APPROACHES TO THE SYNTHESIS OF RARE AMINO SUGARS

by

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PREFACE

This thesis presents some contributions to the synthetic chemistry of nitro and amino sugars.

In the Introduction, the significance of amino sugars in Nature is outlined and a brief account of the utility of nitro sugars for the synthesis of rare amino sugars is given. The specific aims of this thesis are stated, and some general reactions relevant to the project are mentioned. The Introduction is then followed by the discussion of the results and the description of the experiments that were performed.

The thesis is divided into three parts. Part I deals with the synthesis of monoamino, diamino, and triamino sugars from the nitro precursors. In part II, the preparation of the four possible Δ^2 and Δ^3 olefins derivable from methyl 3,6-dideoxy-3-nitro-α-L-hexopyranosides is described, and a stereospecific synthesis of L-desosamine is reported. The last part is concerned with a comparative study of the formation of nitroallylic systems in 3-nitro pyranosides.

ACKNOWLEDGMENT

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ABSTRACTS*

Part I, A

The synthesis of methyl ether derivatives of methyl 3-amino-3,4,6-trideoxy-α-L-xylo-hexopyranoside is described. Methylation of methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (I) using diazomethane and boron trifluoride furnished the monoether II, methyl 3,6-dideoxy-2-O-methyl-3-nitro-α-L-glucopyranoside and the 2,4-dimethylated compound III. Catalytic hydrogenation of III yielded methyl 3-amino-3,6-dideoxy-2,4-di-O-methyl-α-L-glucopyranoside (IV) which was characterized as the N-acetyl derivative V. Acetylation of II with acetic anhydride and boron trifluoride gave, depending on the reaction conditions, either methyl 4-O-acetyl-3,6-dideoxy-2-O-methyl-3-nitro-α-L-glucopyranoside (VI) or the diacetylated derivative VII, 1,4-di-O-acetyl-3,6-dideoxy-2-O-methyl-3-nitro-α-L-glucopyranose. Alternatively, the monoacetate VI was prepared by diazomethane methylation of methyl 4-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (XIII).

When II was treated with triphenylphosphine in carbon tetrachloride, the 4-hydroxy group was substituted by chlorine with inversion of configuration, to give methyl

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* For convenience, compounds in each Part are described using a different set of Roman numerals.

4-chloro-3,4,6-trideoxy-2-O-methyl-nitro-α-L-galacto-pyranoside (VIII), the first vicinal chloronitro sugar to be reported. Action of silica gel upon the chloronitro sugar VIII gave nitroolefin IX, methyl 3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-erythro-hex-3-enopyranoside. Alternatively, IX was obtained by methylation of methyl 3,4,6-trideoxy-3-nitroα-L-erythro-hex-3-enopyranoside (XIV). Sodium borohydride reduction of IX afforded the saturated nitro compound X, methyl 3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-xylo-hexopyrnnoside, which was further reduced to the amino derivative, methyl 3-amino-3,4,6-trideoxy-2-O-methyl-α-L-xylo-hexopyranoside hydrochloride (XI). The latter was transformed into the N-acetylated derivative XII.

Part I, B

Elimination-addition reaction of the acetylated derivative VI with ammonia, followed by treatment with acetic anhydride furnished methyl 4-acetamido-3,4,6-trideoxy-3-nitro-α-L-glucopyranoside (XVI) in high yield. Alternatively, the intermediate amino compound was isolated as hydrochloride XV, and transformed into XVI by N-acetylation. Catalytic hydrogenation of XV afforded the diamino compound XVII, methyl 3,4-diamino-3,4,6-trideoxy-α-L-glucopyranoside dihydrochloride. N-Acetylation of XVII provided the acetamido derivative, methyl 3,4-diacetamido-

3,4,6-trideoxy-α-L-glucopyranoside (XVIII).

Part I, C

The synthesis of methyl 2,3,4-triacetamido-2,3,4,6-tetradeoxy-α-L-glucopyranoside XXII is described. Treatment of diacetate XIX with ammonia and subsequent N-acetylation yielded methyl 2,4-diacetamido-2,3,4,6-tetradeoxy-3-nitro-α-L-glucopyranoside (XX). Catalytic hydrogenation furnished methyl 3-amino-2,4-diacetamido-2,3,4,6-tetradeoxy-α-L-glucopyranoside hydrochloride (XXI) which was further characterized as the fully N-acetylated derivative XXII.

Part II, A

Acetylation of methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (I) and its manno (X) and galacto (XV) isomers with acetic anhydride and boron trifluoride furnished the corresponding diacetates II, XI, and XVI in high yields whereas the talo isomer XVIII gave, depending on the reaction conditions, either its diacetate XIX or a mixture of two nitroolefinic sugars. These nitroolefins were methyl 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (IV) and methyl 4-O-acetyl-2,3,6-trideoxy-α-L-threo-hex-2-enopyranoside (XVII), and they arose in about equal proportions. In addition to IV and XVII a third nitroolefin, 1,4-di-O-acetyl-2,3,6-trideoxy-3-nitro-

α-L-threo-hex-2-enopyranose (XX), was formed under certain conditions.

Base-catalyzed dehydroacetylation (Schmidt-Rutz reaction) of diacetate II resulted in the formation of two nitroolefinic sugars. One of them was an expected product, namely, methyl 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-L-erythro-hex-3-enopyranoside (III), whereas the other was an unexpected 2-epimer (IV). Dehydroacetylation of the diacetates XI, XVI and XIX by the action of silica gel furnished two unsaturated derivatives from each of the isomers, i.e., IV and methyl 4-O-acetyl-2,3,6-trideoxy-3-nitro-α-L-erythro-hex-2-enopyranoside (V) from the manno compound XI; III and XVII from the galacto compound XVI; IV and XVII from the talo compound XIX. The gluco diacetate II gave only one detectable nitroolefin, III.

Deacetylation by controlled methanolysis of the diacetates II and XI yielded only the corresponding 4-O-acetyl derivatives VI and XII, which were then dehydroacetylated by the action of silica gel to give methyl 3,4,6-trideoxy-3-nitro-α-L-erythro-hex-3-enopyranoside (VII) and methyl 3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (XIII), respectively. Controlled acetylation of I using acetyl chloride and triethylamine, which was

followed by chromatography, afforded methyl 2-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (VIII), whereas the manno isomer (X) under similar conditions produced methyl 2,3,6-trideoxy-3-nitro-α-L-erythro-hex-2-enopyranoside (IX).

Part II, B

Nucleophilic addition of methanol to the nitro-olefin VII furnished methyl 3,6-dideoxy-4-O-methyl-3-nitro-α-L-glucopyranoside (XXVIII) in high yield. Reduction of VII with sodium borohydride afforded methyl 3,4,6-trideoxy-3-nitro-α-L-xylo-hexopyranoside (XXII). Catalytic hydrogenation produced methyl 3-amino-3,4,6-trideoxy-α-L-xylo-hexopyranoside (XXIV). Acetylation of XXII resulted in formation of the acetylated derivative XXIII. N,N-Dimethylation of amino compound XXIV with formic acid-formaldehyde led to methyl 3-dimethylamino-3,4,6-trideoxy-α-L-xylo-hexopyranoside (XXVI). L-Desosamine was obtained upon acid hydrolysis of XXVI.

Part III

The speeds of formation of Δ^4 unsaturated 3-aci-nitro salts (nitroallylic systems) in methyl 3-deoxy-3-nitro-β-D-glucopyranoside (I), methyl 3-deoxy-3-nitro-

α-D-arabinopyranoside (II), and methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (III) in the pH range of 7 - 13 were compared by means of ultraviolet spectroscopy, and the results were interpreted in terms of an inductive effect of the C-5 substituent upon deprotonation at that carbon.

I N T R O D U C T I O N

A. The Significance of Amino Sugars in Nature

Amino sugars have long been recognized to play an important role among natural products. Such biological building materials as the chitin of insects and crustaceae, the chondroitin sulfates and hyaluronic acid found in many animal tissues, blood group specific polysaccharides, and glycoproteins present in most body fluids, are some examples of natural products that contain amino sugar components and that have already been studied extensively in the first half of this century. More recently, amino sugars were revealed to be centrally involved in the chemistry of human milk and also in the glycolipids (gangliosides) of brain. It is a most remarkable fact that, in all the diverse materials produced in the animal kingdom, only three different amino sugars have been encountered. These are 2-amino-2-deoxy-D-glucose (glucosamine), 2-amino-2-deoxy-D-galactose (galactosamine), and sialic acid, a nine- carbon amino sugar acid. It is noteworthy, furthermore, that there seem to occur almost no amino sugar in higher plants (1).

However, an entirely different situation exists in the chemistry of microorganisms, a field which was

explored with increasing momentum following World War II. With the discovery and highly successful clinical use of the first antibiotic drugs, chemical research on micro-organisms and their metabolites attracted world-wide attention, and a large share of this research fell in the area of carbohydrate chemistry in general, and of amino sugar chemistry in particular. Numerous antibiotics were discovered which consist partly or wholly of amino carbohydrate building blocks, and certain structural elements in various bacteria and fungi were found to be amino sugars as well (1-4). In contrast to higher animals, microbial chemistry provided an exceedingly diversified spectrum of amino sugars from a viewpoint of both structure and configuration. For example, sugars bearing an amino or substituted amino function in position 3 had not previously been encountered in Nature but have now been detected as constituents of many antibiotics (Table I). Other kinds of newly discovered amino sugars are listed in Table II. Both Tables show the variety in configurations present in these compounds, and they also indicate the wide distribution of sugars having one or two additional deoxy functions, with 6-deoxy derivatives evidently being especially abundant. A few diamino sugars have also been found but no tri- or higher polyamino sugars.

Table I

RARE 3-AMINO SUGARS FOUND IN ANTIBIOTICS

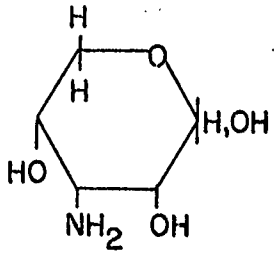
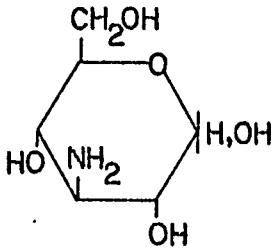
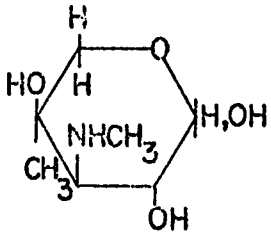
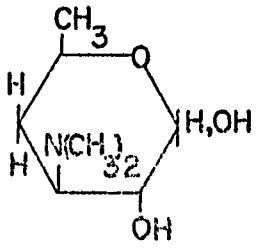
Amino Sugar	Structure	Antibiotic	Reference
3-Amino-3-deoxy-D-ribose		Puromycin	5
3-Amino-3-deoxy-D-glucose (Kanosamine)		Kanamycins A,B,C	6-8
3-deoxy-4-C-methyl-3-methylamino-L-arabinose (Garosamine)		Gentamicin	9-11
3-Dimethylamino-3,4,6-trideoxy-D-xylo-hexose (Desosamine)		Erythromycin Methymycin Narbomycin Neomethymycin Oleandomycin Picromycin	12 13,14 15,16 17 18 13,19,20

Table I (continued)

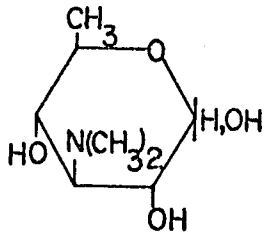
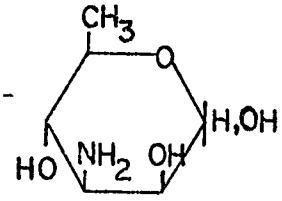
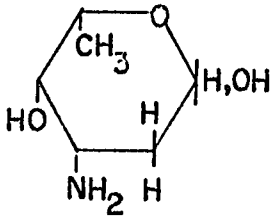
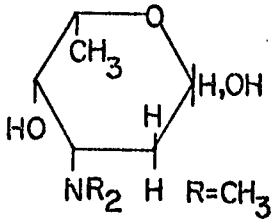
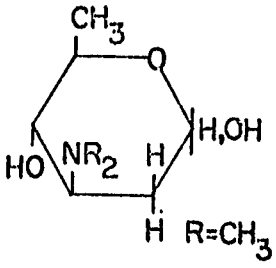
Amino Sugar	Structure	Antibiotic	Reference
3,6-Dideoxy-3-dimethylamino D-glucose (Mycaminose)		Leucomycin	21,22
		Magnamycin	23,24
		Niddamycin	25
		Spiramycin	26
		Tylosin	27
3-Amino-3,6-dideoxy-D-mannose (Mycosamine)		Amphotericin B	28
		Levorin	29
		Lucernosmycin	30
		Nystatin	31
		Pimaricin	32
		Rimocidin	33
		Trichomycin	34
3-Amino-2,3,6-trideoxy-L-lyxo-hexose (Daunosamine)		Daunomycin	35
3-Dimethylamino-2,3,6-trideoxy-L-lyxo-hexose (Rhodosamine)		Cinerubins	36
		Pyrromycin	37,38
		Rhodomycin	36
3-Dimethylamino-2,3,6-trideoxy-D-xylo-hexose (Angolosamine)		Angolamycin	39,40

Table II

OTHER UNUSUAL, NATURALLY-OCCURRING AMINO SUGARS

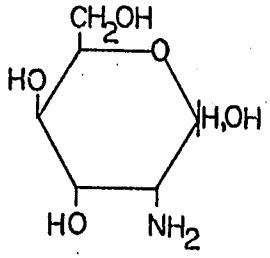
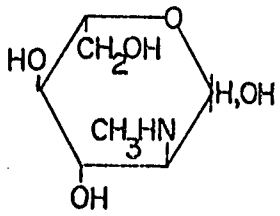
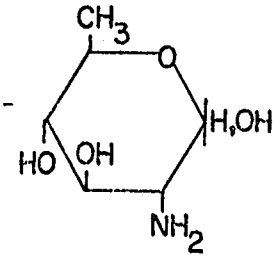
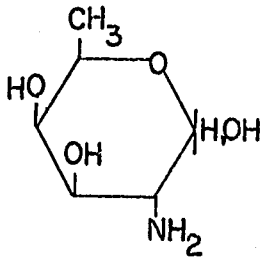
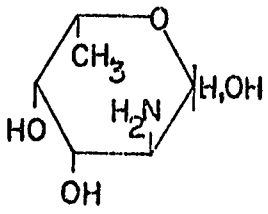
Amino Sugar	Structure	Source	Reference
2-Amino-2-deoxy-D-gulose		Streptothricin	41
2-Methylamino-2-deoxy-L-glucose		Bluensomycin	42
2-Amino-2,6-dideoxy-D-glucose (Chinovosamine)		Moenomycin	43
2-Amino-2,6-dideoxy-D-galactose (D-Fucosamine)		Polysaccharides of: Chromobacterium violaceum Bacillus subtilis Bacillus cerus	44,45 44,45 46
2-Amino-2,6-dideoxy-L-galactose (L-Fucosamine)		Polysaccharides of Pneumococcus type V	47

Table II (continued)

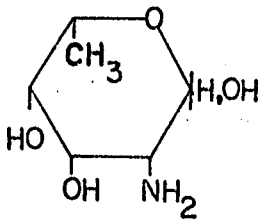
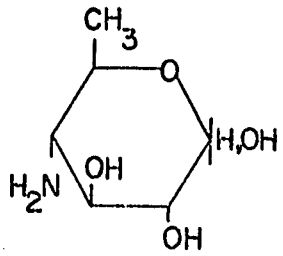
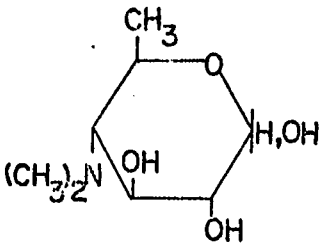
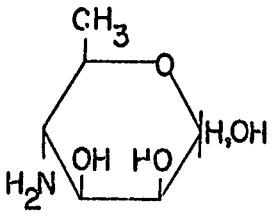
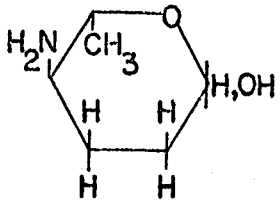
Amino Sugar	Structure	Source	Reference
2-Amino-2,6-dideoxy-L-talose (Pneumosamine)		Polysaccharides of Pneumococcus type V	47,48
4-Amino-4,6-dideoxy-D-glucose (Viosamine)		Lipopolysaccharide of Chromobacterium violaceum	49
4,6-Dideoxy-4-dimethylamino-D-glucose (Amosamine)		Amicetin	50
4-Amino-4,6-dideoxy-D-mannose (Perosamine)		Perimycin	51
4-Amino-2,3,4,6-tetradeoxy-D-erythro-hexose (Tolyposamine)		Tolypomycin	52

Table II (continued)

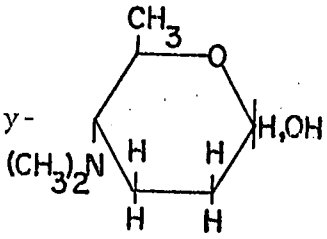
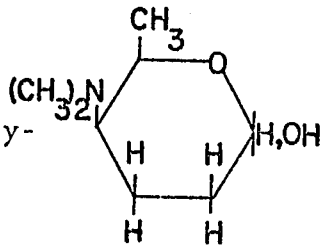
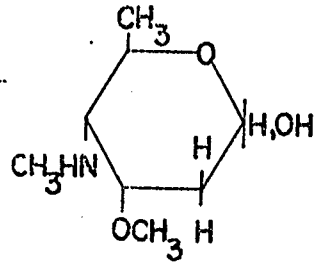
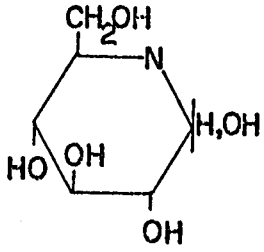
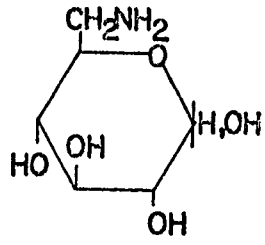
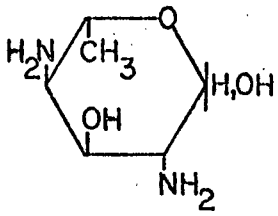
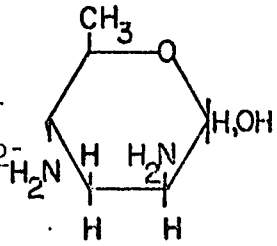
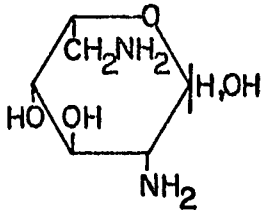
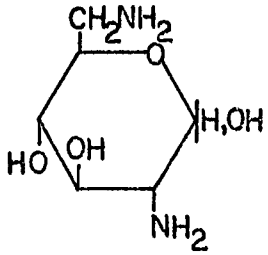
Amino Sugar	Structure	Source	Reference
4-Dimethylamino-2,3,4,6-tetradeoxy-D-erythro-hexose (Forosamine)		Spiramycin	26
4-Dimethylamino-2,3,4,6-tetradeoxy-D-threo-hexose (Ossamine)		Ossamycin	53
4-Methylamino-3-O-methyl-2,4,6-trideoxy-D-ribo-hexose		Apocynacee: Holarrhena curtisii Holarrhena mitis	 54 55
5-Amino-5-deoxy-D-glucose		Nojirimycin	56,57
6-Amino-6-deoxy-D-glucose		Kanamycin A	23

Table II (continued)

Amino Sugar	Structure	Source	Reference
2,4-Diamino-2,4,6-trideoxy-L-altrose (Bacillosamine)		Polysaccharide of Bacillus subtilis	58,59
2,4-Diamino-2,3,4,6-tetradeoxy-D-arabino-hexose (Kasugamine)		Kasugamycin	60
2,6-Diamino-2,6-dideoxy-L-idose (Neosamine B)		Neomycin B Paromomycin I	61 62
2,6-Diamino-2,6-dideoxy-D-glucose (Neosamine C)		Neomycin C Paromomycin II Kanamycin B Kanamycin C	61 63,64 8 7

B. Significance of Nitro Sugars in Synthesis

Stimulated by the discoveries of novel and unusual carbohydrate derivatives in antibiotics and other biologically important materials, chemical synthesis in this area developed rapidly during the past fifteen years. There are many ways of introducing an amino function into a sugar molecule such as, for example, action of ammonia upon epoxides (65, 66), reduction of oximes (67,68), or reduction of azido derivatives generated by nucleophilic displacement in sulfonate esters (69,70). One of the more fruitful approaches, however, is synthesis via nitro sugars (71). Although only one nitro sugar, namely 4-O-methyl-3-C-methyl-3-nitro-2,3,6-trideoxy-L-ribo(or L-arabino)-hexose (evernitrose) has to date been reported as a natural product - a component of the antibiotic everninomycin (72) -, a large number have been synthesized in recent years and many of them have been reduced to the corresponding amines. Only those of the latter which are of a more immediate relevance to antibiotics chemistry are listed in Table III; many stereoisomers and structurally related compounds including di- and triamino derivatives have been obtained in addition. Preparative work has thus aided substantially the elucidation of natural products, by providing compounds

for comparison and identification, and has furnished valuable intermediates for planned, total syntheses of antibiotics, or of analogs and modified derivatives which may find application in biochemical or medical research. Apart from this aspect, nitro sugar chemistry is interesting in its own right because of particular features in reactivity and stereochemistry that are due to the presence of the nitro group. Finally it is worth mentioning that new routes to branched-chain sugars involving nitro derivatives have been elaborated (73,74,75).

Table III

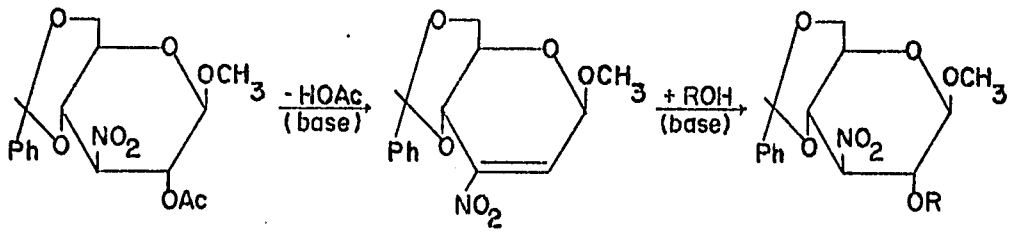
Synthetic Product	Remarks	Reference
3-Amino-3-deoxy-D-ribose	component of puromycin	76
3'-Amino-3'-deoxy-α-L-ribofuranosyl adenine	stereoisomer of 3'-amino-3'-deoxyadenosine	77
3-Amino-3-deoxy-D-glucose	component of kanamycins	78
3-Amino-3,6-dideoxy-D-mannose (mycosamine)	component of several antibiotics (see Table I)	79
3-Dimethylamino-3,6-dideoxy-D-glucose (mycaminose)	component of several antibiotics (see Table I)	80
6-Amino-6-deoxy-D-glucose	component of kanamycin A	81
3-Amino-2,3,6-trideoxy-D-lyxo-hexose	enantiomer of daunosamine from daunomycin	81a

C. Specific Aims of this Thesis

In view of what has been said in the preceding paragraphs it was deemed useful to widen the scope of preparative nitro and hence amino sugar chemistry, as follows. The four methyl 3,6-dideoxy-3-nitro-α-L-hexopyranosides of gluco, manno, galacto, and talo configuration had recently become available in crystalline condition by the method of nitromethane cyclization starting from periodate-oxidized methyl α-L-rhamnopyranoside (82-84). Although the corresponding, simple 3-amino-3-deoxy glycosides were known, it was decided to attempt preparation of some partially O-methylated and O-acetylated derivatives for further reference in structural and synthetic work, to undertake the synthesis of unknown di- and triamino sugars in this series, and also, to elaborate ways of synthesizing polydeoxyamino sugars such as, for example, the enantiomer of the antibiotics component, desosamine. The work contemplated would involve a systematic study of the synthesis of the unknown 2,3- and 3,4-unsaturated nitroolefins derivable from the four nitro glycosides mentioned above.

D. A Short Review of Prior Work Pertinent to the Present Projects

Even though methylation of hydroxyl groups is one of the most common methods used in carbohydrate chemistry for blocking of these groups, it has never been tried in nitro sugars. A few nitro sugar methyl ethers (and certain other ethers) are known, but they have been produced by nucleophilic addition of methanol (and other alcohols) across the double bond of nitroalkenes which were employed either as such or were generated in situ from β-nitro acetates (85,86), e.g.,

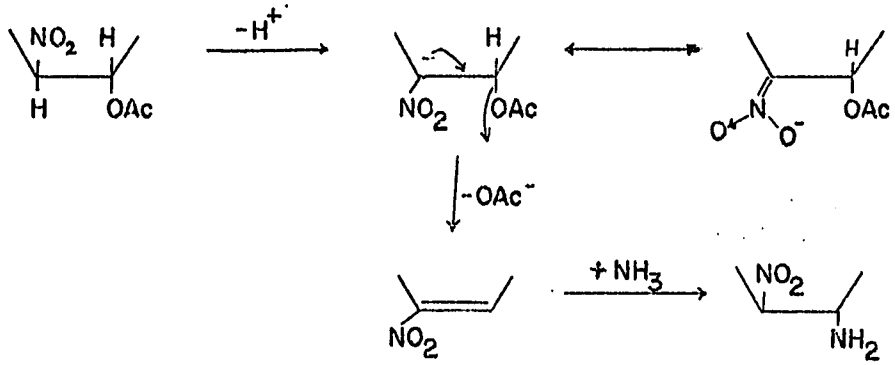


The possibility of direct etherification of nitro sugars remained to be examined.

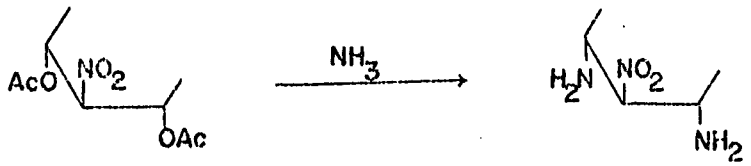
Acetylation of nitro sugars has been accomplished by use of acetic anhydride in the presence of sodium acetate or pyridine but, in some instances, complications arose due to the lability of products in media containing even weakly basic agents (87,88). A satisfactory method proved to be catalysis by boron

trifluoride (89); but here, in at least one instance (90), loss of an acid-labile substituent (a trityl group) was encountered and it was by no means certain whether the method would be generally applicable in the series to be studied, namely, in the di- and trideoxy glycosides which show considerably greater acid sensitivity than normal pyranosides (91).

The replacement by an amino group of an acetoxy function vicinal to a nitro group has been studied as early as 1936 (92) and successfully applied in carbohydrate chemistry many times (93-98). The reaction is regarded as an elimination-addition process:



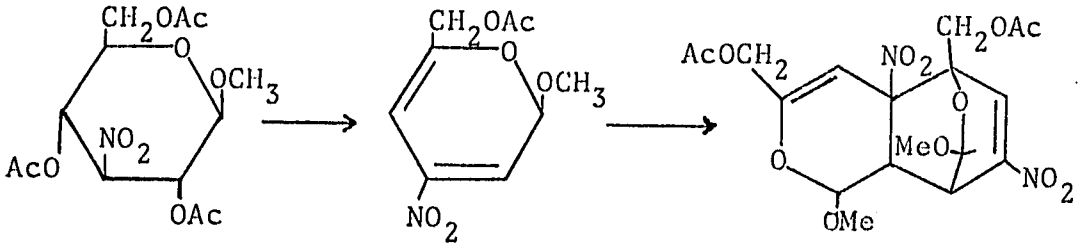
It has been extended to introduce a third nitrogen function (97,99), in which case the elimination-addition process takes place twice.



It was anticipated that this principle of amination should be applicable without trouble to the present project, provided suitable acetates could be made as starting materials. The resulting aminonitro products are usually stabilized by N-acetylation, and subsequent reduction of the nitro group to the amine stage by platinum-catalyzed hydrogenation should offer no difficulties. Concerning the stereochemistry of these reactions it had been observed in most cases that di-equatorial arrangement of the nitro and amino groups prevails and that the catalytic hydrogenation, if it is performed in an acid medium, does not change the configuration of the nitromethylene carbon atom (71).

