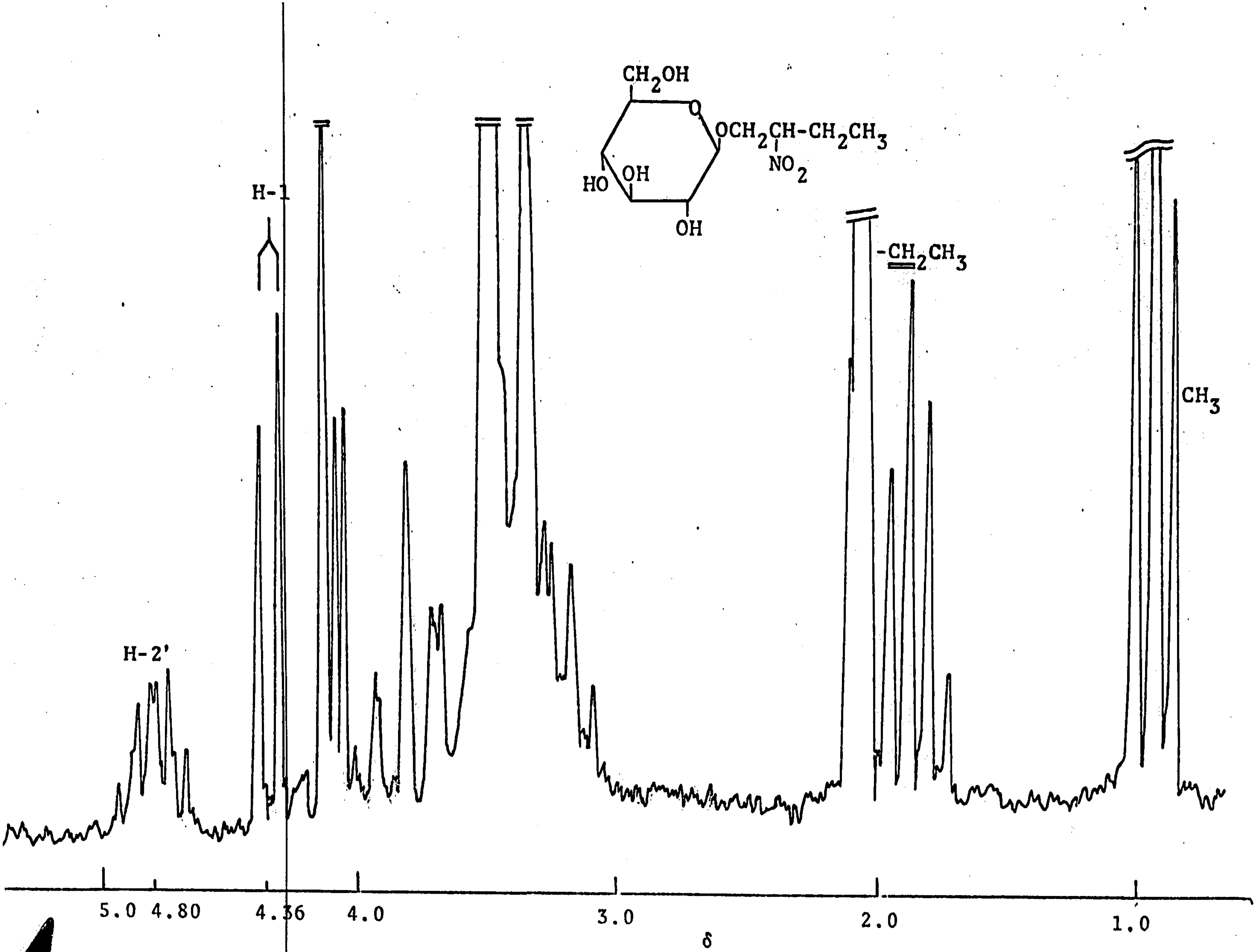


Fig. 8 NMR Spectrum (100 MHz) of XV in acetone-d_6 (+ 0.05 ml D_2O)

glucoside XV and a faint spot for methyl α-D-glucopyranoside. Pure XV was obtained in yields of 60-80% upon column chromatography, and the compound crystallized quite readily (m.p. 130-132°, $[\alpha]_D$ -22.1°). Completeness of deacetylation was shown by the absence of acetyl peaks in infrared and NMR spectra. The NMR spectrum is depicted in Fig. 8. Again, the β-configuration of the glucosidic bond was indicated, in agreement with the levorotation, by the coupling constant of 7.5 Hz found in the anomeric proton signal at 4.36δ . The ethyl moiety of the aglycon produced a triplet at 0.91δ and a quintet at 1.86δ for $\underline{CH_3}$-CH_2- and CH_3-$\underline{CH_2}$-$CH(NO_2)$, respectively, and the nitromethylene proton gave a multiplet at 4.80δ. No signal multiplicities that could be ascribed to different epimers were detected, and it is therefore concluded that crystalline XV was a uniform compound.

1-Ethyl-2-nitropropyl β-D-glucopyranoside (XVI)

Pilot experiments indicated that p-toluenesulfonate-catalyzed methanolysis of the glucoside tetraacetate X required a longer reaction period. With a catalyst to sugar ratio of 1/19, 60 hours of refluxing was required,

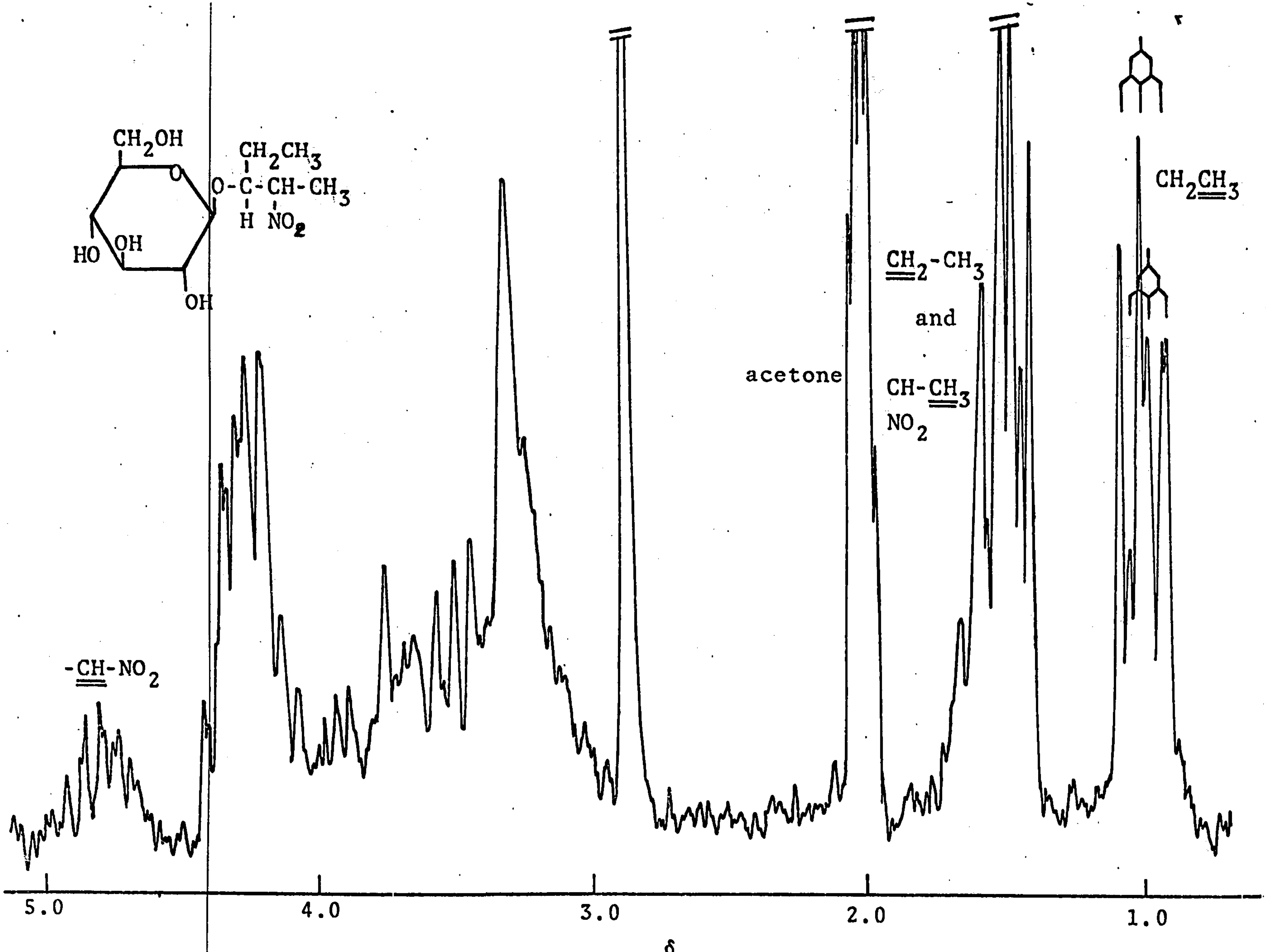


Fig. 9 NMR Spectrum (100 MHz) of XVI in acetone-d_6

while with a ratio of 1/13, this period could be reduced to 45 hours. As in previous deacetylations the production of by-products was noticed. However, they appeared to be present only in minor amounts in the final reaction mixture as judged from their faint t.l.c. spots. Repeated column chromatography furnished XVI as a chromatographically homogeneous syrup that failed to crystallize. It had $[\alpha]_D$ -28.6° and lacked carbonyl absorption in the infrared while showing strong hydroxyl absorption.

Although the NMR spectrum (Fig. 9) was too complicated for a detailed analysis, it showed a three-proton signal at highest field which was attributable to the methyl portion of the aglycon ethyl moiety and which consisted of two overlapping triplets, suggesting a non-uniform product (i.e., the presence of diastereoisomers). A complex multiplet of five-proton intensity adjoining downfield was attributed to the methylene portion of the ethyl group and to the methyl group of the nitropropyl moiety. The one-proton multiplet at lowest field (4.60-5.02δ) presumably represented the nitromethylene proton.

2-Methyl-2-nitropropyl β-D-glucopyranoside (XVII)

The glucoside tetraacetate XI was the only compound having an aglycon with a tertiary nitro group. It could be anticipated that, because of the lack of a hydrogen atom in α-position to the nitro group, the compound would be stable under the basic conditions of Zemplén deacetylation. This proved to be true, and methoxide-catalyzed deacetylation cleanly gave chromatographically pure glucoside XVII in 95% yield. The compound melted sharply at 140.5-141.5° and showed $[\alpha]_D$ -23.3°. The infrared spectrum lacked carbonyl absorption and gave a nitro band at 1535 cm^{-1}, in accord with the tertiary attachment of the nitro group. The NMR spectrum showed a six-proton singlet at high field for the two aglycon methyl groups. It is recalled that these groups had slightly differing shifts due to magnetic nonequivalence in the fully acetylated compound, but the same was not observed in the free glucoside. The anomeric proton signal was located at low field as a doublet with a 7.5 Hz splitting in conformity with the β-glucoside configuration. The remainder of the spectrum was not amenable to analysis.

3-Nitropropyl β-D-glucopyranoside (XVIII, miserotoxin)

This compound was prepared for purposes of comparison in the bioassay of the new glucosides. The procedure of Shields (7) was followed (see also p.8 and 11). The compound was obtained as a syrup showing $[\alpha]_D$ -24° and giving infrared and NMR spectra identical with those recorded by the author just mentioned.

C. Toxicity of the Nitroalkyl β-D-Glucopyranosides XIII-XVIII

A test was designed for a comparison of the toxicity of miserotoxin (XVIII) and the synthetic miserotoxin analogs XIII-XVIII. The tests were carried out on one-week old chickens. The method was similar to that employed by Williams and Binns (5) except that all chemicals were fed as solids or syrup in gelatin capsules whereas the authors (5) used aqueous solutions which they introduced orally by syringe. The nitroalkyl glucosides were weighed into gelatin capsules on the day prior to the test. Each capsule contained 250 μmole of the test chemical. A set of capsules containing equivalent amounts of pure glucose were also prepared.

The chickens were weighed* and coded by marking head, wing and back prior to administering the gelatin capsule. The capsule was dipped in water and placed on the back of the chicken's tongue from where it was swallowed. This procedure was carried out on seven birds, capsules being administered in

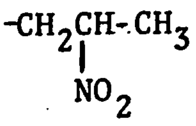
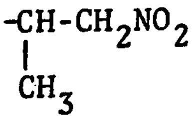
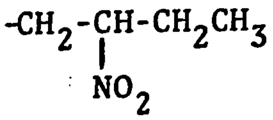
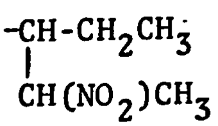
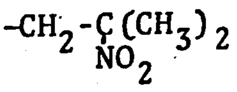
---

* Average body weight was 62.7 g.

the order of glucose, XVIII, XIII, XIV, XV, XVI and XVII in one-minute intervals. The operation was repeated three times on another twenty-one chickens, in three groups in the same order, and the time of administration recorded, The chickens were kept in pairs in separate cages. Four chickens were kept as controls without treatment. Close observation was exercised during the first twelve hours and at the end of the twenty-four hour test period.

The eight groups of chickens showed different symptoms during the first twelve hours. The results were recorded in the following Table. The letter N signifies normal behavior as observed in the controls and in those having received glucose. The letter D indicates that the birds, according to visual judgment, were in a state of depression. They were slow in motion, had their heads lowered, eyes closed, and wings drooped. These symptoms occurred to varying degrees in all the chickens of groups 3-8 during the first 12-hour period. At the end of the twenty-four hour period, death had occurred only in groups 4 and 6, although effects of heavy poisoning persisted

Toxicity of Nitroalkyl β-D-Glucopyranosides *

Group	Test Chemical	Aglycon of Test Chemical	Symptoms	
			in 12 h.	in 24 h.
1	(Control)	-	N.	all alive N.
2	glucose	-	N.	all alive N.
3	XVIII (miserotoxin)	$-(CH_2)_3NO_2$	D.	all alive D.
4	XIII	 $-CH_2\underset{NO_2}{CH}-CH_3$		3/4 dead 1/4
5	XIV	 $-\underset{CH_3}{CH}-CH_2NO_2$	D.	all alive D.
6	XV	 $-CH_2-\underset{NO_2}{CH}-CH_2CH_3$		2/4 dead 2/4
7	XVI	 $-\underset{CH(NO_2)CH_3}{CH}-CH_2CH_3$	D.	all alive D.
8	XVII	 $-CH_2-\underset{NO_2}{C}(CH_3)_2$		all alive N.

* N, Normal; D, depressed.

also in groups 3, 5 and 7. The chickens of group 8 had returned to almost normal behavior.

The results may be classified in three groups as far as toxicity is concerned. Compounds XIII and XV killed 50% or more of the chickens and were clearly more toxic than miserotoxin (XVIII). Compound XVII caused slight poisoning in the first twelve hours, but the symptoms faded after twenty-four hours, suggesting that the compound was less toxic than miserotoxin. Compounds XIV and XVI showed a toxicity roughly similar to that of miserotoxin. It must be realized that these results have certain limitations. They were obtained from qualitative observation of toxic symptons on a relatively small number of animals; exact measurements of physiological parameters such as heart beat and body temperature on larger groups of animals would have been more informative. Furthermore, it must be pointed out that the results refer to products as obtained in the syntheses and not necessarily to stereochemically uniform compounds. At least XIV and XVI are known to be mixtures of diastereoisomers. Diastereoisomers frequently differ greatly in biological activities, and fortuitous isomer ratios in individual preparations may lessen the reliability of the test results.

Miserotoxin (XVIII) had been tested previously as described by Shields (7). The symptoms reported were similar to those observed in the present test. In the former test, an aqueous solution of XVIII with a concentration of 5 mg per gram of body weight (18.7 μmole per gram body weight) was used and the chickens were all killed within ten hours. The present test employed a much lower dose (3.99 μmole per gram of body weight), which made possible a better comparison of the effects of the various gluocosides with reference to miserotoxin. In terms of toxicology, the toxicity of miserotoxin as revealed by the present results must be described as moderate.

PART II

OXIDATION OF AMINO SUGARS TO NITRO SUGARS

RESULTS AND DISCUSSION *

The methods available for introducing a nitro group into carbohydrate molecules have been outlined in the Introduction. It is recalled that so far there has been reported in the literature only one example which involved oxidation of a nitrogenous sugar derivative, namely an oxime (75). Prior to the publication of that report, the present project of oxidizing amino sugars was initiated. 2-Amino-2-deoxy aldoses are easily synthesized by the cyanohydrin method (92), and it would be interesting to explore whether they may be oxidized to 2-nitro aldoses, the synthesis of which has received very little attention to date. For practical reasons, however, it was decided to begin a study of amine oxidation first with a non-carbohydrate model compound and then with 3-amino-3-deoxy sugars. One of the reasons for commencing studies in the 3-amino series was the expectation that nitro products, if obtained, could more readily be identified, by comparison with

---

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

known compounds, and that fewer complications would likely be encountered than with 2-nitro glycosides, the latter expectedly being base-labile (compare the discussion on p. 11).

m-Chloroperbenzoic acid was chosen as an oxidizing agent. It was considered that the relatively mild action and ease of handling of this stable, commercially available reagent would be advantageous. The reagent has been widely used to synthesize epoxides from olefins (93) and sulfones or sulfoxides from sulfides. Only one example could be found for its use in an oxidation of an amino group to a nitro group. Robinson and coworkers (84) were able to oxidize an aminosteroid in 58% yield and established that the reaction proceeded with retention of configuration at the asymmetric carbon atom bearing the nitrogen.

As will be outlined in the subsequent paragraphs, oxidation of <u>trans</u>-2-aminocyclohexanol (resembling aminopyranosides in its structure) and of 3-amino-3-deoxy glycosides proved feasible. However, the reaction proved to be complicated by the fact that nitroso derivatives arose in varying proportions along with nitro derivatives.

known compounds, and that fewer complications would likely be encountered than with 2-nitro glycosides, the latter expectedly being base-labile (compare the discussion on p. 11).

m-Chloroperbenzoic acid was chosen as an oxidizing agent. It was considered that the relatively mild action and ease of handling of this stable, commercially available reagent would be advantageous. The reagent has been widely used to synthesize epoxides from olefins (93) and sulfones or sulfoxides from sulfides. Only one example could be found for its use in an oxidation of an amino group to a nitro group. Robinson and coworkers (84) were able to oxidize an aminosteroid in 58% yield and established that the reaction proceeded with retention of configuration at the asymmetric carbon atom bearing the nitrogen.

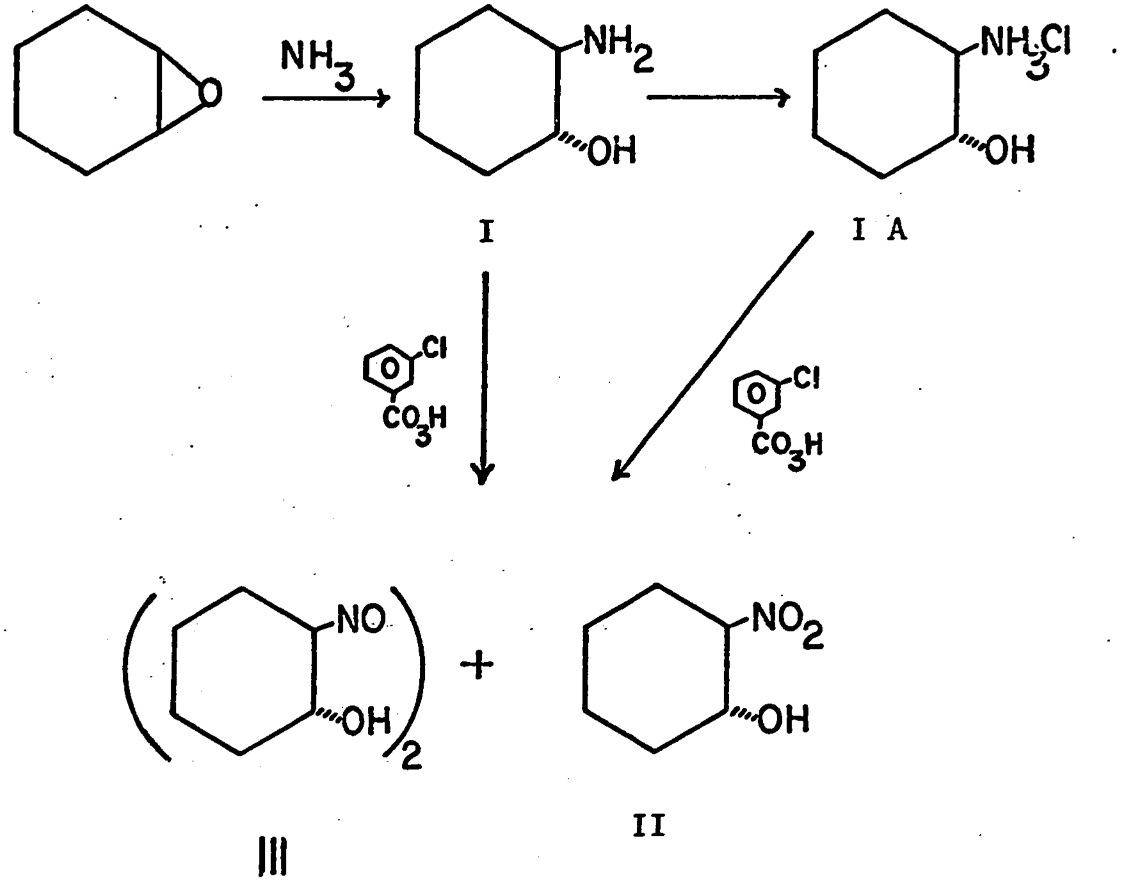
As will be outlined in the subsequent paragraphs, oxidation of trans-2-aminocyclohexanol (resembling aminopyranosides in its structure) and of 3-amino-3-deoxy glycosides proved feasible. However, the reaction proved to be complicated by the fact that nitroso derivatives arose in varying proportions along with nitro derivatives.

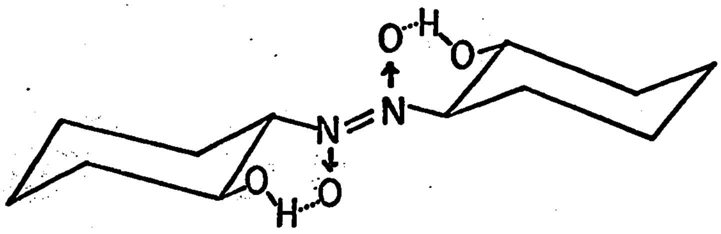
They are evidently produced as intermediates in the oxidation (85, 94) and, depending on conditions, tend to form stable dimers which are oxidized no further. The dimerization must be very rapid since the blue-green color commonly associated with monomeric nitroso compounds (95, 96) was never observed. It was found that the ratio of nitro to nitroso products was influenced by the magnitude of the excess of peracid that was employed. With a relatively low molar ratio of peracid to amine (e.g. 3:1) the nitroso product always preponderated. With an increased ratio (e.g. 6:1), a more even distribution of products could be achieved. Apart from this, the reaction appeared to be rapid and clean, and other substituents such as hydroxyl and methoxyl groups remained intact. One major practical difficulty relating to the work-up procedures had to be overcome. This was the removal of m-chlorobenzoic acid which, of course, was present in large amounts in the crude reaction mixtures. The usual practice of removing it by extraction with aqueous bicarbonate from an organic medium was not applicable in most cases for fear of causing configurational changes in the nitro sugars and also because the nitro sugars are soluble in water. However, chromatographic and extractive procedures were worked out which furnished pure products in satisfactory manner.

A. Oxidation of trans-2-aminocyclohexanol (I)

Trans-2-aminocyclohexanol (I) was prepared by reaction of cyclohexene oxide with liquid ammonia at elevated temperature (97). *Trans*-diaxial opening of the epoxide ring leads to the formation of I as the exclusive product. Its spectral data and melting point agreed with expectations. For further characterization and as an alternative starting material for the oxidation, the amine hydrochloride I A was prepared also.

Oxidation of the amino alcohol I with a threefold molar excess of m-chloroperbenzoic acid in chloroform solution at reflux temperature appeared to be complete after one hour. Thin layer chromatography revealed the formation of two products. Removal of the acid by extraction and separation of the products by column chromatography was attended by losses; however, both products could be isolated in pure form in moderate yields. One product, which was obtained in a yield of 16%, proved to





III

be the desired trans-2-nitrocyclohexanol (II). It was identified by its spectral properties and by its melting point (46-47°) which agreed with the literature value (98).

The second product (m.p. 130-132°) was isolated in 28% yield. Elemental analysis indicated the empirical formula $C_6H_{11}NO_2$. The compound showed strong ultraviolet absorption with λ_{max} 296 nm (ε, 7500) resembling that reported (85) for dimeric nitrosocyclohexane (λ_{max} 290 nm). The infrared spectrum exhibited broad absorption in the 3400 cm^{-1} region attributable to hydrogen-bonded hydroxyl, and a strong band at 1195 cm^{-1} which was characteristic for a trans-nitroso dimer structure (95, 96). There was no absorption in the region 2800-1500 cm^{-1}, indicating absence of such functional groups as NO_2, C=O, NH_2 and C=C. On the basis of these facts the compound was assigned structure III (trans-nitrosocyclohexanol trans-dimer). Similar products were obtained when the amine hydrochloride I A was used as starting material in the oxidation.

Performance of the oxidation with a five-fold excess of oxidant led to similar results. It is noteworthy that oxidation of cyclohexylamine with peracetic acid has been reported (85) to give, in 44% yield, the dimer of nitrosocyclohexane but no nitrocyclohexane. The production of a nitro compound in the present case gave encouragement for trying the reaction with carbohydrates, even though the yield of II in this model reaction was not high.

It was interesting to compare the NMR spectra of II and III. In the nitro alcohol II, the two protons in the α-position to the functional groups had similar chemical shift, giving overlapping broad multiplets near 4.1δ . In the spectrum of III there was a multiplet corresponding to only one proton (the carbinol proton) in the same region whereas a second one-proton multiplet was centered about 5.1δ . The latter was assigned to H-2 (the proton α to nitrogen). A strong deshielding effect by the nitroso group has been noted previously (96, 99).

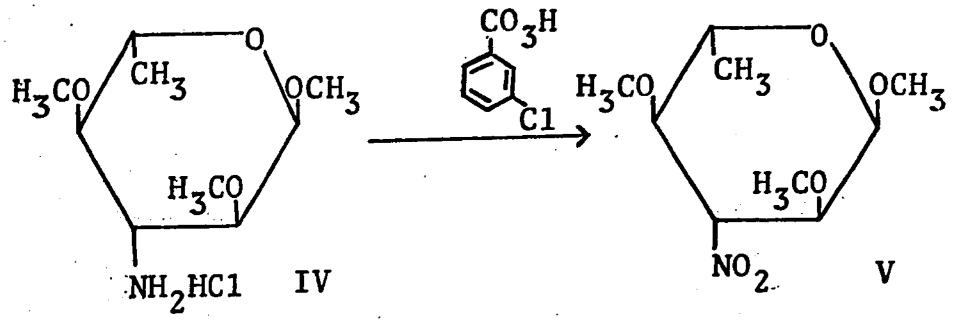
B. Oxidation of 3-Amino-3-deoxy-glycosides

The m-chloroperbenzoic acid oxidation was first applied to an amino pyranoside with protected hydroxyl groups and then to three amino hexopyranosides and one amino pentopyranoside with unprotected hydroxyl groups.

1. Oxidation of methyl 3-amino-3,6-dideoxy-2,4-di-O-methyl-α-L-glucopyranoside hydrochloride (IV)

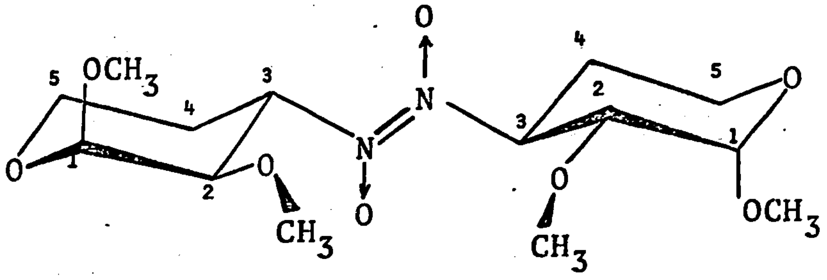
The known (100) amino glucoside dimethyl ether IV was oxidized with m-chloroperbenzoic acid in chloroform containing a small proportion of methanol. Oxidation was rapid, being nearly complete after about half an hour. Thin layer chromatography indicated formation of one main product along with only traces of by-products. The main product was isolated in a yield of 53% and was identified as methyl 3,6-dideoxy-2,4-di-O-methyl-3-nitro-α-L-glucopyranoside (V) by comparison with a sample obtained (100) in an independent synthesis.