Although nitroolefins are intermediates in the elimination-additions just referred to, their actual isolation requires base-catalyzed elimination of the acetoxy substituent (dehydroacetylation) in an aprotic solvent. Normally, action of sodium bicarbonate in refluxing benzene is satisfactory when there is only one acetoxy group next to the nitro group (Schmidt-Rutz reaction) (87, 100,101). Thus, methyl 4,6-O-benzylidenated 3-nitro-2-O-acetyl hexopyranosides have afforded 2,3-unsaturated derivatives (87,101). However, if the nitro group is flanked by two acetoxy groups the course

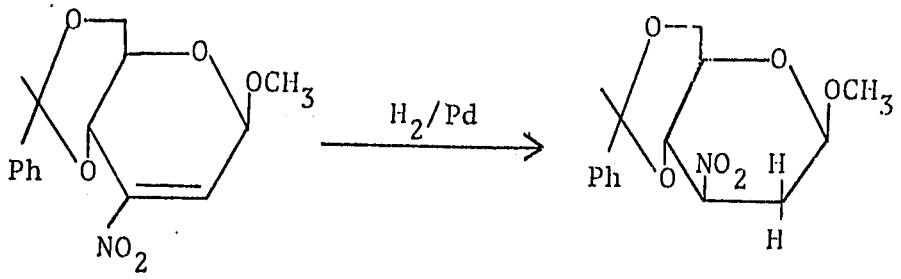
of reaction may be different. Thus, treatment of methyl 2,4,6-tri-O-acetyl-3-deoxy-3-nitro-β-D-glucopyranoside under Schmidt-Rutz conditions resulted in a tricyclic product that arose through a Diels-Alder type self-addition of a nitrodiene primarily formed (102):

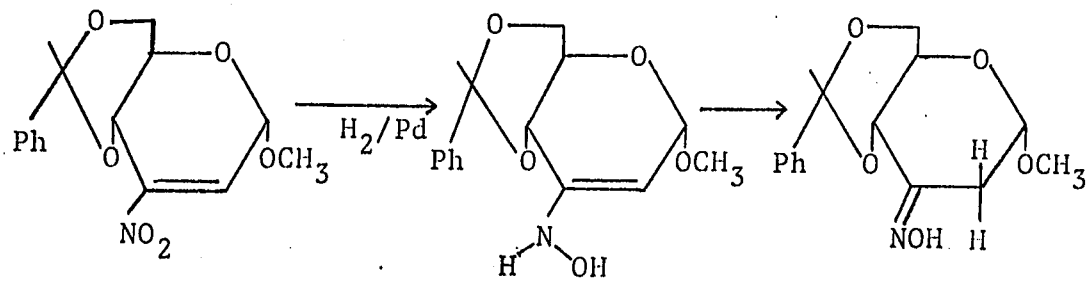


It was interesting to examine whether such a reaction would also occur in the 6-deoxy glycoside series to be studied. If so, ways and means would have to be sought to prevent diene formation by choosing appropriate, monoacetylated compounds as starting materials for the desired nitro monoolefins.

The conversion of nitroolefinic sugars into saturated nitro derivatives has been achieved by selective hydrogenation using a palladium catalyst (101a, 103). In some cases where steric hindrance tended to retard saturation of the olefinic bond, concurrent partial reduction of the nitro group was observed and

the major product was an oxime (101b).





Use of sodium borohydride in ethanol (104) was found to circumvent this difficulty and to give quantitative yields of saturated nitro compounds (105).

PART I

Mono-, Di-, and Triamino Sugars

from

Nitro Sugars

RESULTS and DISCUSSION*

A. Synthesis of O-methylated 3-nitro and 3-amino derivatives in the 3,6-dideoxyhexose series

Methylation is one of the most widely used chemical procedures for the structural elucidation of oligo- and polysaccharides. In the field of nitrogen-containing saccharides, too, a great deal of work has been directed toward the synthesis of methylated derivatives and their use as compounds of comparison in structural studies on natural products (106). However, most of this work pertains to derivatives of 2-amino-2-deoxy sugars that play a role in the animal kingdom, and relatively few methyl ethers of other amino sugars have been described in the literature. The number of known methyl ethers of nitro sugars is even smaller (71). It therefore seemed worthwhile to investigate possibilities for the preparation of various, hitherto unknown O-methyl derivatives in the 3-nitro and 3-amino-3,6-dideoxyhexose series. The recent discovery in an antibiotic (72), of a nitro sugar - the first one in nature - that possesses also an O-methyl function added significance

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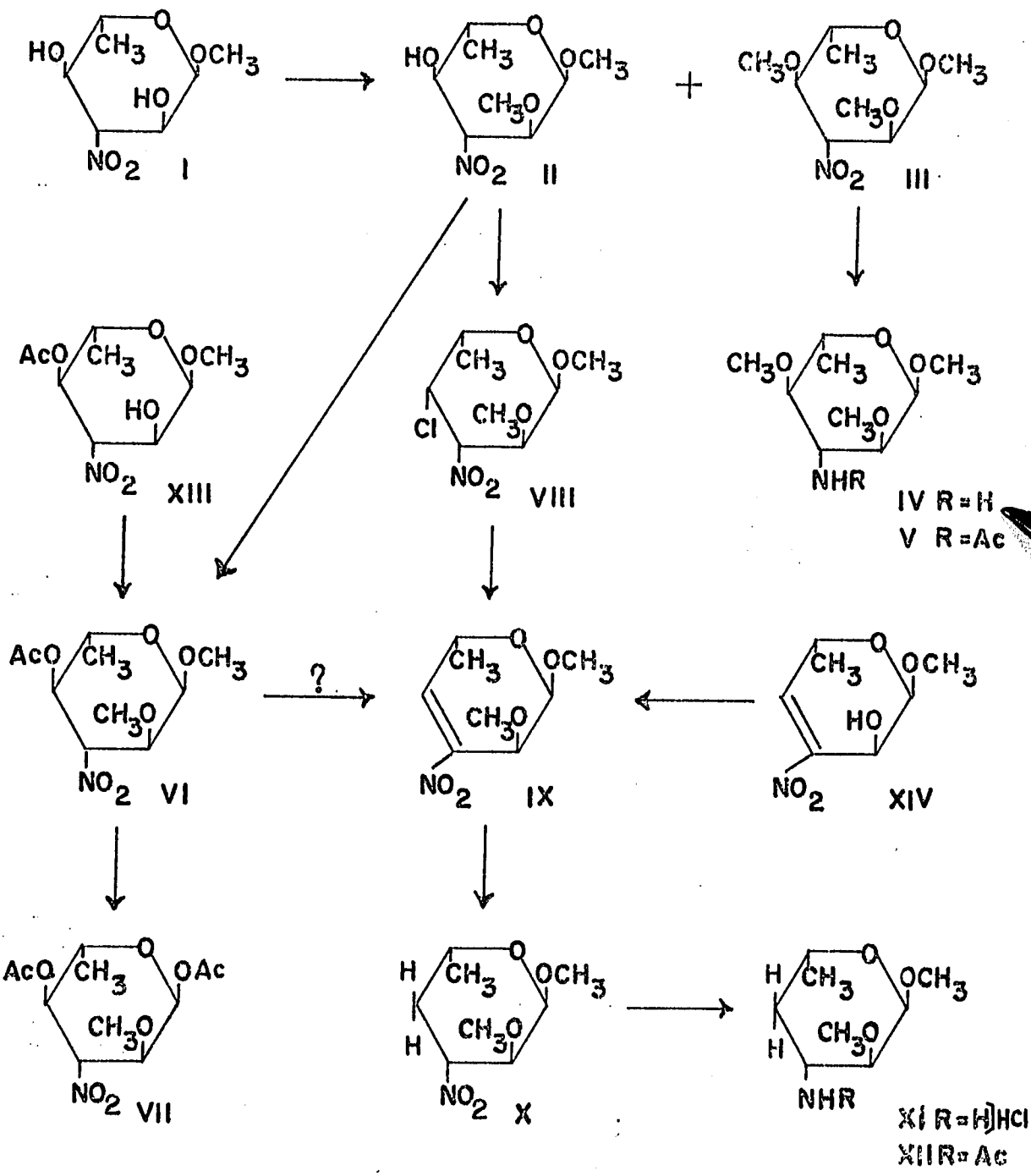
* For convenience, compounds in this chapter are numbered using a new set of Roman numerals.

to this project (see evernitrose, Introduction p.9). It may be anticipated that compounds of the type to be described in the following pages will gain importance in future structural work on newly discovered antibiotics compounds and in their eventual synthesis.

The most frequently employed methods for the methylation of sugars are those of Haworth (dimethyl sulfate and sodium hydroxide) (107), Kuhn (methyl iodide and silver or barium oxide in N,N-dimethyl formamide) (108), and Hakamori (methyl iodide and sodium hydride in dimethyl sulfoxide) (109). However, because of their sensitivity towards alkaline reagents, nitro sugars were considered to be unsuitable substrates for these procedures which were likely to cause unwanted configurational and structural changes. Methylation with diazomethane catalyzed by boron trifluoride (110) appeared to be a more promising approach. This reagent also has the advantage of not affecting such base-labile blocking groups as O-acetyls, thus facilitating certain synthetic sequences.

Methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (I) was prepared from commercially available L-rhamnose according to published procedures(84), and was methylated with a large excess of diazomethane and boron trifluoride at low temperature (Scheme I). Column chromatography



Scheme I. Monoamino sugars from nitro sugars

of the methylated material furnished two products. The faster-moving product was the fully methylated compound III, methyl 3,6-dideoxy-2,4-di-O-methyl-3-nitro-α-L-glucopyranoside, which was obtained in 34% yield. The more slowly moving product was the monoether II, methyl 3,6-dideoxy-2-O-methyl-3-nitro-α-L-glucopyranoside, which was isolated in 62% yield. Structural proof for these compounds and those subsequently to be described will be discussed in a separate section (p.30).

The dimethyl ether III was hydrogenated using platinum catalyst in the presence of hydrochloric acid at room temperature and atmospheric pressure. The hydrogenation proved to be extremely sluggish, and it was incomplete even after three weeks. Nevertheless, the product, methyl 3-amino-3,6-dideoxy-2,4-di-O-methyl-α-L-glucopyranoside hydrochloride (IV), was obtained in 62% yield. The fact that the hydrogenation proceeded much more slowly than in other nitro sugars, where it is usually complete within 24 hours (71), is probably due to the steric effect of the three methoxy groups at C-1, C-2, and C-4. No attempt was made to accelerate the reaction by use of forcing condition.

The amine hydrochloride IV was then N-acetylated with acetic anhydride in methanol-water, in the presence of an anion exchange resin, which afforded the acetamido

derivative V, methyl 3-acetamido-3,6-dideoxy-2,4-di-O-methyl-α-L-glucopyranoside, in 85% yield.

The monomethyl ether II was acetylated with acetic anhydride catalyzed by small amount of boron trifluoride (89) at a temperature about -60°. The reaction was complete within ten minutes and the 4-acetate VI was obtained in almost quantitative yield. Interestingly, when acetylation was performed at 0° over a longer period of time and with a somewhat increased amount of boron trifluoride, a different product was obtained in 86% yield, namely, 1,4-di-O-acetyl-3,6-dideoxy-2-O-methyl-3-nitro-α-L-glucopyranose (VII). Although sulfuric acid-catalyzed acetolyses of glycosidic bonds are fairly common and have been observed also in nitro glycosides (77,90), the present case is the first one to be encountered under conditions of the milder, boron trifluoride-catalyzed acetylation. A considerable number of methyl hexopyranosides, disaccharides, and glycoside benzylidene acetals have been acetylated by the latter method without effect upon the glycosidic center or upon acid-labile benzylidene groups (77,89,90), even though the reactions were not normally performed at lower than ice - bath temperature. One has to remember, however, that 6-deoxy glycosides in general are more readily susceptible to

acid-catalyzed reactions at the anomeric center than their 6-hydroxy analogs. Given the fact that acetolysis in II (or in intermediate VI) has occurred, it is not surprising that the predominant product VII should possess the α-anomeric configuration since the latter is preferred due to the anomeric effect (111).

The 4-O-acetyl-2-O-methyl derivative VI was synthesized also by a different route. It was obtained in 83% yield by diazomethane methylation of methyl 4-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (XIII), the latter having been prepared by partial acid hydrolysis of methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (see p. 70).

It has been mentioned in the Introduction that several nitroolefinic sugars having their unsaturated function between C-2 and C-3 are known and have proved to be useful synthetic intermediates. It was therefore interesting to synthesize and study the properties of 3,4-unsaturated nitro sugars. The 4-acetate VI appeared to offer itself for the synthesis of such an olefin, and attempts were therefore made to subject VI to the Schmidt-Rutz reaction (i.e., base-catalyzed dehydroacetylation). Exploratory experiments were performed with sodium bicarbonate, potassium carbonate, sodium carbonate or triethylamine in inert solvents such as

dry benzene or dry toluene. The reaction mixtures were examined by infrared spectroscopy as well as by thin-layer chromatography. In all cases, the expected nitro-alkene absorption in the infrared region of 1535-1515 cm^{-1} was either weak or absent, and no evidence for formation of the desired product was found on chromatograms. On prolonged refluxing (e.g. overnight) the reaction mixtures turned brownish and seemed to contain small amounts of unidentified material.

Having failed in converting VI into the olefin IX it was thought that, possibly, dehydrohalogenation of an analogous 4-halo derivative might prove more successful. Szarek (112) has recently reported on a facile reaction of this kind in a nitro sugar. In order to prepare a suitable halogen derivative, e.g. the 4-chloro sugar VIII, the method of Lee and coworkers (113) was applied. This method accomplishes conversion of a hydroxy function into a chloro function by reaction with tertiary phosphine (usually triphenylphosphine) in carbon tetrachloride. Alkyl chlorides are thus obtained in good yields from alcohols under mild condition.

$$ROH + CCl_4 + R'_3P \rightarrow RCl + R'_3P(O) + CHCl_3$$

When the nitro alcohol II was for the first

time heated under reflux in dry carbon tetrachloride in the presence of triphenylphosphine, a colorless crystalline product was isolated after column chromatographic separation. However, elemental analysis suggested the formula $C_8H_{13}O_5N$ which did not correspond to the chloro-nitro sugar VIII. Rather, the composition corresponded to the nitroolefin of structure IX, and spectral data were consistent with this structure. Thus, the UV spectrum showed absorption at λ_{max} 245 nm ($\underline{\varepsilon}$,5300), and the infrared spectrum (Fig.1) revealed an absorption at 1515 cm^{-1}, in accord with a nitroalkene grouping.

The structure of IX, methyl 3,4,6-trideoxy-2-$\underline{O}$-methyl-3-nitro-α-L-erythro-hex-3-enopyranoside, was later confirmed by an independent synthesis that will be recorded in a subsequent paragraph.

When the chlorination of II was repeated on a larger scale and only a short column of silica gel was employed in the work-up operation, the chloro compound VIII, methyl 4-chloro-3,4,6-trideoxy-2-$\underline{O}$-methyl-3-nitro-α-L-galactopyranoside, could be isolated in crystalline form in 44% yield. The olefin IX was a by-product detected by NMR spectroscopy in the mother liquor. Evidently VIII suffers dehydrohalogenation quite readily, presumably during work-up. Indeed, when isolated VIII was passed through a silica gel column again, it was converted to the extent of

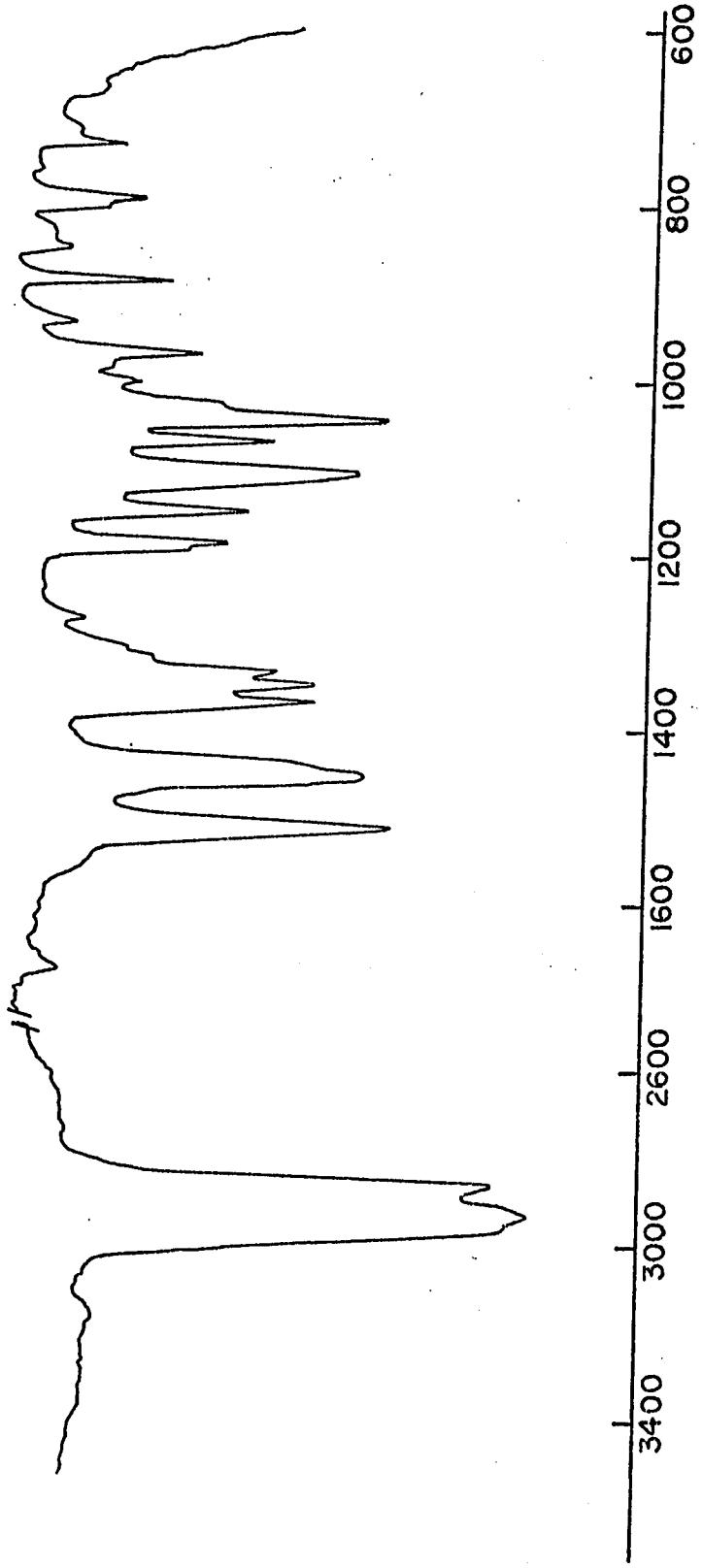


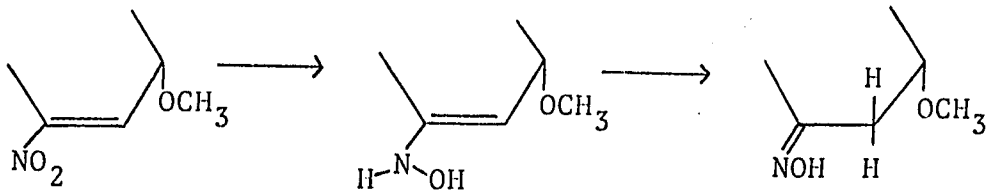
Fig. 1 Infrared spectrum of compound IX in Nujol mull

83% into the olefin IX.

The independent synthesis of IX alluded to above was achieved by diazomethane methylation of the non-methylated nitroolefin XIV, which gave a yield of 93%. The process was conducted in a manner so as to never allow an excess of diazomethane to build up, in order to avoid a possible addition of the reagent across the nitroolefinic double bond. The success of the operation demonstrated that nitroalkenes containing a hydroxy group can well be selectively O-methylated even though diazomethane is known to react readily with the double bond to give pyrazolines (114a). In fact, several pyrazolines derived from nitroolefinic sugars were made in this way in concurrent work in this laboratory (114b). The hydroxynitroolefin XIV required for the methylation had become available by dehydroacetylation of the 4-acetate XIII (see Part II, p.70).

One of the aims of this thesis was to prepare 3-amino sugars containing a deoxy function in position 4, in view of the occurrence of such structures in antibiotics. Consequently, reduction of the nitroolefin IX was studied next. To obtain the saturated nitro compound X, perhaps the simplest approach might be catalytic hydrogenation using a palladium catalyst, which has proved

successful in a number of similar cases (71). However, in certain nitroolefinic glycosides that possessed, like IX, an axial anomeric methoxyl group there arose complications due to partial reduction of the nitro group instead of the ring double bond, and oximes were formed (101b):



When, on the other hand, these particular nitroolefins were treated with sodium borohydride in ethanol according to Shechter (104a), the expected nitroalkanes were the sole products (105). Hence, borohydride reduction was applied to IX. It yielded methyl 3,4,6-trideoxy-3-nitro-α-L-xylo-hexopyranoside (X) as a colorless, chromatographically homogeneous syrup.

Further hydrogenation of X, performed at room temperature and atmospheric pressure in the presence of platinum catalyst and hydrochloric acid, furnished in 95% yield the crystalline compound XI, methyl 3-amino-3,4,6-trideoxy-2-O-methyl-α-L-xylo-hexopyranoside hydrochloride. N-Acetylation of this hydrochloride with acetic anhydride in aqueous methanol in the presence of anion exchange

resin afforded in 84% yield the acetamido derivative XII, methyl 3-acetamido-3,4,6-trideoxy-2-O-methyl-α-L-xylo-hexopyranoside.

In summary, the reaction sequences described above have demonstrated for the first time the utility of diazomethane as a reagent for the preparation of nitro sugar methyl ethers; the feasibility of making a nitroolefinic sugar from a nitro alcohol precursor by the triphenylphosphine-carbon tetrachloride method via a reactive chloronitro intermediate (a method which may find further uses as an alternative to the Schmidt-Rutz reaction); and finally, the sequences constitute the first example of the use of nitro sugars for the synthesis of a 3-amino sugar having a 4-deoxy function.

Proof of Structure and Configuration

All the reactions involved in the synthesis of compounds II-VI, namely boron trifluoride-catalyzed methylation and O-acetylation, catalytic hydrogenation in the presence of acid, and N-acetylation, can safely be assumed to cause no configurational changes, and hence the α-L-gluco configuration of the starting glycoside I applies to these products.

Compounds II and III were revealed to be products of monomethylation and dimethylation, respectively, by their NMR spectra which exhibited sharp singlets near 6.6τ corresponding to two and three methoxyl groups, and by their IR spectra which showed a strong hydroxyl band at 3430 cm^{-1} for II but no such absorption for III. The 2-O-methyl rather than the 4-O-methyl structure was deduced for the partially methylated product II on the basis of the NMR spectrum of its acetate VI (Fig.2). A low-field, one-proton triplet at 5.15τ was assigned to the ring proton at the carbon atom bearing the acetoxy substituent. The large spacing of the triplet (10Hz) requires this proton to be axially oriented and vicinally coupled with two axial protons. This condition is met by H-4 but not by H-2; consequently, the acetoxy group is situated in position 4 and this leaves the position 2 for the methoxy

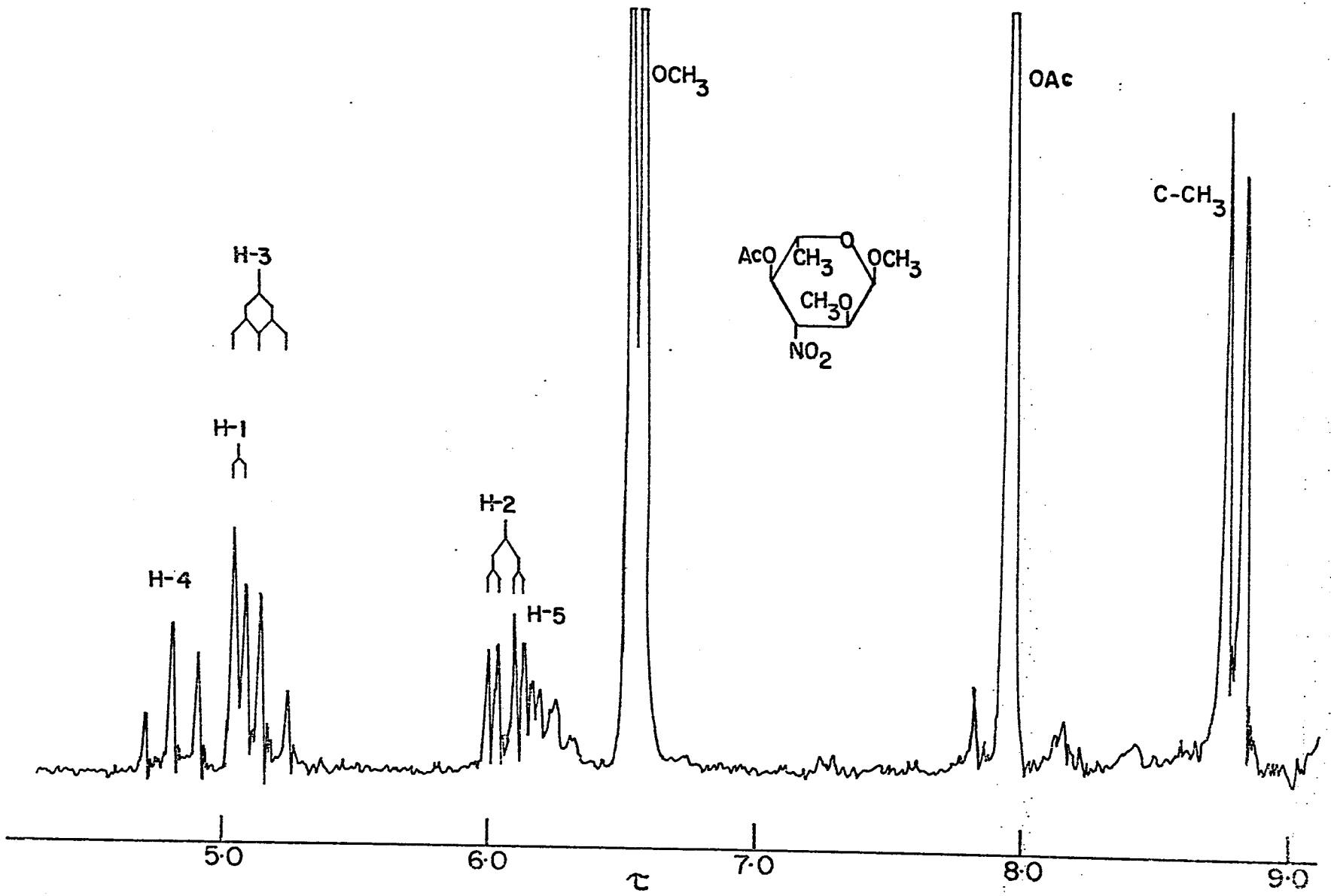


Fig. 2 NMR spectrum of compound VI in deuterated chloroform

group. In accord therewith, a quartet signal at 6.08τ attributable to H-2 exhibited a small splitting (3.5-4Hz) due to axial-equatorial coupling between H-2 and H-1, and a large splitting (10Hz) due to axial-axial coupling between H-2 and H-3. It has been observed in polysaccharides (115) as well as in monosaccharides (116) that the C-2 hydroxyl group generally appears to possess higher reactivity toward methylating agents than C-3 or C-4 hydroxyl groups. The difference has been explained in terms of a higher acidity of the C-2 hydroxy group due to an inductive effect exerted by the acetal oxygen at C-1 (116). The preferred site of methylation observed in I was, therefore, not unexpected.

The anomeric center of the diacetate VII was proved, also by NMR spectrum (Fig.3), to have retained the α-configuration of the precursor VI. The low-field, one-proton doublet at 3.54τ attributable to H-1 showed a small splitting of 3.5Hz in line with the 1,2-equatorial-axial proton relationship required for the α-anomer. The β-anomer would have been expected to show an H-1 signal as a doublet with a larger splitting due to axial-axial coupling between H-1 and H-2.