The oxidation of IV was the only case in which no nitroso compound was isolated. It is of course possible that a small proportion of nitroso compound had arisen but escaped detection. At any rate, the nitro compound V was the preponderant product. Failure of the nitroso intermediate to survive may be explained by assuming that its dimerization is not favored in the present case. At first glance, one might think that dimerization could be hindered sterically by the two methyl ether groups vicinal to the nitroso group. However, a model can be constructed of the dimer in a conformation that appears free from steric strain (A). Perhaps a better explanation is lack of stabilization by hydrogen bonding such as is possible in hydroxy analogs (compare formula III).



IV

V

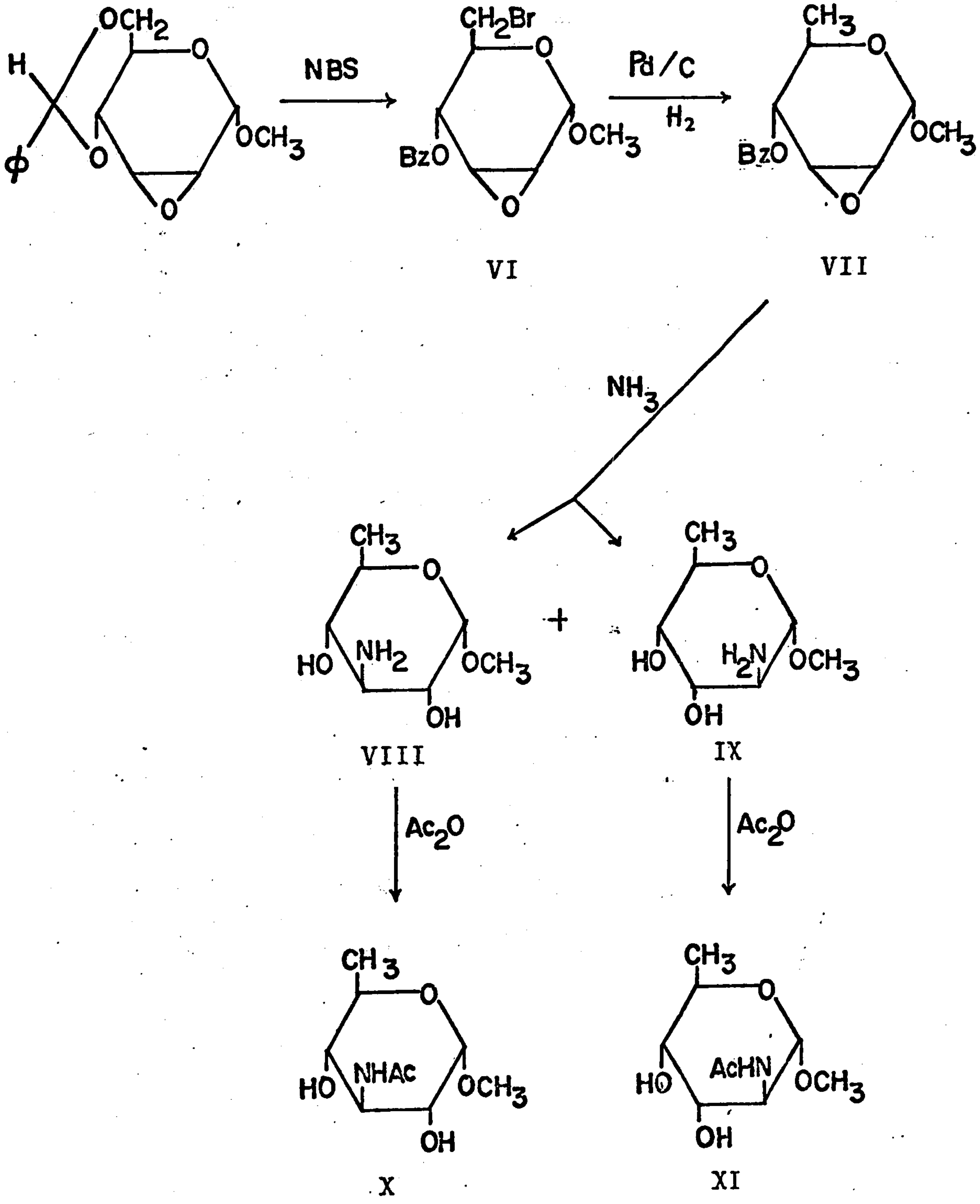


A (substituents on front side of molecule shown only)

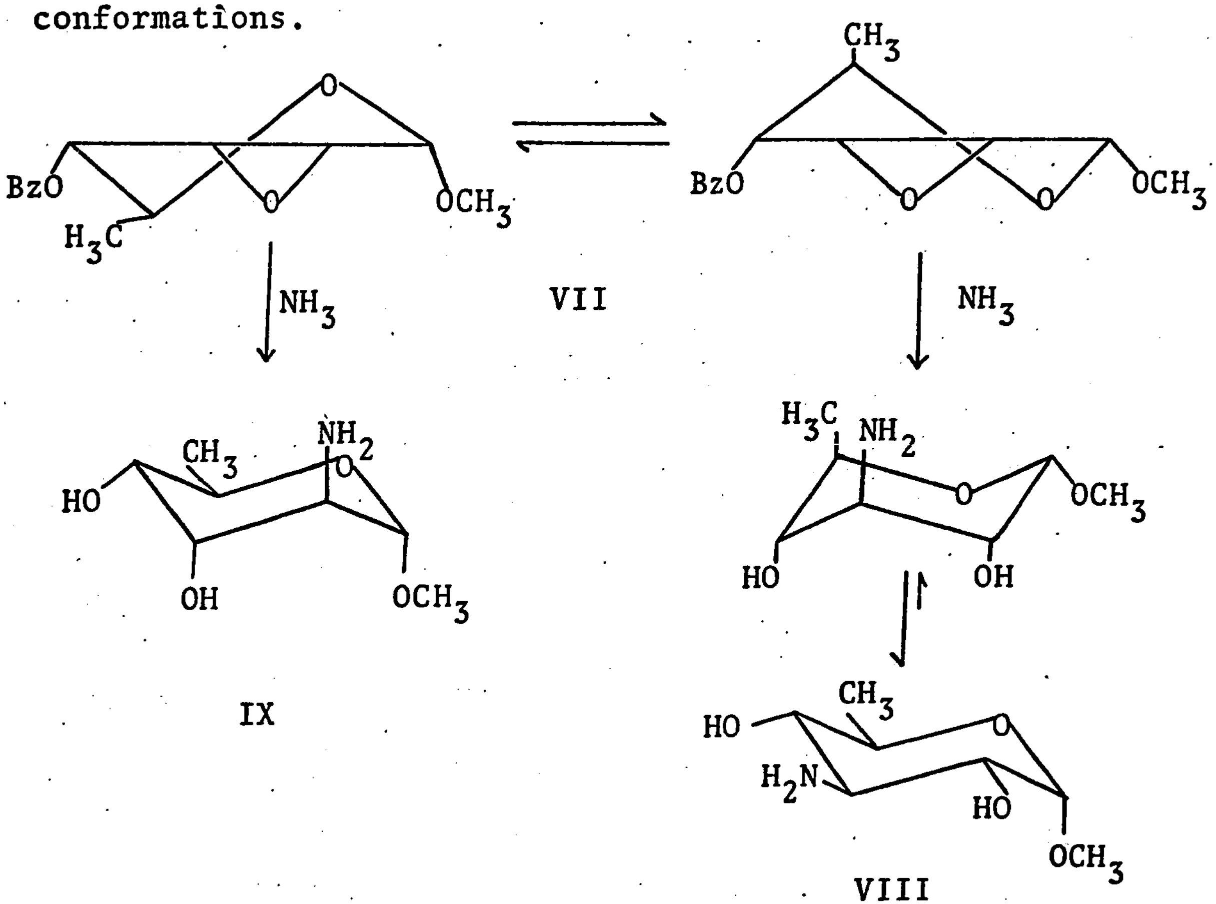
2. Oxidation of methyl 3-amino-3,6-dideoxy-α-D-glucopyranoside (VIII)

(a). Preparation of methyl 3-amino-3,6-dideoxy-α-D-glucopyranoside (VIII) and methyl 2-amino-2,6-dideoxy-α-D-altropyranoside (IX)

It was decided to try the peracid oxidation on a glycoside containing unprotected hydroxyl groups. In order to minimize difficulties that would probably be encountered because of the poor solubility of polyhydroxy compounds in the chloroform reaction medium, a sugar derivative possessing only two hydroxyl groups seemed attractive for the initial studies, and therefore methyl 3-amino-3,6-dideoxy-α-D-glucopyranoside (VIII) was chosen. This glycoside had been prepared previously (101) in a multi-step synthesis involving the nitromethane cyclization method. For the present work another approach to VIII was elaborated. This route involved opening of the epoxide ring in known (102) methyl 2,3-anhydro-4-O-benzoyl-6-deoxy-α-D-allopyranoside (VII), a method which is frequently used for the synthesis of amino sugars (92). Such epoxide ring opening in sugar epoxides generally


OCH2
H
φ
O
O
O
OCH3
NBS
CH2Br
BzO
O
O
OCH3
Pd/C
H2
CH3
BzO
O
O
OCH3
VI
VII
NH3
CH3
O
HO
NH2
OCH3
OH
+
CH3
O
HO
H2N
OCH3
OH
VIII
IX
Ac2O
Ac2O
CH3
O
HO
NHAc
OCH3
OH
CH3
O
HO
AcHN
OCH3
OH
X
XI

obeys the Fürst-Plattner rule, leading to trans diaxial amino and hydroxyl group arrangement. It was therefore possible that two products, namely VIII and the 2-amino-deoxy-α-D-altro isomer IX, could arise from VII, providing the epoxide can react in both of its half-chair conformations.



VII

IX

VIII

When the epoxy glycoside VII was treated with liquid ammonia under pressure at 130° following the procedure given by Jarý et al. (103) for the reaction with an analogous α-D-manno epoxide, two products were formed in addition to benzamide which originated from the ester group at position 4. The preponderant product, which was isolated in crystalline form in a yield of 56%, proved to be the 3-amino glucoside VIII. It exhibited physical constants agreeing with literature values and was further characterized by preparation of its N-acetyl derivative X and by NMR spectroscopy. The second product was obtained as a syrup in a yield of 27%. It was identified as methyl 2-amino-2,6-dideoxy-α-D-altropyranoside by its optical rotation, NMR spectroscopy and preparation of the crystalline (and known) N-acetyl derivative XI (104).

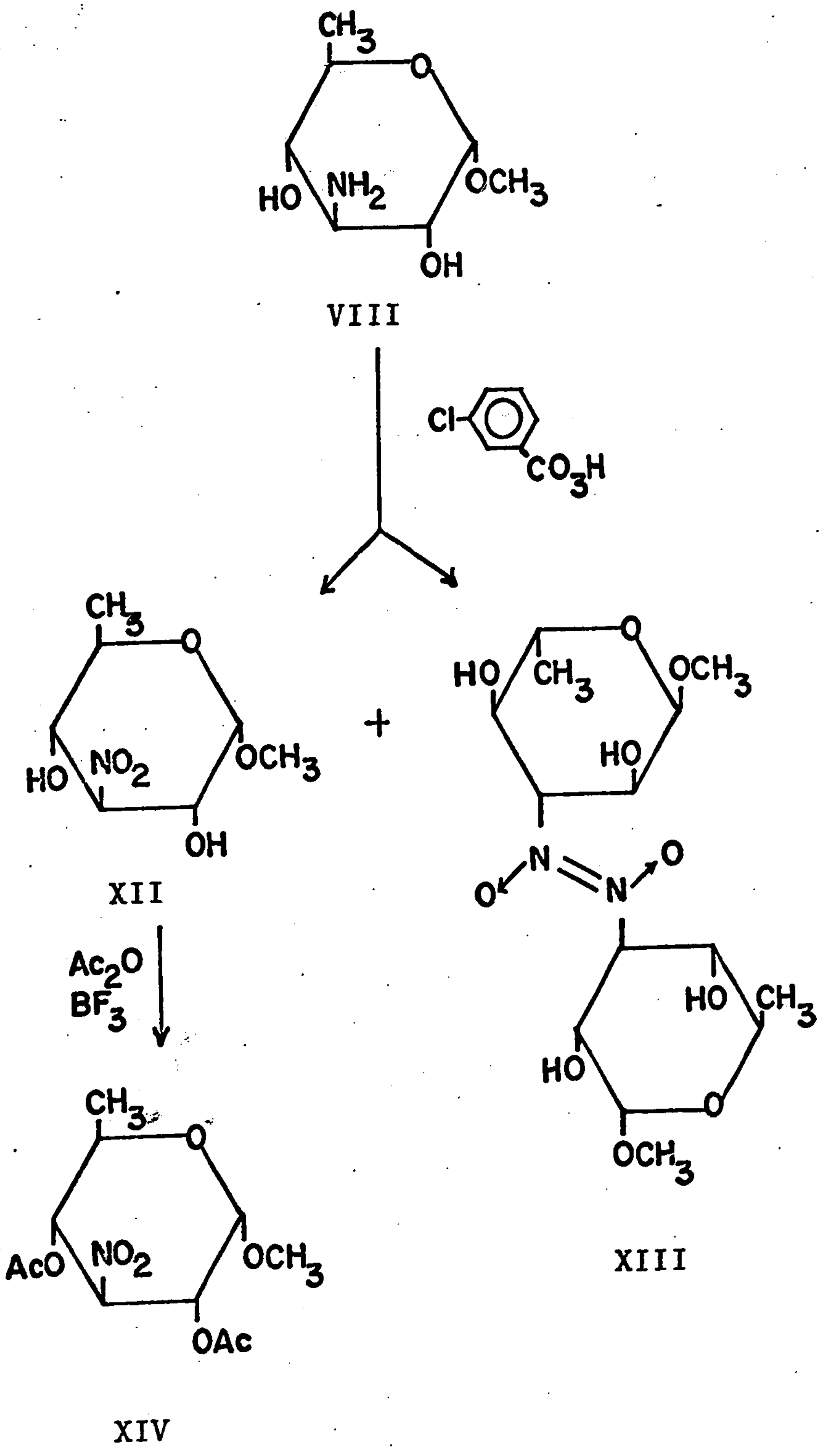
The NMR spectrum of the amino glucoside VIII in deuterium oxide showed as expected a three-proton doublet for the C-methyl group at highest field (1.25δ). Its spacing of 6.5 Hz was repeated in the splitting pattern of a one-proton octet centered at 3.71δ which also revealed a 9 Hz coupling. The octet was assigned to H-5, the larger coupling being due to interaction with H-4. In the region 2.75-3.55δ were two partially overlapping, symmetrical triplets, each having 9 Hz spacings. Neither of these triplets could belong to H-2 which regardless of configuration is required to produce at least one small splitting due to vicinal coupling with the equatorial, α-anomeric proton. Consequently the two triplets must be attributed to H-3 and H-4, and the large spacing of the H-3 triplet indicated axial arrangement of H-2, H-3, and H-4 , thus confirming the <u>gluco</u> configuration. The glycosidic $\underline{O}$-CH_3 group gave a singlet at 3.42δ . Just downfield from it appeared two lines separated by 3.7 Hz which probably represented one half of a quartet produced by H-2, the other half being obscured by the base of the methoxyl peak. The spectrum of the N-acetyl derivative X showed the expected substituent resonances for $\underline{O}$-CH_3, $\underline{N}$-$COCH_3$ and $\underline{C}$-CH_3 at 3.43δ, 1.93 δ and 1.28 δ , respectively. Upfield from the $\underline{O}$-CH_3 signal was one symmetrical triplet (3.16δ, i.e., in the region where the free amine VIII gave two triplets); it was assigned to H-4 ($J_{3,4} = J_{4,5} = 9.5\text{-}10$ Hz). The H-3 signal, previously in the same region, was shifted downfield by the N-acetyl group to below the H-5 multiplet and was seen as a symmetrical triplet with 10 Hz spacing at 4.01δ . The H-2 signal also incurred a (smaller) downfield shift which separated it completely from the $\underline{O}$-CH_3 peak under which it had been partially hidden in the free amine. It was now seen as a quartet at 3.62δ, with spacings of 4 and 10 Hz. Thus the spectrum corroborated the α-D-*gluco* configuration of X.

The spectrum of the 2-amino altroside IX was more difficult to interpret. However, the constitution of the compound received support by the presence of signals attributable to the $\underline{\mathrm{C}}\text{-CH}_3$ and $\underline{\mathrm{O}}\text{-CH}_3$ groups and by the requisite number of signals corresponding to ring protons. The spectrum differed clearly from that of the isomer VIII by the absence of triplets with large spacings, which are caused by axial protons coupled with two axial neighbors, and this accorded with the requirements of the α-D-*altro* configuration.

(b). Oxidation of the amino glucoside VIII

Oxidation of the amino glucoside VIII led to methyl 3,6-dideoxy-3-nitro-α-D-glucopyranoside (XII) and to dimeric methyl 3,6-dideoxy-3-nitroso-α-D-glucopyranoside (XIII) in proportions varying in dependence of the reaction conditions. The total yields of the two products were excellent.

When in a first trial VIII was refluxed for


CH3
O
HO
NH2
OCH3
OH
VIII
Cl
CO3H
CH3
O
HO
NO2
OCH3
OH
XII
+
HO
CH3
O
OCH3
HO
O
N
N
O
HO
CH3
HO
O
OCH3
XIII
Ac2O
BF3
CH3
O
AcO
NO2
OCH3
OAc
XIV

one hour in chloroform containing 3 molar equivalents of oxidant, only the nitroso compound was isolated, in a yield of 75%, although some of the nitro compound was probably formed also. Increase of the amount of oxidant to 4.25 molar equivalents operated in favor of nitro product formation, and although the products were not isolated in that experiment, it could be estimated from the NMR spectrum that the ratio XII to XIII was about 4 : 6.

The best results in terms of preparation of XII were achieved when the amine was not added at once to the oxidation medium but was added gradually, as solution in chloroform-methanol mixtures, to refluxing chloroform containing 6-6.8 molar equivalents of oxidant. Whereas the nitroso product still predominated when addition was carried out over a period of 7 minutes (yields of XII and XIII: 26 and 69%, respectively), the product ratio changed in favor of XII when an addition time of 30 minutes was allowed. Thus, the yields were 44 and 43%, respectively, in one experiment; and 50.5 and 33.5% in another; the two experiments differed insofar as a larger amount of methanol was present in the final reaction medium of the second one (32 vs. 22%).

These results might be explained by assuming that the first reaction step, namely oxidation of the amine to the monomeric nitroso compound, is faster than the oxidation of the latter to the nitro compound. If the nitroso compound accumulates in appreciable concentration it will tend to dimerize and thereby be prevented from further oxidation. Hence, slow introduction of the amine favors nitro product formation. The influence of methanol is probably due to its opposing dimer formation by interfering with hydrogen bond stabilization in the latter.

Methyl 3,6-dideoxy-3-nitro-α-D-glucopyranoside (XII) was identified by comparison of its melting point, optical rotation, and spectral data with the data of its known L-enantiomer (105). The optical rotation was of similar value but opposite in sign. The infrared spectrum of the product showed bands identical with those of the enantiomer. A strong band at 1550 cm^{-1} indicated the presence of a nitro function. The NMR spectrum (Fig. 10) had a high-field doublet centered at 1.20δ with a spacing of 6 Hz. This was assigned to the $\underline{C}$-CH_3 protons. A two-proton

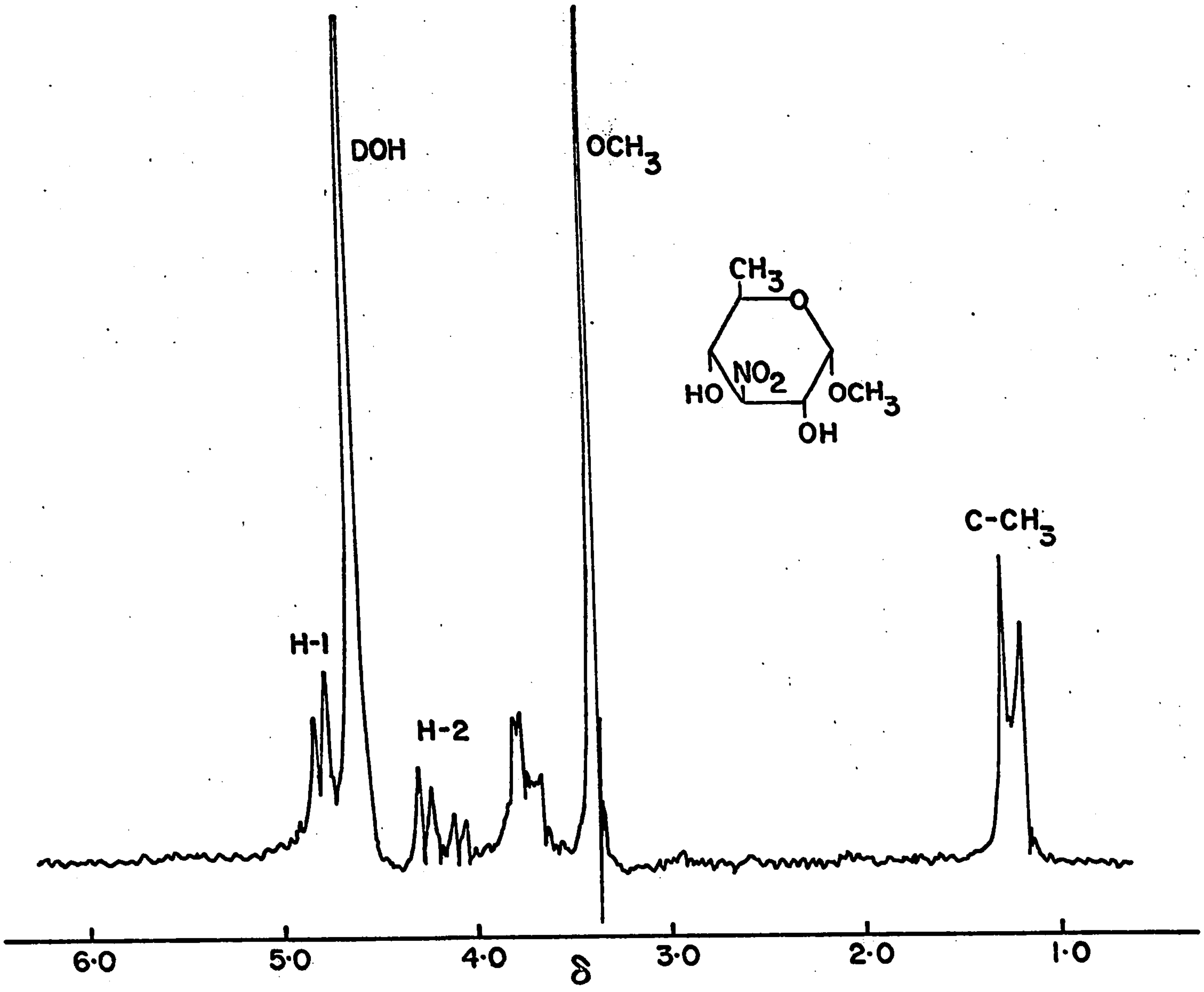


Fig. 10 NMR Spectrum (60 MHz) of XII in D_2O

multiplet in the region 3.6-3.8δ was assigned to H-5 and H-4. A quartet centered at 4.13δ with a large (11 Hz) and a small (4 Hz) coupling was assigned to H-2 which was split with the equatorially oriented H-1 by 4 Hz and with the axially oriented H-3 by 11 Hz. The anomeric proton was located on the slope of the HDO peak as a doublet centered at 4.77δ with a spacing of 4 Hz. The coupling constant agreed with a gauche relationship between H-1 and H-2. The remaining proton H-3 was masked by the broad HDO band.

A diacetate of XII, methyl 3,6-dideoxy-3-nitro-2,4-di-O-acetyl-α-D-glucopyranoside (XIV), was prepared by acetylation with acetic anhydride and boron trifluoride. Its physical constants and infrared spectrum agreed with the values reported (106) for the L-enantiomer.

The nitroso compound XIII exhibited an ultraviolet absorption similar to compound III, with λ_{max} at 298 nm ($\varepsilon = 7400$), as is characteristic for trans-nitroso dimers. Its infrared spectrum showed strong hydroxyl absorption at 3400 cm^{-1}. One strong band was present at 1190 cm^{-1} as the only absorption band in the

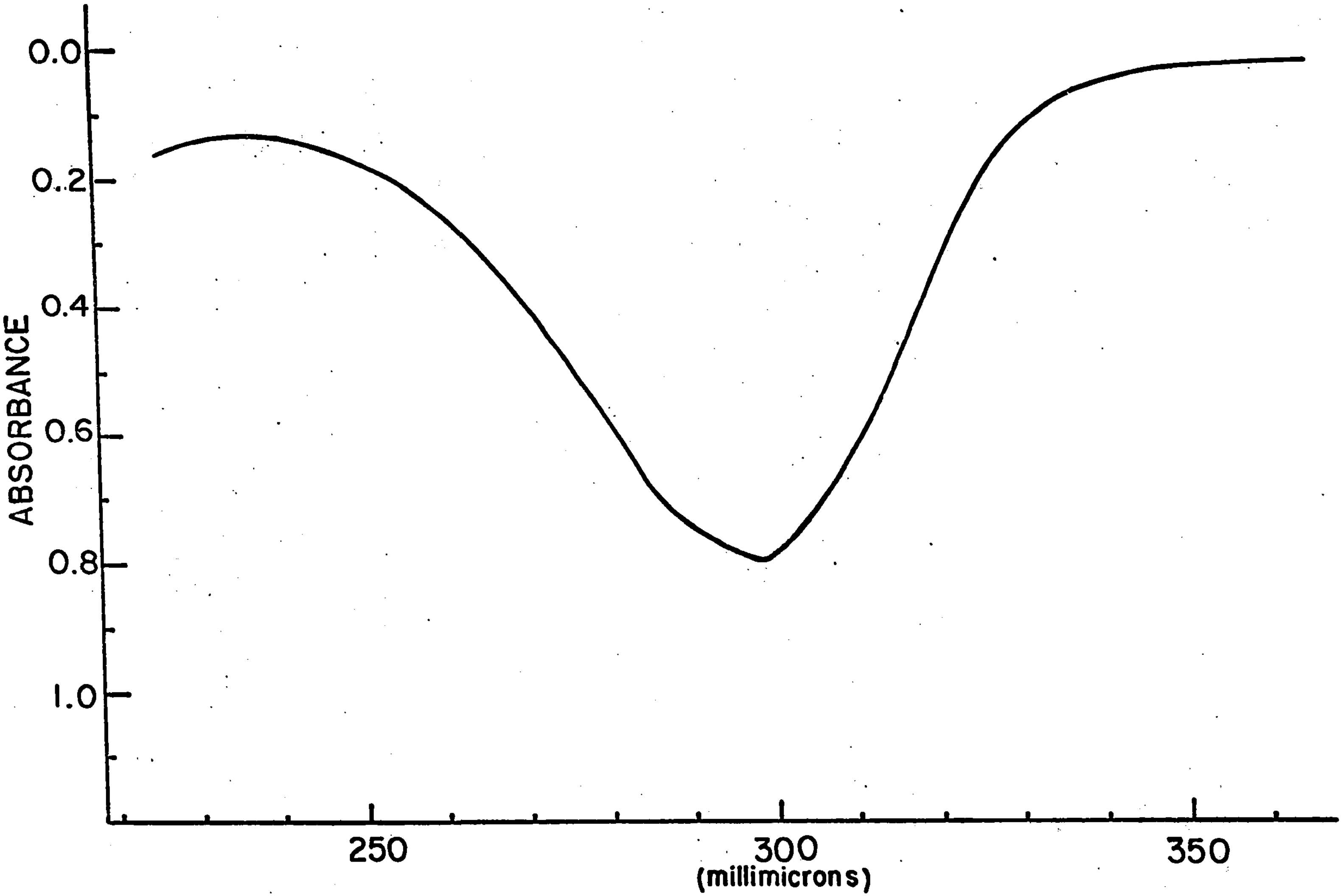


Fig. 11 UV Spectrum of XIII (in water)