The conversion of compound II into the chloro-nitro derivative VIII involved an inversion of configuration at C-4, i.e., from the L-gluco to the L-galacto

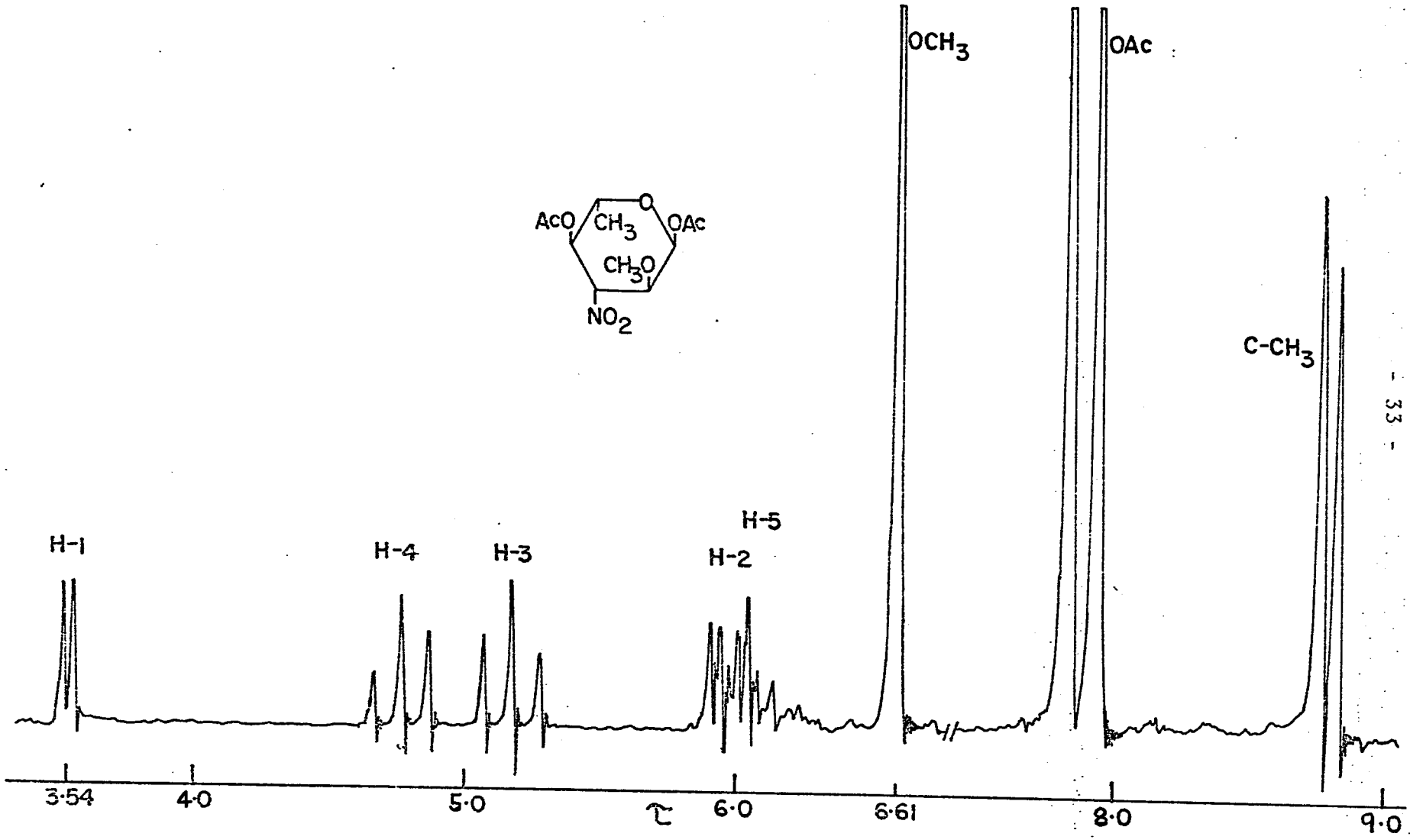
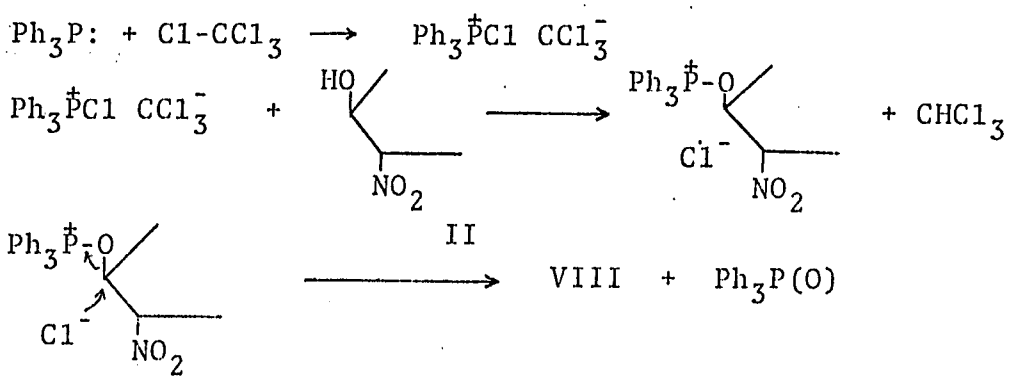


Fig.3 NMR spectrum of compound VII in deuterated chloroform

configuration. This fact was established by studies of the NMR spectrum of VIII. An expanded spectrum of the ring hydrogen resonance region (5.0-6.0τ) is shown in Fig. 4. The well-resolved spectrum showed six peaks centered at 5.05τ , with a total intensity corresponding to two protons. These peaks comprised a quartet assigned to H-3 ($J_{2,3}$=10-10.5Hz, $J_{3,4}$=3.5Hz) and a doublet assigned to H-1 ($J_{1,2}$= 3.5Hz). A quartet ($J_{3,4}$=3.5Hz, $J_{4,5}$=1.5Hz) at 5.46τ was attributable to H-4. The multiplet in the region of 5.8τ consisted of an octet for H-5 ($J_{4,5}$=1.5Hz, $J_{5,6}$=6Hz) centered at 5.77τ and a quartet for H-2 ($J_{1,2}$=3.5Hz, $J_{2,3}$= 10-10.5Hz) at 5.86τ . Spin decoupling of the H-4 signal by double irradiation at 5.46τ changed the H-3 signal at 5.05τ from a quartet to a doublet ($J_{2,3}$=10Hz) while the H-1 doublet remained unchanged. Similarly, the H-5 octet at 5.77τ collapsed to a quartet ($J_{5,6}$=6-6.5Hz) while the H-2 quartet remained unchanged. Thus, the α-L-galacto configuration of VIII was assigned correctly. The reaction mechanism of formation is represented as follows:



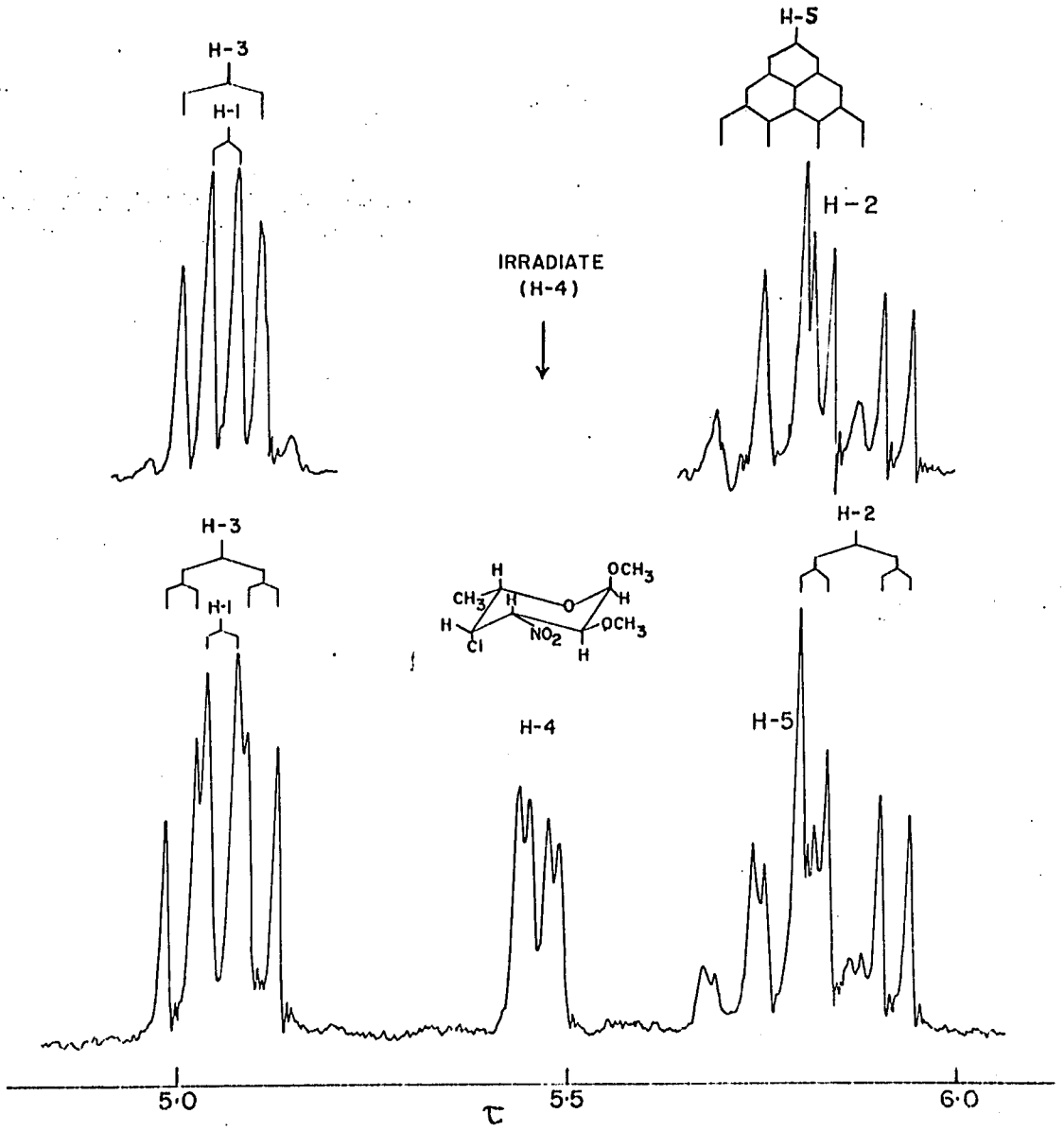
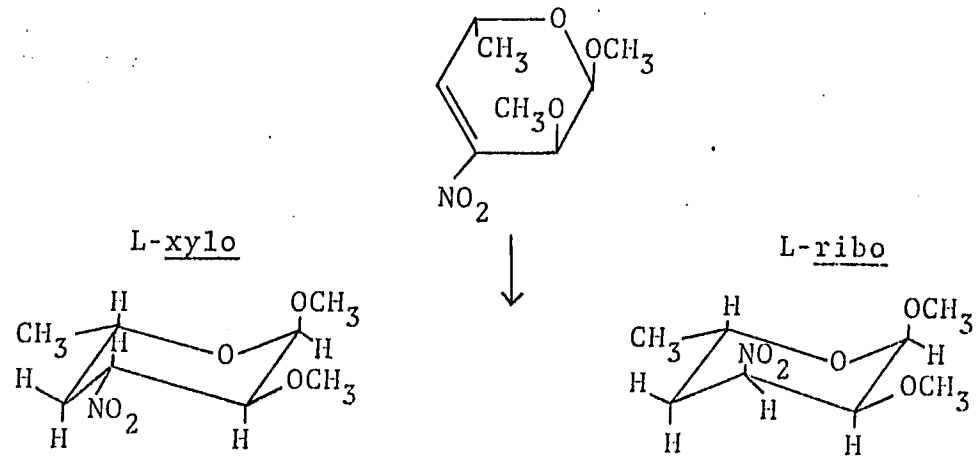


FIG. 4 THE RING HYDROGEN RESONANCES OF COMPOUND VIII IN DEUTERATED CHLOROFORM

The galacto configuration of VIII, with an axial chlorine atom, is perhaps responsible for the special ease with which the compound undergoes elimination (dehydrochlorination).

The structure and configuration of the nitroolefin IX follows from its formation from VIII and XIV. Confirmation was provided by its NMR spectrum (see Experimental) which showed a low-field, one-proton doublet at 2.94τ attributable to the olefinic proton H-4. A doublet at 5.08τ with a spacing of 3Hz was assigned to the anomeric proton. H-2 gave a quartet at 5.59τ , and the multiplet at 5.35τ was due to H-5. Two sharp three-proton singlets at 6.43 and 6.46τ were the signals of the methoxy groups. The remaining doublet at 8.62τ , of three-proton intensity, was assigned to the C-CH_3 group.

Reduction of nitroolefin IX with sodium borohydride generates one asymmetric center at C-3, with the possible formation of two stereoisomers, namely those with the L-xylo and L-ribo configurations.



However, only one product was obtained, and it was assigned the L-xylo configuration on the basis of its NMR spectrum in deuterated chloroform (Fig.5). The L-xylo configuration was revealed by the presence at 6.17τ of a quartet for H-2, with coupling constants $J_{1,2}$= 3.5Hz and $J_{2,3}$=10Hz. The large splitting between H-2 and H-3 requires a diaxial arrangement for these two protons. The L-ribo configuration would have produced a H-2 signal as a narrow quartet or triplet showing small coupling constants only, because of the axial-equatorial arrangement between H-2 and both of its neighbors.

The subsequent products XI and XII should also possess the L-xylo configuration since the reactions involved (catalytic hydrogenation in acidic medium and N-acetylation) are known to proceed without configurational change. This was further supported by NMR data of compound XII (see Experimental) which, in deuterated chloroform, exhibited the acetamido signal at 8.04τ in agreement with an equatorial orientation (117,118).

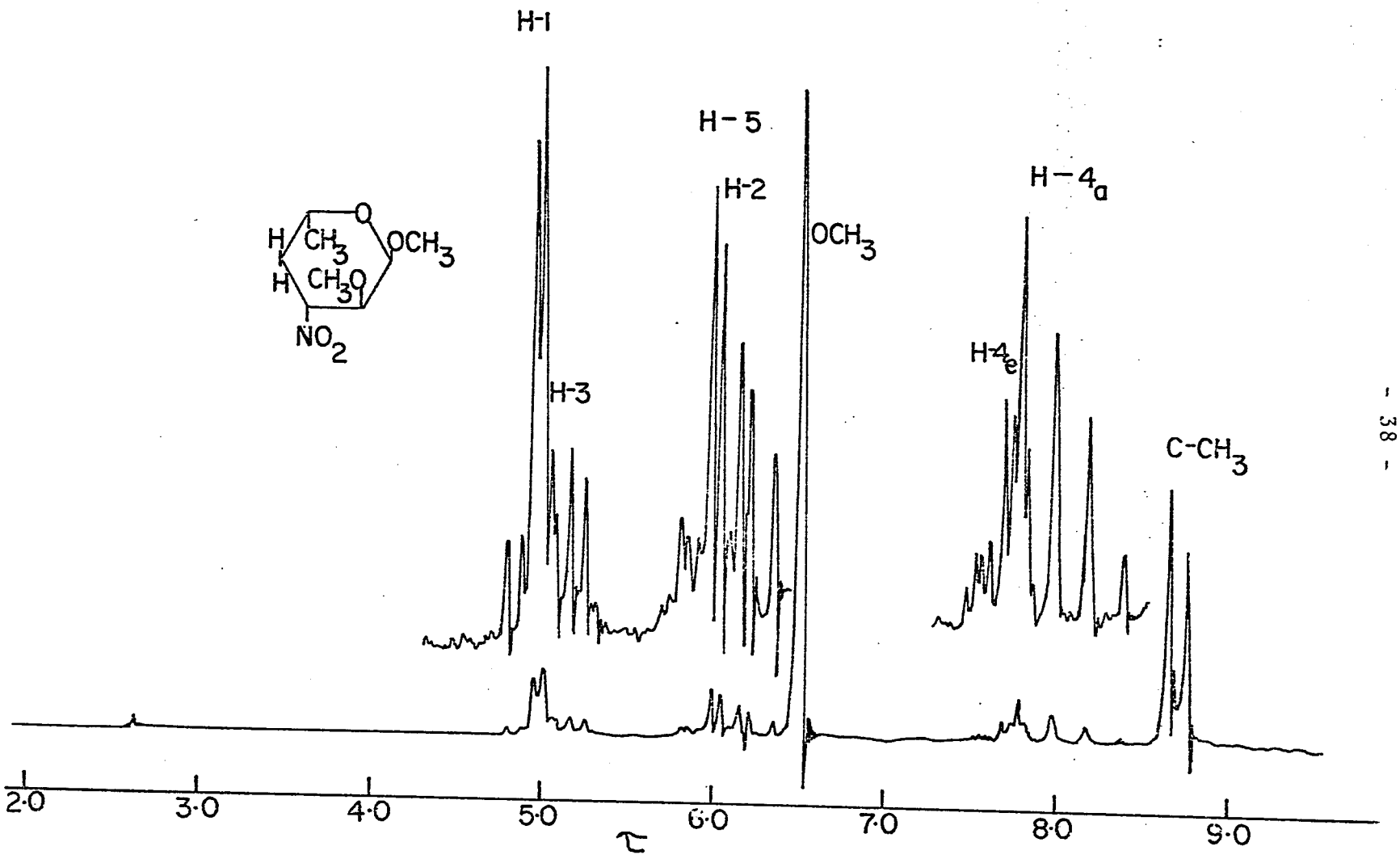


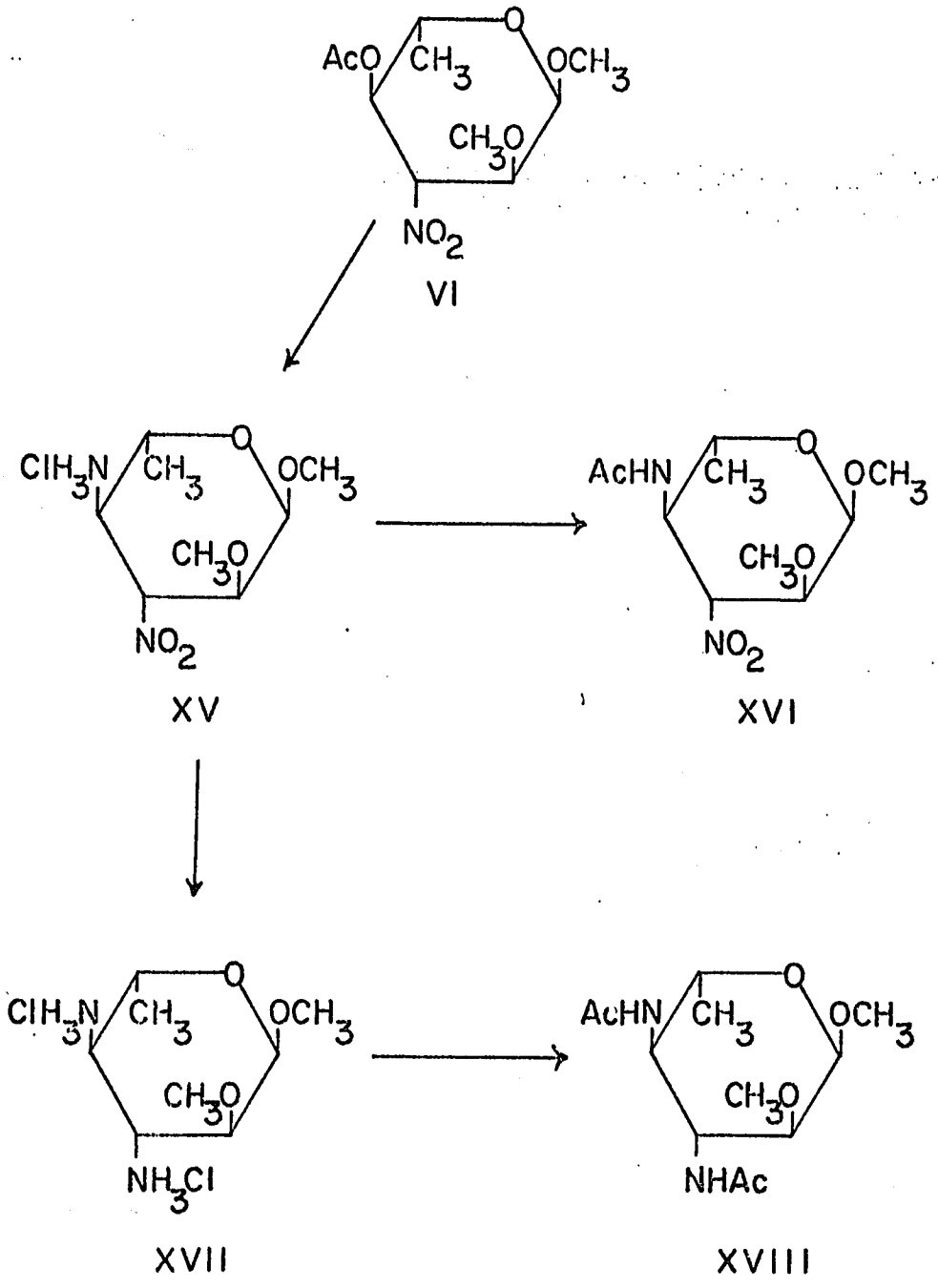
Fig.5 NMR spectrum of compound X in deuterated chloroform

B. Synthesis of Diamino Sugars

Although most diamino sugars known to date have been synthesized by making use of nucleophilic displacement reactions for the introduction of one or both of the nitrogen functions (106b), several have been obtained by the action of ammonia upon suitable nitro sugar derivatives and subsequent hydrogenation of the resulting aminonitro sugars(95, 119). It was decided to study the latter approach in the 6-deoxy hexose series.

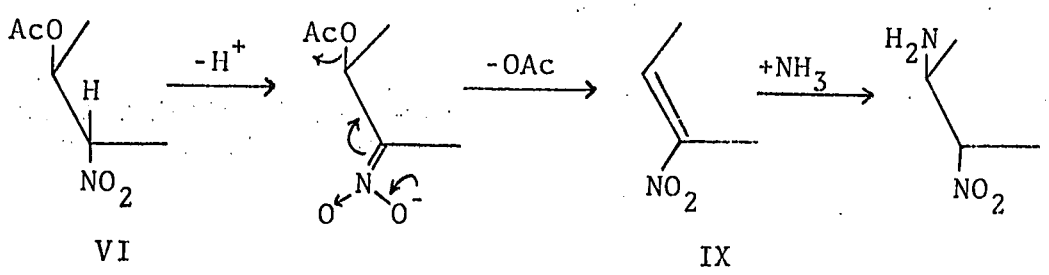
When methyl 4-O-acetyl-3,6-dideoxy-2-O-methyl-α-L-glucopyranoside (VI) (Scheme II) was treated with ammonia at about -60° for six hours, a glassy syrup was obtained. The syrup was unstable at room temperature as indicated by progressive discoloration, and it was therefore rapidly neutralized by titration with an anhydrous solution of hydrogen chloride in ether. A crystalline salt, methyl 4-amino-3,4,6-tetradeoxy-2-O-methyl-3-nitro-α-L-glucopyanoside hydrochloride (XV), was obtained in 96.5% yield. Paper chromatography of the crystalline product showed only one spot. The infrared spectrum of XV showed absorptions at 1590 cm^{-1} and 1505 cm^{-1} corresponding to an amine salt. The ester carbonyl peak (1730 cm^{-1}) of the starting compound had disappeared.

The formation of XV from the β-nitro acetate VI may be visualized as proceeding via the nitroolefin



Scheme II Diamino Sugars from Nitro Sugars

IX which is generated *in situ*:



VI IX

Ammonia abstracts the nitromethylene proton of VI to form a nitronate from which the C-4 acetoxy group is then eliminated to give intermediate IX, and the latter then adds ammonia to give the amine that was isolated as its hydrochloride. An elimination-addition mechanism for such a process was first invoked by Irving and Fuller. (120).

N-Acetylation of XV was effected with acetic anhydride in methanol-water at 0°, in the presence of anion exchange resin, and afforded methyl 4-acetamido-3,4,6-trideoxy-2-*O*-methyl-3-nitro-α-L-glucopyranoside (XVI) in 96% yield. Alternatively, the acetamido derivative XVI could be prepared in 80% yield by direct acetylation of crude aminonitro intermediate without purification via the hydrochloride.

Hydrogenation of the aminonitro derivative XV in the presence of platinum catalyst and dilute hydrochloric acid was complete within four hours, as indicated by thin-layer chromatography, and gave in 93% yield the crystalline diamine XVII, methyl 3,4-diamino-3,4,6-trideoxy-2-O-methyl-α-L-glucopyranoside dihydrochloride. There was no nitro absorption in the infrared region of 1550 cm^{-1}, and elemental analysis agreed with the diamino structure XVII.

Complete N-acetylation was performed as described before and afforded the diacetamido derivative XVIII, methyl 3,4-diacetamido-3,4,6-trideoxy-2-O-methyl-α-L-glucopyranoside, in 88% yield. The compound was moderately soluble in chloroform and sublimed at 298-300°. Its infrared spectrum is shown in Fig.6.

In summary, these studies have demonstrated that synthesis via aminonitro derivatives offers a high-yielding pathway to diamino sugars also in the 6-deoxy series, and they have led to the first example of a 3,4-diamino sugar. Noteworthy in the reaction VI→XV is its high stereoselectivity which is evidenced by the isolation of a single product in 96% yield. The product has the L-gluco configuration as will be shown in the next paragraph. In other words, the substituents at C-3 and C-4

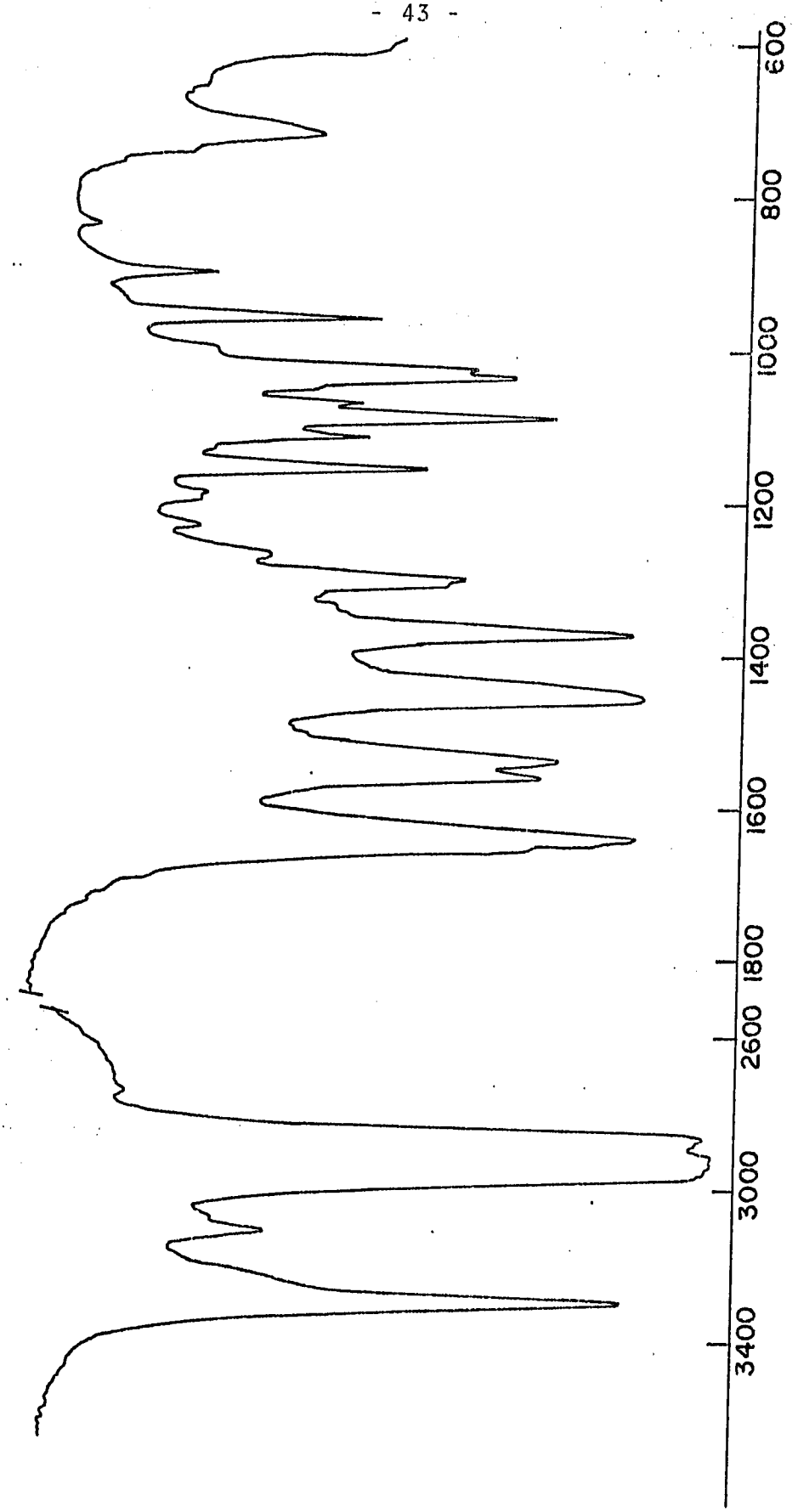


Fig.6 Infrared spectrum of compound XVIII in Nujol mull

have arranged themselves nearly exclusively in diequatorial orientation, even though four different arrangements are theoretically possible. Considering the presumed 3,4-unsaturated intermediate and presupposing kinetic control it would not be immediately obvious why this should be so. However, experience in related cases was precisely the same (95,119). Probably the reaction is controlled thermodynamically, any other epimers primarily engendered being converted into the most stable epimer. Whether this is due to reversibility of the addition reaction or to a subsequent, reversible epimerization by another path must remain unanswered.

Proof of Configuration

Assignment of L-gluco configuration to the reaction products just described was based on the NMR spectra of XVI and XVIII. In deuterated chloroform solution, the nitroacetamido compound XVI (Fig.7) was characterized by the presence of a sharp singlet at 8.05τ, assigned to the methyl protons of an equatorial C-4 acetamido group on the basis of abundant chemical shift data for acetamido groups on six-membered sugar rings (117,118). Valuable information was obtained from the coupling constants of the ring protons. A one-proton

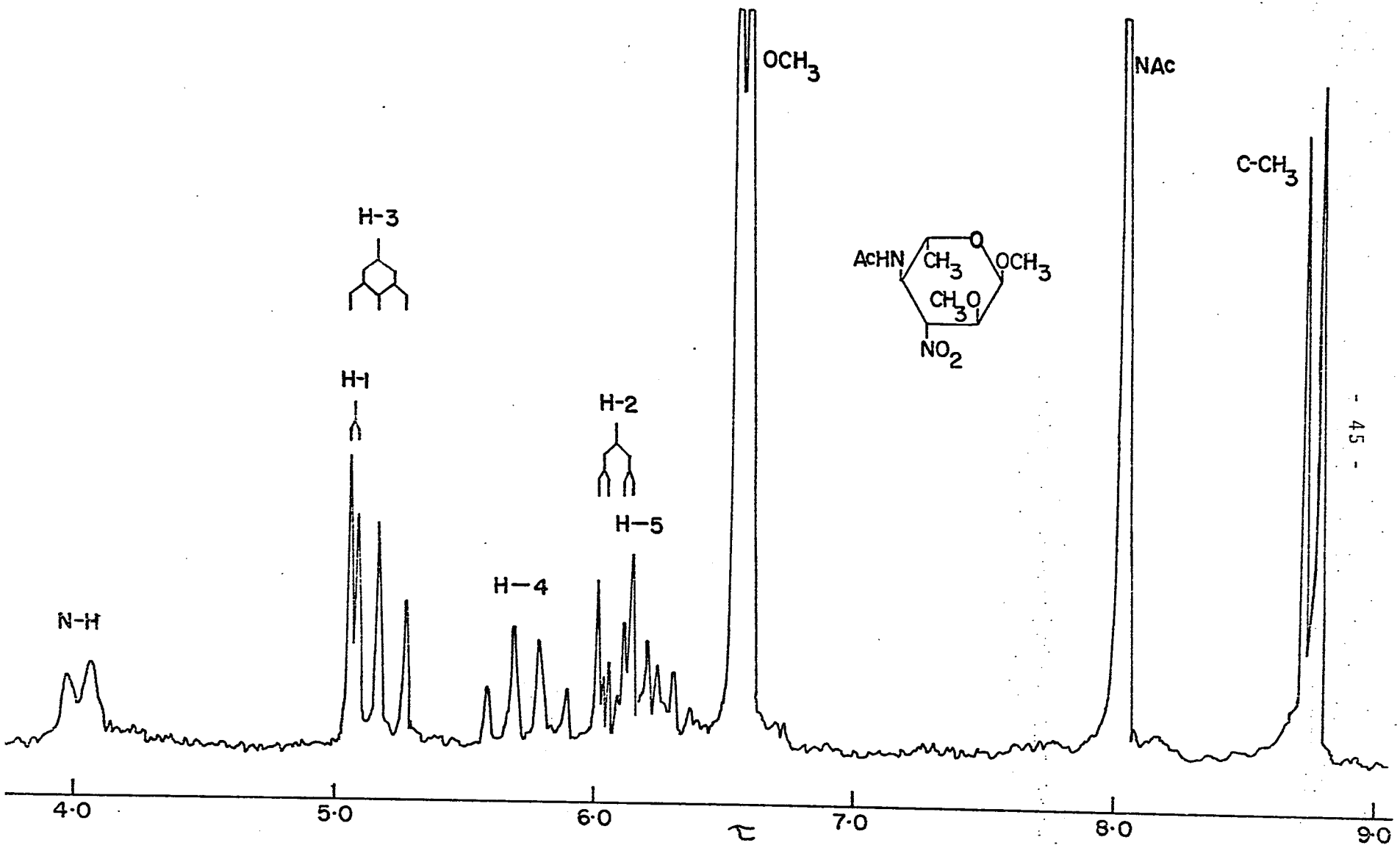


Fig.7 NMR spectrum of compound XYI in deuterated chloroform

signal attributable to H-3 appeared as a symmetrical triplet that was centered at 5.18τ and exhibited large spacing (10Hz), which proved axial-axial coupling with both H-2 and H-4. This was consistent with the nature of the H-4 signal occurring at 5.75τ. The latter was a well resolved quartet produced by diaxial coupling of H-4 with H-3 and H-5 and further coupling with the NH proton, with the same magnitude of 10Hz.

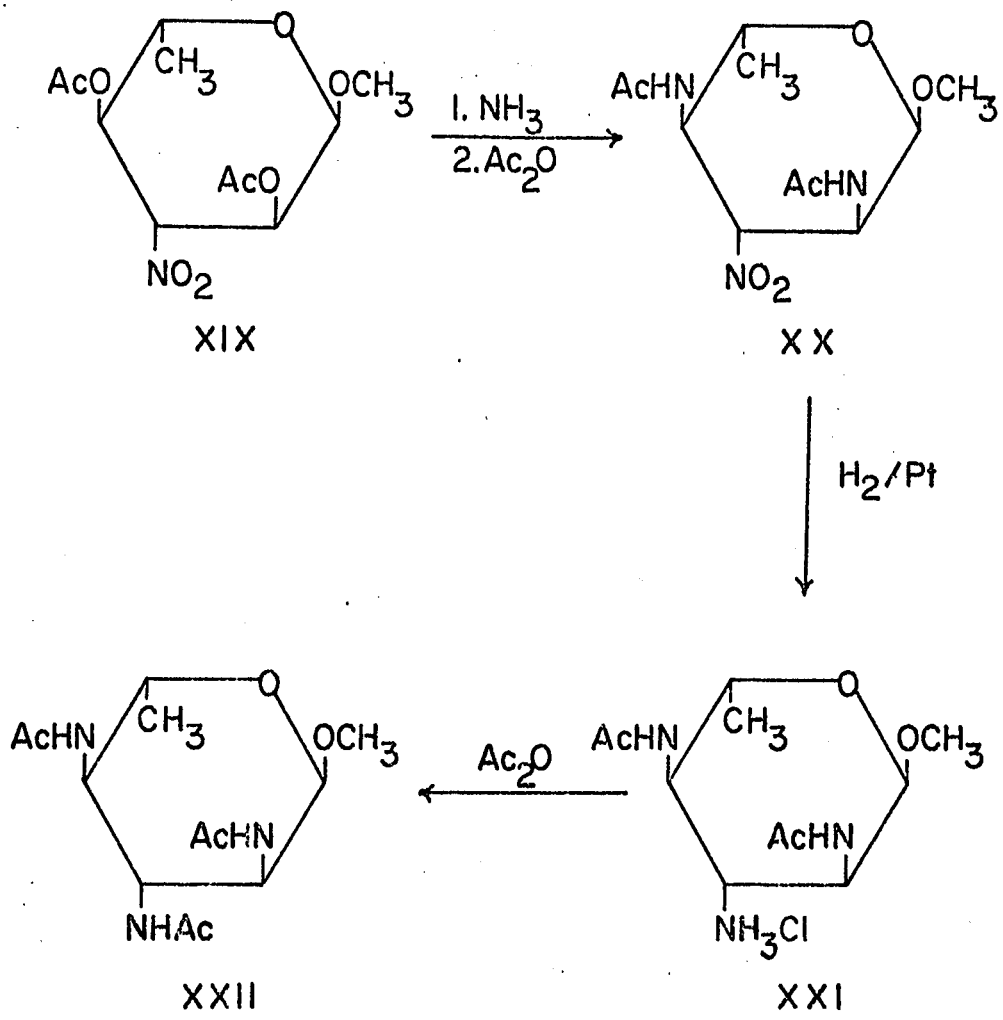
Finally, the equatorial orientation of substituents at C-3 and C-4 was substantiated by the spectrum of the acetylated reduction product XVIII which showed a sharp singlet integrating for six protons at 8.08τ , that is,in the region of equatorial acetamido group resonance (117,118). The H-4 signal again was a quartet as in compound XVI, in the expected position at 5.79τ , with a spacing of 10Hz.

C. Synthesis of Triamino Sugars

Whereas several diamino sugars have been encountered in Nature (see Introduction p.8), triamino sugars have not yet been discovered to occur naturally, and only a few synthetic examples were reported (95b, 121-124). Chemical knowledge in this class of compounds is relatively scarce, and further synthetic studies appeared worthwhile.

In continuation of the work described in Section B, in which an acetoxy group vicinal to a nitro group was replaced stereospecifically by an amino function, it was interesting to investigate the behaviour of the diacetyl compound XIX toward ammonia. The principle of elimination-addition should also apply to this diacetate as it did in the case of the monoacetate VI. In a model reaction, Baer and Wang (99) have synthesized trans,trans-1,3-diacetamido-2-nitrocyclohexane from trans,trans-2-nitro-1,3-cyclohexanediol diacetate. The product was subsequently reduced to the corresponding triamino derivative.

When an ethereal solution of methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (XIX), obtained by acetylation of I (see Part II, p.59), was treated with dry ammonia gas at a temperature of -70° (Scheme III) and the product was subsequently acetylated



Scheme III Triamino Sugars from Nitro Sugars

with acetic anhydride, a white solid was obtained in 60% yield. The compound, which decomposed at 331° and was moderately soluble in methanol, proved to be methyl 2,4-diacetamido-2,3,4,6-tetradeoxy-3-nitro-α-L-gluco-pyranoside (XX)*. The mother liquor contained at least two other distinguishable components as revealed by a thin-layer chromatogram. No attempt was made to isolate these by-products.

Compound XX was suspended in water and hydrogenation was performed in an acid medium, in the presence of Adams catalyst at ordinary temperature and pressure. The reduction, monitored by thin-layer chromatography, was complete after three days and white solid XXI, methyl 3-amino-2,4-diacetamido-2,3,4,6-tetradeoxy-α-L-glucopyranoside hydrochloride, was obtained in 97.5% yield. N-Acetylation of the product gave in high yield methyl 2,3,4-triacetamido-2,3,4,6-tetradeoxy-α-L-glucopyranoside (XXII). This derivative displayed a remarkable thermal stability in that it did not melt or decompose below 360°. It was

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* During the course of this work F.W. Lichtenthaler and W. Fischer (125) reported in a preliminary communication to have carried out the same reaction with liquid ammonia. In addition to XX they claimed to have isolated the α-L-manno epimer. For compound XX they recorded the somewhat lower decomposition point of 309°. No NMR data were given.

sparingly soluble in methanol and insoluble in water and other common solvents. Its infrared spectrum (Fig.8) showed strong absorptions at 1650 and 1550 cm^{-1} in agreement with the assigned structure.

All attempts to hydrolyze, with acid, the glycosidic bond in XXII were unsuccessful and resulted in extensive charring. It is well known that certain amino glycosides are difficult to hydrolyze (106b, pp.92-94), although methyl 2-acetamido-3-amino-2,3-dideoxy-α-D-glucopyranoside hydrochloride was hydrolyzed (95b) to give the reducing diamino sugar dihydrochloride in low yield.

Proof of Configuration

Since the formation of XXII from XIX must be assumed to take place via two successive elimination-addition processes, the original configuration of the starting compound was not necessarily maintained in the product. Three asymmetric centers were involved in the process and therefore, eight stereoisomers could theoretically have arisen; consequently, proof of configuration was necessary.

The triacetamido derivative XXI was unsuitable for NMR analysis because of its solubility characteristics. However, sufficient information was obtained from the

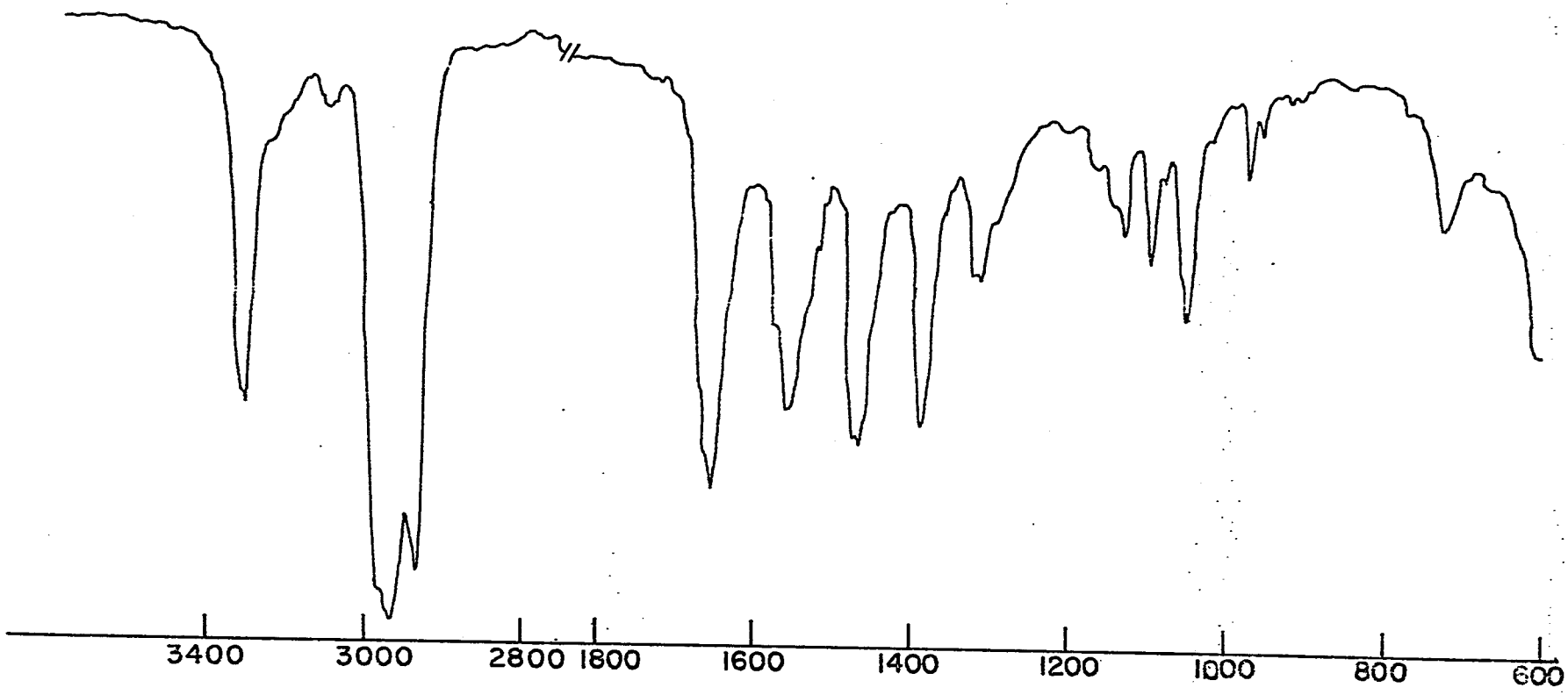

Fig.8 Infrared spectrum of compound XXII in Nujol mull

NMR spectrum of the diacetamidonitro derivative XX in deuterated dimethyl sulfoxide (Fig.9). A six-proton singlet at 8.22τ was attributable to two equatorial acetamido groups at C-2 and C-4, the τ-value falling within the range of 8.21-8.27τ cited by Lichtenthaler and coworkers (117c) for a large number of acetamido sugars in that solvent. For axial acetamido groups the chemical shifts fall in the region of 7.95-8.10τ in the same solvent. Although most of the ring protons were difficult to analyze, a well-resolved triplet in the expected region at 5.13τ was assigned to H-3, the nitromethylene proton. Its splitting ($J_{2,3}=J_{3,4}$=11Hz) required axial arrangement of H-2, H-3 and H-4, consistent with the orientation of the acetamido groups deduced from chemical shift. Finally, the anomeric proton gave a doublet at 5.36τ with $J_{1,2}$= 3-3.5Hz in line with the known stereochemistry at this center. These data confirmed the L-gluco configuration for XX. The derivatives XXI and XXII must have the same configuration since they arose from XX in reactions known to leave configurations unaltered.

Concerning the stereochemistry of the action of ammonia upon the diacetate XIX it is to be concluded, once again, that considerable stereoselectivity prevails, even though the L-gluco product was isolated only to

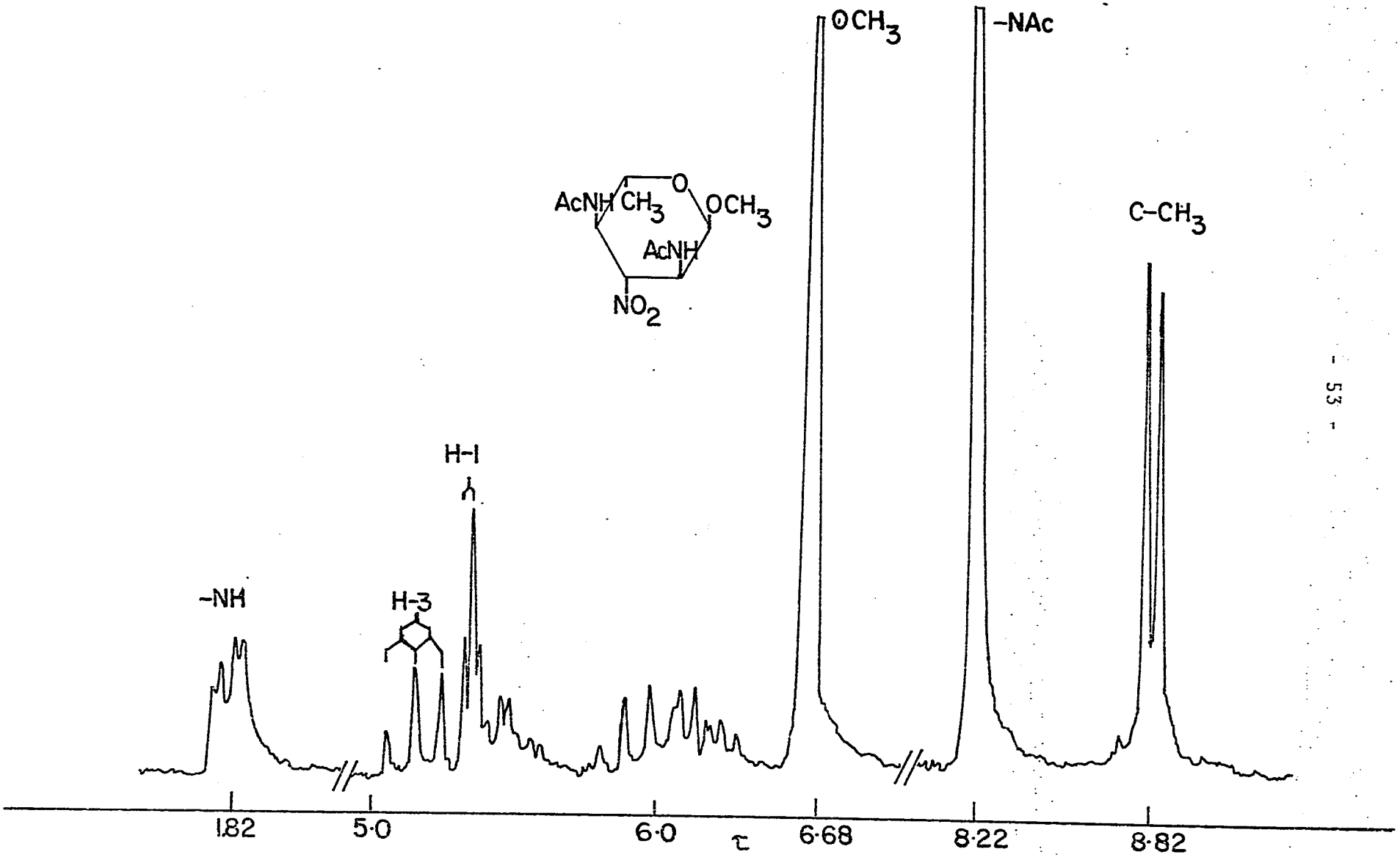

Fig. 9 NMR spectrum of compound XX in deuterated dimethyl sulfoxide

the extent of 60% and there was chromatographic evidence for the formation of by-products which most likely were epimers. Hence the degree of selectivity appeared to be somewhat less than in the reaction of VI under comparable conditions. Assuming thermodynamic control one might perhaps explain this difference by a slower over-all reaction in the case of XIX so that, under the given conditions, equilibrium had not yet been reached. In this connection, reference is made to the configurational equilibration of the non-amino parent compound of XX and its stereoisomers, namely, the methyl 3,6-dideoxy-3-nitro-α-L-hexopyranosides recently examined by Kovář et al. (126). In that analogous series it was found that the α-L-gluco configuration predominates in equilibrium when epimerization is allowed to take place in the presence of a catalytic amount of base; but in the presence of a stoichiometric amount of alkali, the result is determined by the relative stabilities of the nitronates rather than those of the free nitro sugars, and the nitronate of the α-L-talo glycoside is the most stable one. The authors cited have discussed this in detail and have explained the situation in terms of conformational analysis. As far as the diaminonitro compounds generated in an ammoniacal medium are concerned one will have to conclude that the relative thermodynamic stabilities of the free nitro compounds rather than those of their nitronate salts determine the stereochemistry of the reaction.

TABLE IV

CHEMICAL SHIFT (τ) DATA FOR EQUATORIAL ACETAMIDO GROUP SIGNALS OF NEW GLYCOSIDES DESCRIBED IN PART I

Compound	Solvent	2-NHAc	3-NHAc	4-NHAc
V	$CDCl_3$		8.01	
XII	$CDCl_3$		8.04	
XVI	$CDCl_3$		8.05	
XVIII	$CDCl_3$ (+3 drops methanol)		8.08	8.08
XX	DMSO-d_6	8.22		8.22

PART II

Acetylation and Dehydroacetylation of Methyl 3,6-Dideoxy-3-nitro-α-L-glycosides: Synthesis of Nitroolefins and L-Desosamine

RESULTS and DISCUSSION *

The most common method for preparing α-nitroolefinic sugars makes use of the Schmidt-Rutz reaction (100), i.e., the elimination of an acetic acid molecule from acetylated β-nitro alcohols. The reaction has been successfully applied to many blocked nitro sugars that contained a single acetoxy group adjacent to the nitro group (87,101). However in instances where the nitro group was flanked by two acetoxy groups, the reaction took a more complicated course (102), as has been outlined in the Introduction. Since an essential part of the task set for this thesis was the synthesis and utilization of nitroolefins in the 6-deoxyhexose series, the dehydroacetylation of various mono-and diacetates of that series was to be studied.

Most of the nitro sugar acetates required for this investigation have not yet been described in the literature. It was decided to try their preparation, whenever feasible, by the convenient method of acetylation using acetic anhydride and boron trifluoride (89), which

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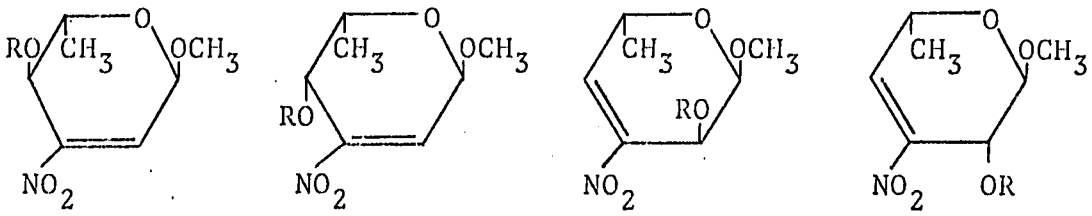
* For convenience, compounds in this chapter are numbered using a new set of Roman numerals.

has proved superior to other methods in this field. An alternative method to be considered, which has likewise been useful in acetylations of nitro sugars, comprises the use of equimolar amounts of acetyl chloride and triethylamine, although in one recent instance this reagent has unexpectedly led to a nitronic acid-acetic acid mixed anhydride (88).

As mentioned earlier in the Introduction, the nitromethane cyclization of L'-methoxy-L-methyldiglycol-aldehyde prepared from methyl α-L-rhamnopyranoside (127) leads to the four methyl 3,6-dideoxy-3-nitro-hexo-pyranosides with the α-L-gluco, α-L-manno, α-L-galacto, and α-L-talo configurations, all of which have been isolated in crystalline form (84). Four nitroolefins could possibly be synthesized from these saturated nitro glycosides via appropriate acetates. They would possess the Δ^2 -α-L-erythro (A), Δ^2 -α-L-threo (B), Δ^3 -α-L-erythro (C) and Δ^3 -α-L-threo (D) configurations.



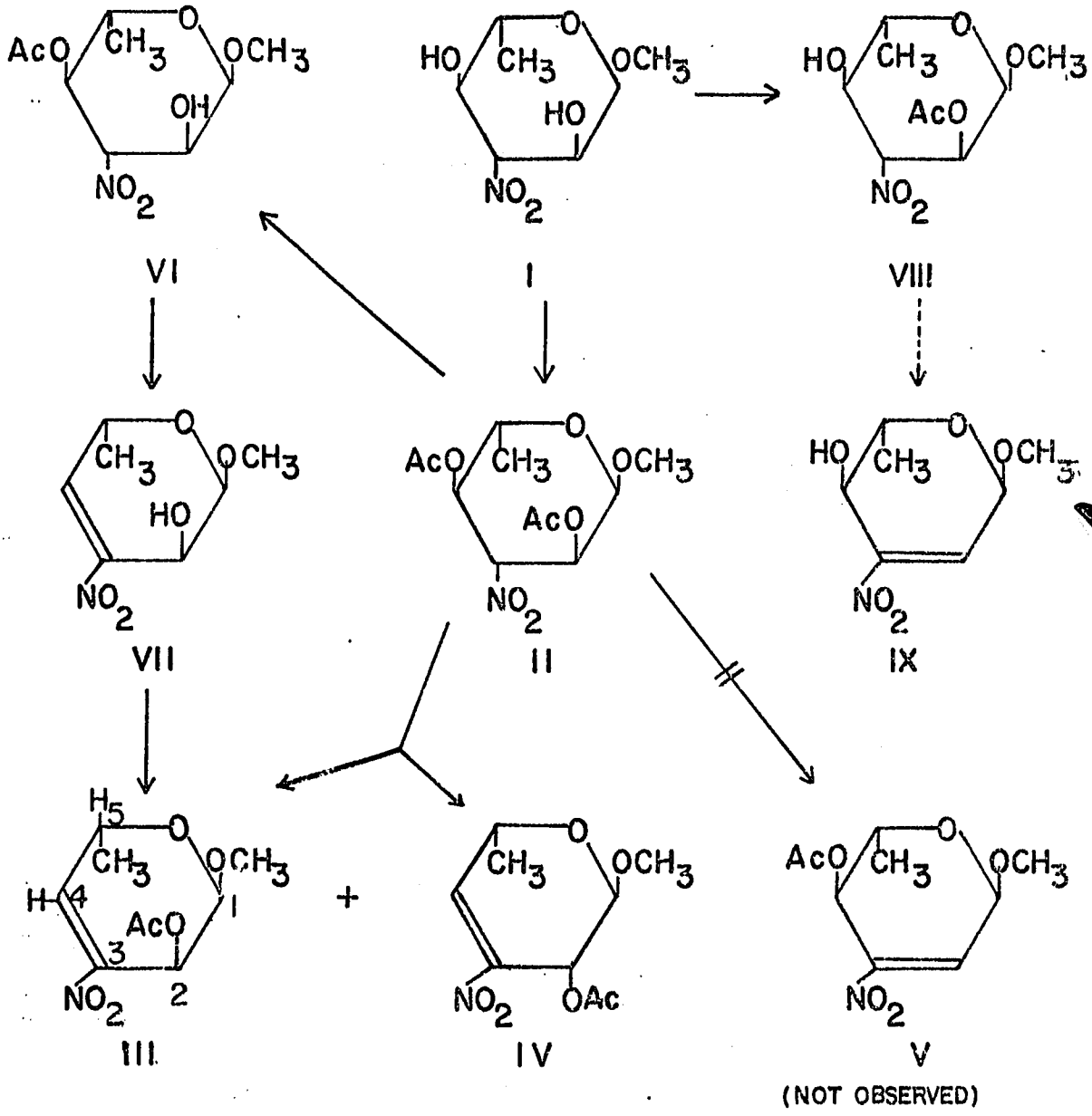
A B C D

This part of the research was devoted to the synthesis of these nitroolefins and to their potential usefulness as preparative precursors for amino and poly-deoxy sugars.

A. Synthesis of Nitroolefins from Methyl 3,6-dideoxy-3-nitro-α-L-hexopyranosides

1. From methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (I)

When methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (I) was acetylated with acetic anhydride and boron trifluoride at 0° (Scheme IV), the diacetate II, methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside was obtained in high yield (95%). This particular compound contains a nitro group flanked on both sides by acetoxy functions. The base-catalyzed dehydroacetylation (Schmidt-Rutz reaction) of II may, therefore, be expected to lead to the formation of either the 2,3- or 3,4-unsaturated derivative or to a mixture of both. A further possibility to be considered would be elimination of two molecules of acetic acid, giving rise to highly reactive dienes that would presumably undergo spontaneous self-addition by Diels-Alder reaction. As was mentioned in the Introduction, such Diels-Alder adducts were the only products isolated


AcO
CH3
OCH3
OH
NO2
VI
HO
HO
VIII
AcO
VII
HO
II
IX
H5
H
4
3
2
1
III
+
OAc
IV
V
(NOT OBSERVED)

Scheme IV

in the analogous dehydroacetylation of methyl 2,4,6-tri-O-acetyl-3-deoxy-3-nitro-β-D-hexopyranosides, no monoolefins having been observed in that case (102). However, in the present case, when methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (II) was heated under reflux with sodium bicarbonate and Drierite in dry benzene, two crystalline monoolefins were obtained. They proved to be methyl 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-L-erythro-hex-3-enopyranoside (III, m.p. 98-99°) and methyl 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (IV, m.p. 81-81.5°), and were isolated in yields of 4 and 21%, respectively.

Both new compounds gave data of elemental analysis corresponding to the formula $C_9H_{13}O_6N$. The olefinic character was indicated by their spectral data. They showed strong UV absorption at λ_{max} 247 nm and a nitroalkene band in the infrared region of 1520 cm^{-1} (see Table V). The NMR spectra of III and IV are shown in Fig.10 and Fig.11. The chemical shifts and coupling constants are compiled in Table VIA and VIB.