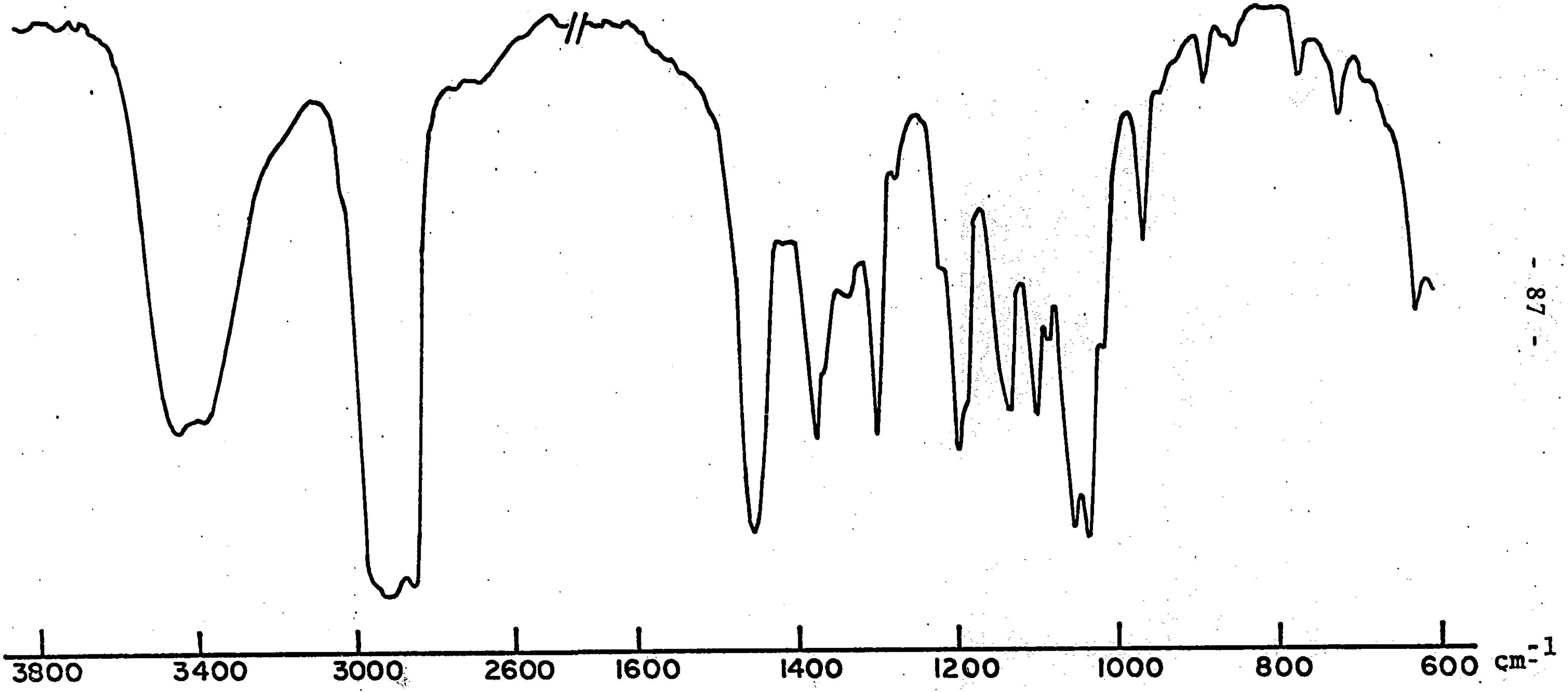


Fig. 12 Infrared Spectrum of XIII (Nujol mull)

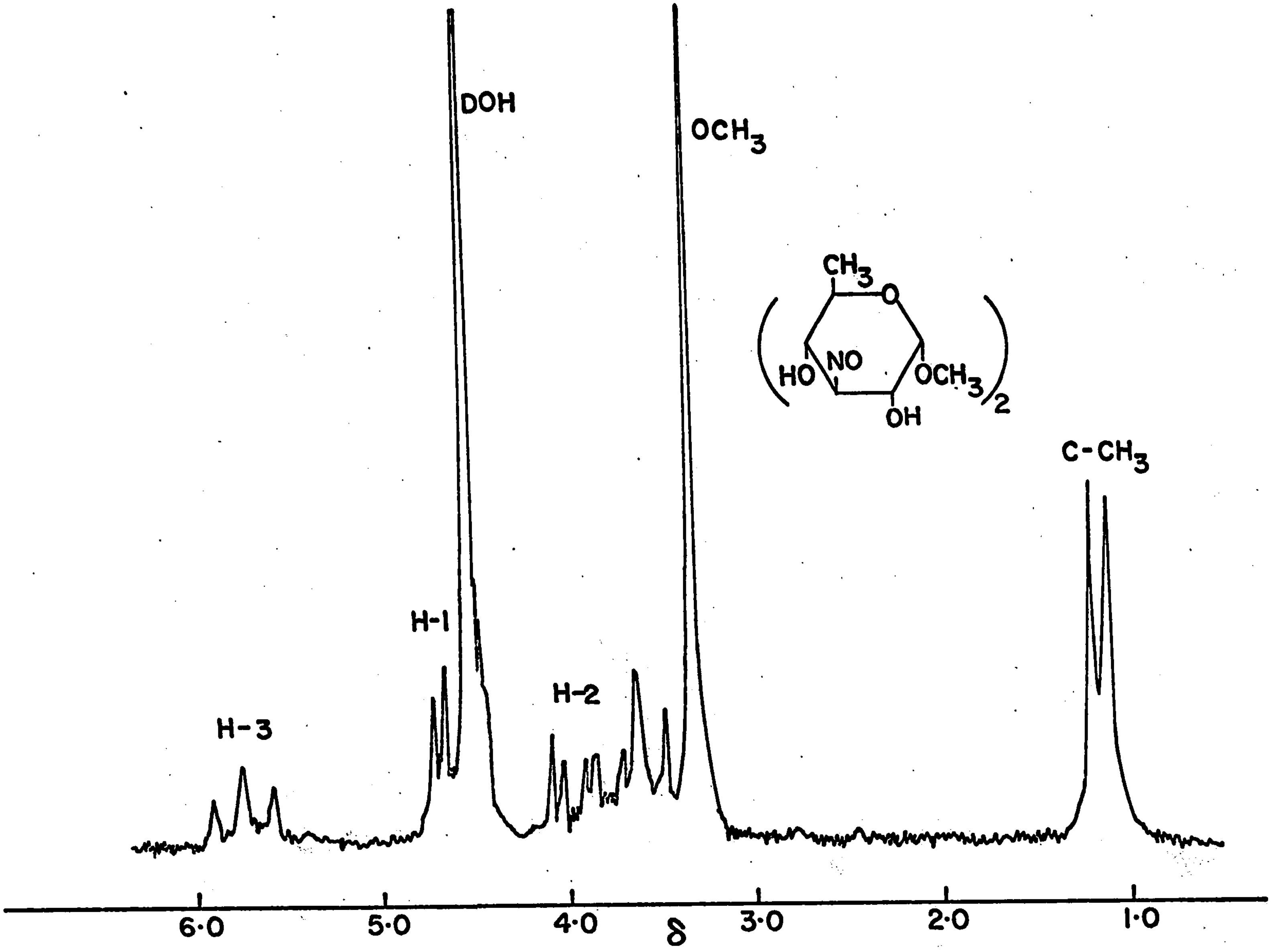


Fig. 13 NMR Spectrum (60 MHz) of XIII in D_2O

region 1160-1290 cm^{-1}. This agreed with the characteristic infrared absorption of <u>trans</u>—nitroso dimers. The NMR spectrum of XIII resembled that of XII in the region upfield from HDO peak. A three-proton doublet centered at 1.23δ was due to the $\underline{C}$-CH_3 protons (coupling constant, 6 Hz). The three-proton <u>O</u>-methyl singlet was at 3.4δ, shifted slightly to lower field compared to that in the spectrum of X. A two-proton multiplet in the region 3.47-3.87δ was assigned to H-4 and H-5, like in XII. A quartet centered at 4.07δ was attributed to H-2; it was slightly shifted to higher field compared to the H-2 signal in XII. This quartet resulted from splitting with H-3 (J = 10 Hz) and H-1 (J = 4 Hz). The anomeric proton (H-1) showed a narrow doublet centered at 4.77δ with a spacing of 4 Hz as a result of coupling with H-2. The low field signal, a one-proton triplet centered at 6.0δ , was assigned to H-3. Equal coupling of H-3 with H-2 and H-4 resulted in a triplet with spacings of 10 Hz. The chemical shift of H-3, the proton in α-position to the nitroso group, was close to values reported by Lemieux and coworkers (66) for 1-chloro-2-nitroso sugar dimers *. Apparently the dimeric nitroso function has a

---

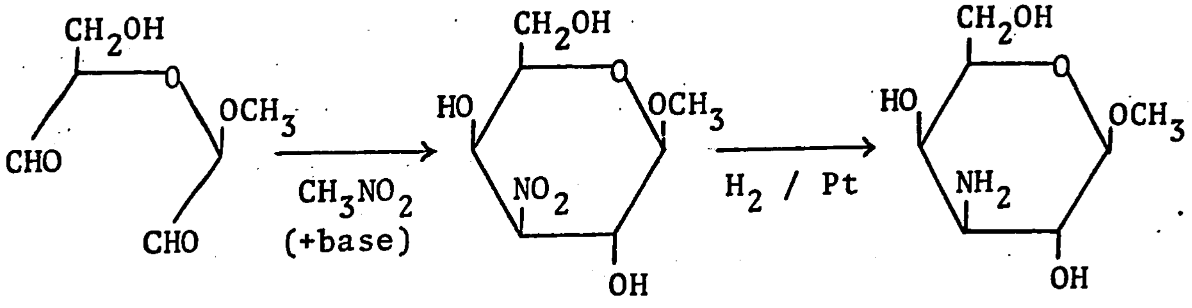
* Reported values were 5.46, 5.53 and 5.38δ.

greater deshielding effect than the nitro group.

Elemental analysis of XIII was attempted twice on recrystallized samples. In each time, a grey residue was found (3.0 and 6.5%). This non-combustible material was suspected to be an inorganic contaminant stemming from the repeated column chromatography. When calculations were adjusted for the residue the analytical values agreed with the structure of compound XIII.

3. Oxidation of methyl 3-amino-3-deoxy-β-D-galactopyranoside (XV)

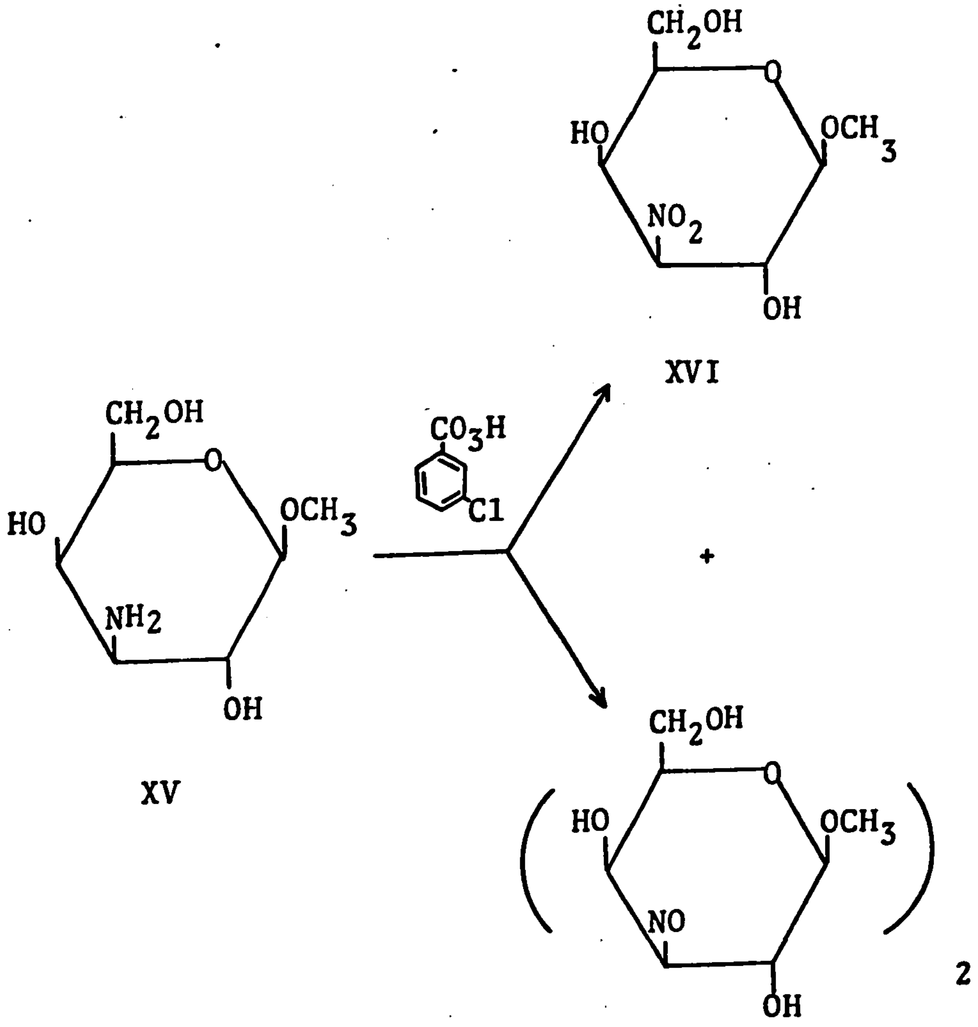
Next, the amine oxidation was to be tested on glycosides possessing three unprotected hydroxyl groups. Methyl 3-amino-3-deoxy-β-D-galactopyranoside (XV) was selected as a first example. This amino sugar is readily available (107) by catalytic hydrogenation of methyl 3-deoxy-3-nitro-β-D-galactopyranoside (XVI) which, in turn, can be made (107) by nitromethane cyclization of a sugar dialdehyde as shown:



XVI

XV

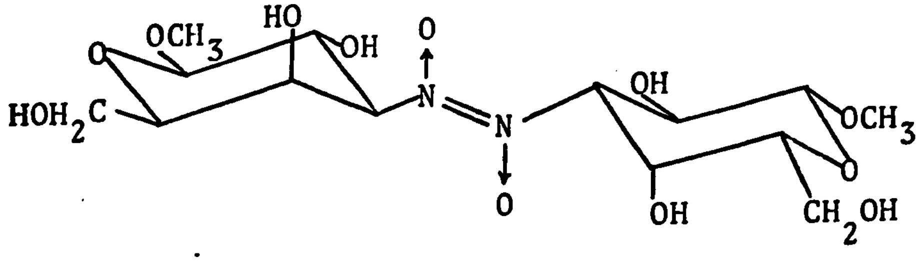
(+stereoisomers)



XVI

XV

XVII



XVII

Oxidation of XV with 6.3 molar equivalents of m-chloroperbenzoic acid in chloroform-methanol (1:1) proceeded rapidly and furnished both the known nitro glycoside XVI and the hitherto unknown methyl 3-deoxy-3-nitroso-β-D-galactopyranoside dimer (XVII) in a combined yield of 75%. However, the nitroso compound (yield, 47%) was obtained as the major product, and the nitro compound (yield, 28%) arose as the minor product. Several attempts to shift the product ratio in favor of the latter, by modifying reaction conditions, were to no avail, compound XVII always being produced predominantly. One experiment was made using pure methanol as the solvent, with the result that an additional, unidentified product arose besides XVI and XVII; the experiment was abandoned.

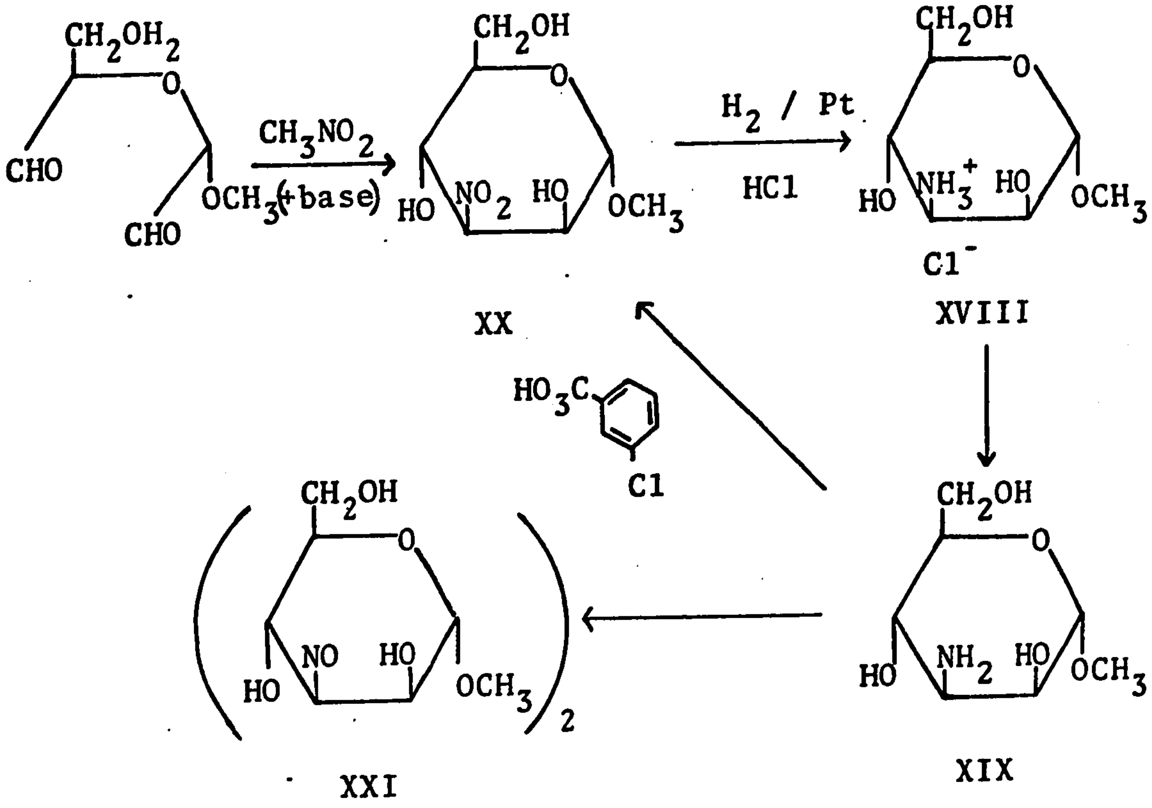
The nitro galactoside XVI was identified by comparison of its melting point, optical rotation, and infrared spectrum with the data of an authentic sample. The NMR spectrum, which had not previously been recorded, clearly showed signals attributable to H-3 (quartet, $J_{3,4}$ = 3.5 and $J_{2,3}$ = 10 Hz), H-2 (quartet, $J_{2,3}$ = 10 and $J_{1,2}$ = 8 Hz), H-1 (doublet, $J_{1,2}$ = 8 Hz) and to the methoxyl group (3-proton singlet), while the remaining signals were not well resolved (see Experimental).

The assignable signals were in agreement with the structure.

The nitroso dimer XVII gave microanalytical values corresponding to the assumed structure, and a molecular weight determination by osmometry revealed the dimeric nature of the compound. Like the nitroso dimers mentioned earlier, XVII exhibited ultraviolet absorption with λ_{max} 295 nm (ε , 7500) and broad infrared absorption at 3400-3200 cm^{-1} (hydrogen-bonded hydroxyl) as well as a sharp, strong band at 1190 cm^{-1} characteristic of the *trans* azodioxy moiety (95, 96). There was no nitro group absorption in the 1550 cm^{-1} region. An NMR spectrum obtained from XVII in D_2O was of poor quality but it did show the signal at lowest field to be a quartet with splittings of 3 and 10 Hz. This signal, which was attributable to H-3, was shifted downfield by 0.45 ppm in comparison to the corresponding signal in the nitro compound XVI, due to the stronger deshielding effect of the C-3 substituent group (96, 99).

4. Oxidation of methyl 3-amino-3-deoxy-α-D-mannopyranoside (XIX)

Methyl 3-amino-3-deoxy-α-D-mannopyranoside (XIX) has been synthesized, but isolated only in the form of its hydrochloride XVIII, by nitromethane cyclization of a sugar dialdehyde followed by catalytic hydrogenation in the presence of hydrochloric acid (108). For the requirements of the present thesis the free amino glycoside XIX was prepared for the first time by anion exchange treatment of its hydrochloride XVIII.



It should be mentioned that in the synthesis of XVIII the nitro mannoside XX shown as an intermediate had originally (108) not been isolated. Without separation from accompanying stereoisomers it had been reduced, and isomer separation had been accomplished on the amine stage. However, most recently the nitro mannoside XX has been isolated in crystalline form by W. Rank (109) in work concurrently pursued in this laboratory.

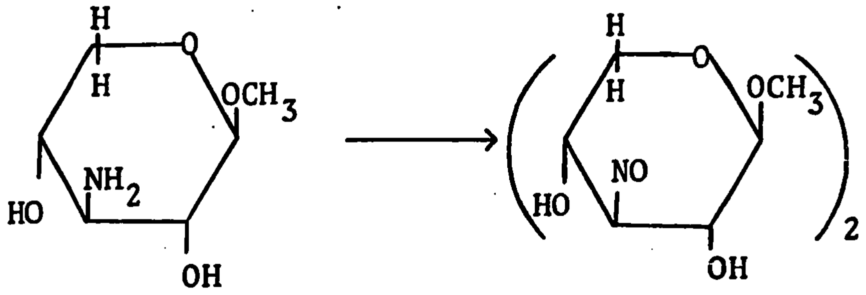
After trying a few oxidations of the amine XIX under conditions which included the use of pure chloroform and pure methanol as solvents, a successful experiment employing a mixture of these solvents gave oxidation products in a combined yield of 72%. Crystalline methyl 3-deoxy-3-nitro-α-D-mannopyranoside (XX) was isolated in 38% yield and identified by comparison with an authentic sample. Dimeric methyl 3-deoxy-3-nitroso-α-D-mannopyranoside (XXI) was obtained in 32% yield as a hygroscopic solid which could not be induced to crystallize despite many attempts. Although it was not submitted to elemental analysis, spectral data and analogy to previous results leave little doubt as to its structure. The product showed ultraviolet absorption at λ_{max} 293 nm (ε , 5000). The infrared spectrum exhibited broad hydroxyl absorption around 3300 cm^{-1} and a medium strong band at 1190 cm^{-1} but lacked nitro group absorption. The NMR spectrum in D_2O again displayed at lowest field (5.45δ) a quartet which was assignable to H-3 at the carbon bearing the nitroso bridge. The signal revealed couplings of 3 Hz (with the equatorial H-2) and of 10.5 Hz (with the axial H-4) as required for the <u>manno</u> configuration. The anomeric proton H-1 gave a doublet at 4.70δ with a spacing of 2 Hz, in accord with equatorial-equatorial coupling. The glycosidic methoxyl group produced a three-proton singlet at 3.46δ .

An attempt was also made to use the amine hydrochloride XVIII in the oxidation reaction. However, thin layer chromatography revealed the product composition to be more complex than in the case of the free base, and the mixture was investigated no further.

5. Oxidation of methyl 3-amino-3-deoxy-β-D-xylopyranoside (XXII)

Methyl 3-amino-3-deoxy-β-D-xylopyranoside (XXII) has been synthesized by Schaub *et al.* (110) and Baer and Fischer (111). Oxidation of this amino pyranoside (XXII) in a chloroform-methanol mixture occurred rapidly and gave largely one product, according to t.l.c.. The reaction differed from the previous ones insofar as the product crystallized directly from the medium during the reflux period. The product, which was thus isolated in 40% yield was sparingly soluble in all solvents that were tried, including water and dimethyl sulfoxide. For this reason, no NMR spectrum could be obtained, and no elemental analysis was performed owing to lack of material. However, ultraviolet and infrared spectra indicated that the compound was a dimeric nitroso derivative. It showed λ_{max} 300 nm (ε, 7000) and broad IR absorption around 3400 cm^{-1} as well as a sharp band at 1195 cm^{-1}. There was no nitro band present, nor any other band between 1500 and 2800 cm^{-1}. It appears reasonable to assume that the compound was dimeric methyl 3-deoxy-3-nitroso-β-D-xylopyranoside (XXIII).

Evidently the high degree of insolubility of the dimer causes the monomer to be removed from solution so rapidly that it fails to be oxidized to the nitro stage.



XXII XXIII

C. Oxidation of Methyl 2-Amino-2,6-dideoxy-α-D-altropyranoside (IX) - An Exploratory Experiment.

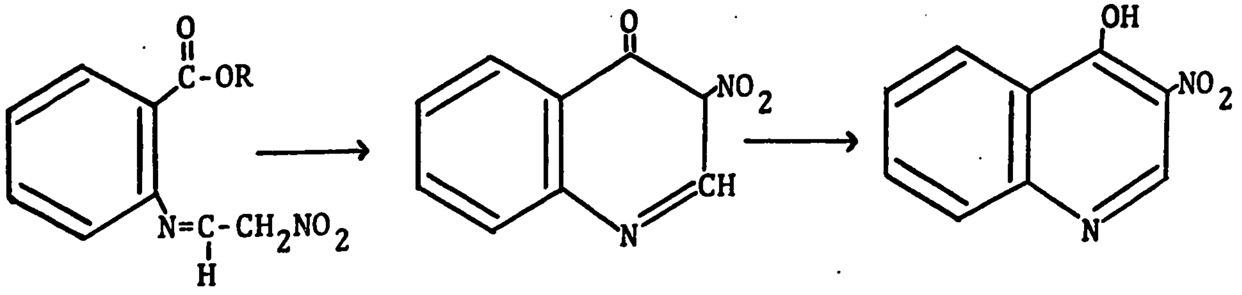
No detailed oxidation studies were performed with glycosides carrying an amino group in position 2. However, oxidation of methyl 2-amino-2,6-dideoxy-α-D-altropyranoside (IX) was examined in a preliminary way. Thin layer chromatography revealed that at least two major and two minor products were formed. One of the major products was isolated in crystalline form (m.p. 120-122°), though in undetermined yield, by laborious chromatography. It was optically active ($[\alpha]_D$ +48.5°) and displayed a strong infrared band at 1570 cm^{-1}, and therefore was in all likelihood a nitro sugar. Although the structure of the product remains to be elucidated in a definitive manner it is quite clear that the 2-amino sugar IX has reacted with m-chloroperbenzoic acid under conditions similar to those applied to the 3-amino sugars, and it appears worthwhile to follow up this reaction at a later date.

PART III

SYNTHESIS OF 4-HYDROXY-3-NITROQUINOLINE

RESULTS AND DISCUSSION *

It was mentioned in the Introduction that only a few examples of Dieckmann-type ester condensations leading to cyclic α-nitro ketones have been reported in the literature. In continuation of work performed in this laboratory, which had provided a route to 2-nitroindanones by such cyclization (16, 17), it was planned to attempt the following synthesis starting with I :



I, R = CH_3 II III

IV, R = H

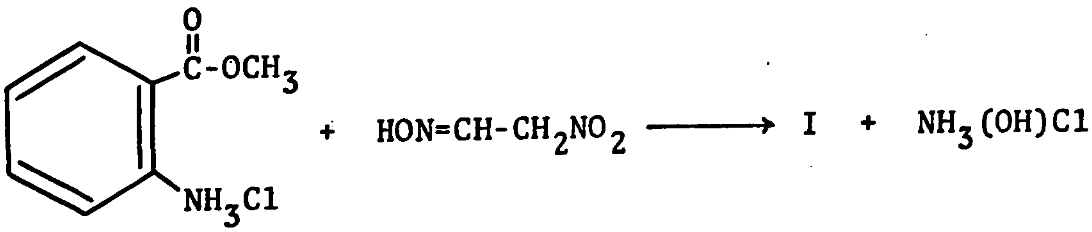
Methyl 2-(2-nitroethylideneamino) benzoate (I) should cyclize to give the nitro ketone II which was expected to tautomerize to 4-hydroxy-3-nitroquinoline (III). In analogy to the nitroindanone synthesis the

---

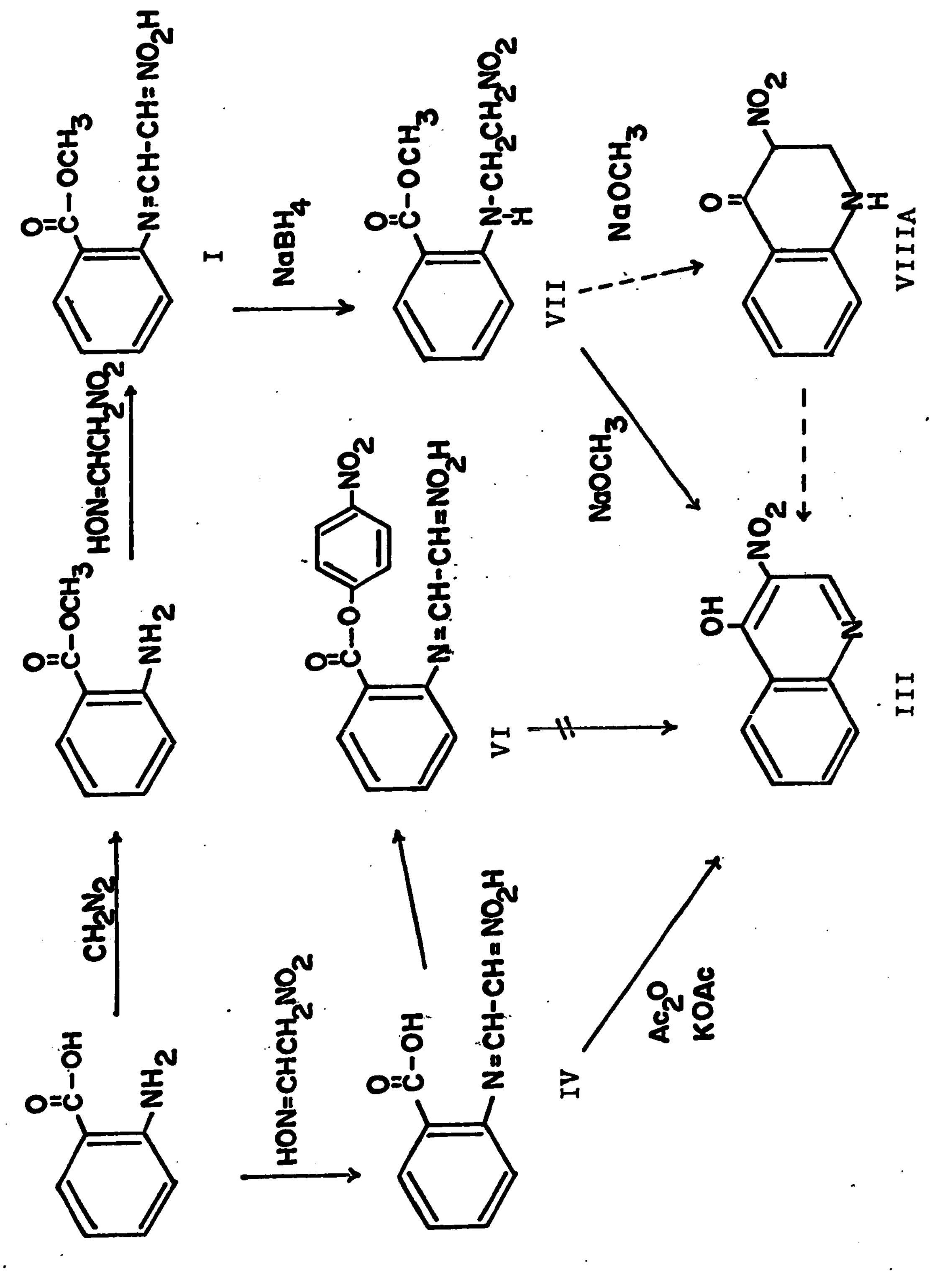
* For convenience, compounds in this Part are numbered with a new set of Roman numerals.

cyclization might have been expected to be promoted by sodium methoxide, although in 1937 Colonna (112) has reported that he was unable to bring about that same cyclization by use of acetic anhydride and potassium acetate. Colonna's observation was later confirmed by Bachman _et_ _al_. (113) who were, however, able to produce III by cyclizing the free acid IV in the presence of acetic anhydride and potassium acetate.