Compound III showed a low-field, one-proton quartet at 2.73τ attributable to the olefinic proton H-4, and H-2 gave a multiplet at 4.08τ . Since each of these protons is vicinally related to only one proton,

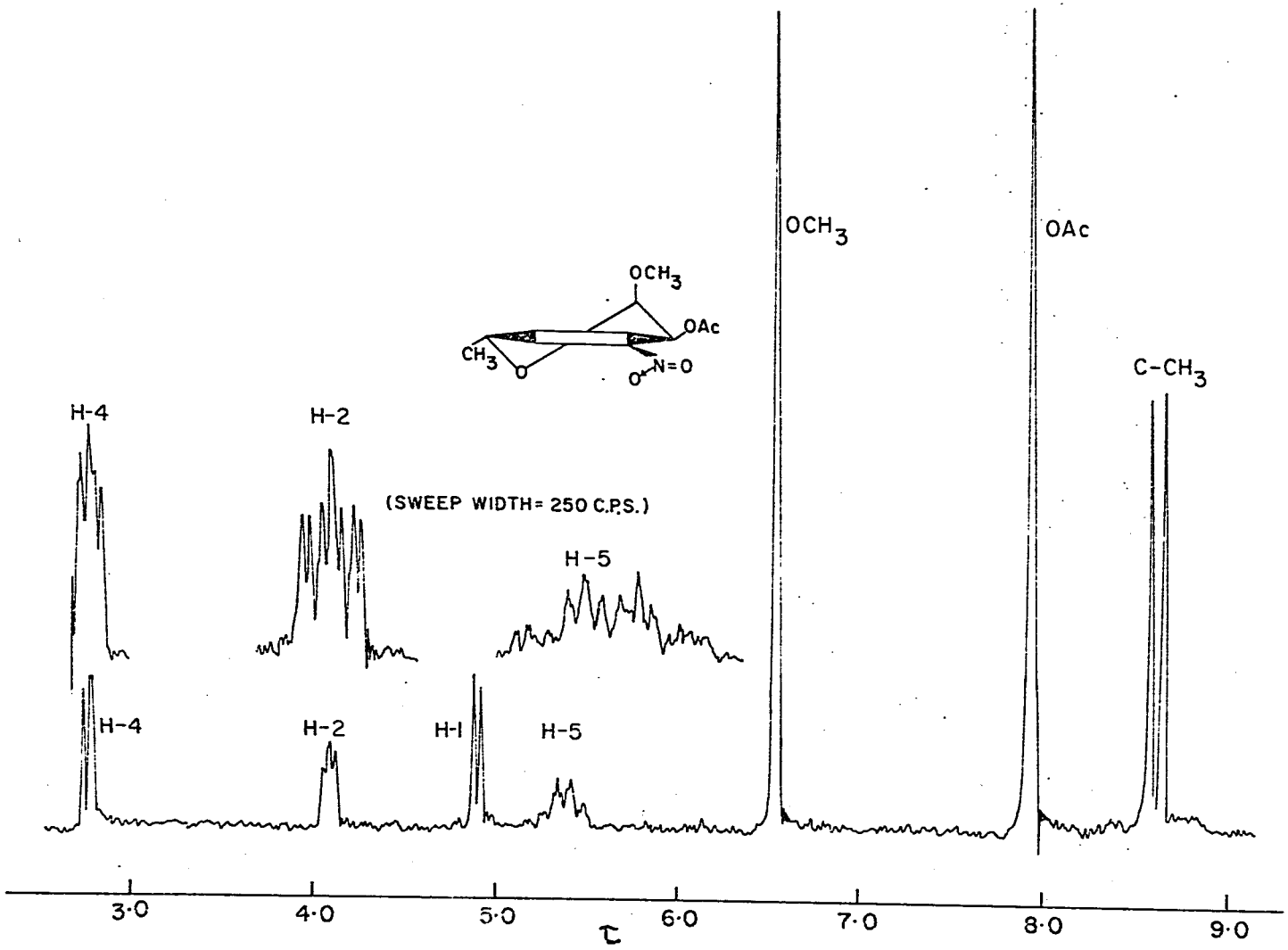


Fig.10 NMR SPECTRUM OF COMPOUND III (IN $CDCl_3$)

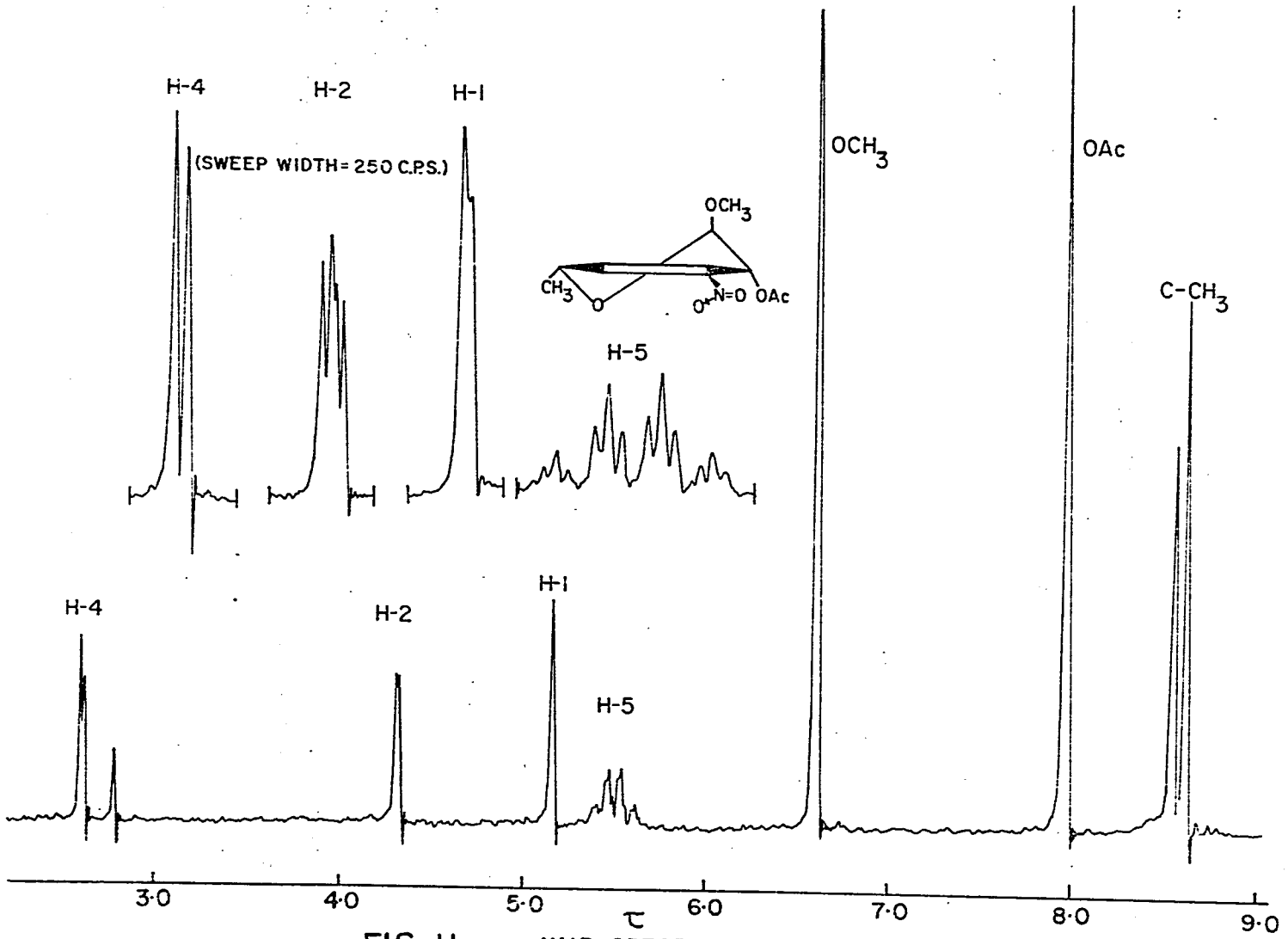


FIG. 11 NMR SPECTRUM OF COMPOUND IV (IN $CDCl_3$)

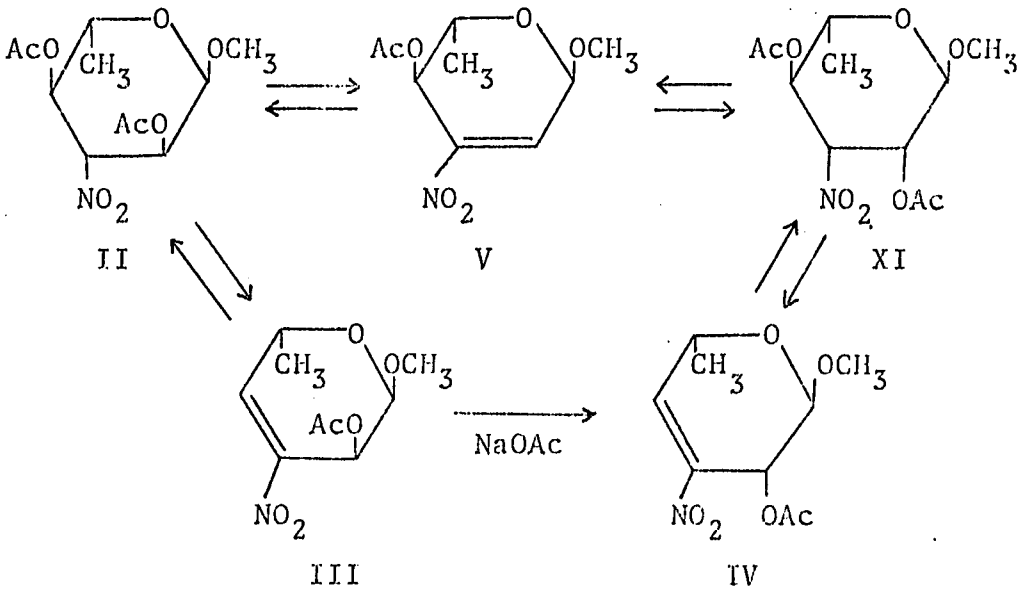
the signals might have been expected to be doublets, and the observed multiplicities appear to be caused by long-range coupling. A doublet at 4.89τ was assigned to the anomeric proton H-1. The multiplet that centered at 5.36τ was due to H-5. Two sharp three-proton singlets at 6.54 and 7.91τ were the signals of the methoxy and acetoxy groups, respectively. The remaining doublet, of three-proton intensity, was due to the $\underline{C}$-CH_3 group. Compound IV showed a similar spectrum with a doublet at 2.56τ (H-4), a quartet at 4.28τ (H-2), a narrowly split signal at 5.12τ (H-1) and a multiplet for H-5 at 5.46τ . The substituent resonances of $\underline{O}$-CH_3, $OCOCH_3$, and $\underline{C}$-CH_3 occurred at 6.57, 7.93, and 8.55τ , respectively. The Δ^3 position of the double bond could be inferred for both III and IV from the chemical shifts of the H-5 signals. These signals were shifted downfield to about 5.4τ from the 5.9-6.3τ region where they occur in saturated nitroacetates (Table VIIA). The shift is attributed to the effect of a nitroalkene grouping in allylic position. The downfield shift is less pronounced in Δ^2 -nitroolefinic structures, the H-5 signals falling in the range of 5.7-6.0τ (Table VIA). The structures of III and IV were confirmed by independent synthesis as will be described later in this section.

Six-membered cyclic olefins are generally assumed to occupy half-chair conformations. The half-chairs depicted for III and IV in Figures 10 and 11 are in accord with the coupling constants observed for H-1, H-2, H-4 and H-5. Both half-chairs project a dihedral angle between H-4 and H-5 close to 90°; therefore small coupling constants are expected. The observed values for $J_{4,5}$ were about 2Hz. Furthermore, the dihedral angles between H-1 and H-2 show approximately 35° and 90° for III and IV, respectively, in harmony with the measured coupling constants 4 and 1Hz. The C-5 proton in both compounds showed a twelve-peak signal. Since H-5 is vicinally related only to H-4 and the $\underline{C}\text{-}CH_3$ protons, an octet would be expected; hence the additional splittings imply long-range coupling. Spin decoupling by double irradiation of the H-2 multiplet of III at 4.08τ collapsed the H-5 signal to an octet ($J_{4,5}$=1.5-2Hz, $J_{5,6}$=7Hz) and changed the H-4 quartet to a doublet, while the H-1 doublet became a singlet. This experiment revealed that coupling across four bonds ($J_{2,4}$= 1Hz) as well as five bonds ($J_{2,5}$= 2.5Hz) exists. There was no allylic coupling (four bonds) between H-2 and H-4 in the spectrum of IV. The H-4 signal showed a doublet with a coupling constant $J_{4,5}$= 2Hz, while the H-2 proton showed a quartet with

$J_{1,2}$= 1Hz and $J_{2,5}$= 2Hz. The absence of observable long-range coupling in the latter compound is in agreement with the prediction that, in the half-chair depicted, the allylic coupling constant between H-4 and a quasi-equatorial proton H-2 will be very small. The dihedral angle between these two protons is estimated to be 40° which corresponds to a coupling constant of 0.3Hz (128).

The observed vicinal and the long-range coupling constants thus support strongly the half-chair conformations of III and IV.

The formation of the 2-epimeric, Δ^3-unsaturated compound IV was rather unexpected. A possible explanation is contained in the following reaction scheme:

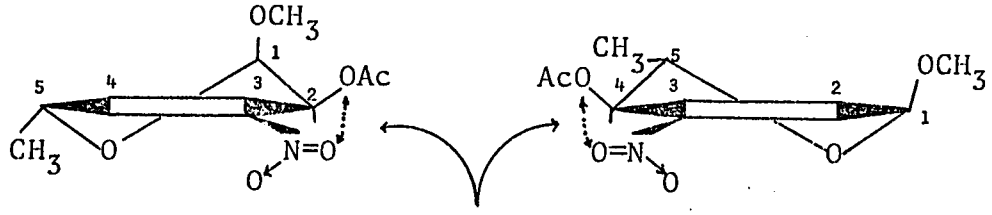


It would appear reasonable to expect that part of the diacetate II undergoes dehydroacetylation to give V. Although V was not isolated, it may have been formed in low concentration, and nucleophilic readdition of acetate could either reform the starting material II or give the epimeric diacetate XI, methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-L-mannopyranoside. Dehydroacetylation involving the 4-acetoxy group in the latter compound would lead to the nitroolefin IV. When the manno diacetate XI was synthesized by an independent route (see p.76), it was in fact found to be quite unstable, losing its 4-acetoxy group under the mild conditions of chromatography on silica gel to furnish IV as an almost exclusive product.

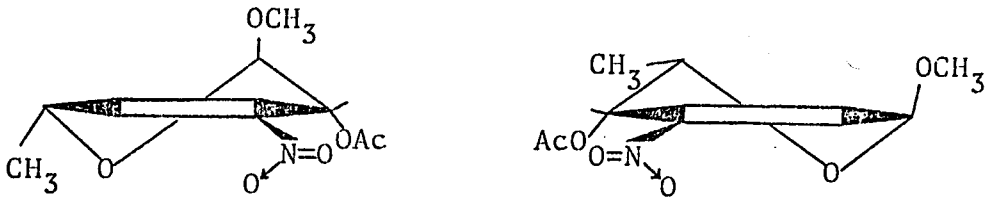
The possibility of IV arising by a displacement reaction from III should also be considered. Although an allylic acetate group is not as good a leaving group as, for example, an allylic halogen (129), acetoxy exchange with configurational inversion at C-2, by attack of acetate anion formed in situ, might occur if the product is more favored sterically. However, a possible conversion of III into IV and its pathway have not been investigated by experiment.

Regardless of the mechanism of formation, it

remains an interesting fact that compound IV arises in the Schmidt-Rutz reaction of II, and that it, instead of III or V, is the major product. It is suggested that III and V are thermodynamically less stable than IV because of the presence, in the two former structures, of $A^{(1,2)}$ interaction between the nitro and adjacent acetoxy substituents. The $A^{(1,2)}$ effect is the non-bonded interaction between a group situated at an endocyclic double bond in a six-membered ring and an adjacent, quasi-equatorial group (130). This interaction is relieved if the adjacent group becomes quasi-axial:



III $A^{(1,2)}$-effect V

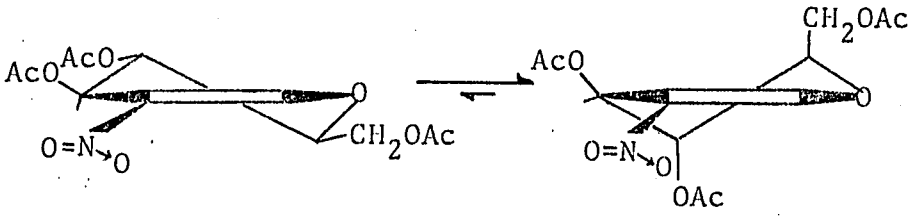


IV free from XVII

$A^{(1,2)}$ interaction

Depicted here is also the 4-epimer of V, namely compound XVII which is to be described in a subsequent section. According to the concept just outlined, this compound is also free from $A^{(1,2)}$ interaction and should, therefore, be relatively stable, as it was indeed found to be. However, it has not been encountered among the products arising from II. Therefore, there is no evidence for C-4 epimerization in the reaction presently under discussion.

The $A^{(1,2)}$ effect has been invoked by Lemieux and coworkers (131) to explain the conformational behavior of 3,4,6-tri-O-acetyl-2-nitro-D-glucal in which non-bonded interaction between the nitro group and the 3-acetoxy group causes predominance of the inverted half-chair as shown:



It should be noted that our compounds, unlike Lemieux's, possess an anomeric methoxyl group which, being axial, will offer resistance to conformational inversion (anomeric effect).

Since the yield of compound III in the above reaction was poor, an alternative synthesis was elaborated. The diacetate II was partially methanolyzed with N methanolic hydrochloric acid. The solution was concentrated without prior neutralization. After column chromatography on silica gel a crystalline monoacetate, methyl 4-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (VI), was obtained in about 35% yield. The infrared spectrum of VI showed strong absorptions at 3460 cm^{-1} and 1746 cm^{-1} of hydroxyl and ester carbonyl groups, respectively. The position of the acetyl group was deduced from the NMR spectrum (see Experimental) which showed H-4 as a triplet at 4.86τ with a large spacing of 10Hz. The chemical shift of the H-4 signal is as expected for a proton attached to a carbon atom bearing an acetoxy grouping (Table VIIA). If the acetoxy substituent had been at C-2, a quartet for H-2 containing a large and a small splitting would have been in the same region, but no such quartet was present. The H-3 signal of VI appeared as a triplet at 5.26τ , with $J_{2,3} = J_{3,4} = 10Hz$.

If, on the other hand, the methanolyzed material was neutralized with silver carbonate prior to chromatographic separation, a mixture of VI and the new product VII,

methyl 3,4,6-trideoxy-3-nitro-α-L-erythro-hex-3-enopyranoside, was obtained. A similar mixture could also be formed from pure VI, simply by passing it through a silica gel column. Obviously, elimination of an acetic acid molecule tends to take place on the column. The elimination is probably catalyzed by traces of basic substances present in the silica gel. The small amount of hydrochloric acid present in the reaction mixture if chromatographed without prior neutralization seems sufficient to offset this catalytic activity. Pure nitroolefin VII was eventually obtained by methanolyzing the reaction mixture once more, with 3% hydrogen chloride in anhydrous methanol, at a temperature of about 45°, and by renewed chromatography. Spectral evidences (Table V, VIA,B) are in agreement with the nitroolefinic structure. The compound showed a low-field, one-proton signal at 2.99τ in the NMR spectrum and a strong nitroalkene absorption in the infrared region of 1515 cm^{-1}. Strong UV absorption was recorded at λ_{max} 247 nm.

Acetylation of nitroolefin VII with acetic anhydride and boron trifluoride gave the monoacetate III in 90% yield, thus confirming the structure of III previously obtained in the Schmidt-Rutz reaction of II.

An attempt has been made to prepare the unsaturated nitro alcohol IX and its acetate V for the purpose of structural comparison. Since partial methylation of the dihydroxy compound I was shown (in Part I) to occur preferentially at C-2, it was thought that monoacetylation at C-2 might likewise be possible. Acetylation of nitroglycoside I with 1 molar equivalent of acetyl chloride and triethylamine led to the isolation of a colorless syrup in 24% yield. Its infrared spectrum indicated the presence of hydroxyl and ester groupings by showing strong absorptions in the regions of 3600-3350 cm^{-1} and 1742 cm^{-1}, respectively. The NMR spectrum (Table VIIA,B) showed a one-proton quartet at 4.80τ assigned to H-2, which, on the basis of the chemical shift, must be due to a ring proton on a carbon bearing an acetoxy group. The splittings of the signal, 3.5 and 9Hz, indicated that the proton was oriented axially and coupled vicinally to an equatorial and an axial proton. This proved that it was position 2 that was acetylated. Hence the product was methyl 2-O-acetyl-3,6-dideoxy-3-nitro-α-L-gluco-pyranoside (VIII).

Chromatography of syrupy VIII on a silica gel column only led to formation of a very samll amount of

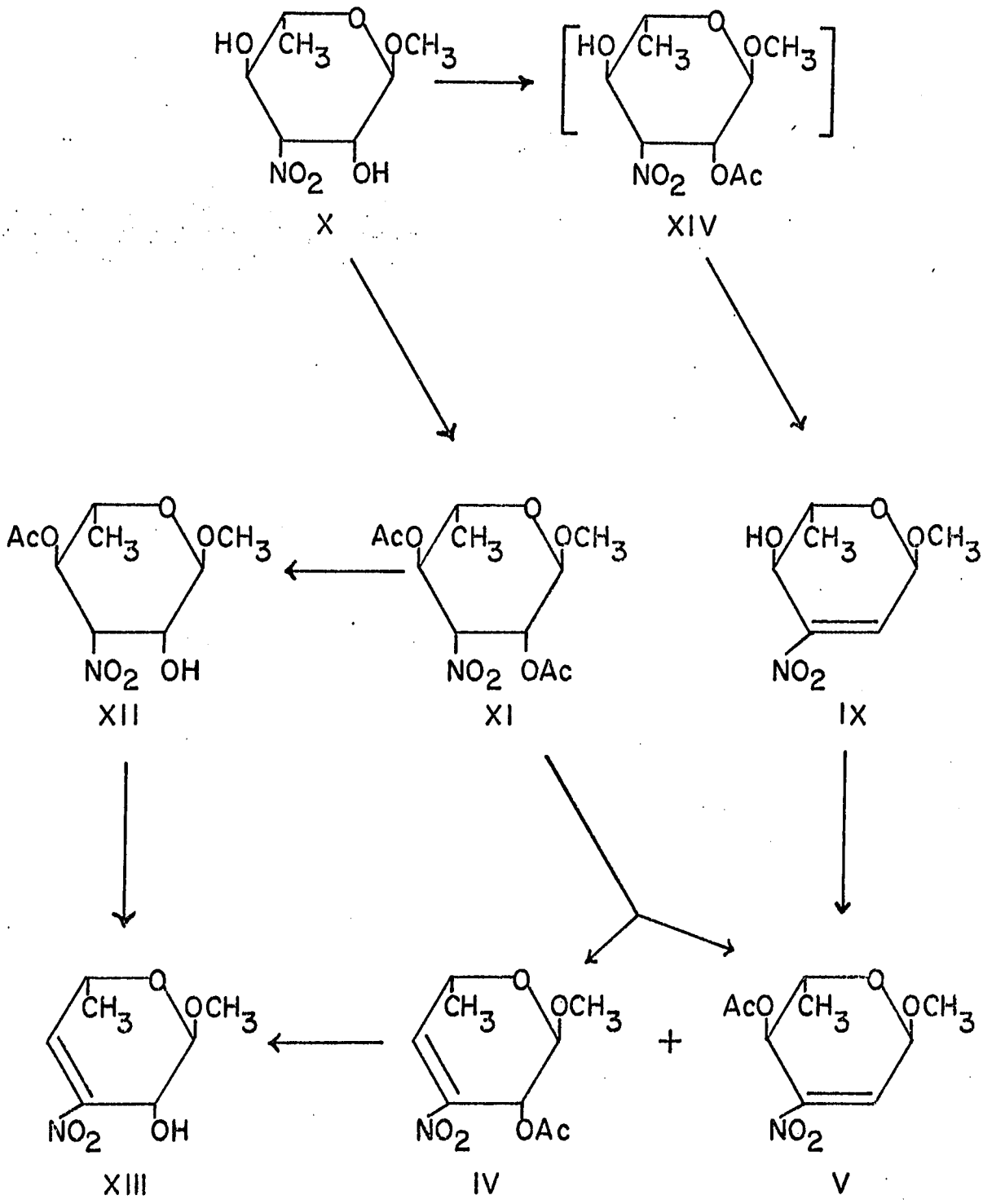
what may have been the dehydroacetylation product IX, as indicated by the NMR spectrum of the resulting mixture. However, the product could not be distinguished from VIII by t.l.c. using a variety of solvent systems, and no attempt was made to isolate it at this stage .

The ease of dehydroacetylation involving the C-4 acetoxy group as compared to that involving the C-2 acetoxy group, was also demonstrated in the following experiment. When diacetate II was slowly passed through a silica gel column, a mixture of nitroolefin III and the starting compound was obtained. No other olefins could be detected.

2. From methyl 3,6-dideoxy-3-nitro-α-L-mannopyranoside (X)

Methyl 3,6-dideoxy-3-nitro-α-L-mannopyranoside (X) was smoothly acetylated with acetic anhydride and boron trifluoride to give in 95% yield the diacetate XI, methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-L-mannopyranoside (Scheme V).

The diacetate XI was methanolyzed with 3% methanolic hydrogen chloride. The reaction mixture was concentrated to a syrup without prior neutralization, and subsequent chromatography on a silica gel column gave the monoacetate XII, methyl 4-O-acetyl-3,6-dideoxy-3-nitro-α-L-mannopyranoside, in 76% yield. The



Scheme V

acetyl substituent was assigned position 4 by the NMR spectrum which showed a triplet with large splitting ($J_{3,4}$= $J_{4,5}$= 10Hz) at 4.41τ . This triplet was due to H-4, indicating two diaxial, vicinal couplings. If position 2 had been acetylated, a quartet or triplet containing two small splittings would have been expected in that region.

When the isolated, crystalline compound XII was put on a silica gel column and eluted slowly with 10% ethyl acetate in benzene, dehydroacetylation occurred and the unsaturated derivative, methyl 3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (XIII) was obtained in 87% yield. This elimination reaction was also observed when the aforementioned, methanolyzed mixture was neutralized with silver carbonate before chromatographic separation.

Compound XIII exhibited strong UV absorption at λ_{max} 251 nm and nitroalkene absorption in the infrared at 1522 cm^{-1}. The NMR spectrum (Table VIA,B) showed a low-field, one-proton signal at 2.74τ for the olefinic proton H-4.

Alternatively, XIII was obtained by methanolysis of the olefin acetate IV that has already been described in the preceding section and that was formed

in the following experiment.

When the diacetate XI was passed through a silica gel column, the NMR spectrum of the resulting crystalline material indicated a mixture of two olefins IV and V, with the former preponderating strongly. Identification of V was achieved by an independent synthesis. This synthesis involved an attempted selective acetylation of the mannoside X in the 2-position. However, upon treatment of X with acetyl chloride and triethylamine (1 mole each) and upon column chromatography of the product, a new unsaturated derivative, methyl 2,3,6-trideoxy-3-nitro-α-L-erythro-hex-2-enopyranoside (IX) was isolated in 54% yield. Again, it showed characteristic absorptions for a nitroolefinic structure in UV and IR spectra. The NMR spectrum is shown in Fig.12. Two quartets (for coupling constants see Table VIB) at 2.97τ and 4.88τ were assigned to the olefinic proton H-2 and the anomeric proton, respectively. The multiplet centered at 5.60τ was due to H-4. The H-5 signal appeared as an octet at 6.00τ and the methoxy group showed a sharp singlet at 6.55τ . The two remaining doublets at 6.95τ and 8.62τ were attributable to the hydroxyl group and the C-CH_3 group, respectively, with the former

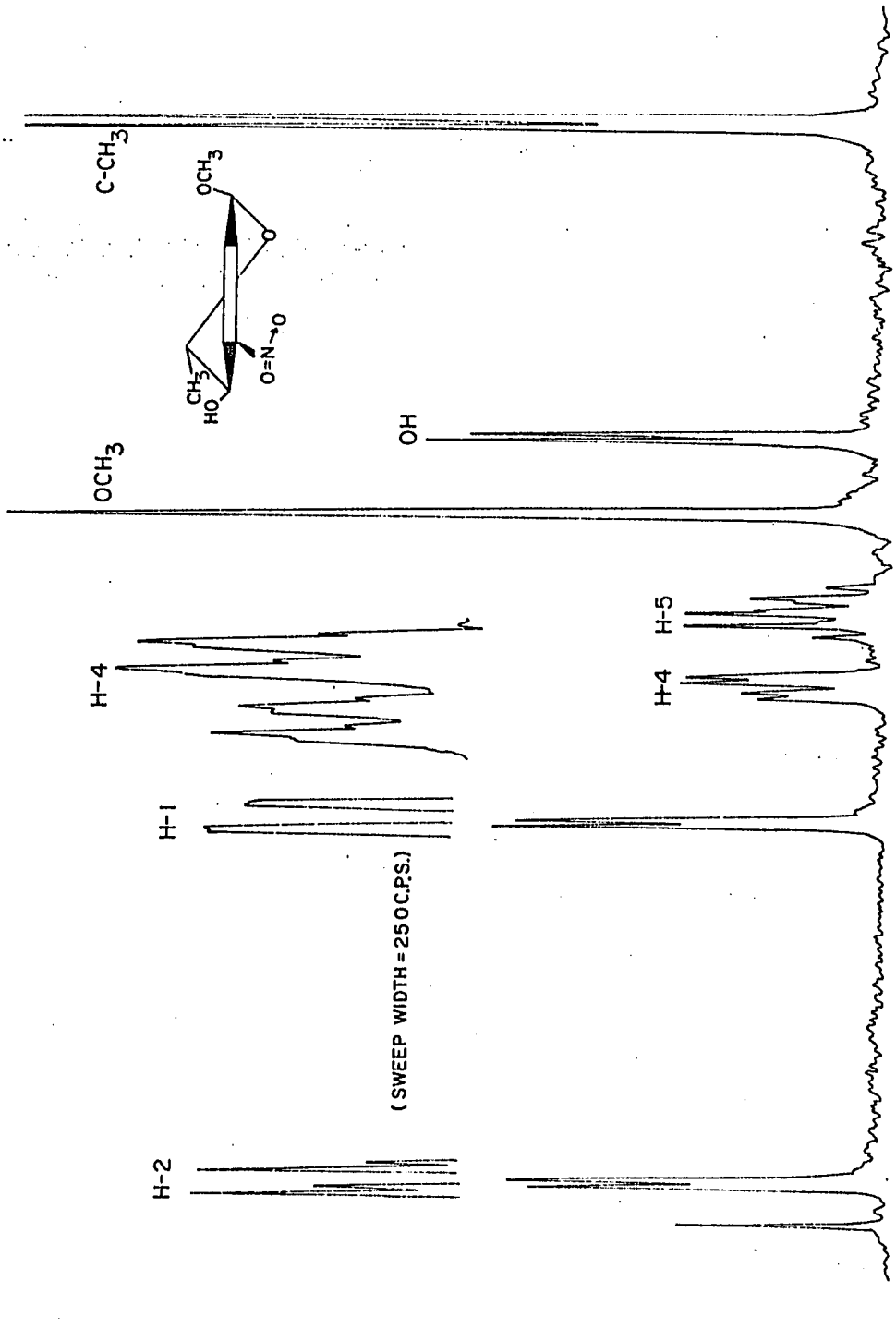


FIG. 12 NMR SPECTRUM OF COMPOUND IX (IN $CDCl_3$)

disappearing upon deuterium exchange. The formation of IX from X may be assumed to have proceeded via the intermediate monoacetate XIV from which a molecule of acetic acid was eliminated by the action of silica gel on the column. It is recalled from the preceding section that the monoacetate VIII, a stereoisomer of XIV, underwent dehydroacetylation to produce IX also although it appeared more stable than XIV.