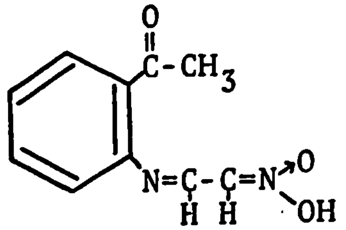
The ester I can be prepared in 60% yield by condensation of methyl anthranilate with methazonic acid (nitroacetaldoxime) in strongly acidic medium (113, 114).



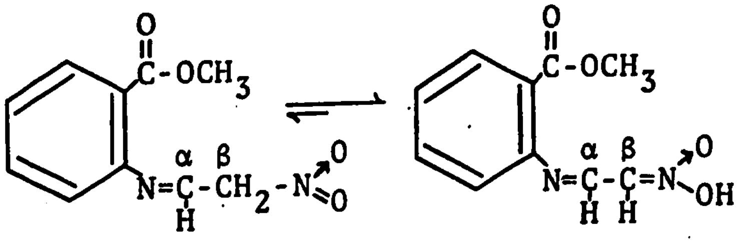
The ester I, a bright yellow, crystalline compound, was readily obtained when the directions given in the literature were followed. However, spectral evidence indicated that the product does not in fact


CH2N2
HON=CHCH2NO2
NaBH4
NaOCH3
NaOCH3
Ac2O
KOAc
I
IV
VI
VII
III
VIIIA

possess the structure depicted above* The IR spectrum did not show any band in the region of 1500-1580 cm^{-1} where the nitro group is normally found to absorb. High-intensity ultraviolet absorption occurred at a wavelength that was considered to be too long for structure I, namely, at λ_{max} 385 nm (ε, 24800 in methanol). The absorption was very similar to that of o-(β-aci-nitro-ethylideneamino)-acetophenone (V) which was reported (115) to show λ_{max} 388 nm (ε , 23700 in methanol). One must therefore assume that I exists predominantly in its tautomeric form, i.e., as the nitronic acid. Conjugation with the N=CH bond and the aromatic ring evidently stabilizes the nitronic acid structure in compounds of this type very strongly. This was borne out by the NMR



V



I

spectrum of I (Fig. 14). At very low field (12.9δ)

---

* see p. 101.

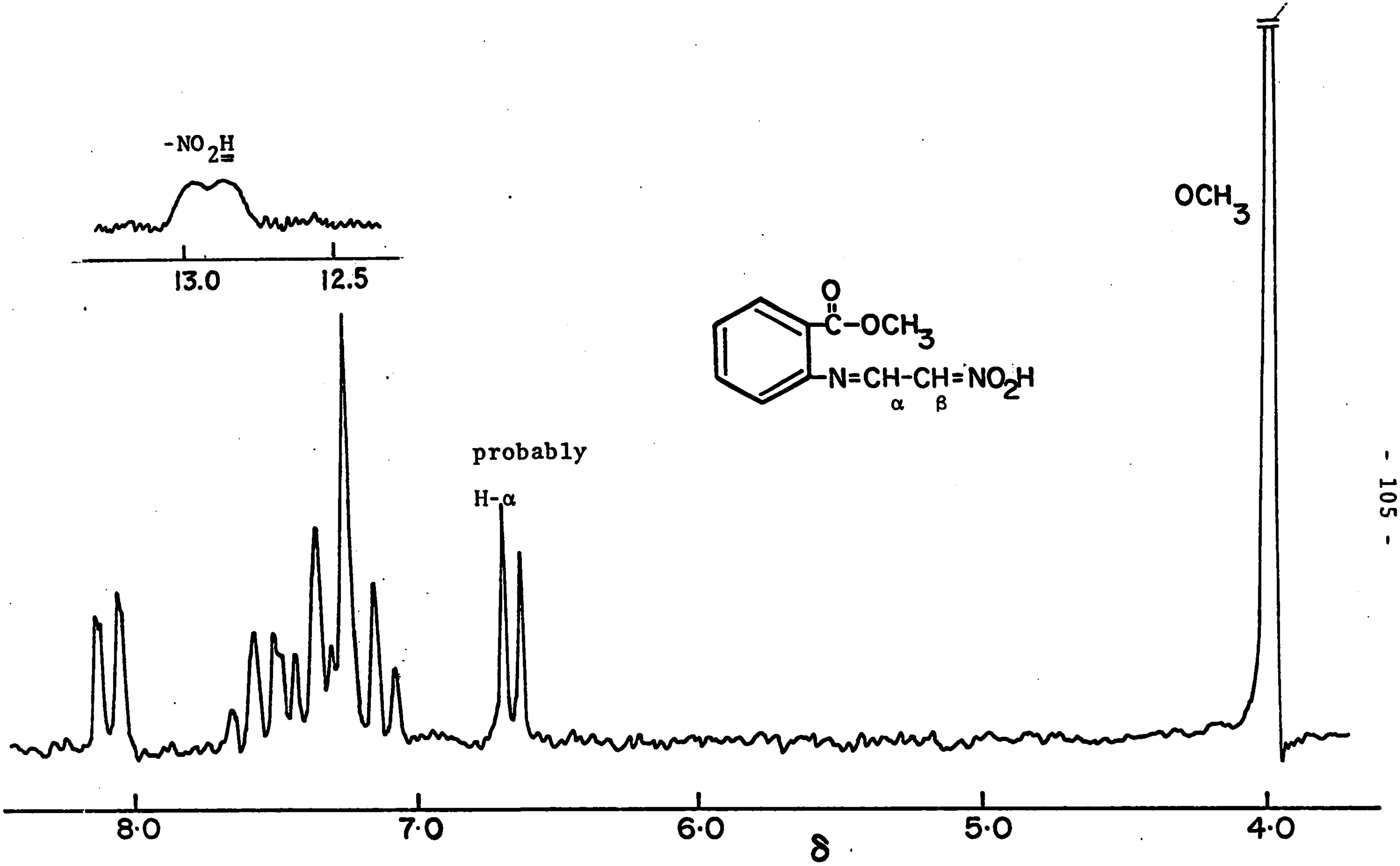
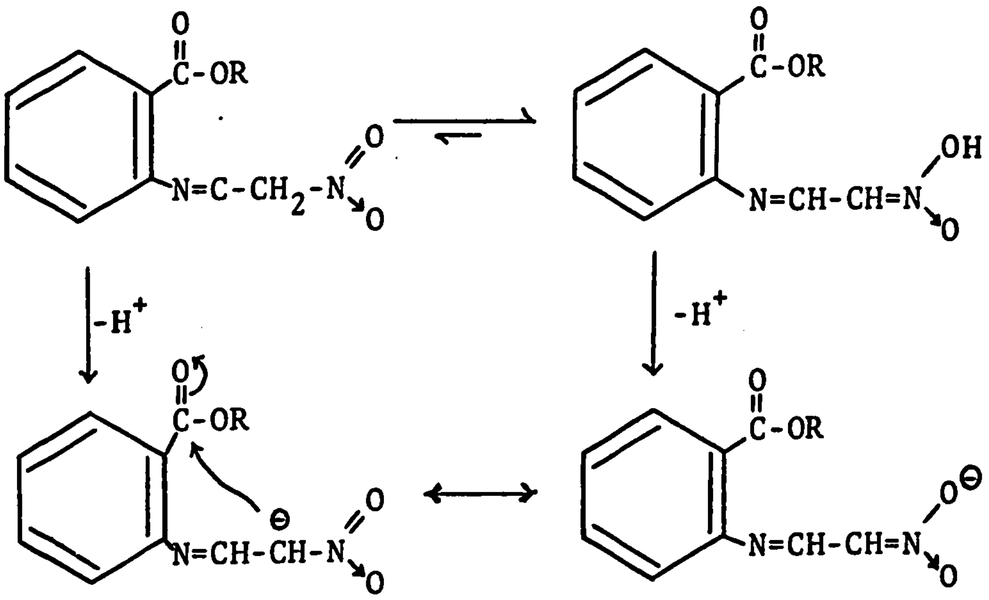


Fig. 14 NMR Spectrum (100 MHz) of I in $CDCl_3$

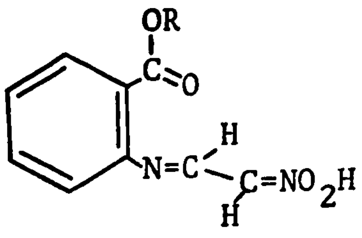
there occurred a one-proton signal that disappeared upon deuterium exchange. It was assigned to the hydrogen of the nitronic acid group. There were no signals in the region of 5-6δ where the two α-protons of the nitro tautomer would be expected to resonate. At lower field, three groups of signals were found, namely, a one-proton doublet at 6.66δ , a complex multiplet corresponding in intensity to four protons in the region of 7.0-7.6δ , and a one-proton quartet at 8.10δ . Presumably the doublet belonged to the α-hydrogen of the side chain and the quartet to one of the ortho-hydrogens in the aromatic ring, whereas the multiplet comprised the signals of the remaining aromatic hydrogens and the β-hydrogen of the side chain. Double irradiation at 8.10δ left the 6.66δ signal unchanged, and vice versa, which means that these two signals were not due to vicinal protons. However, spin decoupling resulted in simplification of the pattern of the complex multiplet. When double irradiation was performed at 6.66 δ, the multiplet was simplified specifically in its central region about 7.34δ , suggesting that this was the resonance position of the β-proton vicinal to the proton resonating at 6.66δ .

For purposes of comparison, the free carboxylic acid IV (113) was also prepared. Like its methyl ester, the carboxylic acid did not show the infrared band in the 1550 cm^{-1} region normally associated with an aliphatic nitro group. The ultraviolet spectrum in methanol exhibited λ_{max} 390 nm (ε , 20000), thus resembling that of the ester. In the NMR spectrum which was taken in dimethyl sulfoxide-d_6, signals assignable to the two protons of a nitromethyl group as required if IV existed in the nitro form could not be found. The signal appearing at lowest field was a one-proton doublet (7.0δ , J = 6.3 Hz) attributable to the α-proton of the side chain. Adjoining downfield in the region of 7.10-8.15δ were three multiplets corresponding in intensity to five protons. Obviously four of these protons were the aromatic ones. The fifth proton resonating in that region must be situated in the side chain, and its chemical shift seemed reasonable for the methine proton of a nitronic acid moiety. The combined evidence from the IR, UV and NMR spectra thus indicated that IV, too, exists in the tautomeric, nitronic acid form rather than in the nitro form. The fact that the ester I preferred the nitronic acid structure was not in itself considered to render cyclization impossible. Base-catalyzed cyclization would proceed via the carbanion which arises from both tautomers :

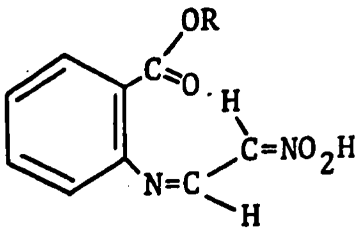


The cyclization was therefore attempted, at first in methanolic solution in the presence of sodium methoxide according to the procedure employed by Baer and Naik for the synthesis of nitroindanones (17). However, all attempts were unsuccessful. Colored products were formed, and the reaction mixtures seemed to contain methyl anthranilate which resulted from cleavage of the side chain. The desired 4-hydroxy-3-nitroquinoline (III) could not be detected among the products even though a sample of III had been prepared, in order to facilitate identification, by the acetic anhydride-potassium acetate procedure starting from the carboxylic acid IV (113). Various modifications of the reaction were tried and proved equally unsuccessful. These attempts included the use of sodium hydroxide and potassium t-butoxide as base catalysts; the starting compound suffered hydrolysis of its methyl carboxylate group and did not undergo cyclization. Use of triethylamine led to recovery of starting material.

Two reasons might be held responsible for the failure of the reaction. Firstly, one may assume that the alkylideneamino double bond in I possesses <u>trans</u> geometry (a), the <u>cis</u> bond (b) being disfavored because of steric hindrance. Yet the <u>cis</u> arrangement is necessary for ring closure to occur. Failure of the molecule to undergo <u>trans</u> → <u>cis</u> isomerization under the reaction conditions would prevent its cyclization.

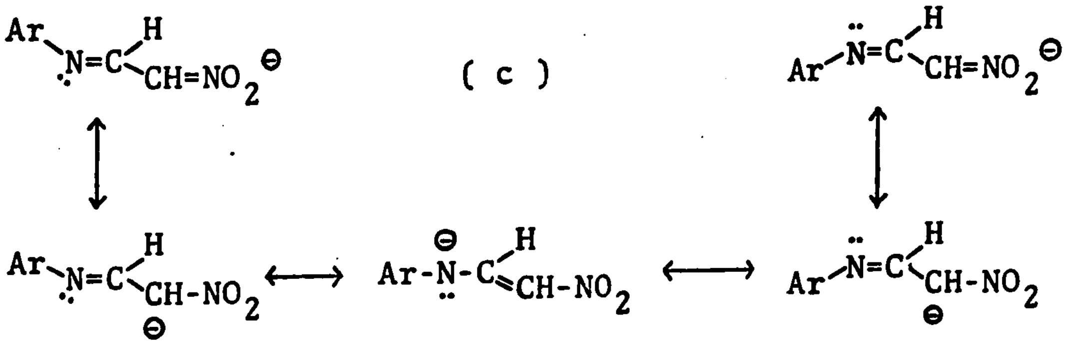


(a)



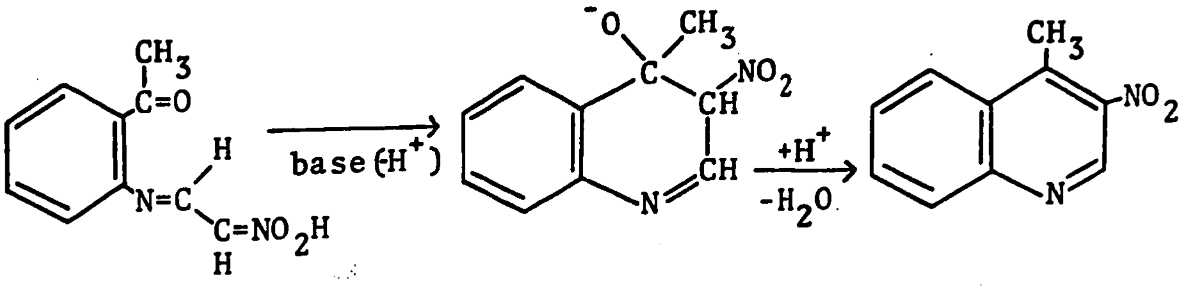
(b)

However, compound I should be quite capable of isomerization by way of resonance in its anion (c).



(c)

Indeed the carboxylic acid IV, to which similar stereochemical considerations should apply, has been cyclized as mentioned above. Furthermore, the acetophenone derivative V, which presumably has also the <u>trans</u> configuration in its alkylideneamino group, has been cyclized in the presence of basic aluminum oxide (116). Hence it is difficult to see that the geometry of I should be the chief obstacle to its cyclization.

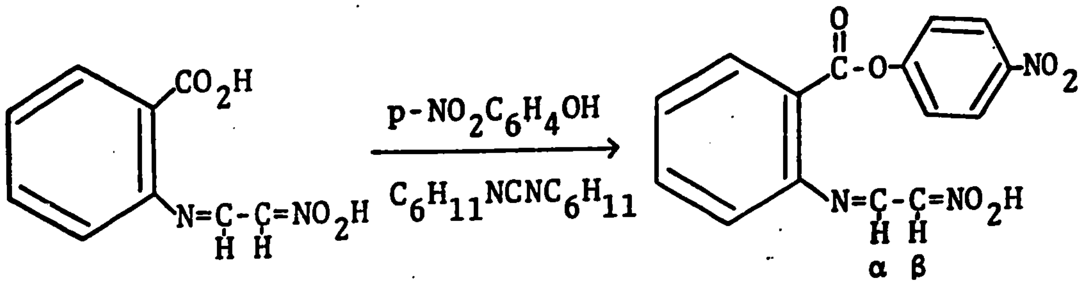


V

The other reason that might be invoked for the failure of the reaction could be a poor nucleophilicity of the carbanion of I, which results from resonance of the negative charge with the aromatic system. Such resonance was not present in the methyl 2-(2-nitroalkyl)-benzoates which cyclized to give nitroindanones (see p. 4). In the cases of IV and V, resonance-diminished nucleophilicity evidently did not prevent cyclization. However, the cyclization of V represents a different reaction type, namely an aldol-type nitroalkane addition (Henry reaction), which generally is more facile than an ester condensation. Cyclization of IV in the presence of acetic anhydride presumably proceeds via a mixed carboxylic-acetic acid anhydride, and one may assume that even a weakly nucleophilic carbanion can successfully attack the anhydride moiety because of the superior leaving group character of acetate ion.

It was therefore decided to try the ester cyclization with an ester containing a group that was expected to be a better leaving group than methoxyl. The p-nitrophenyl ester (VI) of IV was chosen.

In order to prepare this ester, condensation of p-nitrophenyl anthranilate with methazonic acid was tried first, in analogy to the preparation of the methyl ester I. It did not not succeed. However, esterification of the acid IV with p-nitrophenol by the action of dicyclohexylcarbodiimide furnished VI in a yield of 66%.



IV

VI

Like I and IV, the ester VI was suggested by spectral evidence to exist in the nitronic acid form as depicted. The infrared spectrum exhibited a band at 1510 cm^{-1} attributable to the aromatic nitro group, but there was no band in the 1550-1580 cm^{-1} region which would indicate a nitroalkane moiety. The NMR spectrum in DMSO-d$_6$ gave no indication of a nitroethylidene group but, like those of I and IV, showed a one-proton doublet (6.8δ , J = 6.5 Hz) assignable to the α-proton of the side chain. The β-proton signal was shifted downfield and was grouped together with the aromatic resonances (which in this case corresponded in intensity to eight protons).

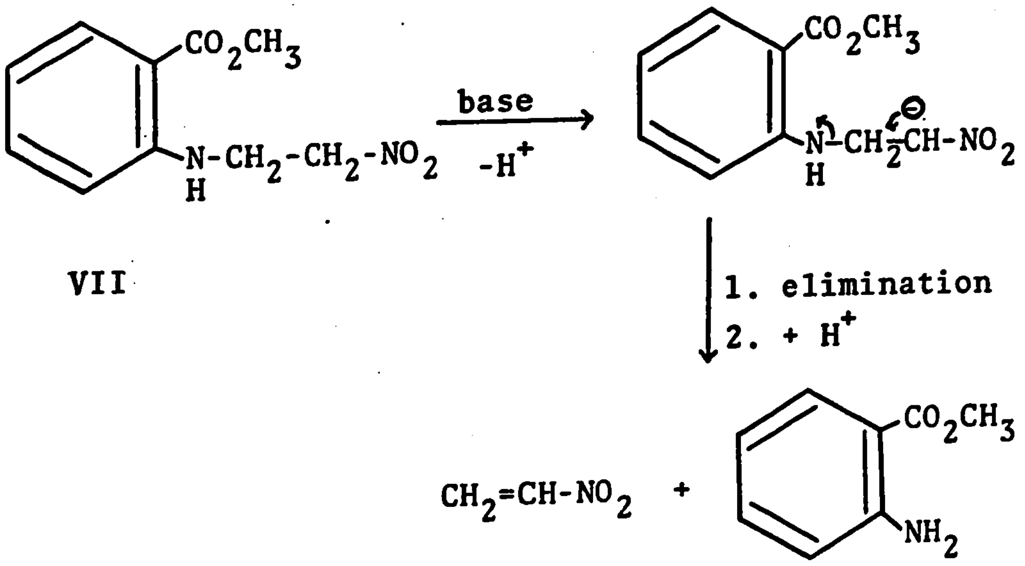
Unfortunately, attempted cyclization of the p-nitrophenyl ester VI did not meet with success either. The reaction, which was carried out at room temperature in methanolic solution containing sodium methoxide, resulted in ester exchange giving I and p-nitrophenol, and no cyclization product was detected.

However, the goal of synthesizing a quinoline derivative by Dieckmann cyclization was eventually reached in the following way. The methyl ester I was treated with sodium borohydride at room temperature according to the procedure given by Walker (117) for the reduction of imines. Reduction occurred rapidly and afforded crystalline methyl 2-(2-nitroethylamino)-benzoate (VII) in yields of 80-90%. As will be shown in a subsequent paragraph, this compound proved amenable to cyclization.

The structure of VII was confirmed by spectral data. The infrared spectrum displayed a strong nitro band at 1550 cm^{-1} as expected for a primary aliphatic nitro group, and it showed a stretching frequency of 3340 cm^{-1} for the secondary amine function. The NMR spectrum was in accord with structure VII. The presence of a methyl ester function was revealed by a three-proton singlet at 3.81δ. Partially overlapping this signal was a triplet of two-proton intensity, which was centered at 3.92δ , and a second triplet of two-proton intensity occurred at 4.58δ . The triplets represented an A_2X_2 spectrum and were assigned to the α-protons and β-protons, respectively, of the nitroethylamino group. The splitting observed was 6 Hz. The four aromatic protons gave three multiplets at low field, and in the same region occurred also the N-H signal which disappeared upon deuterium exchange. For details of the aromatic signals see the Experimental section.

Compound VII was readily recognizable in thin layer chromatography as it produced a characteristic green spot with a brown fringe when the plate was first exposed to iodine vapor and then sprayed with ceric sulfate-sulfuric acid. The color faded on heating.

When methyl 2-(2-nitroethylamino)-benzoate (VII) was allowed to react with sodium methoxide in methanolic solution at room temperature, two products were observed by t.l.c., one of them moving faster than VII and the other remaining near the baseline. The reaction was slow, however, and a large amount of starting material persisted even after 40 hours. When, after that period, the reaction mixture was heated to reflux for an additional six hours, the amount of surviving starting material was substantially reduced. Work-up then gave the slow-moving product (which was identified as a cyclization product, as will be described in the next paragraph), but it also gave residual VII and a by-product which proved to be methyl anthranilate. The latter evidently arose from VII by β-elimination:



VII

The slow-moving, main product of the reaction could be obtained best when the reaction was performed at reflux temperature (65°) for 25 hours. Work-up of the orange colored solution by chromatography on aluminum oxide led to recovery of only a small amount of starting material (which appeared to be contaminated by methyl anthranilate), and furnished a cream-colored, chromatographically homogeneous material in good yield. The product decomposed at 340-345° and was sparingly soluble or insoluble in most of the common organic solvents. Solubility was only moderate even in dimethyl sulfoxide and N,N-dimethylformamide. However, the compound readily dissolved in polar solvents upon addition of alkali, forming a yellow salt. Elemental analysis indicated the composition $C_9H_6N_2O_3$ which corresponded to the constitution of 4-hydroxy-3-nitroquinoline (III), and on this basis the yield of product was calculated to be 45.5%. That the product was indeed 3-nitro-4-hydroxyquinoline was established by spectral and chromatographic comparison with a sample of III that was prepared from IV as previously mentioned (p.109). Strong absorption bands in the ultraviolet and extending into the visible region were found in dimethylformamide solution (λ_{max} 269, 318, and

380 nm) and in aqueous N sodium hydroxide solution (λ_{max} 273 and 369 nm). The well-resolved infrared spectra of the two samples were superimposable. They exhibited hydroxyl absorption in the 3100 cm^{-1} region, the low frequency indicating strong hydrogen bonding between the neighboring hydroxyl and nitro groups. This observation agreed with data reported by Baitinger (118), according to which the hydroxyl group frequency is lowered by 300-500 cm^{-1} in such cases.

The NMR spectrum of III in dimethyl sulfoxide-d_6 in the presence of 1 equivalent of NaOD is shown in Fig. 15. No signals occurred upfield from 7.8δ . A one-proton singlet observed at lowest field (9.67δ) was assigned to H-2 (in the heterocyclic ring), a one-proton doublet at 8.93δ was allocated to H-8 (in the benzene ring *ortho* to the nitrogen atom), and a group of unresolved signals corresponding to three protons was observed in the 7.85-8.55δ region and attributed to the benzene ring protons H-5, H-6 and H-7. These assignments were in concordance with those made by Black (119) for 3-nitroquinoline. The splitting of the H-8 doublet was 8 Hz and was due to *ortho* coupling; *meta* and *para* couplings were not revealed. A spectrum taken in trifluoroacetic acid

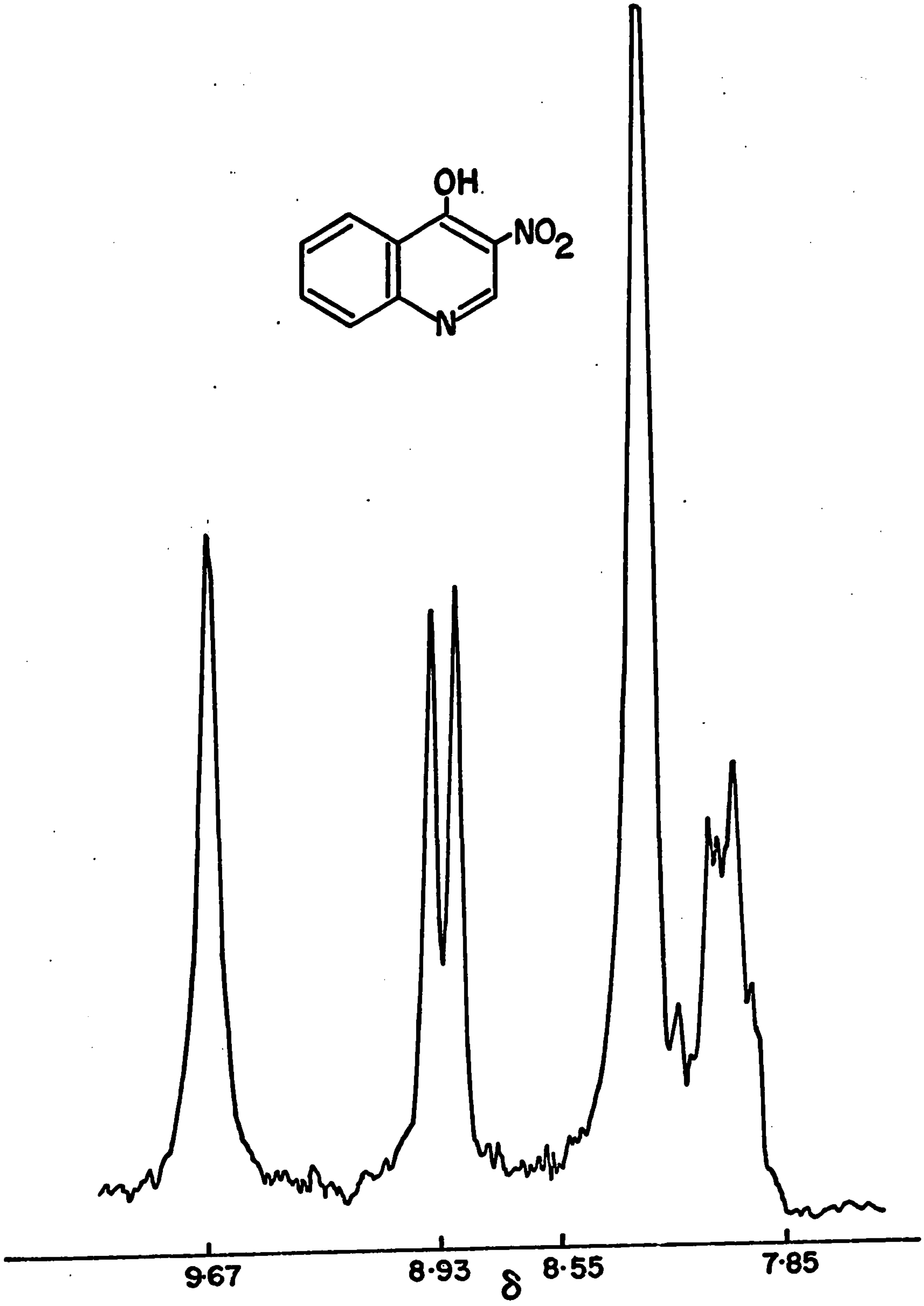
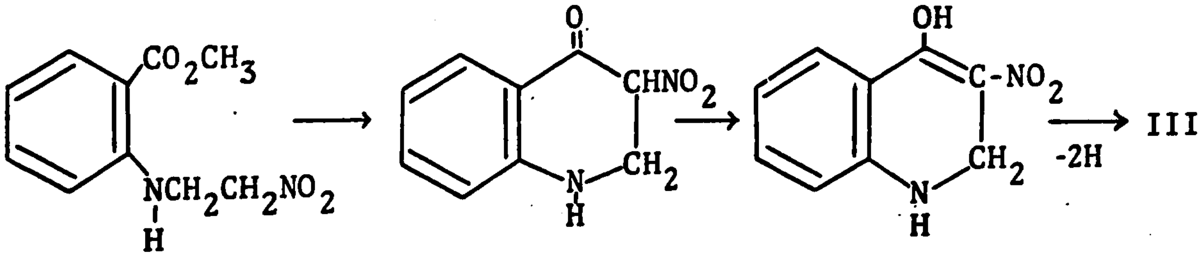


Fig. 15 NMR Spectrum (100 MHz) of III in DMSO-d_6

(with equimolar NaOD solution)

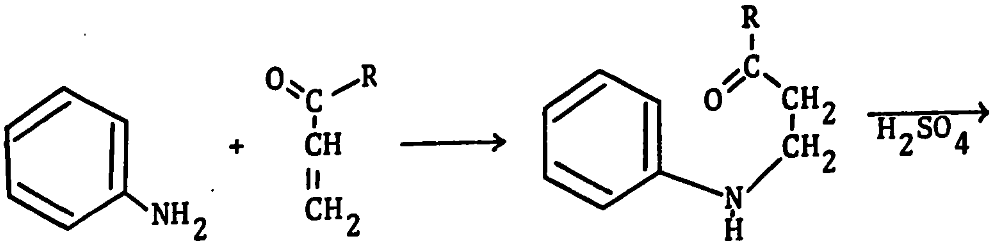
solution showed a similar pattern.

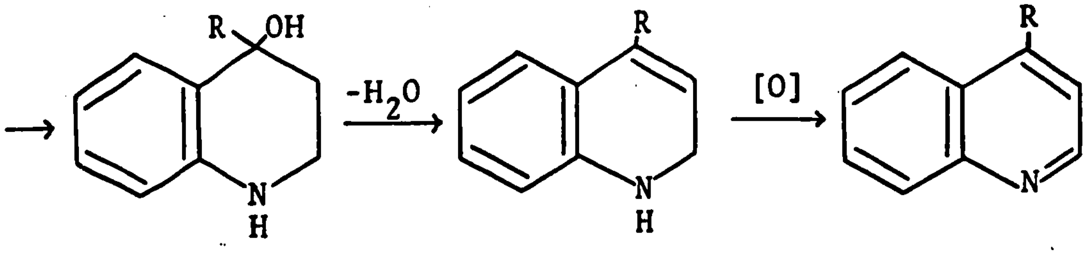
The formation of the quinoline derivative III in the cyclization of VII was surprising insofar as a dihydroquinoline derivative (VIIIB) should have been expected. Clearly an oxidative step must have been



VII VIIIA VIIIB

involved which converted VIIIB (undoubtedly the primary reaction product) into the quinoline III which was isolated. The reaction is reminiscent of the Skraup quinoline synthesis in which a dihydroquinoline intermediate is dehydrogenated to the final product by such oxidizing agents as ferric sulfate, nitrobenzene, stannic chloride, or oxygen (120):





In the present synthesis no external oxidant was added. That oxidation took place by atmospheric oxygen is a possibility which cannot be ruled out. Another possibility might be an intermolecular oxidation-reduction of intermediate VIII or its tautomeric nitro ketone form. The fact that the yield of III was less than 50% would allow for the stoichiometry of such a process. One half of VIII would be reduced to the corresponding 4-hydroxy-3-nitro-1,2,3,4-tetrahydroquinoline. Isolation or identification of the latter was not attempted and it might well prove difficult to do so. If indeed it is formed it could be prone to ring opening by β-elimination under the alkaline reaction conditions, and further complicated transformations might follow.

EXPERIMENTAL

General Remarks

All reactions were monitored by thin layer chromatography (T.L.C.) on silica gel G *, using 7.5-cm plates (Microscopic slides). Unless otherwise stated, the spots were made visible by spraying the plates with a solution of 1% ceric sulfate in 10% sulfuric acid and heating them on a hot plate.

Unless specified otherwise, column chromatography was performed with silica gel 7734 (0.05-0.20 mm, 70-325 mesh ASTM) *.

All evaporations were carried out with a flash evaporator under diminished pressure with a bath temperature at or below 35°.

Melting points of compounds were determined in capillaries in a Gallenkamp melting point apparatus equipped with a calibrated thermometer. They are uncorrected.

---

* A product of E. Merck AG, Darmstadt, Germany.

Infrared spectra were generally taken from Nujol mulls on a Beckman IR-20 spectrophotometer. Relative absorption intensities were estimated visually and were abbreviated as s (strong), m (medium), w (weak) and b (broad). When spectra were obtained from solutions or neat samples, this is explicitly mentioned.

Nuclear magnetic resonance (NMR) spectra were recorded either on a Varian HA-100 or T-60 instrument as specified. Unless a different solvent is stated, deuterated chloroform was used and tetramethylsilane served as internal standard.

Ultraviolet spectra were recorded on a Perkin Elmer spectrophotometer, model 202.

Optical rotations were measured with Perkin Elmer automatic polarimeter, model 141, at room temperature.

Refractive indices were determined with a Carl Zeiss refractometer at room temperature. The instrument was calibrated with monobromonaphthaline (n_D =1.6551).

Microanalyses and molecular weight determinations by the osmometric method were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium, Elbach, Germany.

PART I THE SYNTHESIS OF MISEROTOXIN ANALOGS

A. Synthesis of β-Nitro Alcohols

Preparation of anion exchange resin IRA-401 (OH^-)

Anion exchange resin Amberlite IRA-401 (Cl^-)* fresh from a bottle was soaked in 10% NaOH solution for 4 hours, then washed with 5% NaOH solution in a Büchner funnel, This was followed by repeated washings with distilled water until the filtrate was neutral to pH indicator paper, three washings with 95% ethanol, and finally one washing with 99% ethanol. The resin was left to dry at room temperature for half an hour and was immidiately used in the following reactions.

2-Nitro-1-propanol (I)

Formaldehyde solution (37% aqueous solution, 60 ml, 0.74 mole) and nitromethane(98.5 g, 1.31 mole) were mixed with 99% ethanol (140 ml) in a 500-ml round botton flask. The mixture was cooled externally with water during the addition of anion exchange resin (12 g). The flask was allowed to assume room temperature, sealed,

---

* Obtained from Fisher Chemical Co.

and shaken on an automatic shaker for 16 hours.

The reaction mixture was filtered and the filtrate evaporated to give a yellow liquid which was fractionally distilled under diminished pressure. The main fraction with boiling range 60-62° (0.8 mm) was collected. Yield: 47.5 g (61%); η_D= 1.4338. Reported (86): η_D= 1.4379; b.p. 97-99°/ 10 mm.

Characteristic IR absorption (liquid film, cm^{-1}):3400 s, b (OH); 2980 m; 2940 m; 2880 m; 1550 s (NO_2). Other bands occurred at 1460 m; 1360 s; 1320 m; 1070 s; 1040s; 990 s; 960 w; 920 w; 860 s.

NMR data (60 MHz):

1.37δ (3H, doublet, $J_{2,3}$ = 7 Hz, C-3 methyl protons).

3.07δ (1H, singlet, exchangeable with D_2O, hydroxyl proton).

3.95δ (2H, doublet, $J_{1,2}$ = 6 Hz, C-1 methylene protons).

4.69δ (1H, center of six peaks, C-2 methine proton).

1-Nitro-2-propanol (II)

Acetaldehyde (31.34 g, 40.0 ml, 0.71 mole) was precooled to -5° and added to nitromethane (48.9 g, 0.8 mole) which was contained in a 500 ml round bottom flask in an ice-salt bath. Ethanol (99%, 50 ml) and anion exchange resin (8.0 g) were added to the mixture. The flask was swirled gently for some time with occasional cooling, then brought to room temperature, sealed, and shaken mechanically for 12 hours.

The reaction mixture was filtered to remove the resin, the filtrate was evaporated to a thick liquid and subjected to fractional distillation. Fractions boiling between 60-62°/ 0.4 mm were collected. Yield: 34 g (45.6%). n_D = 1.4330. Reported (121): b.p. 112° (13 mm), n_D = 1.4242.

Characteristic IR absorption (liquid film, cm^{-1}): 3400 s, 3200 s (OH); 1550 s (NO_2). Other bands occurred at: 1380 s; 1260 m; 1130 m; 940 m; 860 m.

NMR data (60 MHz):

1.35δ (3H, doublet, $J_{2,3}$ = 6 Hz, C-3 methyl protons).

3.20δ (1H, doublet, $J_{2,\ 2OH}$ = 4 Hz, exchangeable with D_2O, hydroxyl proton).

4.30-4.80δ (3H, overlapped multiplets of C-1 methylene protons and C-2 methine proton).

2-Nitro-1-butanol (III)

A commercial product was obtained from T. J.

Baker Chemical Co. It was redistilled to yield a colorless liquid, b.p. 83-85°/ 1.8 mm, n_D = 1.4340. Reported (122); b.p. 127-130° / 25 mm.

2-Nitro-3-pentanol (IV)

Freshly distilled propionaldehyde (b.p. 49-50°, 47.8 g, 0.824 mole) and nitroethane (69.7 g, 0.93 mole) were mixed with 99% ethanol (75 ml) in a 500-ml flask. The contents were cooled in a cold water bath and anion exchange resin (16 g) was added. An exothermic reaction was observed. When the reaction mixture had come to room temperature, it was sealed and placed on a shaker for 17 hours.

The reaction mixture was then filtered, evaporated , and distilled under reduced pressure. A crude fraction (72.0 g) boiling between 105-120°/ 18 mm was collected. This was fractionally redistilled, and the bulk of the product was collected at 109-113°/ 20 mm. Yield: 67.0 g (59.2%); n_D = 1.4415. Reported (86): b.p. 107-109°/ 10 mm; n_D = 1.4467.
Characteristic IR absorption (liquid film, cm^{-1}): 3400-3500 s (OH); 1550 s (NO_2). Other bands occurred at:

2980 s; 2960 s; 2900 s; 1390 s; 1450 s; 1100 m; 980 s; 935 w; 880 m.

NMR data (60 MHz):

1.00δ (3H, triplet, $J_{4,5}$ = 7 Hz, C-5 methyl protons).

1.50-1.70δ (5H, overlapped multiplets, C-1 and C-4 protons).

2.90δ (1H, broad doublet, exchangeable with D_2O, hydroxyl proton).

3.90δ (1H, center of a broad multiplet, C-3 proton).

4.6δ (1H, center of multiplet, C-2 proton).

2-Methyl-2-nitro-1-propanol (V)

A cooled formaldehyde solution (37% aqueous solution, 100 ml, 1.23 mole) was added to 2-nitropropane (139.41 g, 1.56 mole), and the mixture was cooled in an ice-bath. The mixture was diluted with ethanol (99%, 120 ml) and anion exchange resin (12 g) was added. The flask was swirled gently for some time while cooled, allowed to assume room temperature, and placed on the automatic shaker for 50 hours.

At the end of the shaking period, the reaction mixture was filtered, the filtrate was evaporated to a

2980 s; 2960 s; 2900 s; 1390 s; 1450 s; 1100 m; 980 s; 935 w; 880 m.

NMR data (60 MHz):

1.00δ (3H, triplet, $J_{4,5}$ = 7 Hz, C-5 methyl protons).

1.50-1.70δ (5H, overlapped multiplets, C-1 and C-4 protons).

2.90δ (1H, broad doublet, exchangeable with D_2O, hydroxyl proton).

3.90δ (1H, center of a broad multiplet, C-3 proton).

4.6δ (1H, center of multiplet, C-2 proton).

2-Methyl-2-nitro-1-propanol (V)

A cooled formaldehyde solution (37% aqueous solution, 100 ml, 1.23 mole) was added to 2-nitropropane (139.41 g, 1.56 mole), and the mixture was cooled in an ice-bath. The mixture was diluted with ethanol (99%, 120 ml) and anion exchange resin (12 g) was added. The flask was swirled gently for some time while cooled, allowed to assume room temperature, and placed on the automatic shaker for 50 hours.

At the end of the shaking period, the reaction mixture was filtered, the filtrate was evaporated to a thick liquid which crystallized on drying <u>in vacuo</u> . Recrystallization from benzene gave colorless needles, m.p. 87-89.5°. Reported (86): m.p. 93-96°. Yield: 35 g, (24%).

Characteristic IR absorption (in CH_3Cl, cm^{-1}): 3600 w, 3400 b (OH); 1535 s (NO_2). Other bands occurred at: 3000 w; 2940 w; 2880 w; 1470 w; 1410 w; 1380 w; 1350 w; 1070 s; 860 w.

NMR data (60 MHz):

1.58δ (6H, singlet, methyl protons).

2.47δ (1H, center of triplet, exchangeable with D_2O, hydroxyl proton).

3.90δ (2H, doublet, $J_{1,1OH}$ = 6 Hz, changed to singlet after addition of D_2O, C-1 methylene protons).

B. Synthesis of Nitroalkyl β-D-Glucopyranoside Tetraacetates

Tetra-O-acetyl-α-D-glucopyranosyl bromide (VI)

This compound was prepared according to the procedure described by Lemieux (88). Colorless needles were obtained in 80% yield. The product was recrystallized from anhydrous ether and showed m.p. 88-89°, $[\alpha]_D$

+ 198° (c, 2, in chloroform).

2-Nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (VII)

2-Nitro-1-propanol (I) (1.491 g, 14.20 mmole), reactive silver carbonate * (3.260g, 11.83 mmole), anhydrous silver perchlorate (2.459 g, 11.83 mmole) and powdered Drierite ** (8.0 g) were mixed with chloroform *** (ethanol-free, 50 ml) in a foil-wrapped, 250-ml round bottom flask and stirred in the dark for half an hour. To this mixture, tetra-O-acetyl-α-D-glucopyranosyl bromide (VI) (8.705 g, 21.2 mmole) was added in three portions in ten-minute intervals. T.L.C. (acetone-benzene, 2:8, v/v) performed 20 minutes after the addition showed that two new spots (R_f = 0.70 and 0.48) and residual VI were present. Additional silver carbonate (0.400 g, 1.445 mmole) and silver perchlorate (0.100 g, 0.484 mmole) were introduced

---

* Prepared according to Methods in Carbohydrate Chemistry, Vol. II, p. 342, Ed. M. L. Wolfrom and R.LWhistler, A.P.1963.

** Dried in oven at 240° for 2 hours.

*** A.I. Vogel, Practical Organic Chemistry, p.176, 3 rd Edition, Longmans, London, 1962.

with vigorous stirring. After 30 minutes, t.l.c. showed a decrease of VI in the reaction mixture. An extra amount of VI (0.80 g, 1.945 mmole) was added to ensure complete reaction of I. The reaction was stopped after a total reaction time of two hours.

The reaction mixture was filtered through a sintered glass funnel and the residue was washed with chloroform. The combined filtrate and washings were evaporated to give a pale yellow liquid (9.85 g). This liquid was placed on a 500-g silica gel column prewashed with benzene, and eluted with benzene (100 ml), 10% acetone in benzene (200 ml), and 20% acetone in benzene (1500 ml). The effluent was collected in 10-ml fractions. The fractions exhibiting one product spot (R_f = 0.70, 20% acetone in benzene) were combined to give a slightly yellow syrup (2.650 g, 42.80%) which crystallized on trituration with 99% ethanol, m.p. 124-127°. One portion of the crystals was recrystallized from ethanol (99%) and petroleum ether (b.p. 60-80°) to give colorless prisms which melted at 126-127° and exhibited $[\alpha]_D$ -18.4° (<u>c</u>, 1.01, in chloroform).

<u>Anal</u>. $C_{17}H_{25}NO_{12}$ (435.38)

Calcd.: C, 46.89; H, 5.79; N, 3.22.

Found: C, 47.03; H, 5.97; N, 3.03.

Characteristic IR absorption of VII (cm^{-1}): 1750 s (C=O); 1550 m (NO_2). Other bands occurred at: 1370 m; 1200-1240 b,m; 1040 s. Hydroxyl absorption was absent.

NMR data (60 MHz):

1.46δ , 1.60δ (3H, centers of two superimposed doublets, C-3' methyl protons, $J_{2',3'}$ = 7 Hz).

1.97δ , 1.99δ , 2.06 δ (12H, three singlets, equatorial O-acetyl groups).

3.59 δ (1H, multiplet, H-5).

4.02-4.29 δ (4H, overlapping multiplets, protons of C-6 and C-1').

4.48 , 4.53 δ (1H, centers of two overlapping doublets, H-1, $J_{1,2}$ = 7.5 Hz).

4.63-4.82 δ (1H, multiplet, H-2').

4.84-5.34 δ (3H, overlapping multiplets, H-2, H-3 and H-4).

Effluent fractions containing the less mobile by-product (R_f = 0.4, 20% acetone in benzene) were combined. The compound was isolated in crystalline form and identified as 2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (XII) by its melting point (129-132°) and

NMR spectrum (27).

1-Methyl-2-nitroethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (VIII)

Lower-melting sample (VIII A)

1-Nitro-2-propanol (II) (1.013 g, 9.64 mmole), reactive silver carbonate (1.508 g, 5.47 mmole), anhydrous silver perchlorate (9.031 g, 1.495 mmole) and powdered Drierite (14.0 g) in chloroform (50 ml, ethanol-free) were stirred for half an hour in the dark. Acetobromoglucose (VI) (3.762 g, 9.64 mmole) dissolved in chloroform (40 ml) was then added to the mixture through a dropping funnel over a period of 15 minutes, with vigorous stirring. An excess of VI (0.500 g, 1.215 mmole) in 5 ml of chloroform was added after a stirring period of 45 minutes. The reaction mixture was then stirred for another 30 minutes before it was filtered. The filtrate and washings were evaporated to give a yellow syrup (4.8 g).

The syrup was placed on a 150-g silica gel column (prepared by suspension in benzene) and eluted with 20% acetone in benzene. Rapid removal of most of the by-product XII was achieved by collecting fractions containing either VIII alone or mixtures of VIII and XII. These were combined and evaporated to give a syrup (3.932 g) containing mainly the desired product and small amounts of XII. This syrup was then rechromatographed on a 225-g silica gel column which was eluted with benzene (100 ml), 10% acetone in benzene (200 ml) and 20% acetone in benzene (300 ml). Chromatographically uniform fractions were combined (R_f = 0.67, solvent system: 20% acetone in benzene). After removal of solvent, a yellow syrup was obtained which crystallized on drying _in vacuo_. Yield: 1.464 g,(35%); m.p. 126-129°. An analytical sample was recrystallized from 99% ethanol and showed m.p. 128-129° (turbid melt, clearing at 134°); $[\alpha]_D$ -14.6° (_c_, 1.1, in chloroform).

Anal. $C_{17}H_{25}NO_{12}$ (435.38)

Calcd., C, 46.89; H, 5.79; N, 3.22.

Found : C, 46.84; H, 5.73; N, 3.40.

Characteristic IR absorption (cm^{-1}): 1750 s (C=O); 1565 m (NO_2). Other bands occurred at: 1230 s, b; 1040 s; 1160 w; 1070 w. Hydroxyl absorption was absent.

NMR data (100 MHz, Fig. 1):

1.26δ, 1.33δ (3H, centers of two overlapping doublets, J = 6 Hz, methyl protons).

1.96δ, 1.98δ, 2.06δ (12H, three singlets, equatorial *O*-acetyl protons).

3.51-4.51δ (6H, overlapping multiplets, H-1', H-2', H-5 and H-6).

4.57δ, 4.59δ (1H, overlapping doublets, $J_{1,2}$ = 7.5 Hz, H-1).

4.78-5.30δ (3H, overlapping multiplets, H-2, H-3 and H-4).

Higher-melting sample (VIII B)

1-Nitro-2-propanol (II) (0.416 g, 3.95 mmole), anhydrous silver perchlorate (0.810 g, 3.91 mmole) and Drierite (5.0 g) in dry nitromethane (35 ml) were stirred in the dark for half an hour. Acetobromoglucose (VI) (1.626 g, 3.95 mmole) was added to the mixture with vigorous stirring. T. l. c. showed, after two hours, the persistence of a trace of VI. An excess of silver perchlorate (0.30 g, 1.44 mmole) was added and the reaction was stopped after another 90 minutes.

The reaction mixture was filtered and the filtrate was evaporated to give a brown liquid (2.211 g,) The liquid was chromatographed on a 115-g silica gel column by elution with 20% acetone in benzene (600 ml). The early effluent fractions (35 ml) were evaporated to afford a yellow liquid (0.25 g) which was identified to be unreacted alcohol II. Later fractions showing a single product spot (R_f = 0.67) were combined and evaporated to a syrup which crystallized on cooling and scratching to yield 0.45 g (26.2%) of solid VIII B. Recrystallization from ethanol (99%) gave colorless crystals, m.p. 139-143°, $[\alpha]_D$ -17.2° (c, 0.68, in chloroform).

Anal. $C_{17}H_{25}NO_{12}$ (435.38)

Cacld., C, 46.89; H, 5.79; N, 3.22.

Found : C, 46.78; H, 5.78; N, 3.29.

NMR data (100 MHz, Fig. 2):

1.33δ, 1.26δ (3H, centers of two overlapping doublets, J = 6 Hz, methyl protons).

1.96δ, 1.99δ, 2.06δ (12H, three singlets, equatorial O-acetyl protons).

3.53-4.56δ (6H, overlapping multiplets, H-1', H-2', H-5 and H-6).

4.57 δ (1H, doublet, H-1, $J_{1,2}$ = 7.5 Hz).

4.77-5.37δ (3H, overlapping multiplets, H-2, H-3 and H-4).

2-Nitrobutyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (IX)

2-Nitro-1-butanol (III) (1.151 g, 9.66 mmole), reactive silver carbonate (3.684 g, 13.400 mmole), anhydrous silver perchlorate (2.815 g, 13.55 mmole), and Drierite (8.0 g)) were stirred in chloroform (50 ml) for half an hour in the dark. Acetobromoglucose (VI) (5.753 g, 14.00 mmole) was added to the mixture in three portions over a period of 20 minutes, and stirring was continued for 90 minutes. The reaction mixture was then filtered and evaporated to give a colorless liquid (6.20 g). This liquid was placed on a 250-g silica gel column which was eluted with benzene (100 ml), 8% acetone in benzene (100 ml), 10% acetone in benzene (100 ml), 15% acetone in benzene (100 ml) and 20% acetone in benzene (500 ml). Effluent was collected in 7-ml fractions.

Fractions containing the fastest moving

product were combined to give a colorless syrup which solidified on trituration with scratching in ethanol (99%) to a colorless powder (1.852 g, 42.6%). An analytical sample was recrystallized from ethanol under slow cooling, m.p. 55-88°, $[\alpha]_D$ -18.8° (c, 1.06, in chloroform).

Anal. $C_{18}H_{27}NO_{12}$ (449.41)

Calcd., C, 48.13; H, 6.06; N, 3.12.

Found : C, 48.05; H, 5.90; N, 3.04.

Characteristic IR absorption (cm^{-1}): 1750 s (C=O); 1550 m (NO_2). Other bands occurred at: 1220 s, b; 1150 m; 1040 b; 960 w; 900 w . No hydroxyl absorption was present.

NMR data (100 MHz):

0.96δ (3H, triplet, $J_{3',4'}$ = 7 Hz, C-4'methyl protons).

1.49-1.90δ (2H, multiplet, C-3' protons).

1097δ, 1.98δ, 2.02δ, 2.07δ (12 H singlets, equatorial O-acetyl protons).

3.54-3.81δ (1H, multiplet, H-5).

3.81-4.29δ (4H, overlapping multiplets, H-1' and H-6).

4.29-4.50δ (1H, multiplet, H-2').

4.53δ (1H, center of doublet, $J_{1,2}$ = 7.5 Hz, H-1).

4.79-5.34δ (3H, overlapping multiplets, H-2, H-3 and H-4).

In one case a crop of m.p. 99-103° was obtained and the mother liquor upon repeated chromatography gave a crop of m.p. 88-90°. These melting points could not be reproduced, however.

1-Ethyl-2-nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (X)

Higher-melting sample (X A)

2-Nitro-3-pentanol (IV) (0.546 g, 4.10 mmole), powdered mercuric cyanide (2.069 g, 8.20 mmole) and Drierite (3.0 g) were stirred in a 100-ml round bottom flask containing 40 ml of dry dichloroethane *. To this mixture, acetobromoglucose (VI) (3.376 g, 8.23 mmole) was added and the reaction mixture was stirred vigorously for 30 hours **. T.l.c. (ethyl acetate: ethanol: benzene = 20: 5: 75, v/v) showed the presence of three spots. The fastest moving spot (R_f = 0.82) corresponded to compound X, the slowest moving spot was

---

* Dried with P_2O_5 and distilled at 81-82°.

** The flask was flushed with nitrogen gas occasionally to remove accumulated hydrogen cyanide.

identical with XII, and the middle spot was not identified. The reaction mixture was diluted with chloroform and washed three times with water. The chloroform layer was dried with anhydrous sodium sulfate and evaporated to furnish a yellow liquid (3.422 g). The liquid was brought onto a 130-g silica gel column which was eluted with 20% ethyl acetate in benzene. Fractions showing a single product spot were combined to give a syrup (0.30 g). Fractions containing mixed spots were rechromatographed on a 30-g silica gel column eluted with the same solvent system, to give a pure syrup (0.58 g). The total yield was 0.88 g (46.4%). Crystallization from 99% ethanol gave X A as a white powder (0.56 g); m.p. 133-139°. An analytical sample was recrystallized from the same solvent and showed m.p. 136-139° (melt turbid, completely clear at 142°), $[\alpha]_D$ -21.6° (c, 1.20, in chloroform).

Anal. $C_{17}H_{29}NO_{12}$ (463.43)

Calcd.: C, 49.24; H, 6.31; N, 3.02.

Found : C, 49.08; H, 6.14; N, 3.28.

Characteristic IR absorption (cm^{-1}): 1750 s (C=O), 1550 m (NO_2). Other bands occurred at: 1230-1200 s, b; 1040 m; 1090 w; 910 w; 1170 w. Hydroxyl absorption was absent.

NMR data (100 MHz, Fig. 3):

0.93δ (3H, center of a triplet, J = 7.0 Hz, methyl protons on the ethyl moiety).

1.44-1.95δ (5H, overlapping multiplets, methylene group of the ethyl moiety and methyl protons on C-3').

1.95δ, 1.98δ, 2.03δ (12H, three singlets, equatorial acetyl protons).

3.54-4.33δ (4H, overlapping multiplets, H-5, H-6 and H-1').

4.47δ (1H, center of doublet, $J_{1,2}$ = 7.5 Hz, H-1).

4.50-4.72 δ (1H, multiplet, partially superimposed with the prominent doublet of H-1).

4.78-5.38δ (3H, overlapping multiplets, H-2, H-3 and H-4).