Boron trifluoride - catalyzed acetylation of IX gave its acetate V, methyl 4-O-acetyl-2,3,6-trideoxy-3-nitro-α-L-erythro-hex-2-enopyranoside, in 68% yield. The NMR spectrum of pure V is shown in Fig.13 and proved by spectral comparison the existence of V in the reaction mixture obtained when the diacetate XI was passed through a silica gel column. Long-range couplings were observed between H-1 and H-4 ($J_{1,4}$ = 1.0Hz) and between H-2 and H-4 ($J_{2,4}$= 1.3Hz). The former coupling, that extends across four single bonds and one double bond, has been termed " homoallylic coupling " by Pinhey and Sternhell (132). Five-bond coupling, it is recalled from the preceding section, was also observed in compounds III and IV, with $J_{2,5}$ = 2Hz which is within the predicted range of 0 - 4Hz (133).

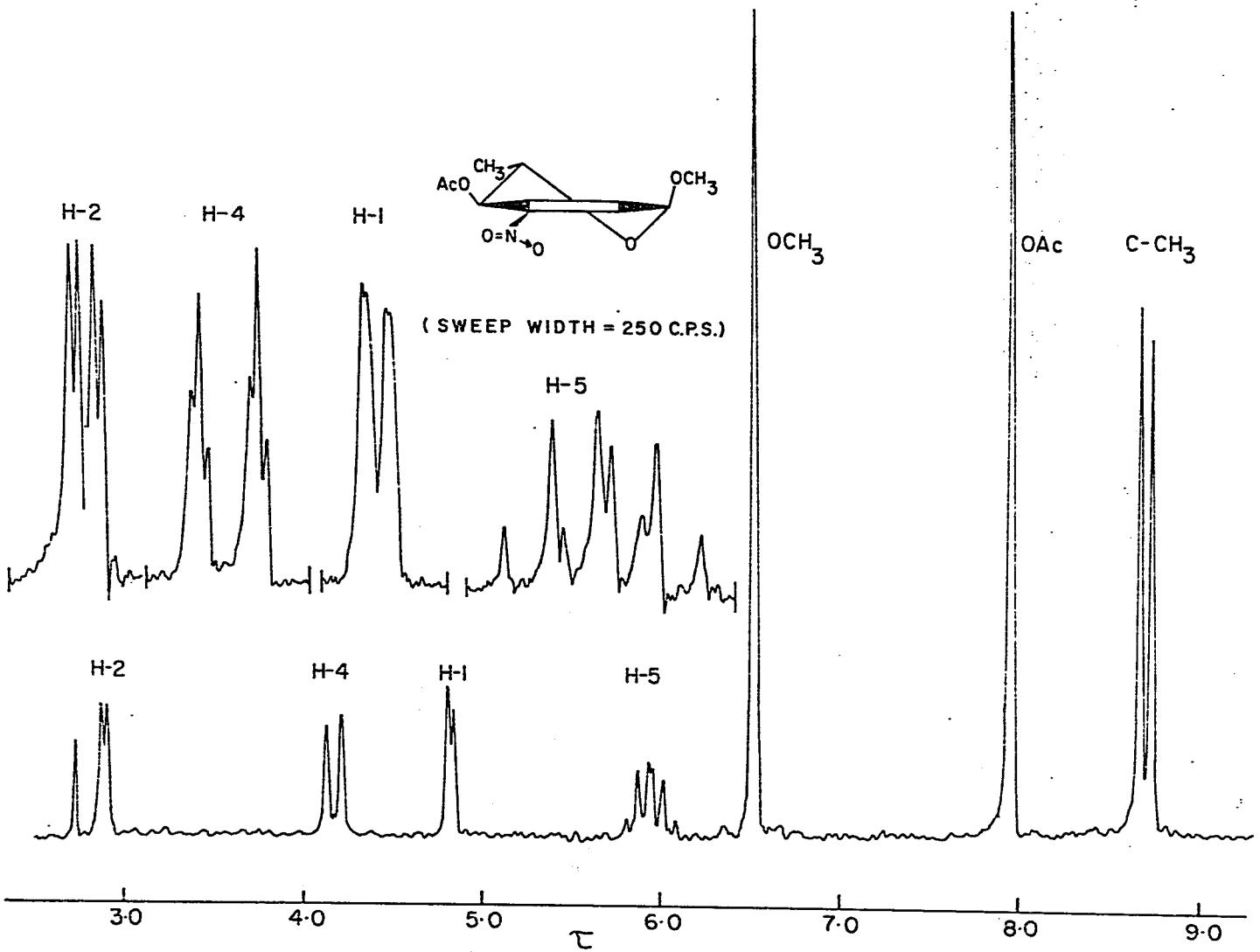


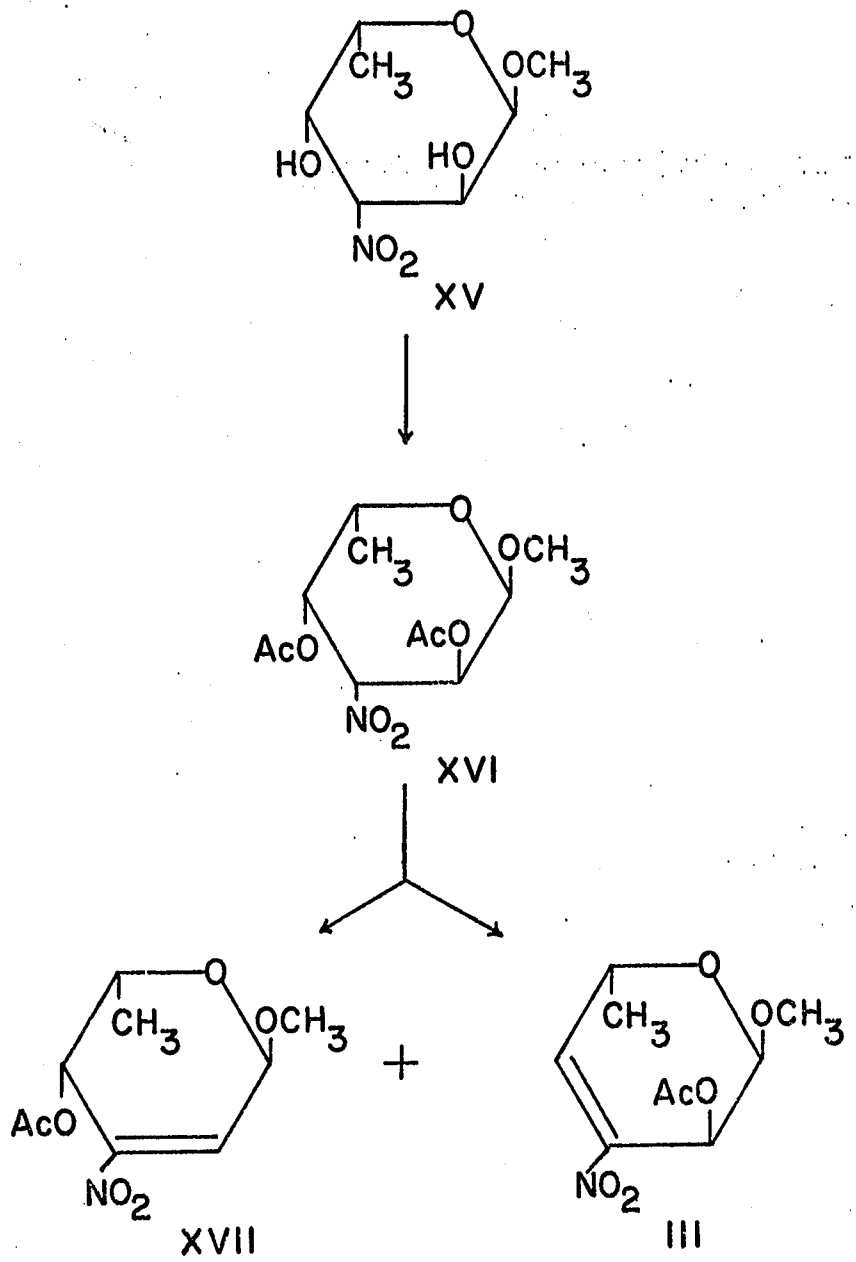
FIG. 13 NMR SPECTRUM OF COMPOUND V (IN $CDCl_3$)

3. From methyl 3,6-dideoxy-3-nitro-α-L-galactopyranoside (XV)

When methyl 3,6-dideoxy-3-nitro-α-L-galactopyranoside (XV) was acetylated with acetic anhydride and boron trifluoride, methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-L-galactopyranoside (XVI) was obtained as a crystalline product in a yield of 92.5% (Scheme VI).

Dehydroacetylation of XVI by the action of silica gel as described previously afforded two separable products. The fast-moving compound was a new nitroolefin, methyl 4-O-acetyl-2,3,6-trideoxy-3-nitro-α-L-threo-hex-2-enopyranoside (XVII), and the slow-moving product proved according to its physical constants and spectral evidences to be the isomer III previously encountered. They were formed in a ratio of 1.3 : 1.

Compound XVII exhibited the typical UV absorption at λ_{max} 247 nm and a nitroalkene band in the infrared at 1530 cm^{-1}. The NMR spectrum of XVII is shown in Fig.14. The chemical shifts and the coupling constants (Table VIA,B) are in agreement with the assigned structure.


CH3
OCH3
HO
HO
NO2
XV
CH3
OCH3
AcO
AcO
NO2
XVI
CH3
OCH3
AcO
NO2
XVII
+
CH3
OCH3
AcO
NO2
III

Scheme VI

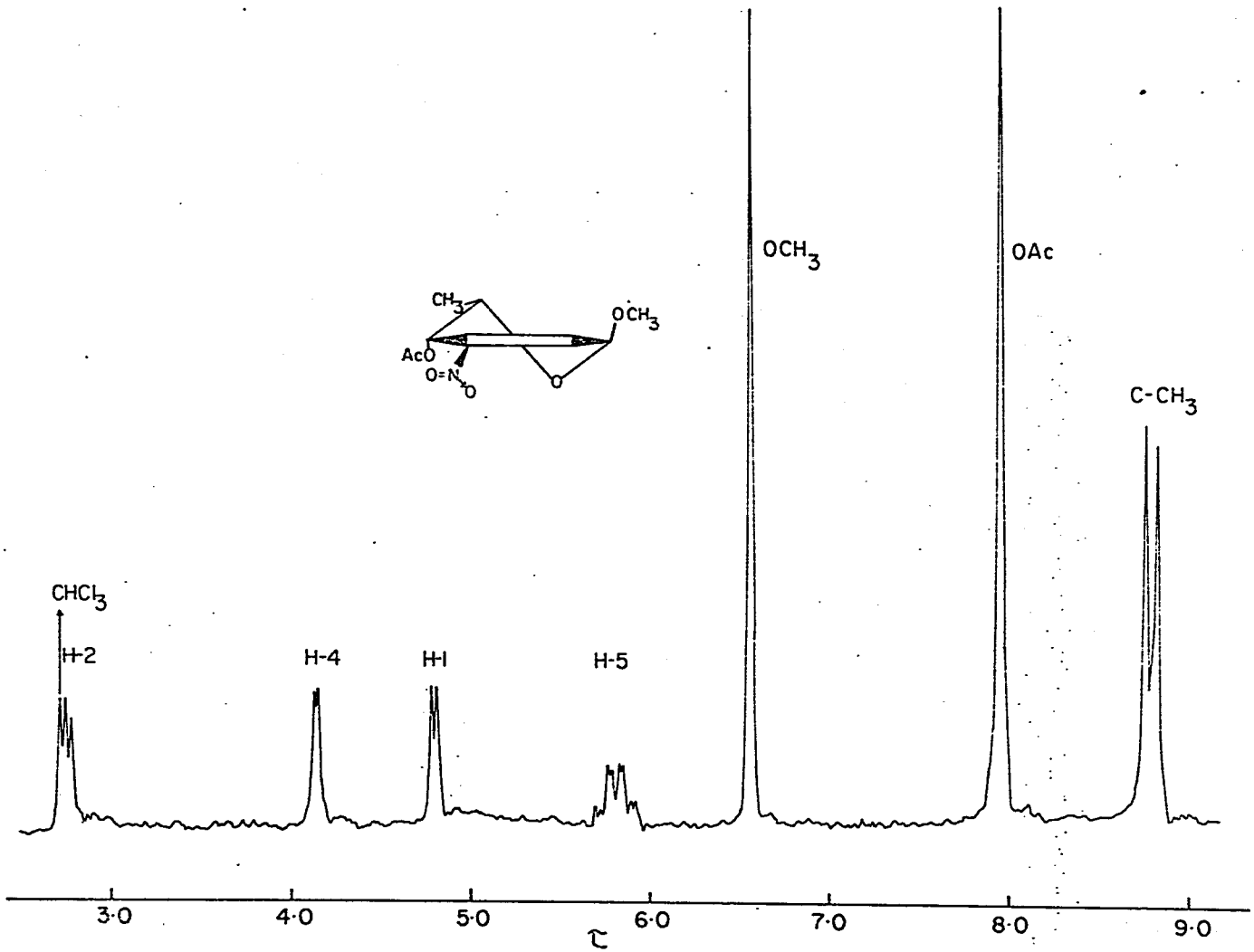
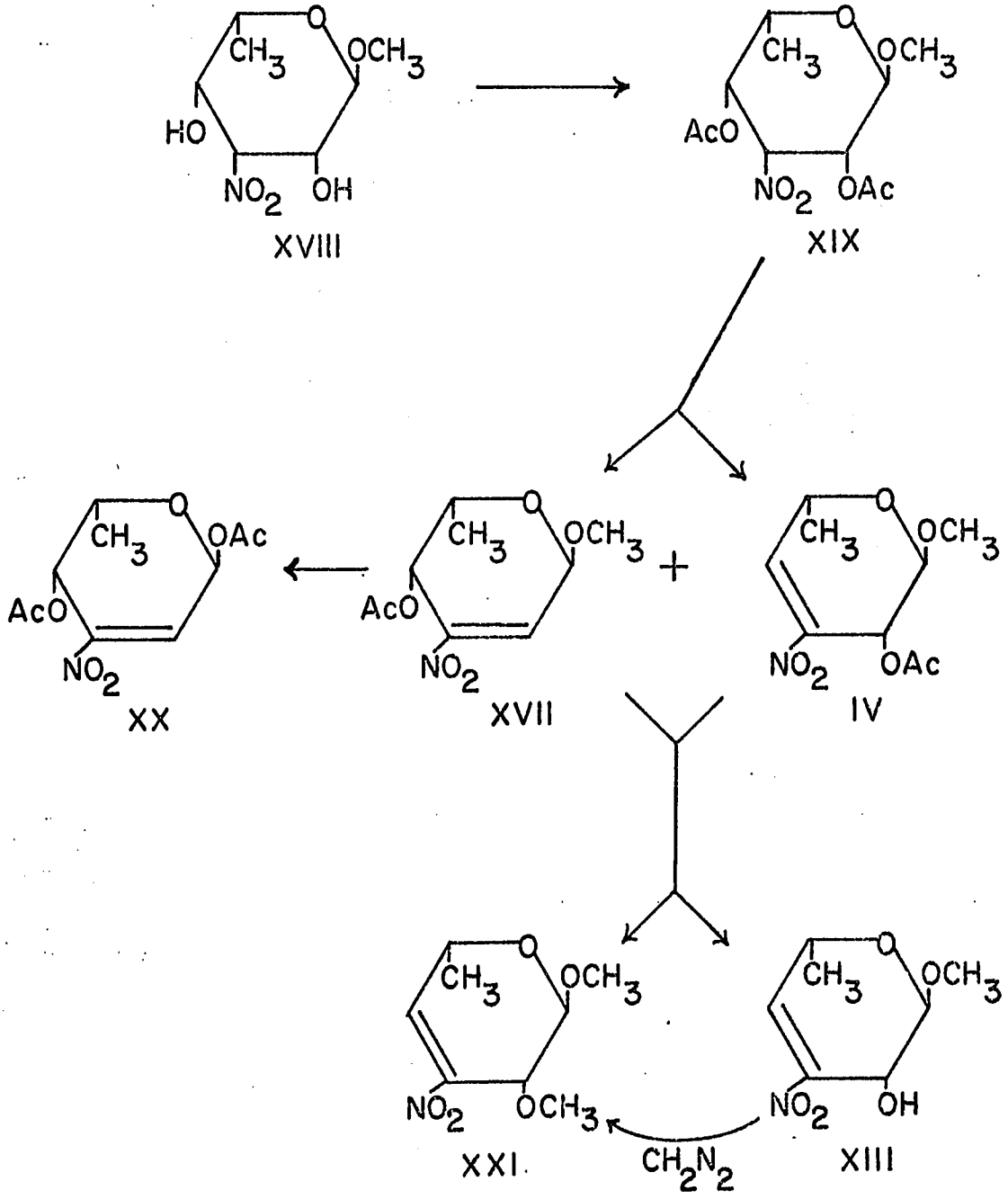


FIG. 14 NMR SPECTRUM OF COMPOUND XVII (IN $CDCl_3$)

4. From methyl 3,6-dideoxy-3-nitro-α-L-talopyranoside (XVIII)

Difficulty was encountered in the boron trifluoride - catalyzed acetylation of methyl 3,6-dideoxy-3-nitro-α-L-talopyranoside (XVIII). The diacetate XIX, methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-L-talopyranoside was obtained once as a crystalline compound. However, in subsequent experiments it failed to crystallize. The compound showed IR and NMR spectra (see Experimental) characteristic of the fully acetylated structure, and it gave a correct elemental analysis. The failure of crystallization was possibly due to contamination by a small amount of nitroolefin which was detected by UV spectroscopy.

When the acetylation reaction was performed with an increased amount of catalyst and longer time, two nitroolefins, IV and XVII, were formed (Scheme VII). According to the NMR spectrum (Fig.15) they arose in approximately equal proportions. It appears that the diacetate XIX, with its two meta-diaxial acetoxy groups, is particularly prone to eliminative loss of an acetic acid molecule. The elimination seems to occur, in this case, not only by base catalysis but also by acid catalysis as depicted (Z = H^+ or BF_3):



Scheme VII

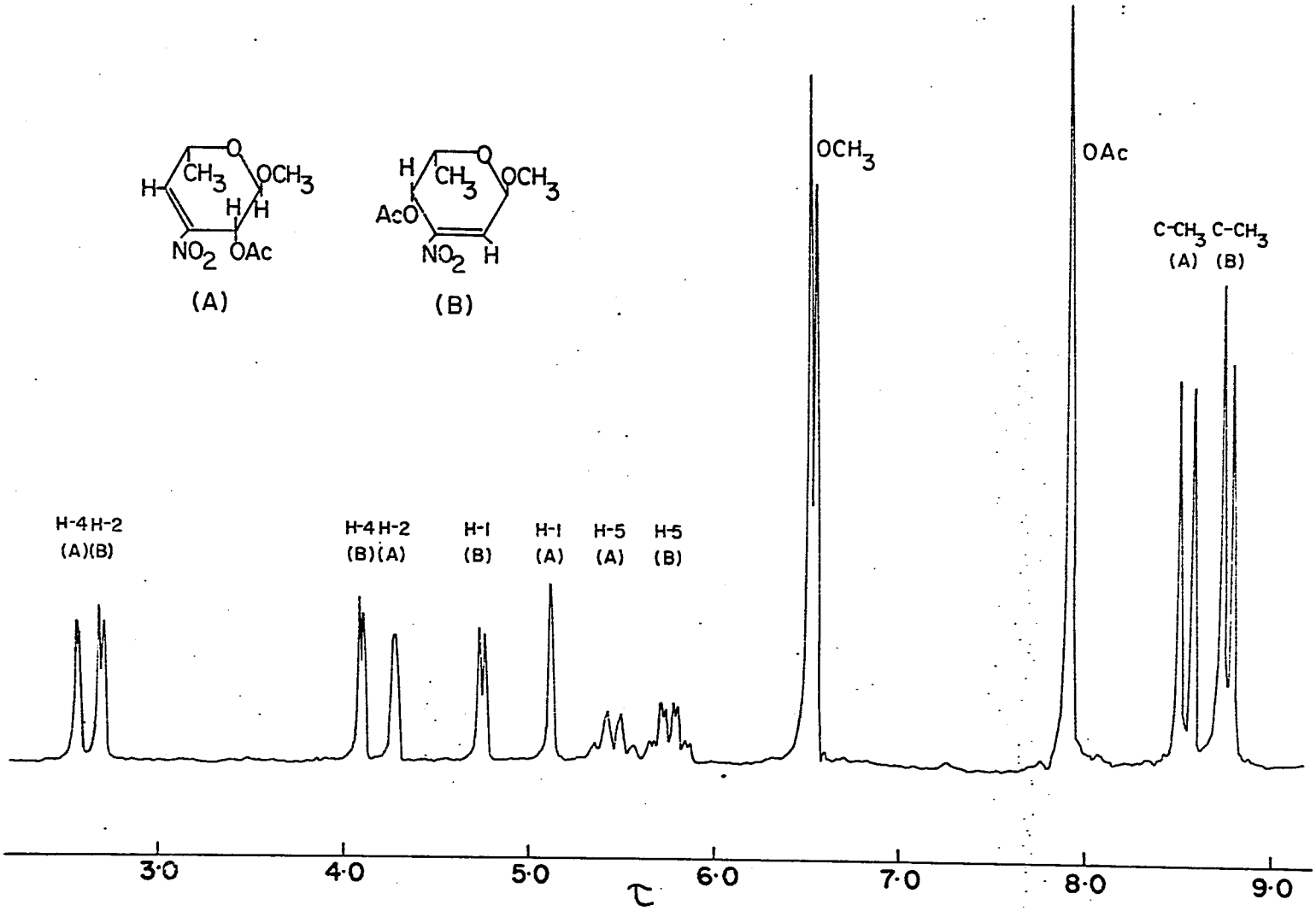
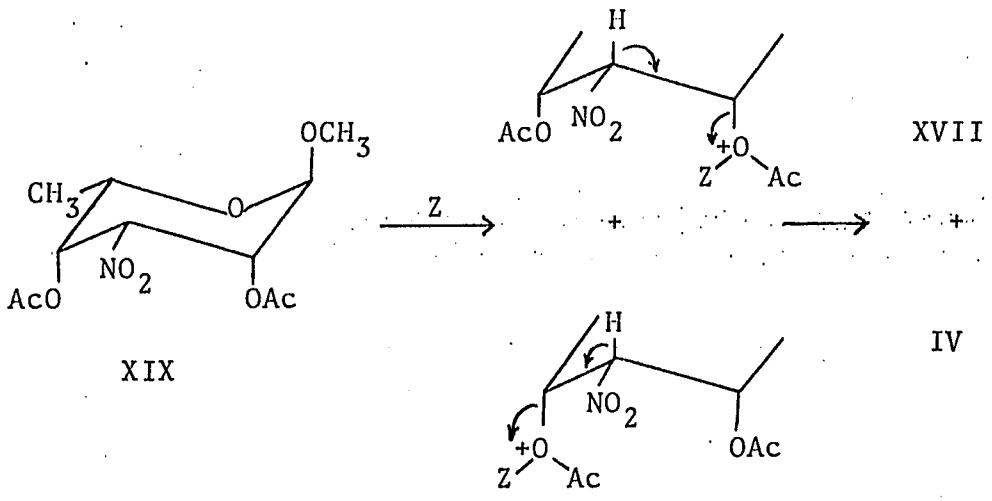


FIG. 15 NMR SPECTRUM OF IV(A) AND XVII(B) OBTAINED BY ACETYLATION (IN $CDCl_3$)



XIX

A mixture of IV and XVII could also be obtained from XIX by the action of silica gel in a procedure similar to that described for the gluco, manno and galacto isomers.

Prolonged treatment of the mixture of olefin monoacetates with a comparatively large excess of acetic anhydride and boron trifluoride at low temperature resulted in acetolysis of the glycosidic bond and afforded a diacetyl nitroolefin, 1,4-di-O-acetyl-2,3,6-trideoxy-3-nitro-α-L-threo-hex-2-enopyranose (XX). The NMR spectrum of XX (Fig.16) showed a six-proton singlet at 7.92τ for the two acetoxy groups

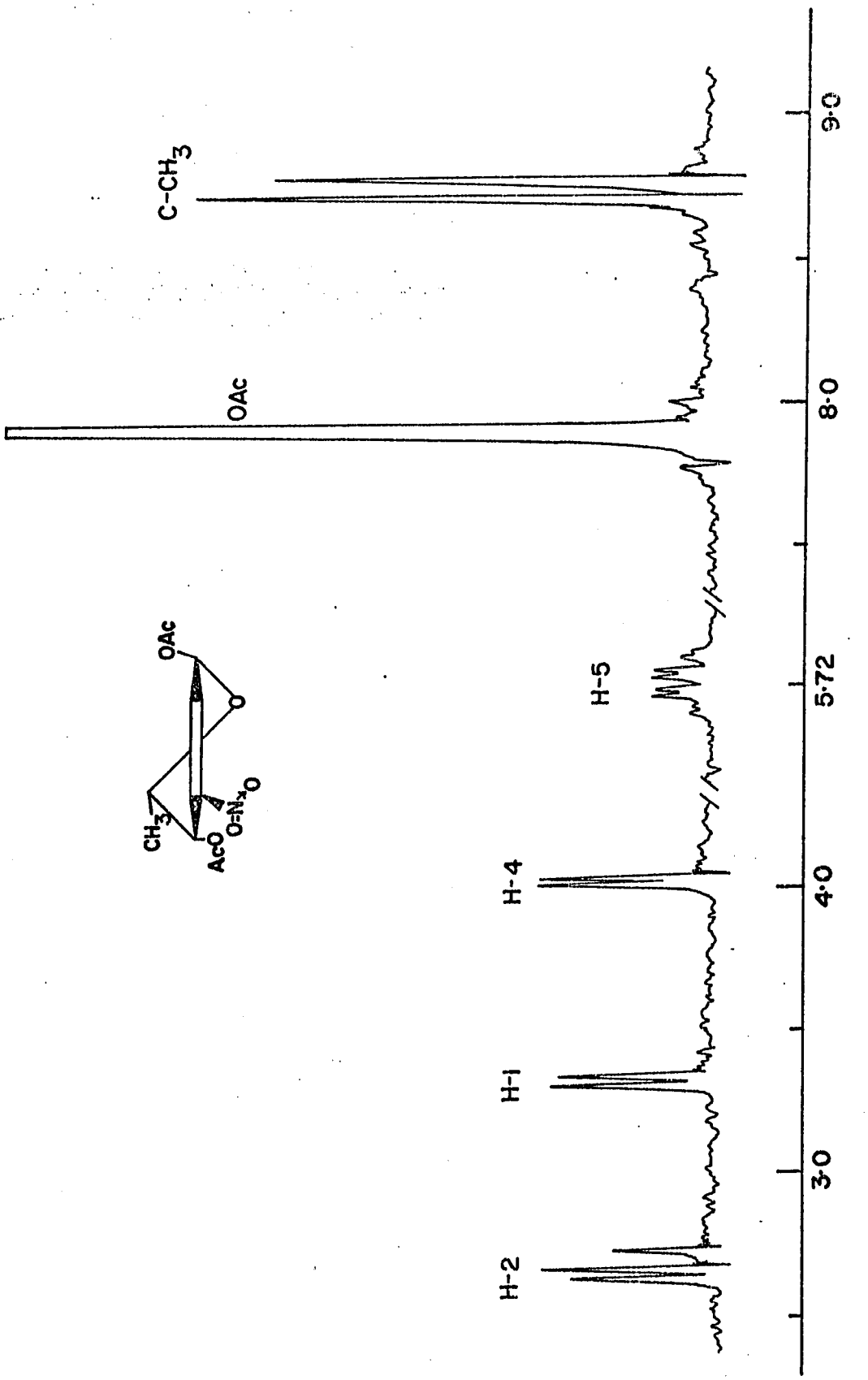
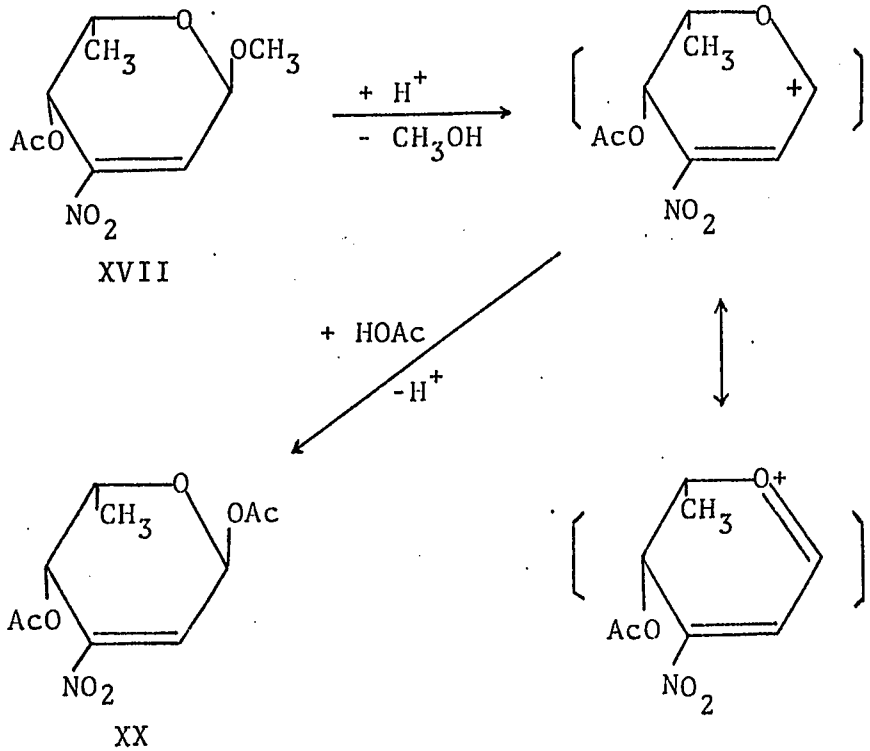


Fig.16 NMR spectrum of compound XX in deuterated chloroform

and no methoxy group signal. The splitting pattern (see Table VIB) suggested that XX possesses the same configuration as XVII (α-L-threo).