Lower-melting sample (X B)

2-Nitro-3-pentanol (IV) (2.033 g, 15.35 mmole), reactive silver carbonate (3.037 g, 17.00 mmole), anhydrous silver perchlorate (4.55 g, 22.00 mmole) and Drierite (12.0 g) were stirred in ethanol-free chloroform (150 ml) for 30 minutes in the dark. Acetobromoglucose (VI) (9.757 g, 23.75 mmole) was added to the mixture in three portions in 15-minute intervals. The reaction mixture was stirred vigorously for one hour, then filtered through a sintered glass funnel. The filtrate was evaporated to give a pale yellow liquid (11.0 g). The liquid was dissolved in 15 ml of benzene and placed on a 500-g silica gel column packed in benzene. The column was eluted with benzene (100 ml), 20% acetone in benzene (1600 ml) and 10 ml fractions were collected. Fractions showing a single t.l.c. spot of X B (R_f=0.72) were combined (250 ml) to give upon evaporation a pure syrup (3.564 g) which crystallized on drying. Fractions containing mixtures of product X B and by-product XII (140 ml) were combined and evaporated to a syrup which crystallized to give 0.11 g of X B as colorless powder. Total yield of the glucoside was 3.674 g (51.7%). An analytical sample was recrystallized from ethanol; m.p. 124-125°, $[\alpha]_D$ -19.6° (_c_, 1.03, in chloroform)

Anal. $C_{19}H_{29}NO_{12}$ (463.43)

Calcd.: C, 49.24; H, 6.31; N, 3.02.

Found : C, 49.02; H, 6.20; N, 3.10.

Characteristic IR absorptions were identical with those of the higher-melting sample, X A.

NMR data (100 MHz, Fig. 4):

0.92δ, 0.96δ (3H, centers of two overlapping triplets, methyl protons on the ethyl moiety).

1.44-1.95δ (5H, overlapping multiplets, methylene group on the ethyl moiety and methyl protons on C-3').

1.97δ, 1.99δ, 2.15δ (12H, three singlets, equatorial acetyl protons).

3.54-4.33δ (4H, overlapping multiplets, H-5, H-6 and H-1').

4.38-4.72δ (2H, overlapping multiplets, H-1 and H-2', a prominent doublet due to H-1 was at 4.47δ, $J_{1,2}$ = 7.5 Hz).

4.77-5.33δ (3H, overlapping multiplets, H-2, H-3 and H-4).

2-Methyl-2-nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (XI)

2-Methyl-2-nitro-1-propanol (V) (2.382 g, 20.00 mmole), reactive silver carbonate (10.00 g, 36.30 mmole), silver perchlorate (1.00 g, 4.84 mmole) and powdered Drierite (20.0 g) were stirred for half an hour in chloroform (100 ml). To this mixture was added acetobromoglucose (VI) (8.226 g, 20.00 mmole), with vigorous stirring. Thirty minutes after the addition, another portion of VI (7.18 g,17.48 mmole) was added together with silver carbonate (3.65 g, 13.25 mmole). The reaction mixture was stirred for 15 hours before it was filtered through a sintered glass funnel. The residue was washed with chloroform, the filtrate and washings were combined and evaporated to give a yellow liquid (14.60 g). The liquid mixture was divided into two portions and both were subjected to column chromatography. One portion (8.14 g) was placed on a column containing 500 g silica gel, prepared in 15% acetone in benzene and eluted with the same solvent system. The other portion (6.46 g) was separated on a 400-g silica gel column prepared and eluted with the solvent system just mentioned. Fractions of 10 ml were collected from both columns. Fractions exhibiting single product spot (R_f = 0.56, 15% acetone in benzene) or one major spot with a trace of impurity (XII, R_f = 0.34) were combined and evaporated to give 4.85 g of a syrup. Crystallization from ethanol (99%) gave colorless prisms. The yield was

3.759 g (41.8%); m.p. 157-159°; $[\alpha]_D$ -20.1° (*c*, 1.0, in chloroform).

Anal. $C_{18}H_{27}NO_{12}$ (449.41)

Calcd.: C, 48.10; H, 6.06; N, 3.12.

Found : C, 48.03; H, 5.98; N, 3.30.

Characteristic IR absorption (in chloroform, cm^{-1}): 1750 s, b (C=O); 1535 m (tertiary NO_2). Other bands occurred at: 2950 w; 1370 m; 1230 s,b; 1030 s,b; 900w.Hydroxyl absorption was absent.

NMR data (100 MHz, Fig. 5):

1.50δ, 1.56δ (6H, two singlets, methyl protons).

1.96δ, 1.98δ, 2.06δ (12H, three singlets, equatorial acetyl protons).

3.98δ (2H, singlet, H-1').

4.20δ (2H, center of multiplet, H-6).

4.49δ (1H, center of doublet, $J_{1,2}$ = 7.5 Hz, H-1).

4.84-5.30δ (3H, overlapping multiplets, H-2, H-3 and H-4).

C. Deacetylation of Glucoside Tetraacetates

2-Nitropropyl β-D-glucopyranoside (XIII)

2-Nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (VII) (1.672 g, 3.84 mmole) was suspended in anhydrous methanol (30 ml) in a flask equipped with reflux condenser, drying tube and magnetic stirrer. A methanolic solution of methyl p-toluenesulfonate was prepared by dissolving 0.936 g of freshly distilled methyl p-toluenesulfonate in 10 ml anhydrous methanol (c = 0.503 M), and 0.585 ml of this solution, corresponding to 0.295 mmole of the catalyst, was added to the reaction mixture which was heated to reflux for 29 hours. After that time t.l.c. (30% ethanol in benzene) showed the presence of one major product (R_f = 0.35) and traces of impurities below and above it. The reaction was stopped by cooling the solution and evaporating it to give a light yellow syrup (1.15 g). The syrup was placed on a 60-g silica gel column which was eluted with 20% ethanol in benzene. Good separation was achieved. Fractions containing the major product were combined and evaporated to give a syrup (0.668 g, 65%) which was chromatographically pure. The syrup was dissolved in a minimum volume of anhydrous methanol, then anhydrous diethyl ether was added dropwise until a slight turbidity appeared. After prolonged cooling, rosette-type crystals of XIII were obtained. It showed m.p. 115-117°, $[\alpha]_D$ -12.3° (c, 1.02, in methanol).

Anal. $C_9H_{17}NO_8$ (267.23)

Calcd.: C, 40.45; H, 6.41; N, 5.24.

Found : C, 40.26; H, 6.58; N, 5.09.

Characteristic IR absorption (cm^{-1}): 3540, 3300 s,b (OH); 1550 s (NO_2).Other bands occurred at: 1200 w; 1160 s; 1070 s; 1030 s; 900 m; 860 m. Ester carbonyl absorption was absent.

NMR data (100 MHz, in acetone-d_6 + 0.05 ml D_2O, Fig. 6):

1.49δ (3H, center of doublet, C-3' methyl protons, $J_{2',3'}$ = 7 Hz).

3.36δ (3H, center of multiplet, H-5 and H-6).

3.48-4.18δ (9H, overlapping signals ascribed to H-2, H-3, H-4, H-1' and the hydroxyl protons).

4.36δ (1H, center of doublet, H-1, $J_{1,2}$ = 7.5 Hz).

4.94δ (1H, center of miltiplet, H-2').

A minor product of the reaction was obtained when later fractions from the column, showing a spot of $R_f = 0.25$, were combined and gave upon evaporation a syrup which crystallized readily on drying. This product was identified as methyl α-D-glucopyranoside by its melting point (163-165°), optical rotation, and by comparing its IR spectrum with that of an authentic sample.

1-Methyl-2-nitroethyl β-D-glucopyranoside (XIV)

1-Methyl-2-nitroethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (VIII) (0.874 g, 2.00 mmole) in anhydrous methanol (20 ml) was methanolyzed in the presence of 0.25 ml (0.169 mmole) of the catalyst solution as described for XIII above. Refluxing was stopped after 18 hours at a stage when the reaction was nearly complete as indicated by t.l.c. (20% ethanol in benzene). The solution was cooled and evaporated and the syrup obtained was chromatographed on a 30-g silica gel column which was eluted with 20% ethanol in benzene (300 ml). Effluent fractions containing the major product were combined and evaporated to afford a colorless syrup (0.30 g, 56%) that was chromatographically pure glucoside XIV. Many attempts to crystallize this syrup did not succeed. It showed $[\alpha]_D$ -18.3° (c, 1.07, in methanol).

Anal. $C_9H_{17}NO_8$ (267.23)

Calcd.: C, 40.45; H, 6.41.

Found : C, 40.84; H, 6.39.

Characteristic IR absorption (liquid film, cm^{-1}): 3400-3200 s,b (OH); 1550 s (NO_2). Other bands occurred at: 2950 w; 1420 w; 1380 m; 1230 w; 1160 w; 1080 s; 1040 s; 890 w; 860 w. Ester absorption was absent.

NMR data (100 MHz, in acetone-d_6, TMS as lock signal):

1.29δ, 1.32δ (3H, centers of two doublets, methyl protons on C-1').

4.41δ, 4.44δ (1H, centers of two overlapping doublets, H-1, $J_{1,2}$ = 7.5 Hz).

4.60δ (2H, center of triplet, H-2').

2.88-4.00δ (11H, multiplets ascribed to ring protons H-2, H-3, H-4, H-5, H-6, hydroxyl protons and H-1').

2-Nitrobutyl β-D-glucopyranoside (XV)

2-Nitrobutyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (IX) (1.016 g, 2.26 mmole) in anhydrous methanol (20 ml) was methanolyzed in the presence of 0.44 ml (0.22 mmole) of catalyst solution as previously described for XIII. After a refluxing period of 23 hours, it was shown by t.l.c. that one major product (R_f = 0.35, 30% ethanol in benzene) was present. A faint spot (R_f = 0.28) corresponded to methyl α-D-glucopyranoside. The reaction mixture was cooled and evaporated to give a colorless syrup (0.592 g). This syrup was dissolved in 5 ml of a solvent mixture (ethanol:benzene, 3:7, v/v) and placed on a column containing 50 g of silica gel. Sequential elution with pure benzene (50 ml), 15% ethanol in benzene (50 ml), and 20% ethanol in benzene (250 ml) resulted in good separation. Effluent fractions containing the major product furnished a colorless syrup (0.537 g). The syrup was dissolved in a minimum volume of anhydrous methanol to which was then added a few drops of ethyl acetate and anhydrous diethyl ether until a slight turbidity appeared. By cooling the mixture overnight in the refrigerator, colorless crystals were obtained (0.253 g); m.p. 130-132°; $[\alpha]_D$ -22.1° (c, 0.33, in water). The mother liquor afforded an additional crop (0.202 g) upon concentration and seeding; m.p. 129-132°. The total yield of XV was 0.455 g (71.7%). The mother liquor from the second crop contained mostly compound XV and traces of side products, according to t.l.c.

Anal. $C_{10}H_{19}NO_8$ (281.26)

Calcd.: C, 42.70; H, 6.81; N, 4.98.

Found : C, 42.81; H, 6.63; N, 4.94.

Characteristic IR absorption (cm^{-1}): 3560, 3400-3200 s (OH); 1550 s (NO_2). Other bands occurred at: 1200 w; 1165 m; 1030 s; 900 w; 860 w; 800 w. Ester absorption was absent.

NMR data (100 MHz, in acetone-d_6 with addition of 0.05 ml of D_2O, TMS as internal standard, Fig. 8).

0.91δ (3H, center of triplet, methyl protons on C-4').

1.86δ (2H, quintet, methylene protons on C-3').

4.36δ (1H, center of doublet, H-1, $J_{1,2}$ = 7.5 Hz).

4.80δ (1H, center of multiplet, H-2').

3.00-4.19δ (12H, overlapping multiplets, ascribed to ring protons H-2, H-3, H-4, H-5 and H-6; hydroxyl protons and H-1').

1-Ethyl-2-nitropropyl β-D-glucopyranoside (XVI)

1-Ethyl-2-nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (X) (1.463 g, 3.16 mmole) in anhydrous methanol (20 ml) was refluxed for 20 hours in the presence of catalyst solution (0.48 ml, 0.244 mmole) as described above for XIII. T.l.c. (20% ethanol in benzene) at this stage showed four spots in addition to a spot of the starting compound. Heating was continued for another 25 hours at which time t.l.c. indicated the presence of one major product (R_f = 0.38). There were two faint shadows above (R_f = 0.5 and 0.7) and one below (R_f = 0.15) the major spot. The solution was cooled and evaporated to a colorless syrup (0.920 g) which was chromatographed on a 60-g silica gel column by elution with 20% ethanol in benzene. Effluent fractions containing the pure major product or mixtures of major product and traces of the less mobile side product (methyl α-D-glucopyranoside) were combined to give a syrup (0.711 g) which was rechromatographed in the same way. Clean separation resulted giving the major product XVI as a chromaographically pure, colorless syrup. Attempts to crystallize this syrup did not prove successful. Yield: 0.565 g (60.5%), $[\alpha]_D$ -28.6° (c, 1.85, in methanol).

Anal. $C_{11}H_{21}NO_8$ (295.29)

Calcd.: C, 44.74; H, 7.17.

Found : C, 44.51, H, 7.39.

Characteristic IR absorption (liquid film, cm^{-1}): 3500 s (OH); 1550 s (NO_2). Other bands occurred at : 1450 m; 1380 m; 1350 w; 1150 m; 1060 b, s; 1030 b. Ester absorption was absent.

NMR data (100 MHz, in acetone-d_6, TMS as internal standard):

1.00δ, 1.02δ (3H, centers of overlapping triplets, methyl protons of the ethyl moiety).

1.42-1.71δ (5H, multiplets, C-3' methyl protons and methylene protons of the ethyl moiety).

3.02-4.46δ (14H, complicated overlapping multiplets, ascribed to all ring protons, hydroxyl protons and H-1').

4.58-5.02δ (1H, multiplet, H-2').

2-Methyl-2-nitropropyl β-D-glucopyranoside (XVII)

2-Methyl-2-nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (XI) (1.01 g, 2.23 mmole) was suspended in anhydrous methanol (12 ml) in a 25-ml round bottom flask with vigorous stirring. A solution of sodium methoxide (3.5 ml, 0.76 mmole, prepared by dissolving 0.153 g of sodium in 30.5 ml of anhydrous methanol) was added to the suspension. The turbid mixture became clear within 5 minutes. The pH of the solution at this stage was 8.5 and t.l.c. (20% ethanol in benzene) after 15 minutes showed a single product spot (R_f = 0.25). The reaction was stopped after another 10 minutes by neutralizing the solution with cation exchange resin Amberite IR-120 (H^+). The resin was removed by filtration and repeatedly washed with ethanol. Filtrate and washings were combined and evaporated to give a white solid (0.610 g, 95%) which was chromatographically pure glucoside XVII. On recrystallization from methanol and diethyl ether, large colorless prisms were obtained (0.428 g); m.p. 140.5-141.5°. Another crop of crystals was obtained by working up the mother liquor. The total yield was 0.549 g (87.5%); $[\alpha]_D$ -23.3° (c, 1.08, in methanol).

Anal. $C_{10}H_{19}NO_8$ (281.26)

Calcd.: C, 42.70; H, 6.81; N, 4.98.

Found : C, 42.89; H, 6.80; N, 5.10.

Characteristic IR absorption (KBr pellet, cm^{-1}): 3500-3200 s, b (OH); 1535 s (tertiary NO_2). Other bands occurred at : 2940 w; 2920 w; 2880 w; 1290 m; 1210 m; 1160 s; 1050-1010 b; 890 m; 860 m; 830 m; 620 m; 550 m. Ester absorption was absent.

NMR data (100 MHz, in D_2O, 0.05 ml of acetone added as internal reference):

0.60 ppm upfield from acetone (6H, singlet, methyl protons).

0.86-1.46 ppm downfield from acetone (5H, overlapping multiplets ascribed to H-5, H-6 and H-1').

2.21 ppm downfield from acetone (1H, doublet, $J_{1,2}$ = 7.5 Hz, H-1).

1.46-2.17 ppm downfield from acetone (3H, complicated overlapping multiplets, H-2, H-3 and H-4).

PART II OXIDATION OF AMINO SUGARS TO NITRO SUGARS

A. Oxidation of trans-2-Aminocyclohexanol(I)

1. Preparation of trans-2-aminocyclohexanol (I)

Cyclohexene oxide (5.3 ml) was dissolved in anhydrous methanol (50 ml) and placed in a stainless steel bomb (32.5×4.8 cm) that was cooled in a dry-ice/acetone bath. Liquid ammonia (40 ml) was added, and the bomb was sealed, allowed to attain room temperature, and heated in an oven at 80° for two hours. It was then allowed to stand at room temperature for twelve hours, cooled with dry-ice/acetone, and opened. Evaporation of the reaction mixture furnished a yellowish-white solid residue. Sublimation of the residue at 45° and 2 Torr gave I as colorless needles, m.p. 67-69°, in a yield of 3.5 g (63%). Recorded (97): m.p. 67-68°. Characteristic IR absorption (liquid film, cm^{-1}): 3360 s (hydrogen-bonded OH); 2940 s, 2860 s (C-H); 1590 m (N-H). Other bands occurred at: 1450 s; 1350-1380 b, w; 1070 s; 970 m; 920 w; 870 w; 840 m.

NMR data (60 MHz):

0.9-1.9 δ (8H, broad signal, ring protons on C-3, -4, -5 and -6).

2.30 δ (1H, singlet, exchangeable with D_2O, superimposed with H-1, hydroxyl proton).

2.20-2.70 δ (1H, broad singlet, H-1).

2.87-3.40 δ (1H, broad signal, H-2).

2. Preparation of trans-2-aminocyclohexanol hydrochloride (I A)

Compound I (1.146 g, 9.95 mmole) was dissolved in 15 ml of ethanol (99%). To this solution, 2N hydrochloric acid was added dropwise until it was slightly acidic (≈ 10 ml). The slightly yellow solution was evaporated to give a powder which on recrystallization from 95% ethanol afforded colorless hydrochloride I A, m.p. 178.5-180°. Lit. (97): m.p. 175°.

Characteristic IR absorption (cm^{-1}):

1600 m, 1570 m (NH_3^+), 1500 s; 1300 m; 1250 w; 1220 w; 1160 w; 1100 w; 1080 s; 1040 s; 1015 s (shoulder); 930 w; 840 m.

3. Synthesis of trans-2-nitrocyclohexanol (II) and trans-2-nitrosocyclohexanol dimer (III)

m-Chloroperbenzoic acid*(0.448 g, 2.61 mmole) was dissolved in chloroform (5 ml) which was heated to reflux in a two-necked flask. A partial suspension of trans-2-aminocyclohexanol (I) (0.100 g, 0.865 mmole) in chloroform (8 ml) was added to the boiling solution through a dropping funnel over a period of five minutes, with vigorous magnetic stirring. The reaction was stopped after one hour. Thin layer chromatography (10% ethyl acetate in benzene, v/v) at this point showed two reaction products (R_f, 0.62 and 0.28). The reaction mixture was cooled in a refrigerator, and m-chlorobenzoic acid which deposited was removed by filtration. The filtrate was washed with ice-cooled sodium bicarbonate solution (5%) and water, dried with anhydrous sodium sulfate, and evaporated to a semi-solid.

---

* m-Chloroperbenzoic acid was purchased from Aldrich Chemical Co. The reagent is specified to be of 85% purity, and this was taken into account throughout the thesis whenever quantities were expressed in molar terms.

The semi-solid was dissolved in a small volume of benzene and brought onto a 5.0-g silica gel column. The column was eluted with 5% ethyl acetate in benzene (20 ml), 10% ethyl acetate in benzene (20 ml), 25% ethyl acetate plus 5% ethanol in benzene (20 ml), and 20% ethyl acetate plus 10% ethanol in benzene (40 ml). The faster moving product obtained after evaporating the early effluent fractions showing a single t.l.c. spot was a yellow oil which crystallized as needles upon trituration with benzene and petroleum ether (30-60°) followed by cooling. The product (20 mg, 16%) was the desired trans-2-nitrocyclohexanol (II), m.p. 46-47°. Lit. (98): m.p. 47-48°.

Characteristic IR absorption (liquid film, cm^{-1}):
3370-3300 s (OH); 2930 s; 2860 s (C-H); 1550 s (NO_2).
Other bands occurred at: 1450 m; 1370 m; 1240 m; 1190 w; 1120 b, w; 1065 s; 970 m; 900 m; 860 m; 730 w.

NMR data (100 MHz):
0.99-2.45δ (8H, unresolved multiplet, ring protons on C-3, -4, -5 and -6).
2.74δ (1H, singlet, exchangeable with D_2O, hydroxyl proton on C-1).

3.85-4.49 δ (2H, broad multiplet, overlapping signals
of H-1 and H-2).

The effluent fractions from the column containing the second product were evaporated to give a white solid which was chromatographically pure; m.p. 118-122°. Recrystallization from ethyl acetate and petroleum ether (60-80°) gave the nitroso dimer III as fine needles melting at 130-132°. The yield was 31 mg (28%).

Anal. $C_{12}H_{22}N_2O_4$ (258.31)

Calcd.: C, 55.79; H, 8.59; O, 24.78.

Found : C, 55.54; H, 8.38; O, 24.95.

Characteristic IR absorption (cm^{-1}): 3400-3200 s (hydrogen-bonded OH); 1195 s (*trans* nitroso dimer); Other bands occurred at: 1300 w; 1270 w; 1240 w; 1070 s; 980 w; 950 w; 910 w; 870 w; 860 w; 840 w; 690 m.

Ultra-violet absorption (in methanol): λ_{max} 296 nm (ε, 7500).

NMR data (60 MHz):

1.0-2.50δ (8H, broad multiplet, ring protons on C-3,
-4, -5 and -6).

3.43δ (1H, broad signal, exchangeable with D_2O, hydroxyl proton on C-1).

4.10δ (1H, center of a broad multiplet, proton on C-1).

4.73-5.53δ (1H, multiplet, proton on C-2).

B. Oxidation of 3-Amino-3-deoxy-glycosides

1. Oxidation of methyl 3-amino-3,6-dideoxy-2,4-di-O-methyl-α-L-glucopyranoside hydrochloride (IV). Synthesis of methyl 3,6-dideoxy-3-nitro-2,4-di-O-methyl-α-L-glucopyranoside (V)

m-Chloroperbenzoic acid (312 mg, 1.81 mmole) was dissolved in chloroform (10 ml) and the solution was heated to reflux. A solution of methyl 3-amino-3,6-dideoxy-2,4-di-O-methyl-α-L-glucopyranoside hydrochloride (IV) (50 mg, 0.207 mmole) in methanol (3 ml) and chloroform (8 ml) was added over aperiod of 20 minutes. The reaction was shown by t.l.c. to be nearly complete (15% ethyl acetate in benzene) five minutes after the end of addition, with only a trace of IV left at the baseline. The reaction was stopped after another 20 minutes, and t.l.c. at this stage showed one major spot (R_f 0.70). A very faint shadow was also visible just above the baseline.

The reaction mixture was cooled, then evaporated to dryness. Chloroform (10 ml) was added to the dry solid, and the mixture was cooled to -19° for some time. Filtration of the resulting suspension removed some of the m-chlorobenzoic acid. The filtrate was evaporated to dryness, dissolved in a small volume of 10% ethyl acetate in benzene and placed on a column of silica gel (17 g). The column was eluted with 15% ethyl acetate in benzene (150 ml). Effluent fractions containing the major product were combined and evaporated to a semi-solid which was a mixture of the product V and some residual m-chlorobenzoic acid. This semi-solid was dissolved in benzene (20 ml) and passed through a small aluminum oxide column (1.5×2.0 cm) which was eluted with benzene. The first two fractions gave upon evaporation the product V as a yellow syrup (26 mg, 53%). It showed $[\alpha]_D$ -144.3° (c,0.55, in chloroform) and spectral data identical with those of an independently prepared sample for which $[\alpha]_D$ -141.3° (c, 1.60, in chloroform) has been recorded (100).

Characteristic IR absorption (liquid film, cm^{-1}):

2920 m, b; 2840 w (C-H); 1555 s (NO_2). Other bands occurred at : 1450 m; 1370 m, b; 1260 w; 1200 m; 1150 m; 1100 s; 1050 s; 990 m; 790 w.

NMR data (60 MHz):

1.31δ (3H, doublet, C-methyl protons).

3.43δ , 3.47δ (9H, two singlets, O-methyl groups on C-1, C-2 and C-4).

3.81δ (1H, center of quartet, H-2, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 10.5 Hz).

4.83δ (1H, center of triplet, H-3, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 10.5 Hz).

4.90δ (1H, center of doublet, H-1, $J_{1,2}$ = 3.5 Hz).

2. Oxidation of methyl 3-amino-3,6-dideoxy-α-D-glucopyranoside (VIII)

a. Preparation of methyl 2,3-anhydro-4-O-benzoyl-6-bromo-6-deoxy-α-D-allopyranoside (VI)

A benzene solution (30 ml) containing

methyl 2,3-anhydro-4,6-benzylidene-α-D-allopyranoside* (1.32 g, 5.0 mmole), N-bromosuccinimide (1.00 g, 5.62 mmole) and benzoyl peroxide (40 mg, 0.165 mmole) was refluxed with stirring for two hours. A transient red color was observed which faded after ten minutes. The solution was evaporated giving a mixture of a solid and a syrup. Ether was added and the resulting solution was filtered. The clear yellow filtrate was washed three times with small amounts of water, dried with anhydrous magnesium sulfate, and evaporated to give a syrup (1.4 g). Thin layer chromatography of the syrup showed one major spot and traces of less mobile impurities (15% ethyl acetate in benzene, v/v). The syrup was dissolved in benzene, the solution treated with activated charcoal and further purified by passing through a silica gel column (70 g). The column was eluted with 20% ethyl acetate in benzene. The product obtained was a syrup which crystallized upon scratching in ether and pentane. Yield: 1.235 g (72%). The crystals showed a melting point of 59.5-

---

* Methods Carbohyd. Chem., Vol.II, p. 189, Ed. M. L. Wolfrom and R.L.Whistler, Academic Press, N. Y.,1963.

60° and $[\alpha]_D$ +175° (c, 1.10, in chloroform), which confirmed the product to be methyl 2,3-anhydro-4-O-benzoyl-6-bromo-6-deoxy-α-D- allopyranoside (VI). Lit. (102): m.p. 60-61°, $[\alpha]_D$ +177° (c, 1.03, in chloroform).

Characteristic IR absorption (liquid film, cm^{-1}):
3080 w; 2900-3000 b; 2840 m; 1720 b, s (C=O); 1600 m; 1580 m (aromatic C-H); 1450 s; 1420 m; 1380 m; 1320 m; 1100-1000 b; 950 s; 980 m; 830 m; 780 w; 760 s; 700 s; 680 m.

NMR data (100 MHz);
3.52δ (3H, singlet, O-methyl protons).
3.42-3.68δ (2H, overlapping multiplets, H-2 and H-3).
4.28δ (1H, center of seven peaks, H-5, $J_{5,6}$ = 3.0 Hz, $J_{5,6}$ = 6.5 Hz, $J_{4,5}$ = 9.5 Hz).
4.98δ (1H, center of doublet, $J_{1,2}$ = 3.0 Hz)
5.28δ (1H, center of quartet, H-4, $J_{4,5}$ = 9.5 Hz, $J_{3,4}$ = 1.5 Hz).
7.48δ (3H, center of multiplet, aromatic protons on C-3', C-4' and C-5').
8.06δ (2H, quartet, aromatic protons on C-2' and C-6').

b. Preparation of methyl 2,3-anhydro-4-O-benzoyl-6-deoxy-α-D—allopyranoside (VII)

Palladium on charcoal (4.0 g, 10%) was carefully introduced into a 500-ml hydrogenation flask containing methanol (150 ml), barium carbonate (18 g), and methyl 2,3-anhydro-4-*O*-benzoyl-6-bromo-6-deoxy-α-D-allopyranoside (VI) (4.436 g, 12.95 mmole). Hydrogenation was allowed to proceed at ordinary temperature and pressure for 19 hours. The reaction mixture was shown by t.l.c. to contain a major product (which gave a greenish spot) and two minor, less mobile products. Inorganic material was filtered off, the filtrate was evaporated, and the residue of evaporation was extracted with chloroform. The chloroform solution was dried with anhydrous sodium sulfate and evaporated to a syrup (2.942 g). Purification of the syrup was effected by using a 150-g silica gel column that was eluted with 15% ethyl acetate in benzene. Effluent fractions containing the major product were combined to give a pale yellow syrup (2.414 g, 71.5%) which was chromatographically pure. Attempts to crystallize this syrup did not succeed. The product was confirmed to be methyl 2,3-anhydro-4-O-benzoyl-6-deoxy-α-D-allopyranoside (VII) by comparison of its spectra with reported data (102). NMR data (100 MHz):

1.20δ (3H, center of doublet, C-6 methyl protons, $J_{5,6}$ = 6.5 Hz).

3.47δ (3H, singlet, O-methyl protons).

3.57δ (2H, overlapping multiplet, H-2 and H-3).

4.14δ (1H, center of multiplet, H-5, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 6.5 Hz).

4.89δ (1H, center of doublet, H-1, $J_{1,2}$ = 3 Hz).

5.05δ (1H, center of quartet, H-4, $J_{4,5}$ = 9.5 Hz, $J_{3,4}$ = 1.5 Hz).

7.37-7.67δ (3H, center of multiplet, aromatic protons on C-3', -4' and -5'.).

8.07δ (3H, center of multiplet, aromatic protons on C-2' and -6').

c. Synthesis of methyl 3-amino-3,6-dideoxy-α-D-glucopyranoside (VIII) and methyl 2-amino-2,6-dideoxy-α-D-altropyranoside (IX)

Methyl 2,3-anhydro-4-O-benzoyl-6-deoxy-α-D-allopyranoside (VII) (2.414 g, 9.17 mmole) was dissolved in methanol (35 ml) in a stainless steel bomb (32.5×4.8 cm) cooled in a dry-ice/acetone bath, and liquid ammonia (60 ml) was added. After the sealed bomb had attained room temperature it was placed in an oven at 130° for thirty-six hours. At the end of this heating period, the bomb was cooled again in dry-ice/acetone before opening, and residual ammonia was then allowed to escape freely at room temperature. The remaining solution was evaporated to give a brown syrup. Addition of water (20 ml) to the syrup resulted in a brown solution containing some undissolved crystalline material. The crystals were filtered off (320 mg) and identified to be benzamide. The remaining aqueous solution was extracted repeatedly with ether. The colorless ethereal solution was dried and thereafter deposited an additional amount (290 mg) of crystalline benzamide. Evaporation of the aqueous layer resulted in a syrup which on addition of ethanol, ethyl acetate and petroleum ether (60-80°) crystallized in colorless prisms, m.p. 174-176° (430 mg). This product was identified as compound VIII by comparison of its melting point and optical rotation, $[\alpha]_D$ +144.4°

(c, 0.34, in water), with the literature values. Lit. (101):m.p. 175-177°, $[\alpha]_D$ +148° (c, 0.57, in water).

The mother liquor from VIII was combined with the previous filtrate of the ether extract and evaporated to a syrup (1.587 g) which was subjected to further separation. The syrup was placed onto a column prepared from a suspension of silica gel (80 g) in methanol-chloroform (3:7, v/v), and elution was performed with the same solvent system. Benzamide (480 mg) was obtained from early effluent fractions. A product (340 mg) which charred to greenish color on t.l.c. appeared after several blank fractions. It appeared homogeneous on t.l.c.; crystallization of the product was difficult and succeeded only once, from a mixture of ethanol, ethyl acetate, and petroleum ether (60-80°), when a small part of it was obtained as a microcrystalline powder melting at 44-46° and showing $[\alpha]_D$ +54° (c, 0.43, in water). This product was identified as methyl 2-amino-2,6-dideoxy-α-D-altropyranoside (IX) by its spectral data and by preparation of its N-acetyl derivative (XI).

Further elution of the column gave fractions containing both VIII and IX, and these were followed by fractions that afforded, upon evaporation and crystallization, pure VIII (273 mg) which was identical with the first crop according to melting point and infrared spectrum. The mother liquor thereof was combined with the chromatographic fractions containing mixtures of VIII and IX, and the syrup (390 mg) obtained upon evaporation was chromatographed again on a 30-g silica gel column. Elution of the column with 30% methanol in chloroform resulted in separation of the two major products, 170 mg of VIII and 85 mg of IX being obtained. Thus the total yield of VIII was 910 mg (56.2%) and that of IX was 430 mg (26.6%). A total of 1.009 g(91%) of benzamide was recovered.

Spectral data of VIII:

Chacacteristic IR absorption (cm^{-1}): 3420 s (N-H); 3340 s, 3300 s (hydrogen-bonded hydroxyl); 1590 m (N-H). Other bands occurred at : 1510 w; 1330 w; 1260 w; 1240 w; 1180 m; 1150 w; 1115 s; 1090 m; 1040 s; 1000 m; 890 w; 840 w; 735 m.

NMR data [100 MHz, in D_2O, chemical shifts were calculated by taking lock signal HDO at 4.75δ(124)]:

1.25δ (3H, center of doublet, C-5 methyl protons, $J_{5,6}$ = 6.5 Hz).

2.90δ (1H, center of triplet, H-4, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz).

3.05δ (1H, center of triplet, H-3, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.5 Hz).

3.42δ (3H, singlet, O-methyl protons).

3.48δ (1H, center of quartet, H-2, partially overlapped by HDO, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 9.5 Hz).

3.71δ (1H, center of octet, H-5, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 6.5 Hz).

Spectral data of IX :

Characteristic IR absorption (cm^{-1}):

3500-3100 m, b; 1600 w; 1540 m; 1050 m, b; 1100 w; 950 w; 850 w; 720 m.

NMR data (100 MHz, in D_2O, lock signal as in VIII):

1.28δ (3H, center of doublet, C-methyl protons, $J_{5,6}$ = 7 Hz).

3.10δ (1H, quartet, H-2, $J_{1,2}$ = 4.Hz, $J_{2,3}$ = 3.5 Hz).

3.43δ (3H, singlet, O-methyl protons).

3.66δ (1H, center of quartet, H-3, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 7 Hz).

3.89δ (1H, center of quartet, H-5, $J_{4,5}$ = 7 Hz).

4.05δ (1H, center of quartet, H-4, $J_{3,4}$ = 7 Hz, $J_{4,5}$ = 7 Hz).

N-Acetyl derivative (X) of VIII :

A sample of VIII (32 mg) in acetic anhydride (2 ml) was warmed on a steam bath for 3 minutes. The excess anhydride was removed by repeated coevaporations with toluene under reduced pressure. The brown syrup obtained was triturated with ethyl acetate and petroleum ether, with addition of a drop of ethanol, whereby it solidified. The yellowish solid was recrystallized from a similar solvent combination, giving 31 mg (78.5%) of colorless needles of methyl 3-acetamido-3,6-dideoxy-α-D-glucopyranoside (X), m.p. 227-228°, $[\alpha]_D$ +146° (c, 0.79, in water). Reported (101) : m.p. 224°, $[\alpha]_D$ +145°.

N-Acetyl derivative (XI) of IX :

The N-acetyl derivative was prepared by dissolving IX (syrup, 40 mg) in 99% ethanol (4 ml), to which acetic anhydride (10 ml) was then added. The mixture was stirred for two minutes at room temperature. After coevaporation with toluene to remove acetic anhydride, a crystalline solid melting at 121-125° was obtained. Recrystallization raised the melting point to 135-137°, and the product showed $[\alpha]_D$ +51° (c, 0.3, in water). The product was methyl 2-acetamido-2,6-dideoxy-α-D-altropyranoside (XI). Reported (104) : m.p. 138-139°, $[\alpha]_D$ +60.4° (c, 0.3, in water).

d. Oxidation of methyl 3-amino-3,6-dideoxy-α-D-glucopyranoside (VIII). Synthesis of methyl 3,6-dideoxy-3-nitro-α-D-glucopyranoside (XII) and methyl 3,6-dideoxy-3-nitroso-α-D-glucopyranoside dimer (XIII)

A solution of m-chloroperbenzoic acid (1.352 g, (6.67 mmole) in chloroform (12 ml) was heated to reflux in a 50-ml two-necked flask equipped with dropping funnel, reflux condenser and magnetic stirrer. A solution of methyl 3-amino-3,6-dideoxy-α-D-glucopyranoside (VIII) (169 mg, 0.955 mmole) in a mixture of methanol (7 ml) and chloroform (10 ml) was added over a period of 30 minutes. Ten minutes after the end of the addition it was found by t.l.c. (5% ethanol in benzene) that all the starting glycoside had disappeared and that two new products (R_f = 0.23 and 0.11) had been formed. Another 45 minutes of refluxing was allowed before the reaction was stopped and the solution was cooled and evaporated to dryness. The residue was extracted with four portions (5 ml each) of water, the clear aqueous extract being removed each time with the aid of a pipette. The combined aqueous solutions were evaporated to give a solid material (212 mg). The solid residue left in the reaction flask after water extraction was mainly m-chlorobenzoic acid and was discarded.

The solid material obtained by extraction was dissolved in a small volume of 5% methanol in chloroform and passed through an aluminum oxide column (5 g neutral Al_2O_3 , deactivated to grade III) which was eluted with the same solvent system. The effluent was evaporated to a white solid (160 mg) which contained the two oxidation products and a trace of m-chlorobenzoic acid. This mixture was chromatographed on a 9.0-g silica gel column eluted with 8% ethanol in benzene (120 ml) and 10% ethanol in benzene (50 ml). Good separation of the two products was achieved. Effluent containing the faster moving product was evaporated to furnish syrupy nitro compound (XII) which crystallized in needle form on drying *in vacuo* (87 mg, 44%). Recrystallization from warm chloroform and petroleum ether (60-80°) readily gave long needles of m.p. 140-141° and $[\alpha]_D$ +159.7° (*c*, 1.05, in water). Reported (105) for the enantiomer of XII : m.p. 142-145°, $[\alpha]_D$ -162° (*c*, 1, in water). The infrared spectrum was identical with that of a sample of the enantiomer.

Characteristic absorption (cm^{-1}): 3520, 3400 s, b (OH); 1550 s (NO_2). Other bands occurred at : 1330 w; 1270 w; 1180 w; 1130 m; 1100 m; 1050 s; 1020 m; 950 w; 930 w; 890 m; 840 w; 790 m.

NMR data (60 MHz, in D_2O, chemical shifts were calculated by taking the HDO lock signal at 4.75δ):

1.20δ (3H, center of doublet, methyl protons, $J_{5,6} = 6$ Hz).

3.35δ (3H, singlet, *O*-methyl protons).

3.60-3.80δ (2H, overlapping multiplets, H-4 and H-5).

4.13δ (1H, center of quartet, H-2, $J_{1,2} = 4$ Hz, $J_{2,3} = 11$ Hz).

4.77δ (1H, center of doublet, H-1, $J_{1,2} = 4$ Hz).

(The NMR spectrum was identical with that of methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside.)

Fractions containing the more slowly moving product from the column were evaporated to give colorless crystals (78 mg, 43%) that were chromatographically pure and melted at 148-152°. Recrystallization from a small volume of ethyl acetate containing a few drops of absolute ethanol was achieved by adding a few drops of petroleum ether (60-80°) and cooling overnight. The fine prisms of the nitroso dimer (XIII) showed a melting point of 154-156° (The liquid turned dark red and decomposed with foaming on raising the temperature to 165°). The optical rotation of the product was $[\alpha]_D$ +151.9° (c, 0.4, in water).

Characteristic IR absorption (cm^{-1}) :

3360-3440 s (hydrogen-bonded OH); 1190 s (trans nitroso dimer). Other bands occurred at : 1300 s; 1140 m; 1100 m; 1040 s; 1060 s; 970 m; 880 w; 850 w; 780 w; 730 w; 630 w.

The NMR spectrum is shown in Fig. 13.

Anal. $C_{14}H_{26}N_2O_{10}$ (382.4)

Calcd.: C, 43.97; H, 6.85; O, 41.85.

Found : C, 43.85 *; H, 6.70 *; O, 41.87**.

e. Methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-D-glucopyranoside (XIV) by acetylation of XII.

Compound XII (35 mg) and acetic anhydride (1.o ml) were stirred at 0°, and two small drops of ethereal boron trifluoride were added. Thin layer chromatography after 30 minutes showed that a fast moving spot was present and the starting material was absent. The reaction mixture was poured into ice water (30 ml) and stirred until all the ice had melted. The aqueous solution was then extracted repeatedly with chloroform. The combined chloroform extracts were dried with anhydrous sodium sulfate and evaporated with added toluene. A yellow syrup was obtained which exhibited on t.l.c. one major spot (R_f 0.8) and traces of a less mobile impurity

---

* These values were recalculated by taking into account 3% of incombustible inorganic residue found in the analytical sample. The values actually were C, 42.53 and H, 6.50.

** This value was obtained from a separate sample.

(15% ethyl acetate in benzene). Crystallization was achieved by trituration of the dry syrup with petroleum ether. Recrystallization from ethyl acetate-petroleum ether gave colorless needles of the diacetate XIV (40 mg, 81.5%) showing a melting point of 108-111° and $[\alpha]_D$ +154.1° (c, 0.3, in chloroform). The known enantiomer of XIV showed (106) m.p. 109-110° and $[\alpha]_D$ -154° (c, 1.0, in chloroform). The infrared spectrum of XIV was identical in every respect with that of a sample of its enantiomer.

2. Oxidation of Methyl 3-Amino-3-deoxy-β-D-galactopyranoside (XV). Synthesis of Methyl 3-Deoxy-3-nitro-β-D-galactopyranoside (XVI) and Methyl 3-Deoxy-3-nitroso-β-D-galactopyranoside Dimer (XVII).

m-Chloroperbenzoic acid (1.284 g, 6.32 mmole) was dissolved in a mixture of methanol (9.5 ml) and chloroform (9.5 ml). A solution of methyl 3-amino-3-deoxy-β-D-galactopyranoside (XV) (195 mg, 1.01 mmole) in methanol (4 ml) and chloroform (4 ml) was added to the refluxing peracid solution over a period of twenty-two minutes. Ten minutes after the end of the addition, thin layer chromatography (20% methanol in chloroform) showed the complete absence of XV and the presence of two faster moving spots (R_f, 0.5 and 0.25) of similar intensity. Heating was stopped after another five minutes. The reaction mixture was cooled and evaporated to give a white solid which was extracted twice with 10 ml of ether. The remaining solid was dealt with as described further below. The ether extract was washed three times with 5 ml of water and was thereafter shown by t.l.c. to contain only m-chlorobenzoic acid; it was discarded. The combined aqueous solution was evaporated to a semi-solid material (89 mg) which was passed through a small (2×2 cm) column by rapid elution with 5% methanol in chloroform. Evaporation of the effluent yielded a colorless syrup (36 mg). This syrup crystallized from a mixture of ethanol (99%) and chloroform. The white powder melted at 80-82° when air-dried, but at 125-128° when dried in vacuo at 56° for twelve hours. It had a rotation of $[\alpha]_D$ +32.6° (c, 0.5, in water). For methyl 3-deoxy-3-nitro-β-D-galactopyranoside (XVI) has been reported (107) : m.p. 87-89° before, and 131-132° after drying *in vacuo*; $[\alpha]_D$ +32.6° (in water). Infrared spectra of the present product and previously obtained XVI were identical. The data were as follows (cm^{-1}) : 3610 w (free OH); 3460 m (hydrogen-bonded OH); 1550 s (NO_2). Other bands occurred at : 1290 w; 1240 w; 1200 w; 1130 m; 1080 s; 1050 m; 1030 m; 980 w; 770 w.

NMR data (60 MHz, in D_2O):
1.07 ppm upfield from HDO (3H, singlet, *O*-methyl protons).
0.87 ppm upfield from HDO (3H, overlapping signals of H-6 and H-5).
0.55 ppm upfield from HDO (1H, center of quartet, H-2, $J_{1,2}$ = 8 Hz, $J_{2,3}$ = 10 Hz).
0.21 ppm upfield from HDO (1H, center of doublet, H-1, $J_{1,2}$ = 8 Hz).
0.22 ppm downfield from HDO (1H, center of quartet, H-3, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 3.5 Hz).

The solid residue left after ether extraction was suspended in methanol (5 ml). The undissolved part (80 mg) proved to be pure by t.l.c. It was recrystallized from methanol-water to give colorless needles (55 mg) of the nitroso dimer XVII, m.p. 141-143°; $[\alpha]_D$ +164.7° (c, 0.57, in water). The methanolic solution from which XVII had been filtered off showed the same two spots as the crude, original reaction mixture before work-up. It was evaporated to dryness and the residue (84 mg) was placed on a 8.0-g silica gel column and eluted with 5% methanol in chloroform (20 ml), 10% methanol in chloroform (20 ml), 25% methanol in chloroform (20 ml) and 30% methanol in chloroform (40 ml). There was obtained 26 mg of the faster moving component (XVI) and 17 mg of the more slowly moving XVII. Thus the total yield of XVI was 62 mg (28%) and that of XVII was 97 mg (47%).

Compound XVII showed the following spectral data :

Characteristic IR absorption (cm^{-1}): 3400-3200 s, b (hydrogen-bonded OH); 1190 s (*trans* nitroso dimer). Other bands occurred at : 1620 w; 1310 m; 1270 m; 1240 m; 1160 m; 1130 m; 1050 s; 1020 s; 980 s; 890 b; 760 w; 720 w.

Ultra-violet absorption in water : λ_{max} 295 nm (ε , 7500).

NMR data (60 MHz, in D_2O) :

1.08 ppm upfield from HDO (3H, singlet, *O*-methyl protons), 0.89 ppm upfield from HDO (3H, overlapping singlet of H-6 and multiplet of H-5).

0.69 ppm downfield from HDO (1H, center of quartet, H-3, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 3 Hz).

0.58 ppm upfield from and under HDO signal (unresolved signals ascribed to the rest of the ring protons).

Anal. $C_{14}H_{26}N_2O_{10}$ (414.36)

Calcd.: C, 40.58; H, 6.42; O, 46.34.

Found : C, 40.64; H, 6.42; O, 46.26.

Molecular weight (osmometric method in H_2O): 423.

3. Oxidation of Methyl 3-Amino-3-deoxy-α-D-mannopyranoside (XIX)

a. Preparation of methyl 3-amino-3-deoxy-α-D-mannopyranoside (XIX)

Methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (XVIII) (0.33 g, 14.3 mmole) was dissolved in 95% ethanol (25 ml) and passed through a column containing 10 g of dry Dowex 1x2 (OH^-) anion exchange resin. The column was eluted with the same solvent. The effluent was evaporated, and the remaining material was purified by recrystallization from 95% ethanol to give colorless needles of the free amino glycoside XIX (0.24 g, 86%) which showed a melting point of 160-162° and rotations of $[\alpha]_D$ +69.9° (c, 1.16, in water) and $[\alpha]_D$ +91.1° (c, 1.0, in methanol).

Anal. $C_7H_{15}NO_5$ (193.20)

Calcd.: C, 43.51; H, 7.83; N, 7.25.

Found : C, 43.48; H, 7.80; N, 7.21.

Characteristic IR absorption (cm^{-1}) : 3400 m, 3380 m (primary N-H); 3360 m (hydrogen-bonded OH); 1570 w (N-H bending). Other bands occurred at : 1170 w; 1140 m; 1065 s; 1025 m; 990 m; 970 m; 940 m; 850 w; 800 w; 720 m.

b. Synthesis of methyl 3-deoxy-3-nitro-α-D-mannopyranoside (XX) and methyl 3-deoxy-3-nitroso-α-D-mannopyranoside dimer (XXI)

A solution of m-chloroperbenzoic acid (0.802 g, 3.95 mmole) in chloroform (8 ml) was heated to reflux and a solution of methyl 3-amino-3-deoxy-α-D-mannopyranoside (XIX) (0.11 g, 0.57 mmole) in methanol (9 ml) and chloroform (4 ml) was added over a period of 20 minutes. The reaction was shown by thin layer chromatography (25% ethanol in benzene) to be complete ten minutes after the addition period. Two spots (R_f, 0.6 and 0.23) of similar intensities were seen. Heating was continued for another ten minutes before the reaction mixture was worked up by evaporation.

The crude mixture of reaction products (0.905 g) was extracted four times with 10 ml portions of ether. The combined ether extract was shaken four times with 5 ml of a 1:1 mixture of water and tetrahydrofuran. The aqueous phase which separated showed a single product spot on t.l.c., but m-chlorobenzoic acid was also present. The water was evaporated and solute was passed through a 5.0-g silica gel column by elution with chloroform, 5%, 10% and 15% methanol in chloroform. m-Chlorobenzoic acid was thereby separated from the product which was obtained as a colorless syrup (23 mg). Crystallization from ethyl acetate and petroleum ether (60-80°) afforded large crystals in rosette form after prolonged cooling. This product was identified as methyl 3-deoxy-3-nitro-α-D-mannopyranoside (XX) by comparison with an

independently prepared sample of proven structure (109). It showed a melting point of 120-120.5° and $[\alpha]_D$ +37.2° (c, 0.58, in water). Reported (109) : m.p. 113-115°, $[\alpha]_D$ +44.5°.
Characteristic IR absorption (cm^{-1}) : 3460 s, 3340 s (OH); 1550 s (NO_2). Other absorption occurred at : 1290 w; 1270 w; 1250 w; 1230 m (with shoulder); 1100 m; 1050 m, b; 975 s; 900 m (with shoulder); 830 w; 770 w.

The solid residue left in the ether extraction of the crude reaction product was fractionated on a 8.0-g silica gel column which was eluted with chloroform (20 ml), 5% methanol in chloroform (20 ml), 10% methanol in chloroform (20 ml), 15% methanol in chloroform (60 ml), and 20% methanol in chloroform (40 ml). Clean separation was achieved giving two products. The faster moving product was obtained as a crystalline solid (26 mg) and was identical with the previously obtained compound XX. It was combined with the mother liquor from the first crop of XX and recrystallized from a mixture of ethyl acetate and petroleum ether. The total yield of XX was 49 mg (38%). Effluent fractions containing the more slowly moving product were evaporated to a foam which upon drying and scratching gave a colorless powder. Attempts to recrystallize this material did not succeed although many solvent systems were tried. The hygroscopic powder melted at 93-96° and showed $[\alpha]_D$ -14° (c, 0.2, in water). This product was judged to be methyl 3-deoxy-3-nitroso-α-D-mannopyranoside dimer XXI by spectroscopic evidence. Characteristic IR avsorption (cm^{-1}) : 3500-3200 s, b (hydrogen-bonded OH); 1195 m (trans nitroso dimer). Other bands occurred at : 1140 m; 1060 s, b (with shoulder); 970 m.

Ultraviolet absorption in water : λ_{max} 293 nm (ε, 5000).

NMR data (100 MHz, in D_2O, chemical shifts calculated by taking the HDO lock signal at 4.75δ):

3.46δ (3H, singlet, O-methyl protons).

3.30-3.50δ (1H, multiplet beneath O-methyl signal).

3.58-3.97δ (4H, multiplets, ascribed to H-2, H-4 and H-6).

4.85δ (1H, doublet, H-1, $J_{1,2}$ = 2 Hz).

5.45δ (2H, center of quartet, H-3, $J_{3,4}$ = 10.5 Hz, $J_{2,3}$ = 3.0 Hz).

4. Oxidation of Methyl 3-Amino-3-deoxy-β-D-xylopyranoside (XXII)

m-Chloroperbenzoic acid (200 mg, 1.16 mmole) was refluxed in chloroform (6 ml), and a solution of methyl 3-amino-3-deoxy-β-D-xylopyranoside (XXII) (26.5 mg, 0.159 mmole) in methanol (2 ml) and chloroform (4 ml) was added over a period of 10 minutes. The clear solution became turbid by separation of crystals during the addition period; the turbidity persisted even when more methanol was added to the reaction mixture. Thin layer chromatography showed that all the starting material had reacted after 10 minutes. Only one product spot (R_f 0.27) was seen (10% methanol in chloroform). The dried product weighed 11 mg (40%). It was recrystallized from hot methanol-water to give fine colorless needles which melted at 168-170°, turning dark red in the process. The product was assumed to be the nitroso compound, methyl 3-deoxy-3-nitroso-β-D-xylopyranoside dimer (XXIII) by virtue of its infrared and ultraviolet spectra.

Characteristic IR absorption (cm^{-1}) : 3400 s, b (OH); 1195 m (trans nitroso dimer). Other bands occurred at :

1320 m; 1300 m; 1220 m; 1160 m; 1120 m; 1060 s (with shoulder); 1020 s; 980 s (with shoulder); 880 w; 720 w; 660 w.

Ultraviolet absorption in water : λ_{max} 300 nm (ε, 7000).

Compound XXIII was hardly soluble in organic solvents. Its low solubility in water and dimethyl sulfoxide at ordinary temperature made it difficult to record an NMR spectrum.

5. Attempted Oxidation of Methyl 2-Amino-2,6-dideoxy-α-D-altropyranoside (IX)

m-Chloroperbenzoic acid (1.506 g, 7.42 mmole) was dissolved in chloroform (12 ml), and the solution was heated to reflux while methyl 2-amino-2,6-dideoxy-α-D-altropyranoside (IX) (197 mg, 1.11 mmole) in chloroform (15 ml) and methanol (2 ml) was added dropwise over a period of 22 minutes. Thin layer chromatography showed that at the end of the addition period a major spot (R_f, 0.47; 5% methanol in benzene) and some faint spots of lower mobility were present. Ten minutes later, two major spots (R_f, 0.47 and 0.18) of similar intensities and two faint spots of intermediate mobility were seen. The reaction was stopped after another 10 minutes and the mixture was evaporated to dryness. Small volumes of water (3x5 ml) were used to extract the solid residue, and the clear aqueous extracts were combined and evaporated to give a white solid material (200 mg). Thin layer chromatography showed that mainly one carbohydrate product and m-chlorobenzoic acid were present. The material was chromatographed on a 15-g silica gel column (length 20 cm) by elution with 8% ethanol in benzene. Fractions of 4 ml were collected. Inspection of the effluent fractions by t.l.c. revealed that chemical changes in the product must have occurred on the column because the number of spots found was greater than before chromatography. Thus, the first eight fractions contained two products which were obtained as a semi-solid mixture (0.373 g) upon evaporation; later fractions eluted with 30% ethanol in chloroform gave two slow-moving products which were not investigated further.

The semi-solid mixture from the early effluent contained a large amount of m-chlorobenzoic acid. It was rechromatographed twice on a silica gel and an aluminum oxide column. The fastest moving product was finally obtained in crystalline form and free from chlorobenzoic acid. It showed a melting point of 120-122° and $[\alpha]_D$ +48.5° (c, 0.165, in methanol). Its characteristic infrared absorptions were at 3430 s; 1570 s (NO_2); 1210 w; 1100 m; 1050 s (two bands); 1000 w; 900 m (two bands); 800 w. The ultraviolet absorption in methanol occurred at λ_{max} 224 nm (ε , 1000). From the spectral data it appears that the compound was a nitro glycoside.

PART III SYNTHESIS OF 4-HYDROXY-3-NITROQUINOLINE

Methyl Anthranilate Hydrochloride

Anthranilic acid * (1.84 g) was dissolved in diethyl ether (20 ml). An ice cooled ethereal solution of diazomethane was added dropwise with continual stirring. Addition was complete when a permanent pale yellow color was observed. The solution was evaporated to a brown liquid (2.3 ml) which was identified by spectral data to be the methyl anthranilate. This liquid was dissolved in 99% ethanol (10 ml) to which 2N hydrochloric acid was added dropwise until the solution was slightly acidic. The solution was evaporated to dryness (bath temperature, 40°). Recrystallization of the solid residue from ethanol-acetone give needles (m.p. 180-181.5°) of methyl anthranilate hydrochloride. Reported (123)m.p.181°. The yield obtained was 1.63 g (65%).

Methazonic Acid

Methazonic acid was prepared as described by Bachmann (113).

---

* Recrystallized from 99% ethanol-petroleum ether (30-60°); m.p. 150-152°.

Sodium hydroxide pellets (20.0 g) were dissolved in water (40 ml) in a 250 ml round bottom flask equipped with dropping funnel, thermometer and mechanical stirrer. The sodium hydroxide solution was warmed in a water bath to adjust its temperature to 45°. Nitromethane (20.0 g) was added through the dropping funnel slowly while the temperature of the solution was kept strictly between 47-50°. After the addition of all the nitromethane the solution temperature was allowed to rise freely above 55°. When the temperature began to drop again, the flask was cooled in ice-bath to 5°. The cooled solution was neutralized by dropwise addition of concentrated hydrochloric acid, temperature being maintained below 10°. Thirty-five milliliters of acid was consumed to bring the pH to 4-5. The resulting mixture consisted of a cream-colored paste in a deep red supernatant liquid. The paste was pressed dry on a Büchner funnel as much as possible, then dried in the air for 30 minutes and afterwards in an evacuated desiccator for two hours. At the end of the drying period, the color of the solid had changed from a light cream to orange. It decomposed with evolution of gas at 85°. The yield was 11 g. Since methazonic acid is unstable in storage it was freshly prepared and used immediately for reactions.

2-(2-*aci*-Nitroethylideneamino)-benzoate (I)

Methyl anthranilate hydrochloride (2.626 g, 0.014 mmole) was dissolved in water (50 ml). Concentrated hydrochloric acid (5.5 ml) was added, and methazonic acid (1.559 g, 0.015 mmole) was then introduced in small portions with vigorous stirring. The yellow, clear solution turned orange and gradually became turbid towards the end of addition. Concentrated hydrochloric acid (6.0 ml) was added and the mixture was stirred for another ten minutes. The suspension was stored in a refrigerator for ten hours, then filtered, and the precipitate was washed with water until the filtrate was neutral. The yellow solid was dried at room temperature to give silky yellow needles which melted at 153-155°. A yield of 1.85 g (60%) was obtained. Recrystallization from warm methanol raised the melting point to 159-160°.
Lit. (112) : m.p. 153°
Characteristic infrared absorptions (cm^{-1}, in chloroform): 1700 m (aromatic ester C=O); 1640 s (C=N); 1600 m (aromatic C-H). Other bands occurred at : 1470 s ;

1435 m ; 1375 m (with shoulder); 1330 w ; 1300 m ; 1280 s ; 1250 s (with shoulder); 1165 w ; 1145 w ; 1080 m ; 960 m . No nitro group asymmetric stretching band was observed.