The ease of formation of XX (at about -15°) provided a hint that it was formed from a Δ^2 -olefin (XVII) since allylic ethers are known to be acid labile (129). It is assumed that a resonance-stabilized carbonium ion was formed, by acid-catalyzed removal of the glycosidic methoxy group. Reaction with acetic acid then generated XX.

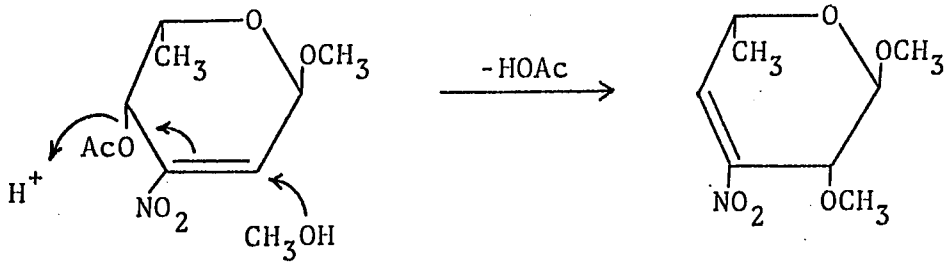


The stereospecific addition of acetic acid to the carbonium ion intermediate is seen as a thermodynamically controlled process giving the more stable α-acetate as a consequence of the anomeric effect (111).

Methanolysis of the mixture of monoacetates IV and XVII gave, in addition to the expected and known (p.75) nitroolefinic alcohol XIII, a new unsaturated derivative, namely, methyl 3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-threo-hex-3-enopyranoside (XXI). This new product showed nitroolefinic absorptions at λ_{max} 247 nm in the UV spectrum and 1520 cm^{-1} in the infrared spectrum.

The NMR spectrum (see Table VIA,B) exhibited an olefinic proton signal at 2.72τ and two methoxy group signals at 6.51τ and 6.58τ . No acetoxy group was detected by IR or NMR spectroscopy. Again, the chemical shift of H-5 (5.53τ) and the coupling constants of the ring protons supported the structure XXI as that of a Δ^3 -nitroolefin with α-L-threo configuration. Furthermore, the compound was not identical with the 2-O-methyl derivative described in Part I, namely, methyl 3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-erythro-hex-3-enopyranoside.

Compound XXI is presumably formed by acid-catalyzed isomerization of the allylic ester XVII, with concurrent addition of solvent methanol.



XVII XXI

A similar reaction had been observed when 3-acetoxy-2-nitro-cyclohexene was refluxed in methanol for 10 hours, the product being 3-methoxy-2-nitro-cyclohexene (134).

Finally, the structure of XXI was confirmed by methylation of XIII with diazomethane catalyzed by boron trifluoride.

Table V

INFRARED FREQUENCIES (cm^{-1}), IN CHLOROFORM,

OF THE NITROOLEFINS DESCRIBED IN PART II*

Compd.	OH	C=O	C=C	NO_2	Other prominent peaks
III		1745s	1680w	1522s	1442m[b], 1370s, 1340s, 1200s[b], 1152ms, 1128s[b], 1050s, 985m, 956m, 910m, 890m, 860w.
IV		1735s	1675w	1520s	1425m[b], 1368ms, 1343s, 1195s[b], 1153ms, 1120ms, 1080s, 1028ms, 1000w, 980w, 913m.
V		1750s	1680w	1535s	1430w[b], 1372m, 1350s, 1200s[b], 1131s, 1092s, 1050s, 978m, 918m.
VII**	3380s		1680w	1515s	1300m, 1278m, 1218m, 1198m, 1153ms, 1130ms, 1100ms, 1072s, 1040ms, 900m, 860w, 810m, 750w.
IX	3600s			1523s	1470w, 1338s, 1285w, 1190ms[b], 1131s, 1088s, 1070s, 1050s, 972ms, 925w, 890w.

* Designations are strong (s), medium-strong (ms), medium (m), weak (w), broad (b).

** in Nujol.

Table V (continued)

Compd.	OH	C=O	C=C	NO_2	Other prominent peaks
XIII	3600m		1675s	1522s	1348s, 1198s[b], 1158ms, 1122ms, 1078s, 1050ms, 1010m, 998m, 972m, 925w, 890w.
XVII		1750s		1530s	1445m, 1390m, 1372s, 1342s, 1200s[b], 1160m, 1131s, 1090s, 1050s, 1000s, 976s, 928m, 912m, 892m, 870w.
		1760s 1738s		1540s	1358s, 1340m, 1316m, 1215s, 1146s, 1120m, 1073m, 1038m, 992s, 948s, 910m, 880w, 800m, 680m.
XXI			1670w	1520s	1445m[b], 1346s, 1188m, 1155m, 1100s, 1070s, 1052s, 1028m, 998m, 940m, 900m.
IX***			1670w	1515s	1350s, 1185s, 1150m, 1110s, 1070m, 970m, 890m, 800m.

*** This compound is from Part I and in Nujol mull.

Table VIA

CHEMICAL SHIFT DATA (τ, in $CDCl_3$) OF NITROOLEFINS DESCRIBED IN PART II*

Compd.	H-1	H-2	H-4	H-5	$C-CH_3$	$1-OCH_3$	2-OAc	4-OAc	Others
III	4.89d	$4.08m_2$	2.73q	$5.36m_3$	8.59d	6.54s	7.91s		
IV	4.88d	4.28q	2.56d	$5.46m_3$	8.55d	6.57s	7.93s		
V	4.83q	2.90q	$4.18m_3$	$5.93m_2$	8.71d	6.54s		7.97s	
VII	5.02d	$5.22m_1$	2.99q	$5.46m_3$	8.64q	6.47s			2-OH 7.20d
IX	4.88q	2.97q	$4.40m_3$	$6.00m_2$	8.62d	6.55s			4-OH 6.95d
XIII	5.08s	5.46s	2.72d	$5.51m_3$	8.57d	6.58s			2-OH 7.08s
XVII	4.76d	2.73d	4.11d	$5.77m_2$	8.75d	6.55s		7.92s	
XX	3.33d	2.65d	4.13d	$5.72m_2$	8.75d			7.92s	1-OAc 7.92s
XXI	5.04d	5.79q	2.72d	$5.53m_3$	8.57d	6.51s			$2-OCH_3$ 6.58s
IX**	5.08d	5.59q	2.94d	$5.35m_3$	8.62d	6.43s			$2-OCH_3$ 6.46s

* Splitting patterns were obtained from expanded spectra (sweep width=250Hz). Designations are s for singlet; d, doublet; q, quartet; m_1, sextet; m_2, octet; m_3, 12 peaks.

** This compound is from Part I.

Table VIB

COUPLING CONSTANTS (Hz) OF NITROOLEFINS DESCRIBED IN PART II*

Compd.	$J_{1,2}$	$J_{1,4}$	$J_{2,4}$	$J_{2,5}$	$J_{4,5}$	$J_{5,6}$
III	4.0	--	1.0	2.5	1.5-2.0	7.0
IV	1.0	--	--	2.0	2.0	7.0
V	3.3	1.0	1.3	--	8.3	6.5
VII	4.5	--	1.0	2.5	1.5-2.0	6.0
IX	3.5	1.0	1.0	--	8.5	6.0
XIII	1.0	--	--	2.0	1.5	7.0
XVII	3.5	--	--	--	2.5	6.5
XX	3.5	--	--	--	2.5	6.5
XXI	1.0	--	--	1.8	1.8	7.0
IX**	3.0	--	--	2.0	2.0	7.0

* Coupling constants are measured from expanded spectra (sweep width=250Hz).

** This compound is from Part I.

Table VIIA

CHEMICAL SHIFT DATA (τ, in $CDCl_3$) OF ACETYL DERIVATIVES IN PART I AND PART II*

Compd.	H-1	H-2	H-3	H-4	H-5	C-CH_3	1-OCH_3	2-OAc	4-OAc	Others	
Part I											
VI	5.07d	6.08q	5.15t	4.82t	6.19m	8.82d	6.59s		7.97s	2-OCH_3	6.55s
VII	3.54d	5.98q	5.17t	4.76t	6.03m	8.79d			7.94s	1-OAc	7.84s
Part II										2-OCH_3	6.61s
II	5.01d	4.74q	5.07t	4.81t	6.16m_1	8.79d	6.62s	7.98s	7.98s		
VI	5.22d	5.80q	5.26t	4.86t	6.20m_1	8.83d	6.56s		8.00s	2-OH	7.22b
VIII	5.06d	4.80q	5.14t	6.24m	6.36m	8.68d	6.64s	7.98s		4-OH	6.84b
XI	5.26d	4.49q	5.10q	4.40t	6.25m_1	8.75d	6.62s	7.94s	7.97s		
XII	5.27d	5.54q	5.21q	4.41t	6.26m_1	8.76d	6.61s		7.98s	2-OH	7.11d
XVI	4.96d	4.40q	4.96q	4.31q	5.88m_1	8.84d	6.63s	7.96s	7.92s		
XIX	5.10d	4.40q	5.15t	4.19q	5.95m_1	8.78d	6.61s	7.94s	7.92s		

* Designations are s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; m_1, octet; b, broad.

COUPLING CONSTANTS (Hz) OF ACETYL DERIVATIVES IN PART I AND PART II*

Compd.	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
Part I					
VI	3.5	10.0	10.0	10.0	6.0
VII	3.5	10.0	10.0	10.0	6.0
Part II					
II	3.5	10.0	10.0	10.0	6.0
VI	4.0	10.0	10.0	10.0	6.0
VIII	3.5	11.0	9.0	**	6.0
XI	1.5	3.5	10.5	10.0	6.0
XII	2.0	3.0	10.5	10.0	6.0
XVI	3.5	11.0	11.0	1.0	6.0
XIX	1.5	3.5	3.5	1.0	6.0

* Coupling constants are measured from expanded spectra (sweep width = 250Hz).

** Could not be measured due to overlapping of proton signals.

B. Stereospecific Synthesis of L-Desosamine

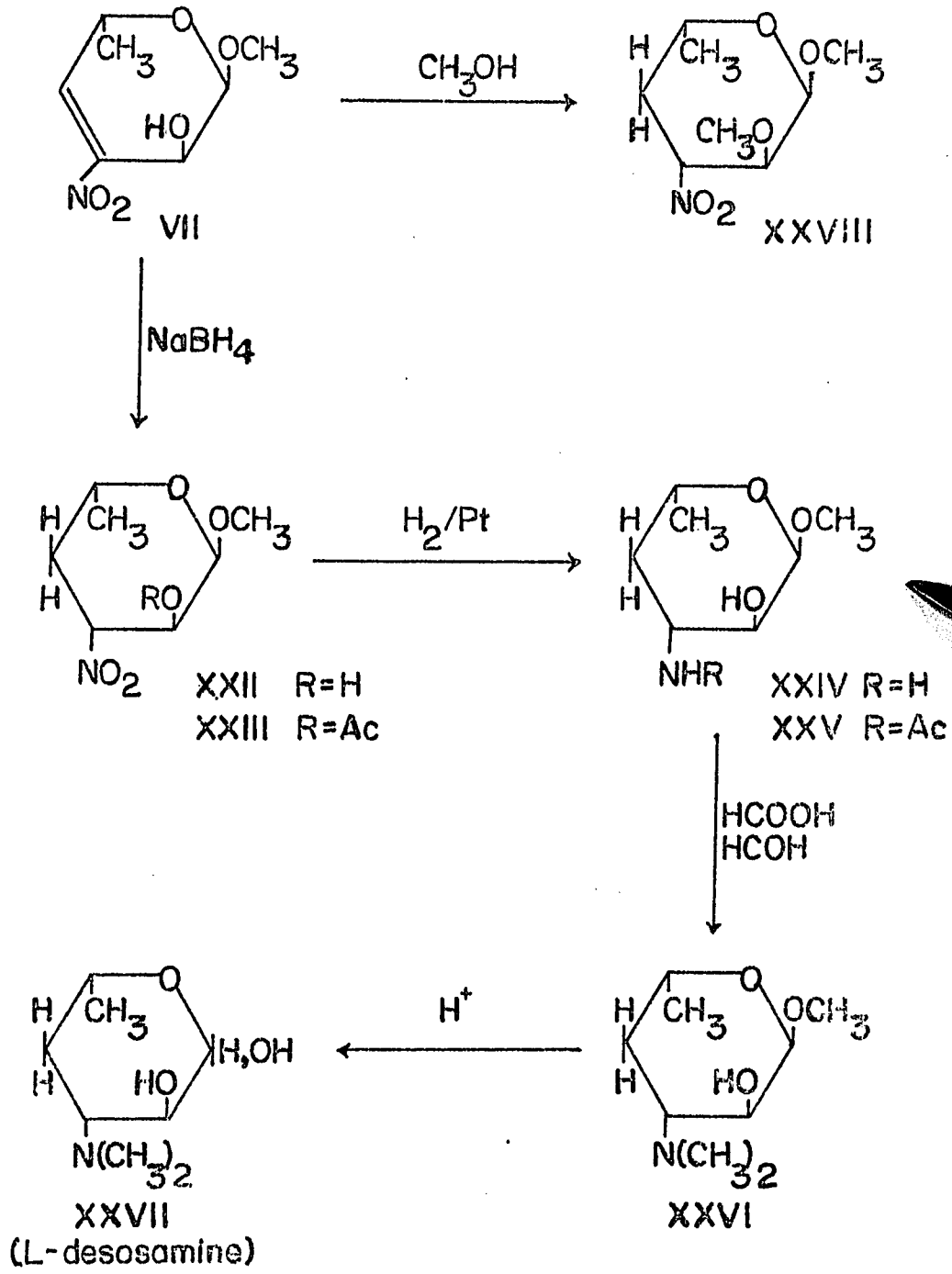
Nitroolefinic sugars having their unsaturation between C-2 and C-3 have served as intermediates for the synthesis of several 2,3-dideoxy-3-amino sugars (101,103b). In part IA of this thesis, the synthesis of a 3,4-dideoxy-3-amino sugar from a blocked 3,4-nitroolefin has been described. The present section embodies a further exploration of the utility of nitroolefinic sugars as potential intermediates for the synthesis of amino sugars that may command interest in the chemistry of antibiotics.

Desosamine has been found to be a component common to such macrolide antibiotics as erythromycin, methymycin, narbomycin, neomethmycin, picromycin and oleandomycin (see Introduction, p.3). Assignment of structure as 3-dimethylamino-3,4,6-trideoxy-D-xylo-hexose was based on chemical degradation (42, 135,136), NMR spectral studies (137,138), and synthesis (139-141). A low-yield stereospecific synthesis of the natural product was achieved by Richardson (140) starting from methyl 3-amino-3-deoxy-D-glucopyranoside. Two non-stereospecific syntheses starting from optically inactive non-carbohydrate materials and leading to the DL sugar have also been accomplished (139,141).

A stereospecific synthesis of the L-enantiomorph of desosamine has not yet been reported, and such a synthesis has now been performed as illustrated in Scheme VIII.

The nitroolefin VII, methyl 3,4,6-trideoxy-3-nitro-α-L-erythro-hex-3-enopyranoside, which is now readily available (see p.71), served as a starting material. Selective reduction of VII with sodium borohydride in ethanol at 0° for 15 minutes furnished the saturated nitro derivative XXII, methyl 3,4,6-trideoxy-3-nitro-α-L-xylo-hexopyranoside, in almost quantitative yield. Hydrogenation of the nitro compound XXII over Adams catalyst was then performed in the presence of dilute hydrochloric acid at ordinary temperature and pressure. The reduction was completed after four hours and quantitatively gave the hydrochloride of methyl 3-amino-3,4,6-trideoxy-α-L-xylo-hexopyranoside (XXIV), as a hygroscopic solid. The hydrochloride was transformed into the free amino compound XXIV by treating it with anion exchange resin. The yield was 96%.

A facile and economical method for the conversion of an amino group into a dimethylamino function (Eschweiler-Clarke reaction) consists of reacting the amino compound with a mixture of formaldehyde



Scheme VIII Synthesis of L-Desosamine

and formic acid (142). N,N-Dimethylation of some amino alcohols has been investigated (143) and, in amino sugars, has led to good yield of the corresponding N,N-dimethyl derivatives in several instances (80). The method was applied to the amino glycoside XXIV, and although the product, methyl 3-dimethylamino-3,4,6-trideoxy-α-L-xylo-hexopyranoside (XXVI), was obtained as an impure syrup only, it could be hydrolyzed with 6 N hydrochloric acid to give L-desosamine hydrochloride. The latter was purified via the free base XXVII, 3-dimethylamino-3,4,6-trideoxy-L-xylo-hexose (L-desosamine), by treatment with anion exchange resin followed by reconversion into the hydrochloride. L-Desosamine was obtained in 66% yield.

Proof of Configuration

It was shown in Part I that sodium borohydride reduction of methyl 3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-erythro-hex-3-enopyranoside (i.e., the methyl ether of VII) stereoselectively gave that saturated product which had an equatorial nitro group, i.e., which had the α-L-xylo configuration (see Scheme I on p.20). It was quite reasonable to assume the same steric course

for the reduction of VII, but such a prediction could not be made with certainty. The free hydroxy group in VII might conceivably exert a directive influence not existing in the methyl ether; furthermore, the product might possibly undergo base-catalyzed epimerization at the secondary carbinol carbon (C-2), as is often observed in β-nitro alcohols. At any rate, proof of configuration for the reduction product XXII was desirable.

The NMR spectrum of XXII in deuterated chloroform (see Experimental) exhibited a one-proton multiplet at 5.90τ which was reduced to a quartet upon deuterium exchange. The signal was attributable to H-2, its coupling constant $J_{2,3}$= 10Hz indicating a diaxial orientation of H-2 and H-3 and its coupling constant $J_{1,2}$= 3.5Hz being in line with an axial-equatorial relationship of H-2 and H-1. The latter relationship was confirmed by the splitting of the doublet at 5.20τ which was assigned to the anomeric proton. The assignment was further substantiated by the NMR data (see Experimental) of the acetylated derivative XXIII, methyl 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-L-xylo-hexopyranoside, obtained by acetylation of XXII with acetic anhydride and boron trifluoride. The H-2 signal was shifted from 5.90τ for XXII to 4.74τ , and the coupling constants were $J_{1,2}$ = 3.5 Hz and $J_{2,3}$ = 11 Hz.

The H-1 and H-3 signals were a doublet and a sextet superimposed at 5.01τ , with $J_{1,2}$= 3.5Hz, $J_{2,3}$= $J_{3,4a}$= 11Hz, $J_{3,4e}$= 4.5Hz. Thus it was proved that no epimerization had occurred at C-2 and assignment of the α-L-xylo configuration was correct. This conclusion was borne out when the dimethylamino sugar resulting at the end of the synthesis proved in fact to be the enantiomorph of natural desosamine for which the D-xylo configuration had been established. Thus, the NMR spectrum of XXVII (Fig.17) was identical with the published spectrum of the D-enantiomorph (138). The infrared spectrum (Fig.18) of L-desosamine hydrochloride also coincided with that of D-desosamine hydrochloride (141). Finally, comparison of the melting points and specific rotations of D-desosamine and the new product (Table VIII) confirms the enantiomorphism.

As a corollary to the stereospecific saturation of the nitroolefin VII it was observed that addition of methanol across the double bond also reveals the tendency of the nitro group to become equatorially oriented. Thus, when VII was gently refluxed overnight in anhydrous methanol, the product obtained in 92% yield was methyl 3,6-dideoxy-4-O-methyl-3-nitro-α-L-gluco-

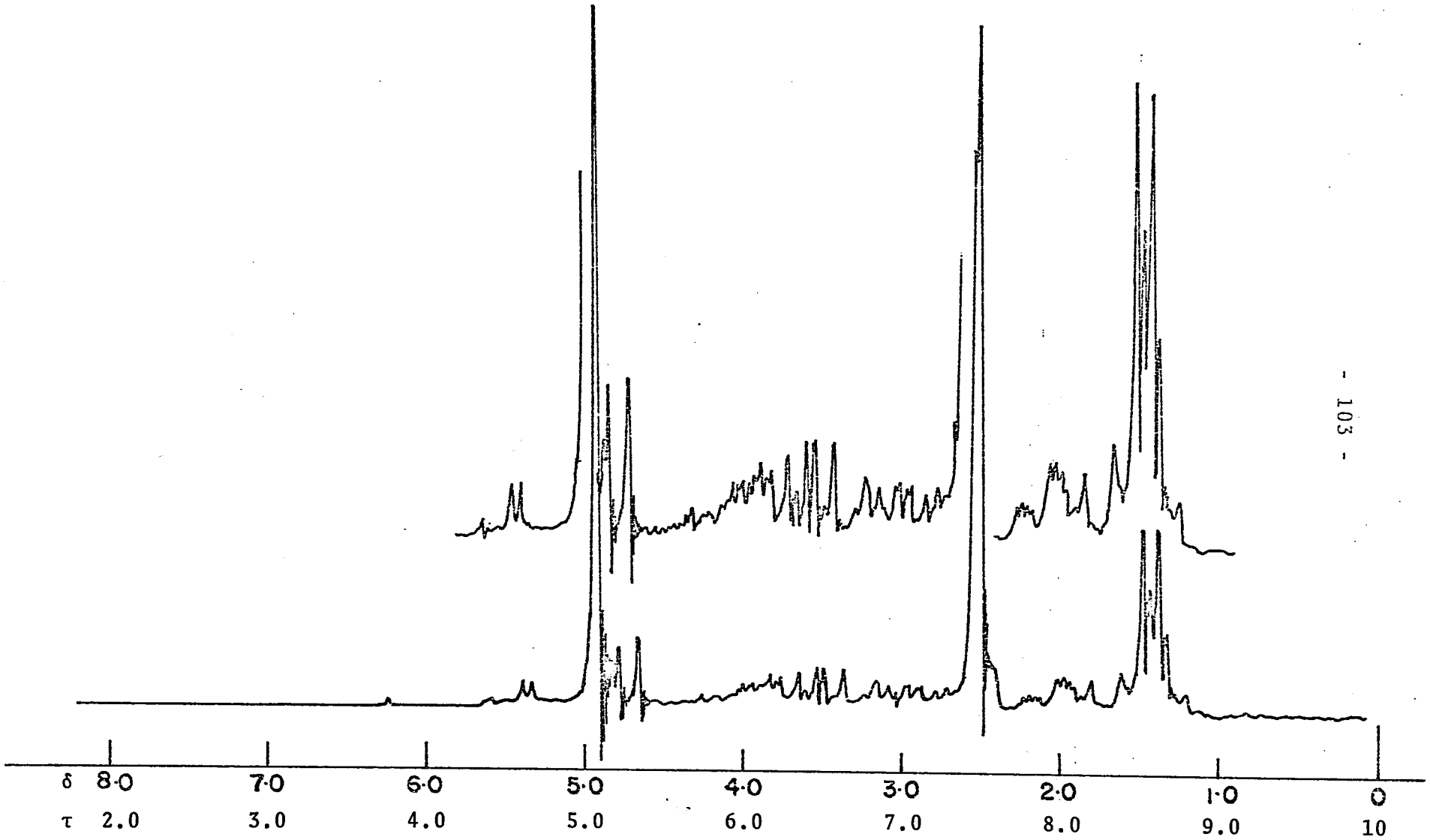


Fig.17 NMR spectrum of L-desosamine in deuterium oxide (60 MHz)

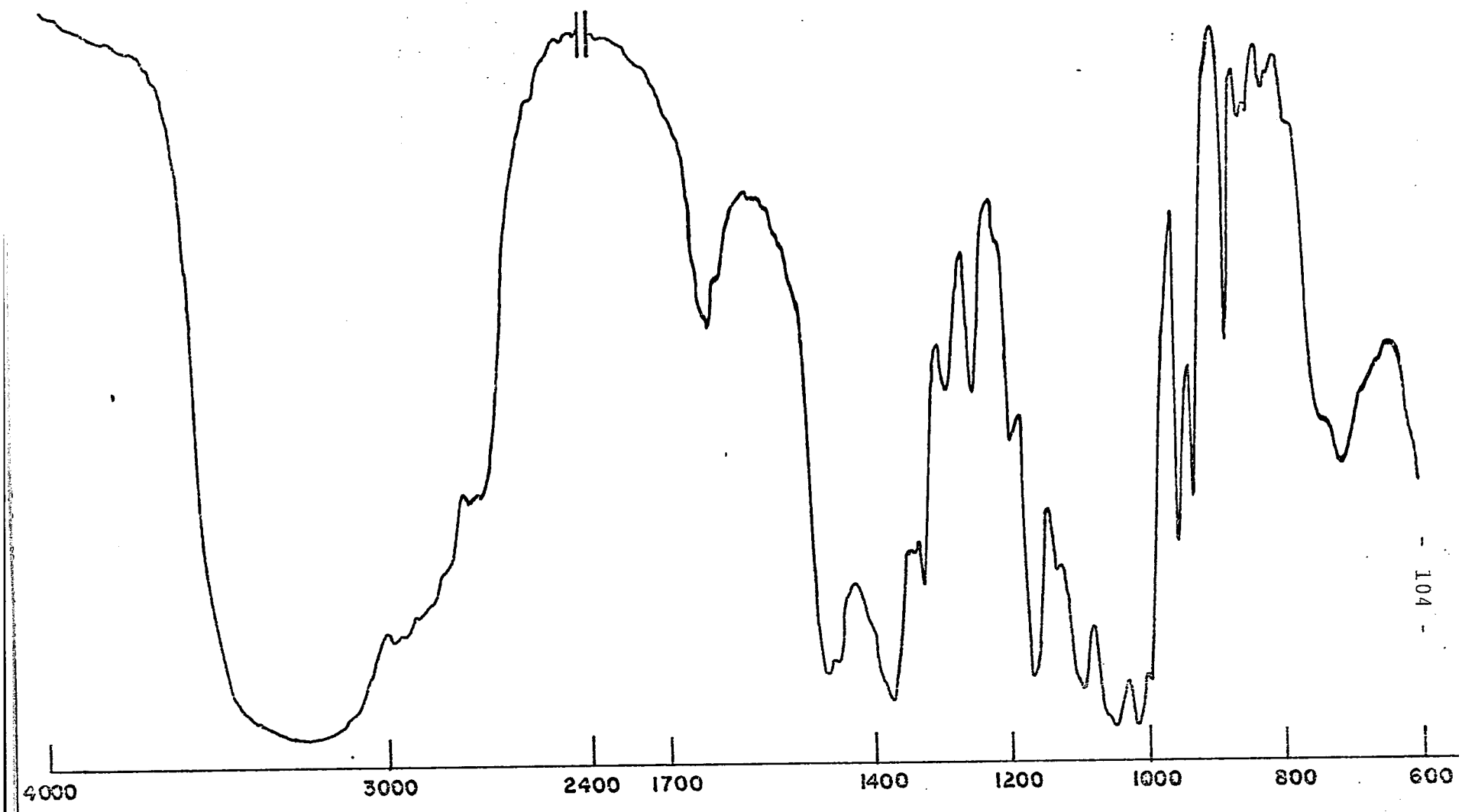


Fig. 18 Infrared spectrum of L-desosamine hydrochloride (in KBr)

pyranoside (XXVIII). The configuration of XXVIII was elucidated by its NMR spectrum (see Experimental) which displayed a triplet for H-3 with $J_{2,3} = J_{3,4} =$ 10Hz, indicative of axial H-2, H-3, and H-4.