The NMR spectrum is shown in Fig. 14.

2-(2-*aci*-Nitroethylideneamino)-benzoic Acid (IV)

Anthranilic acid (1.072 g, 7.82 mmole) was dissolved in water (30 ml), and concentrated hydrochloric acid (9 ml) was added with swirling. This was followed by the addition of methazonic acid (1.30 g, 12.5 mmole) with vigorous stirring. A precipitate occurred after 20 minutes. Stirring was continued for another 20 minutes before the reaction mixture was stored in the refrigerator for 12 hours. The precipitate was then filtered on a Büchner funnel, washed with a large volume of distilled water until the filtrate was neutral, and then dried in a vacuum to give a dull yellow solid. Recrystallization from ethanol (99%) gave IV as silky yellow crystals (1.21 g, 74%) melting at 198-200°. Reported (113) : m.p. 196-197°. Characteristic infrared absorptions (cm^{-1}; KBr pellet): 3200 s, b (carboxylic acid hydroxyl, hydrogen-bonded); 3090 s, b (aromatic C-H); 1680 s (aromatic carboxylic acid C=O); 1650 s (C=N); 1610 s (aromatic C-H). Others : 1480 s ; 1430 m ; 1410 m ; 1380 s ; 1350 m ; 1270 s, b ; 1210 s ; 1160 m ; 970 s ; 900 m ; 780 s ; 750 s ; 720 w ; 700 w ; 670 m ; 650 w ; (no NO_2 group asymmetric stretching absorption).

p-Nitrophenyl 2-(2-aci-Nitroethylideneamino)-benzoate (VI)

p-Nitrophenol (0.366 g, 2.63 mmole) and dicyclohexylcarbodiimide (566 mg, 2.75 mmole) were dissolved by stirring in tetrahydrofuran (45 ml). Methyl 2-(2-aci-nitroethylideneamino)benzoic acid (IV) (549 mg, 2.63 mmole) was added to the solution at an initial bath temperature of 0°. The solution was then allowed to assume room temperature and was stirred for 20 hours. Thin layer chromatography (20% ethyl acetate in benzene) showed that a trace of starting compound IV and some unreacted p-nitrophenol were present. The reaction mixture was filtered to remove dicyclohexylurea (m.p. 224-226°), the filtrate was evaporated to dryness, and further dried under vacuum. The red material was washed by trituration with 99% ethanol whereby it became yellow in color. The washed and dried product melted at 215-217° and weighed 450 mg. The alcoholic washing liquid was allowed to evaporate partially at room temperature in an open vessel. Crystals deposited after one day. They were filtered, washed with water, and dried (126 mg; m.p. 222-223°). This crop and the previous one were jointly recrystallized from acetone-ethyl acetate to give VI as a bright yellow, crystalline powder, m.p. 228°. A total yield of 66.5% was obtained.

<u>Anal</u>. $C_{15}H_{11}N_3O_6$ (329.26)

Calcd. : C, 54.71; H, 3.37; N, 12.76.

Found : C, 54.62; H, 3.55; N, 12.59.

Characteristic infrared absorptions (cm^{-1}, KBr pellet):
3100 w - 2960 w (aromatic and aliphatic C-H); 1715 s ; (aromatic ester C=O) ; 1630 s (C=N) ; 1600 s (aromatic C-H); 1510 s (aromatic NO_2). Others : 1465 s ; 1370 s ; 1340 s ; 1270 s ; 1210 s, b ; 1155 m ; 1100 m ; 1040 s ; 960 m ; 860 s ; 830 w ; 760 m ; 750 s ; 740 s ; 680 m.

NMR data (in DMSO-d_6, TMS as lock signal) :

6.68 δ (1H, center of doublet, ascribed to H-α, J = 6.5 Hz).

7.40 δ (1H, multiplet).

7.72 δ (2H, center of multiplet, H-2' and H-6', $J_{2',3'} = J_{5',6'}$ = 9.0 Hz).

7.8-8.0 δ (2H, overlapped signal, broad multiplet probably due to H-6 and β-H).

8.1-8.4 δ (2H, overlapping multiplets).

8.44 δ (2H, center of doublet, H-3' and H-5', $J_{2',3'} = J_{5',6'}$ = 9.0 Hz).

Methyl 2-(2-Nitroethylamino)-benzoate (VII)

Methyl 2-(2-*aci*-nitroethylideneamino)-benzoate (I) (2.196 g, 9.87 mmole) was suspended in anhydrous methanol (50 ml). The suspension was warmed to 30-35° in a water bath, which was followed by the addition of sodium borohydride (891 mg, 23.5 mmole) over a period of five minutes, with vigorous stirring. The water bath was removed at the end of the addition period. Initial liberation of heat was observed. Stirring was continued for another five minutes, then water (40 ml) was added to the reaction mixture, causing some solid material to precipitate. The mixture was extracted three times with 20 ml of diethyl ether. The combined ether layers were dried with anhydrous magnesium sulfate and evaporated to remove most of the methanol, then repeatedly extracted with diethyl ether. The ether extract was processed as before to give a second crop of the crystalline product (0.17 g), the total yield of crystalline material thus being 1.911 g (86.4%). Recrystallization from warm benzene-petroleum ether (60-80°) gave methyl 2-(2-nitroethylamino)-benzoate (VII) as long needles which showed a melting point of 84-85°.

Anal. $C_{10}H_{12}N_2O_4$ (224.21)

Calcd. : C, 53.57; H, 5.39; N, 12.50.

Found : C, 53.46; H, 5.47; N, 12.52.

Characteristic infrared absorptions (cm^{-1}, in chloroform): 3340 m (bonded secondary N-H); 3040 w (aromatic C-H); 2950 w (aliphtic C-H); 1680 s (aromatic ester C=O); 1570 s (aromatic C-C); 1550s (NO_2). Others : 1510 m ; 1430 m ; 1350 w ; 1315 s ; 1240 s, b ; 1160 m ; 1150 w ; 1110 s ; 1070 m .

NMR data (100 MHz):

3.81 δ (3H, singlet, O-methyl protons).

3.92 δ (2H, center of triplet partially overlapped by O-methyl signal, α-methylene protons, $J_{\alpha,\beta}$= 6.0Hz).

4.58 δ (2H, center of triplet, β-methylene protons, $J_{\alpha,\beta}$= 6.0 Hz).

6.54-7.26 δ (3H, overlapping multiplets ascribed to H-4, H-5 and H-6).

7.89 δ (1H, center of quartet, H-3, $J_{3,4}$ = 8.0 Hz, $J_{3,5}$ = 1.5 Hz).

7.78-8.18 δ (1H, broad signal superimposed by H-6, exchangeable with D_2O, N-H proton).

4-Hydroxy-3-nitroquinoline (III)

A. By base-catalyzed cyclization of methyl 2-(2-nitroethylamino)-benzoate (VII)

Methyl 2-(2-nitroethylamino)-benzoate (VII) (233 mg, 1.04 mmole) was dissolved in anhydrous methanol (30 ml), and a sodium methoxide solution (2.62 mmole of sodium metal in 5.0 ml of anhydrous methanol) was added. The mixture was heated to reflux. The yellow solution turned to orange after five hours. Starting material VII was shown to persist by thin layer chromatography (20% ethyl acetate in benzene)* after 20 hours of heating while a new spot at the baseline increased in intensity gradually. The reaction was stopped after 25 hours. The orange brownish solution deposited a precipitate upon cooling. Filtration gave a yellow solid (28 mg).

---

* The t.l.c. spot was made visible in an iodine chamber and then sprayed with ceric sulfate / sulfuric acid to show VII as a greenish spot.

The filtrate was evaporated to a brownish solid (0.28 g) which was dissolved in a small volume of methanol and placed on an aluminum oxide column (30 g)*. On elution with methanol, yellow bands were visible. The first, light yellow band eluted gave 27 mg of the fast moving material, identified to be a mixture of starting compound VII and a small amount of methyl anthranilate. The second yellow band was collected in 150 ml of effluent which on evaporation gave a yellow solid showing one spot on a thin layer chromatogram. This material which showed alkaline reaction was stirred in methanol with an excess of cation exchange resin Amberlite IR-120 (H^+). The neutralized methanol solution was turbid and faintly yellowish. On evaporation it produced a cream-colored solid which decomposed at 340-345°. A yield of 70 mg was obtained. The later effluent fractions from the second yellow zone were contaminated by some more slowly moving material of red color. These fractions were combined with the yellow solid obtained by filtration at the beginning of the work-up, and evaporation gave a yellowish orange product which was rechromatographed on a column containing 10 g of Al_2O_3. In this way another 20 mg of cream-

---

* Aluminum oxide (neutral) was deactivated to grade III by addition of 6% of water.

colored substance was obtained, after neutralization with cation exchange resin. Thus the total yield was 90 mg (45.5%). The product was identified as 4-hydroxy-3-nitroquinoline (III).

Anal. $C_9H_6O_3N_2$ (190.15)

Calcd. : C, 56.84; H, 3.18; N, 14.73.

Found : C, 56.99; H, 3.35; N, 14.49.

Characteristic infrared absorptions (cm^{-1}):

3200-3040 b (strongly hydrogen-bonded OH); 1620 s (C=N); 1610 s (aromatic C-H); 1535 s (aromatic NO_2).

Others : 1555 s ; 1490 s ; 1450 s ; 1340 s ; 1280 m ; 1260 m ; 1200 m ; 1150 w ; 870 m ; 850 m ; 800 m ; 780 m ; 760 s ; 740 m ; 670 m ; (ester carbonyl was absent).

NMR data (100 MHz, in dimethyl sulfoxide-d_6 with the addition of an equimolar amount of NaOD).

7.85-8.55δ (3H, multiplet, H-5, H-6 and H-7).

8.93δ (1H, center of doublet, H-8, $J_{7,8}$ = 8.0 Hz).

9.67δ (1H, singlet, H-2).

The spectrum is shown in Fig. 15.

Ultraviolet absorption in N,N-dimethylformamide : λ_{max} 269 nm, 318 nm (ε, 4100), 380 nm (ε, 5600) ; in N NaOH solution : λ_{max} , 273 nm (ε,4000), 369 nm (ε,6000).

B. By cyclization of IV with acetic anhydride and potassium acetate

A mixture of 2-(2-*aci*-nitroethylideneamino)-benzoic acid (IV) (502 mg, 2.4 mmole) and acetic anhydride (15 ml) were placed in a 25-ml three-necked round bottom flask equipped with thermometer, reflux condenser and magnetic stirrer. The mixture was stirred and heated to 100-105° until a clear solution was obtained. Heating was then discontinued and powdered, dry potassium acetate * (236 mg, 2.4 mmole) was added with vigorous stirring. The color of the solution changed spontaneously to red. The temperature began to drop after two minutes. Heating was resumed to allow reflux (143°) for an additional 15 minutes. The color of the solution darkened to a deep brown. At the end of the reflux period the reaction mixture was cooled to room temperature and filtered through a sintered glass funnel. The tan colored residue was washed with glacial acetic acid until the filtrate was colorless. (The initial filtrate was reddish brown). It was then washed with water by repeated

---

* Freshly fused and kept in oven at 110° before use.

trituration until the water was neutral to pH paper. The solid was dried in an oven at 105° for half an hour and weighed 200 mg (43.8%). It showed a decomposition range of 340-345°.

Infrared and NMR spectra were identical with those of compound III obtained by method A.

CLAIMS TO ORIGINAL RESEARCH

PART I

1. The synthesis of 2-nitroalkyl β-D-glucopyranoside tetraacetates by the Koenigs-Knorr reaction was studied. Conditions suitable for the synthesis of these base-sensitive glucosides were determined.
2. Deacetylation of the glucoside tetraacetates catalyzed by methyl p-toluenesulfonate in methanolic solution gave the free 2-nitroalkyl β-D-glucopyranosides. This was the first instance of the synthesis of alkali-labile nitro glycosides.
3. The following new compounds were obtained:
   a. 2-Nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (VII).
   b. 1-Methyl-2-nitroethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (VIII) (two epimers).
   c. 2-Nitrobutyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (IX).
   d. 1-Ethyl-2-nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (X) (two epimers)
   e. 2-Methyl-2-nitropropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (XI)

f. 2-Nitropropyl β-D-glucopyranoside (XIII).
g. 1-Methyl-2-nitroethyl β-D-glucopyranoside (XIV).
h. 2-Nitrobutyl β-D-glucopyranoside (XV).
i. 1-Ethyl-2-nitropropyl β-D-glucopyranoside (XVI).
j. 2-Methyl-2-nitropropyl β-D-glucopyranoside (XVII).

PART II

1. The reaction of ammonia with methyl 2,3-anhydro-4-O-benzoyl-6-deoxy-α-D-allopyranoside was studied for the first time.
2. The oxidation of cyclic secondary carbinamines to nitro compounds by m-chloroperbenzoic acid was investigated for the first time. Oxidation of a series of 3-amino sugars possessing either free or protected hydroxyl groups proved to be a useful method for the synthesis of nitro sugars as well as nitroso sugars.
3. The oxidation was successfully carried out to give the following known nitro compounds from the corresponding amino precursors:
    a. *Trans*-2-nitrocyclohexanol (II).
    b. Methyl 3,6-dideoxy-3-nitro-2,4-di-O-methyl-α-L-glucopyranoside (V).
    c. Methyl 3,6-dideoxy-3-nitro-α-D-glucopyranoside (XII).

d. Methyl 3-deoxy-3-nitro-β-D-galactopyranoside (XVI).
e. Methyl 3-deoxy-3-nitro-α-D-mannopyranoside (XX).

4. The following new compounds were obtained:
   a. Trans-2-nitrosocyclohexanol dimer (III).
   b. Methyl 3,6-dideoxy-3-nitroso-α-D-glucopyranoside dimer (XIII).
   c. Methyl 3-deoxy-3-nitroso-β-D-galactopyranoside dimer (XVII).
   d. Methyl 3-deoxy-3-nitroso-α-D-mannopyranoside dimer (XXI).
   e. Methyl 3-deoxy-3-nitroso-β-D-xylopyranoside dimer (XXIII).

PART III

The Dieckmann-type, cyclizing ester condensation of nitro esters was applied to a compound possessing a 2-nitroethylamino group as the reactive methylene function. The reaction represents a new synthesis of the quinoline ring. Two new compounds were prepared in this connection:

a. Methyl 2-(2-nitroethylamino)-benzoate (VII).
b. p-Nitrophenyl 2-(2-*aci*-nitroethylideneamino) benzoate (VII).

REFERENCES

1. C. L. Carter and W. J. McChesney, Nature, <u>164</u>, 575 (1949).
2. M. C. Rebstock, H. M. Crooks, J. Controulis and Q. R. Bartz, J. Amer. Chem. Soc., <u>71</u>, 2458 (1949).
3. Z. Eckstein, Österr. Chemiker Ztg., <u>66</u>, 111 (1965).
4. F. R. Stermitz, F. A. Norris and M. C. Williams, J. Amer. Chem. Soc., <u>91</u>, 4599 (1969).
5. M. C. Williams and W. Binns, Weeds, <u>15</u>, 359 (1967).
6. M. C. Williams and F. A. Norris, Weed Science, <u>17</u>, 236 (1969).
7. D. Shields, M. Sc. Thesis, Univ. of Ottawa, 1970.
8. A. K. Ganguly, O. Z. Sarre and H. Reimann, J. Amer. Chem. Soc., <u>90</u>, 7129 (1968).
9. H. H. Baer, Advan. Carbohyd. Chem., <u>24</u>, 67 (1969).
10. L. Henry, Compt. Rend., <u>120</u>, 1265 (1895).
11. H. H. Baer and L. Urbas, in <u>The Chemistry of the Nitro and Nitroso Groups</u>, Part 2, p. 75, Ed. H. Feuer, Interscience Publishers, N. Y., 1970.
12. J. C. Sowden and H. O. L. Fischer, J. Amer. Chem. Soc., <u>66</u>, 1312 (1944).
13. J. C. Sowden, Advan. Carbohyd. Chem., <u>6</u>, 291 (1951).
14. J. M. Grosheintz and H. O. L. Fischer, J. Amer. Chem.

Soc., 70, 1479 (1948).

15. H. H. Baer and H. O. L. Fischer, J. Amer. Chem. Soc., 81, 5184 (1959).
16. S. Naik, Ph. D. Thesis, Univ. of Ottawa, 1967.
17. H. H. Baer and S. Naik, J. Org. Chem., 35, 2927 (1970).
18. T. Severin, B. Brueck and P. Adhikary, Ber., 99, 3097 (1966).
19. P. L. Southwick, J. A. Fitzgerald, R. Madhav and D. A. Welsh, J. Org. Chem., 34, 3279 (1969).
20. W. Koenigs and E. Knorr, Ber., 34, 957 (1901).
21. W. L. Evans, D. D. Reynolds and E. A. Talley, Advan. Carbohyd. Chem., 6, 27 (1951).
22. J. Conchie, G. A. Levvy and C. A. Marsh, ibid., 12, 157 (1957).
23. Rodd's Chemistry of Carbon Compounds, Vol. 1, Part F, p. 327, Ed. S. Coffey, Elsevier Publishing Co., London, 1967.
24. W. J. Hickinbottom, J. Chem. Soc., 1676 (1929).
25. M. L. Wolfrom, A. O. Pittet and I. C. Gillam, Proc. Natl. Acad. Sci. U. S., 47, 700 (1961).
26. H. H. Baer, W. Rank and F. Kienzle, Can. J. Chem., 48, 1302 (1970).
27. C. M. McCloskey and G. H. Coleman, Org. Syntheses,

Coll. Vol., 3,434 (1955).

28. L. C. Kreider and W. L. Evans, J. Amer. Chem. Soc., 58, 797 (1936).

29. P. F. Lloyd and G. P. Roberts, J. Chem. Soc., 2962 (1963).

30. E. Fischer and M. Bergmann,Ber.,50, 711 (1917).

31. B. Helferich, A. Doppstadt and A. Gottschlich, Naturwissenschaften, 40, 441 (1953).

32. K. Kum, Carbohyd. Res., 11, 269 (1969).

33. H. S. Isbell and H. L. Frush, J. Research Natl. Bur. Standards, 43, 161 (1949).

34. G. Zemplén, Ber., 59, 1254 (1926).

35. R. Kuhn and W. Kirschenlohr, Ber., 86, 1331 (1953).

36. R. Kuhn, F. Zilliken and A. Gauhe, Ber., 86, 466 (1953).

37. B. Helferich, A. Löwa, W. Nippe and H. Riedel, Ber., 46, 1083 (1923).

38. C. E. Ballou, Advan. Carbohyd. Chem., 9, 59 (1954).

39. C. F. Huebner, S. A. Karjala, W. R. Sullivan and K. P. Link, J. Amer. Chem. Soc., 66, 906 (1944).

40. C. E. Ballou and K. P. Link, J. Amer. Chem. Soc., 71, 3743 (1949).

41. C. E. Ballou and K. P. Link, ibid., 72, 3147 (1950).

42. B. Helferich and M. Hase, Ann., 554, 261 (1943).

43. H. O. L. Fischer and H. H. Baer, Ann., 619, 53 (1958).

44. H. H. Baer and W. Rank, Can. J. Chem., 43, 3330 (1965).

45. B. Lindberg and S. Svensson, Acta Chem. Scand., 21, 299 (1967).

46. H. H. Baer, W. Rank and F. Kienzle, Can. J. Chem., 48, 1302 (1970).

47. H. H. Baer and I. Furić, J. Org. Chem., 33, 3731 (1968).

48. E. Fischer, Ber., 26, 2400 (1893).

49. J. E. Cadotte, F. Smith and D. Spriestersbach, J. Amer. Chem. Soc., 74, 1501 (1954).

50. C. T. Bishop and F. P. Cooper, Can. J. Chem., 40, 224 (1962); ibid., 41, 2743 (1963).

51. a. R. D. Guthrie, R. J. Ferrier and M. J. How, Carbohydrate Chemistry, Vol. 1, p. 18, The Chemical Society, Burlington House, London, 1968.
    b. ibid., vol. 3, p.16 (1970).

52. N. K. Kochetkov, A. J. Khorlin and A. F. Bochkov, Tetrahedron Lett., 289 (1964).

53. N. K. Kochetkov, A. J. Khorlin and A. F. Bochkov, Tetrahedron, 23, 693 (1967).

54. V. A. Derevitskaya, E. M. Klimov and N. K. Kochetkov, Carbohyd. Res., 7, 7 (1968).

55. G. B. Howarth, D. G. Lance, W. A. Szarek and J. K. N.

Jones, Can. J. Chem., 47, 75 (1969).

56. S. W. Gunner, W. G. Overend and N. R. Williams, Chem. Ind. (London), 1523 (1964).

57. H. H. Baer and G. V. Rao, Ann., 686, 210 (1965).

58. S. W. Gunner, R. D. King and W. G. Overend, J. Chem. Soc., 1954 (1970).

59. a.A.Rosenthal, K. S. Ong and D. A. Baker, Carbohyd. Res., 13, 113 (1970).

b. A. Rosenthal and K. S. Ong, Can. J. Chem., 48, 3034 (1970).

60. H. H. Baer and K. S. Ong, Can. J. Chem., 46, 2511 (1968).

61. H. H. Baer and J. Kovář, Can. J. Chem., 49, 1940 (1971).

62. H. H. Baer and W. Rank, Can. J. Chem., (in press).

63. J. Kovář, K. Čapek and H. H. Baer, Can. J. Chem., in press, 1971.

64. W. J. Serfontein, J. H. Jordaan and J. White, Tetrahedron Lett., 1069 (1964).

65. R. U. Lemieux, T. L. Nagabhushan and I. K. O'Neill, Tetrahedron Lett., 1909 (1964).

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

67. R. U. Lemieux, T. L. Nagabhushan and S. W. Gunner,

Can. J. Chem., 46, 405 (1968).

68. W. A. Szarek, D. G. Lance and R. L. Beach, Carbohyd. Res., 13, 75 (1970).

69. J. C. Sugihara, W. J. Teerlink, R. Macleod, S. M. Dorrence and C. H. Springer, J. Org. Chem., 28, 2079 (1963).

70. V. Meyer and O. Stüber, Ber., 5, 203, 399, 514 (1872).

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

72. N. Kornblum, Org. Reactions, 12, 101 (1962).

73. N. Kornblum, R. J. Clutter and W. J. Jones, J. Amer. Chem. Soc., 78, 4003 (1956).

74. W. D. Emmons and A. S. Pagano, J. Amer. Chem. Soc., 77, 4557 (1955).

75. T. Takamoto and R. Sudoh, Tetrahedron Lett., 2053 (1971).

76. W. D. Emmons and A. S. Pagano, J. Amer. Chem. Soc., 77, 89 (1955).

77. H. O. Larson, in The Chemistry of the Nitro and Nitroso groups, Part 1, p. 301. Ed. H. Feuer, Interscience Publishers, 1970.

78. E. S. Shanley and E. P. Greenspan, Ind. Eng. Chem., 39, 1536 (1947).

79. D. C. Iffland and T. F. Yen, J. Amer. Chem. Soc., 76, 4083 (1954).

80. A. A. Patchett, F.Hoffman, F. F. Giazzusso, H. Schwann and G. E. Arth, J. Org. Chem., 27 , 3822 (1962).

81. J. R. Bull, Sir E. R. H. Jones, G. D. Meakins, J. Chem. Soc., 2601 (1965).

82. W. D. Emmons, J. Amer. Chem. Soc., 79, 5528 (1957).

83. L. N. Nysted and R. R. Burtner, J. Org. Chem., 27, 3175 (1962).

84. C. H. Robinson, L. M. Milewich and P. Hofer, J. Org. Chem., 31, 524 (1966).

85. W. D. Emmons, J. Chem. Soc., 79, 6522 (1957).

86. M. J. Astle and F. P. Abbott, J. Org. Chem., 21, 1228 (1956).

87. N. Kornblum, H. E. Ungnade and R. A. Smiley, J. Org. Chem., 21, 377 (1956).

88. R. U. Lemieux, Methods Carbohyd. Chem., Vol. II 211, Ed. M. L. Wolfrom and R.L.Whistler, Academic Press, New York, 1963.

89. L. D. Hall, Advan. Carbohyd. Chem., 19, 51 (1966).

90. R. U. Lemieux and J. D. Stevens, Can. J. Chem., 44, 249 (1966).

91. B. Helferich and E. Schmitz-Hillebrecht, Ber., 66, 378 (1933).

92. J. Staněk, M. Černý, J. Kocourek, J. Pacák, The Monosaccharides, Academic Press, New York, and Publishing House of the Czechoslovak Academy of Science, Prague, 1963.

93. L. Fieser and M. Fieser, Reagents for Organic Synthesis, p. 135, John Wiley, New York, 1967.

94. N. Kornblum, R. J. Clutter and W. J. Jones, J. Amer. Chem. Soc., 78, 4003 (1956).

95. B. G. Gowenlock and W. Luttke, Quart. Rev. (London), 12, 321 (1958).

96. C. N. R. Rao in The Chemistry of Nitro and Nitroso Groups, Ed. H. Feuer, Interscience, 1970.

97. L. Brunnel, Ann. Chim., 6, 213 (1905).

98. T. E. Stevens and W. D. Emmons, J. Amer. Chem. Soc., 79, 6008 (1957).

99. J. P. Freeman, J. Org. Chem., 28, 2508 (1963).

100. C. W. Chiu, Ph. D. Thesis, University of Ottawa, 1971.

101. A. C. Richardson, J. Chem. Soc., 2758 (1962).

102. S. Hanessian and N. P. Plessas, J. Org. Chem., 34, 1045 (1969).

103. J. Jarý, J. Kovář and K. Čapek, Coll. Czech. Chem. Commun., 30, 1144 (1965).

104. A. Zobáčová, V. Heřmáncová and J. Jarý, Coll. Czech. Chem. Commun., 32, 3560 (1967).

105. H. H. Baer and K. Čapek, Can. J. Chem., 47, 99 (1969).

106. F. W. Lichtenthaler and W. Fischer, Chem. Comm. 1081 (1970).

107. H. H. Baer and F. Kienzle, Can. J. Chem., 41, 1606 (1963).

108. H. H. Baer and H. O. L. Fischer, J. Amer. Chem. Soc., 82, 3709 (1960).

109. W. Rank, Ph. D. Thesis, University of Ottawa, 1971.

110. R. E. Schaub and M. J. Weiss, J. Amer. Chem. Soc., 80, 4683 (1958).

111. H. H. Baer and H. O. L. Fischer, ibid., 81, 5184 (1959).

112. M. Colonna, Gazz. Chim. Ital., 67, 222 (1937).

113. G. B. Bachman, D. E. Welton, G. L. Jenkins and J. E. Christian, J. Amer. Chem. Soc., 69, 365 (1947).

114. German Patent, 347,375 (to Badische Anilin- and Soda Fabrik). Jan., 17 1922.

115. W. L. F. Armarego, T. J. Batterham, K. Schofield and R. S. Theobald, J. Chem. Soc., 1433 (1966).

116. H. E. Baumgarten and S. H. Lee Chiu, unpublished result.

117. G. N. Walker, J. Org. Chem., 36, 305 (1971)

118. W. F. Batinger, Tetrahedron, 20, 1635 (1964).

119. P. J. Black, Aust. J. Chem., 17, 558 (1964).

120. L. A. Paquette, Modern Heterocyclic Chemistry , p. 275, Benjamin, N. Y. 1968.

121. L. Henry, Chem. Zentr., II, 887 (1898).

122. L. Henry, Bull. Soc. Chim., 15, 1225 (1896).

123. E. Erdmann and H. Erdmann, Chem. Zentr. 11,461 (1900).

124. R. M. Silverstein and G. C. Bassler, Spectrometric Identification of Organic Compounds, p. 135, John Wiley, N. Y. 1967.

116. H. E. Baumgarten and S. H. Lee Chiu, unpublished result.

117. G. N. Walker, J. Org. Chem., 36, 305 (1971)

118. W. F. Batinger, Tetrahedron, 20, 1635 (1964).

119. P. J. Black, Aust. J. Chem., 17, 558 (1964).

120. L. A. Paquette, Modern Heterocyclic Chemistry , p. 275, Benjamin, N. Y. 1968.

121. L. Henry, Chem. Zentr., II, 887 (1898).

122. L. Henry, Bull. Soc. Chim., 15, 1225 (1896).

123. E. Erdmann and H. Erdmann, Chem. Zentr. 11,461 (1900).

124. R. M. Silverstein and G. C. Bassler, Spectrometric Identification of Organic Compounds, p. 135, John Wiley, N. Y. 1967.