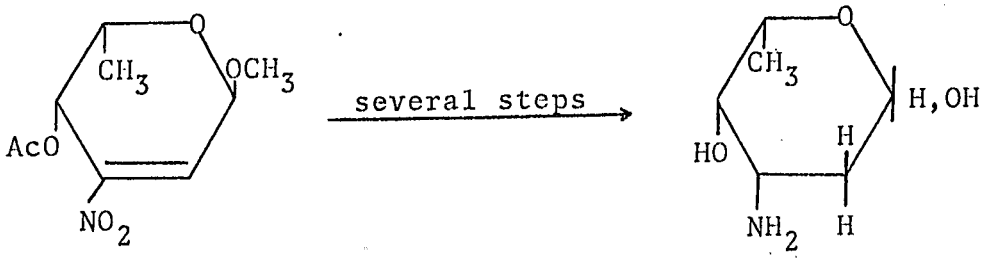
Table VIII

PHYSICAL CONSTANTS OF D- AND L-DESOSAMINE

	D-desosamine (ref.)		L-desosamine
m.p.	182°	(136)	183-184°
	183-184°	(42)	
	185-187°	(141)	
	189-191°	(138)	
$[\alpha]_D$	+ 49.5°	(138)	- 52°
	+ 51°	(141)	
	+ 48°	(136)	

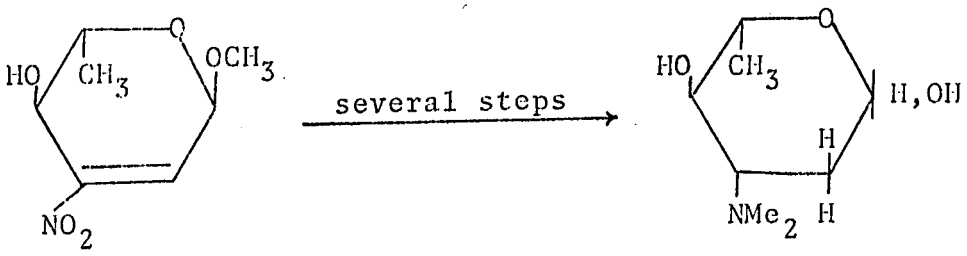
C. Prospects

The four isomeric sugar nitroolefins which have become available as a result of this work should lend themselves to a variety of synthetically useful reactions in addition to those already performed. Thus, in analogy to the synthesis of L-desosamine, the nitroolefin XVII should prove a convenient starting point for a synthesis of daunosamine (a naturally occurring antibiotic constituent), and the nitroolefin IX should be able to serve for a synthesis of L-angolosamine (the enantiomer of an antibiotic constituent):



XVII

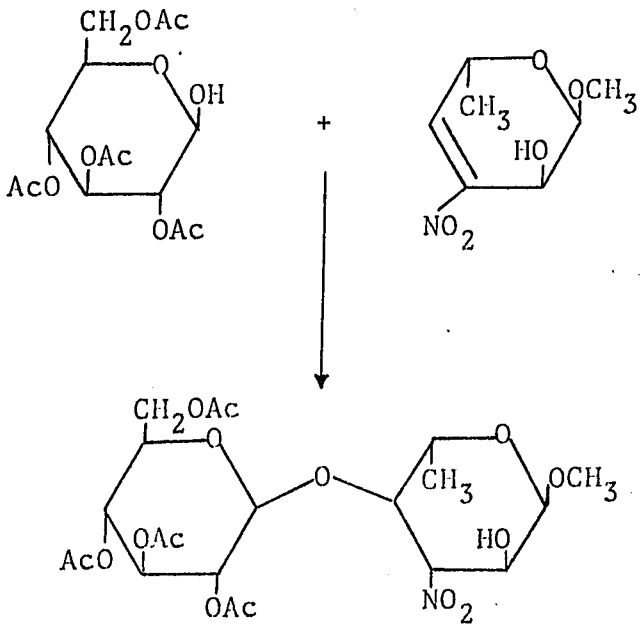
Daunosamine



IX

L-Angolosamine

Other 3-amino and 3-dimethylamino sugars, both of the 2,3,6- and of the 3,4,6-trideoxy type, no doubt would be accessible in similar fashion and might be made in anticipation of their discovery in nature. Furthermore, since 3,4-unsaturated 3-nitro sugars are capable of adding nucleophiles to give 4-substituted derivatives (compare the reaction VII → XXVIII), the synthesis of 1→4 linked oligosaccharides by the recently-developed nucleophilic addition method (86) may be contemplated, e.g. :



PART III

Formation of Allylic Nitronates

RESULTS and DISCUSSION*

It had been observed that the sodium nitronates of 3-deoxy-3-nitroglycosides in aqueous solution exhibit mutarotations which are due to epimerizations occurring at carbon atoms adjacent to the aci-nitro group (76,144). An epimeric equilibrium is established within a few hours, at room temperature. However, if these epimeric equilibrium mixtures are allowed to stand for prolonged periods of time, the occurrence of a secondary, and comparatively slow, chemical reaction is noticed (145). This reaction is reflected in a further mutarotation and, especially, in a striking change in the ultraviolet spectrum. The characteristic nitronate absorption at 250 nm decreases, with concurrent appearance of a new peak at about 295 nm which reaches its maximum intensity after several days when the original peak has completely disappeared. The spectral change is accelerated at higher temperatures; in hexosides (Ia) previously investigated (145) it was complete within 15 minutes at 98°. The reaction products

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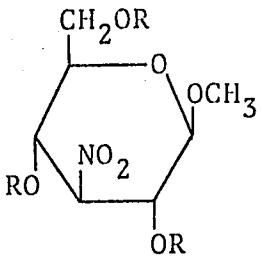
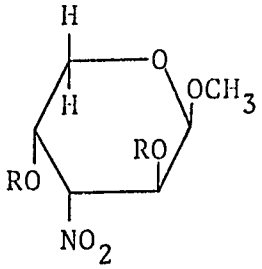
* For convenience, compounds in this chapter are numbered using a new set of Roman numerals.

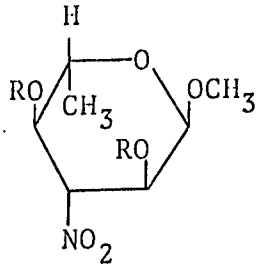
from hexosides (Ia and epimers) and pentosides (IIa and epimers) were isolated and shown to possess the allylic nitronate structures IV and V, respectively (145).



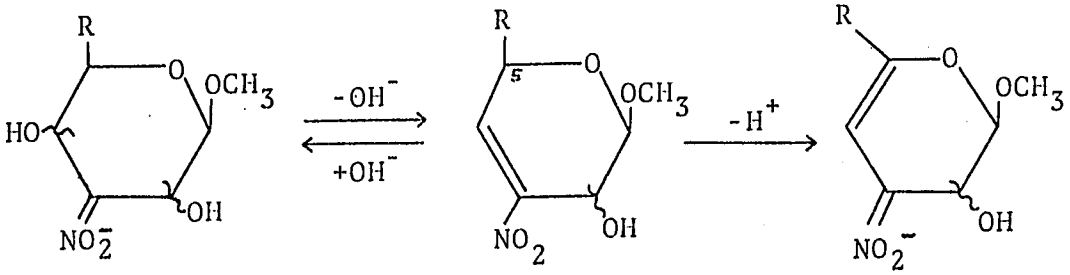
Ia) R=H
b) R=Ac



IIa) R=H
b) R=Ac



IIIa) R=H
b) R=Ac



Ia (and epimers)
$R=CH_2OH$

IIa (and epimers)
R=H

IV $R=CH_2OH$
V R=H

It is considered that formation of these dehydration products proceeds by way of proton abstraction from the allylic position (C-5) in nitroolefins presumed to be in equilibrium with the epimerized nitronates. It has been observed (89), moreover, that the rate of

forming unsaturated nitronate is greatly accelerated when the triacetate (Ib) is used as a substrate instead of Ia itself. In that case, treatment with 0.01 N NaOH at room temperature produced the aforementioned spectral change within 4 minutes.

In this thesis the studies were extended to the 6-deoxy hexoside series, and a qualitative comparison of the ease of allylic nitronate formation in the glycosides Ia - IIIa and their acetates Ib - IIIb was undertaken.

When methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (IIIa) was dissolved in water containing one equivalent of sodium hydroxide, an ultraviolet peak at 250 nm corresponding to the saturated nitronate was seen immediately, but it reached its maximum intensity (ε= 12000) only upon heating on a steam bath for two minutes. Further heating caused the peak to degenerate, with concurrent development of a new peak at 295 nm. After 90 minutes, the new peak had reached its maximum intensity (ε= 19000) and the original peak had disappeared completely (Fig.19).

The reaction product formed was isolated as a brownish powder which could not be purified for microanalysis. However, a 60-MHz NMR spectrum (Fig.20)

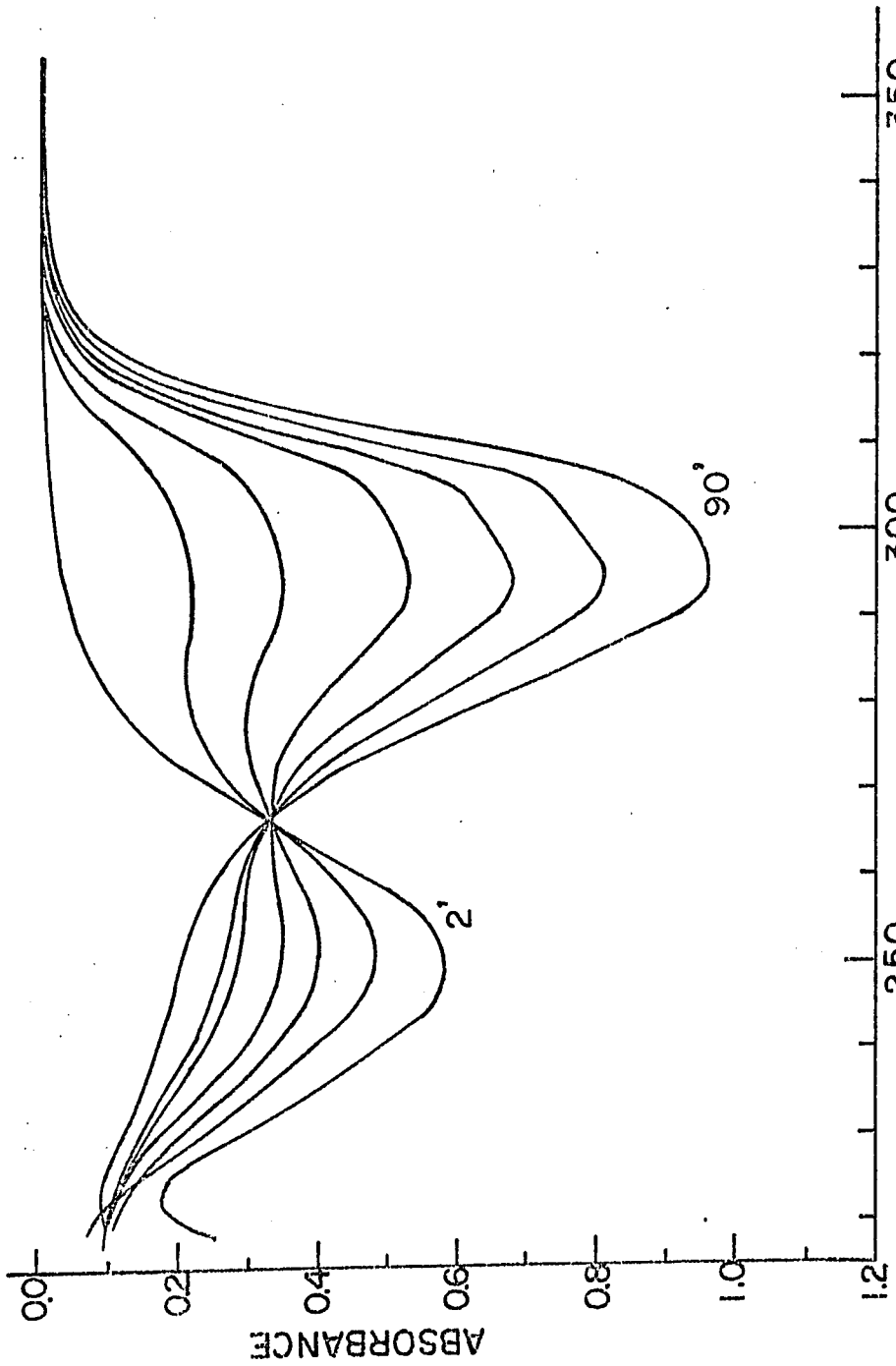


Fig.19 UV spectrum of compound IIIa in the presence of one equivalent of NaOH at 100° (C= $5x10^{-5}$ M)

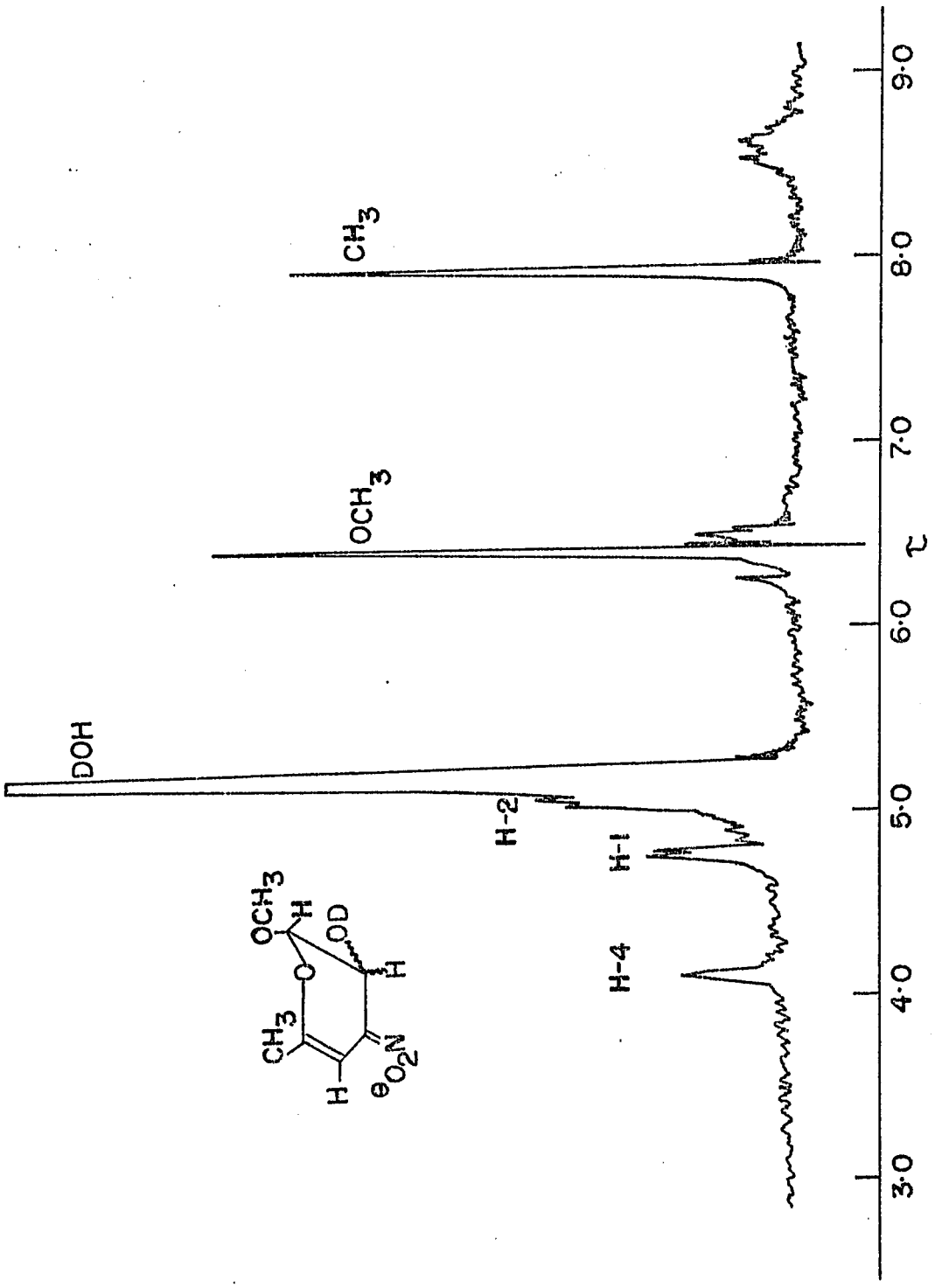


Fig.20 NMR spectrum of compound VI (impure) in deuterium oxide

of this crude product in deuterium oxide did suggest the allylic nitronate structure VI. A one-proton singlet at 4.10τ suggested the presence of an olefinic proton. Two doublets at 4.79τ and 5.05τ were assigned to the protons at C-1 and C-2, the coupling constant being 2Hz. The glycosidic methoxy group gave a three-proton singlet at 6.42τ . Another sharp three-proton singlet at 7.93τ was assigned to the C-methyl group in position 5.

As it appeared that formation of an allylic nitronate from IIIa was less facile than that from I (which required only 15 minutes of heating), it became of interest to perform also a comparison with the reaction of II, under various conditions. The ultraviolet spectra generated from IIa and IIIa and their diacetates IIb and IIIb were recorded after varying reaction times at different pH of the medium. The results are compiled in Table IX.

At pH 10-13, unsaturated nitronate V was formed when nitroalcohol IIa was heated for about 20 minutes, whereas formation of VI required at least one hour under the same experimental conditions.

In media of lower alkalinity (pH 7-9), in which the glycosides predominantly exist as free nitro

Table IX*

Time (in min.) for maximum UV absorption at different pH values ($C=5x10^{-5}$ M)

λ_{max} (nm)	250		295		250		295	
Compound	IIa	IIb	IIa	IIb	IIIa	IIIb	IIIa	IIIb
pH								
13	1	***	20	20	2	***	90	90
12	2	***	20	20	2	***	90	90
11	2	***	20	20	2	***	80	80
10	2	***	22	22	4	***	60	60
9	**	***	25	25	**	***	30	10
8	**	***	20	20	**	1	40	20
7	**	***	25	20	**	1	20	10

* Heating at 100°.

** Absence or very small absorption.

*** Maximum absorption immediately after the solution is prepared.

compounds rather than as nitronates (71), the ultraviolet absorption at 250 nm was very small or absent, so that no accurate measurements were possible in this range.

Room temperature studies of compounds Ia, IIa and IIIa in 0.1 N sodium hydroxide solution (C= 10^{-4}M) showed a similar trend, with the maximum intensity occurring at 295 nm within about 22 days in compound Ia (λ_{max} = 300 nm) and 30 days in compound IIa, while compound IIIa showed only a small absorption in the region even after 40 days (Fig.21). Slightly different rates were observed for the generation of maximum absorption at 250 nm.

Interesting results were obtained when the acetylated derivatives (IIb and IIIb) were treated with alkali under the same conditions. The presence of acetoxy groups at C-2 and C-4 did not seem to affect the overall rate of the allylic nitronates formation (Table IX). However, formation of the saturated nitronate absorbing at 250 nm was accelerated, which appears to reflect an inductive effect of the acetoxy groups upon the deprotonation at C-3.

Because of the electron-donating character of the methyl group at C-5, one would expect VI to be

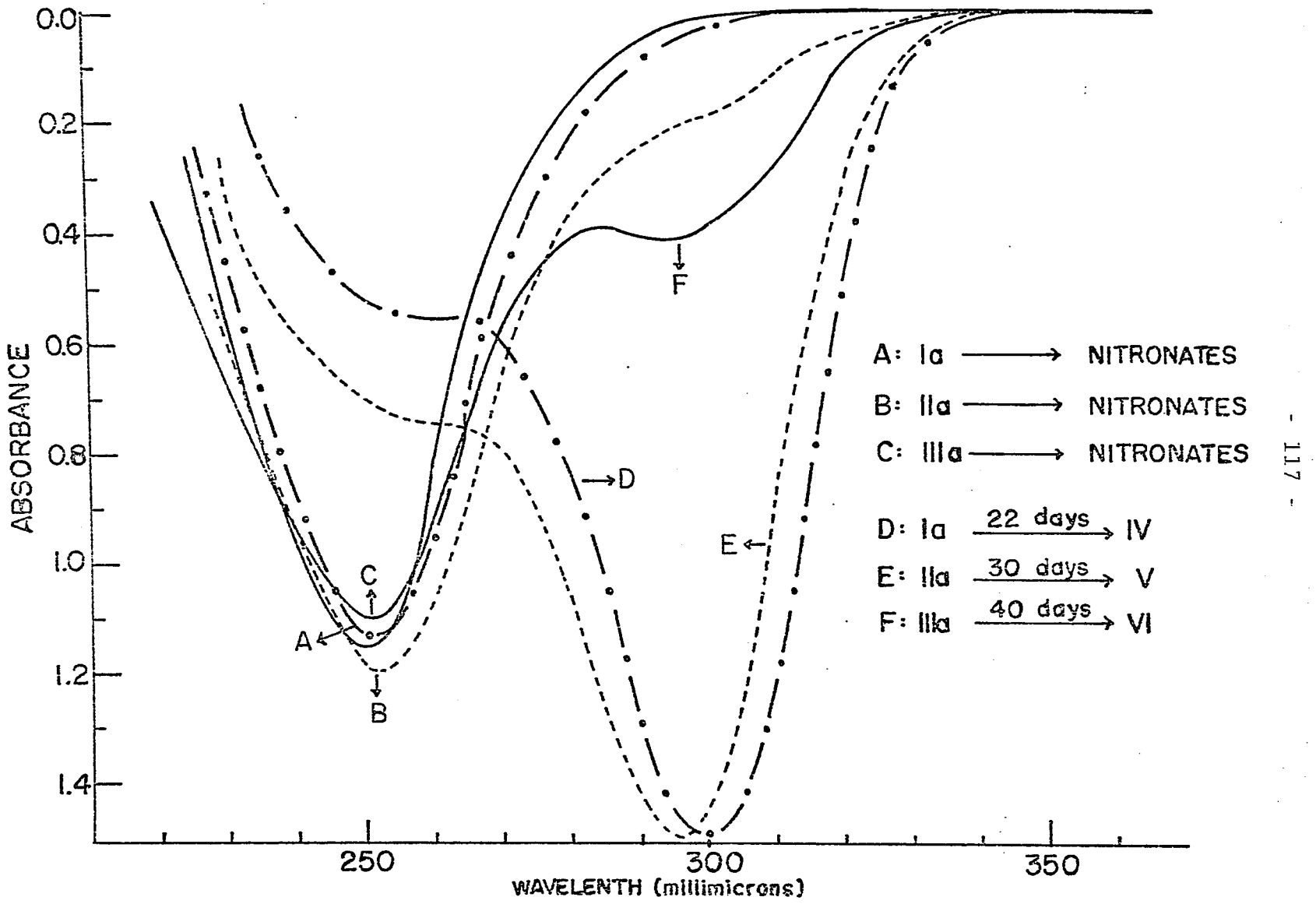


Fig.21 Formation of Nitronates and Allylic Nitronates from Compounds Ia, IIa and IIIa

formed more slowly than V. This is in agreement with the experimental results. A steric influence exerted by the C-methyl group is probably not responsible for the retardation of the reaction, since a hydroxymethyl or acetoxymethyl group at C-5 does not have a similar effect. It now appears that, as compared to II, substitution at C-5 by an acetoxymethyl group causes a great acceleration and substitution by an hydroxymethyl group causes a slight acceleration, whereas substitution by a methyl group effects a deceleration, of allylic nitronate formation. It is concluded that the reaction rate is influenced by inductive assistance or retardation, due to the C-5 substituent, of the base-catalyzed removal of H-5.

EXPERIMENTAL

General Remarks

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

Ultraviolet absorptions were recorded on a Perkin Elmer spectrophotometer, Model 202.

Unless otherwise specified, infrared spectra were obtained from Nujol mulls on a Beckman IR-20 spectrophotometer. Relative band intensities were estimated visually and were given as s (strong), m (medium), w (weak), b (broad).

Except where stated otherwise, nuclear magnetic resonance (NMR) spectra were recorded on a Varian HA-100 instrument, deuterated chloroform was used as solvent, and the lock signal was obtained with tetramethylsilane. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad.

Optical rotations were measured using a Perkin Elmer automatic polarimeter, Model 141, at room temperature.

Paper chromatography of amino sugars was performed by the descending technique on Whatman No.1 paper. The irrigating solvent mixture was acetic acid-ethyl acetate-pyridine-water (1:5:5:3, v/v). The spots were made visible

by spraying with ninhydrin solution. R_{GN} means mobility relative to D-glucosamine hydrochloride.

All reactions were monitored by T.L.C. on silica gel G (E. Merck AG, Darmstadt, Germany), using 7.5-cm plates (microscope slides). The spots were made visible by spraying the plates with a solution of 1% ceric sulfate in 10% sulfuric acid and heating on a hot plate. Column chromatography was performed on Silica gel 7734 (0.05-0.20 mm, 70-325 mesh ASTM).

Unless otherwise stated, solutions were evaporated under diminished pressure in a rotary evaporator with a bath temperature at or below 35°.

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

Microanalyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium, Elbach, Germany.

Part I

A. SYNTHESIS OF O-METHYLATED 3-NITRO AND 3-AMINO DERIVATIVES IN THE 3,6-DIDEOXYHEXOSE SERIES

Methyl 3,6-Dideoxy-2-O-methyl-3-nitro-α-L-glucopyranoside (II) and Methyl 3,6-Dideoxy-2,4-di-O-methyl-3-nitro-α-L-glucopyranoside (III)

A solution of methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (I) (2.0 g) in anhydrous ether (50 ml) was stirred in a dry-ice bath for about 10 minutes. Then, an ethereal solution of diazomethane (generated from 40 g of N-nitrosomethylurea) and 3 ml of boron trifluoride etherate solution were added dropwise, in alternating sequence, in the course of 3 h. The rate of addition was such that an excess of diazomethane was always present, as evidenced by the pale yellow color of the reaction mixture. A white flocculent precipitate of polymethylene was filtered off and washed thrice with ether, and evaporation of the filtrate furnished a slightly yellow syrup. Thin layer chromatography using the solvent system of carbon tetrachloride-ethanol (92:8,v/v) showed a small amount of slow-moving starting material to be still present in addition to two faster-moving products. The

syrup was dissolved in a small amount of the solvent mixture just mentioned, applied to a column containing 250 g of silica gel, and eluted with the same solvent mixture. Fractions of 5 ml were collected, inspected by t.l.c., appropriately pooled, and evaporated to dryness.

The dimethyl ether III, which appeared in early fractions, was obtained as an oil (0.783 g, 34.4%) that solidified after standing in the open air for one week. The compound melted at 54-55° and showed $[\alpha]_D$ -141.3° (c, 1.6, in chloroform).

Anal. Calcd for $C_9H_{17}O_6N$ (235.2): C, 45.95; H, 7.28; OCH_3, 39.57. Found: C, 46.52; H, 7.18; OCH_3 39.33.

The infrared spectrum was taken from a liquid film. The most prominent frequencies (cm^{-1}) were at 1555s (nitroalkane); 1450m; 1360m; 1190m; 1150m; 1100s; 1050s; 1000s; 935w; 900w; 850w; 795w; 650w. Hydroxyl absorption was absent.

NMR data ($CDCl_3$): τ 5.15 (1H, d, $J_{1,2}$= 3Hz, τ 5.23 (1H, t, $J_{2,3}$= $J_{3,4}$= 10Hz, H-3); τ 6.20 (1H,q, $J_{1,2}$= 3Hz, $J_{2,3}$= 10Hz, H-2); τ 6.32-6.78 (1H, m, H-5); τ 6.51 (1H, t, $J_{3,4}$= $J_{4,5}$= 10Hz, H-4); τ 6.60, 6.64 (9H, 2s, OCH_3); τ 8.71 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

From subsequent fractions of the column, the monomethyl ether II was obtained in crystalline form

(1.314 g, 61.5%). Recrystallization from carbon tetrachloride and petroleum ether afforded colorless, flaky crystal which melted at 87.5-88.5° and exhibited $[\alpha]_D$ -160.3° (c, 1.27, in chloroform).

Anal. Calcd for $C_8H_{15}O_6N$ (221.2): C, 43.43; H, 6.84; N, 6.33. Found: C, 43.50; H, 6.95; N, 6.14.

Characteristic infrared absorptions (cm^{-1}) occurred at 3430s (hydroxyl); 1550s (nitroalkane); 1335m; 1260m; 1200m; 1100-1020s (several bands); 960w; 950w; 840w; 790m; 650w.

NMR data ($CDCl_3$); τ 5.12 (1H, d, $J_{1,2}$= 3.5-4 Hz, H-1); τ 5.26 (1H, t, $J_{2,3}$= $J_{3,4}$= 10-11Hz, H-3); τ 6.19 (1H, q, $J_{1,2}$= 3.5-4Hz, $J_{2,3}$= 10-11Hz, H-2); τ 6.18-6.46 (2H, m, H-4 and H-5); τ 6.58, 6.62 (6H, 2s, OCH_3); τ 7.51 (1H, b, disappeared on deuteration, OH); τ 8.71 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

By further elution of the column, 108 mg of the starting compound I was recovered.

Methyl 3-Amino-3,6-dideoxy-2,4-di-Omethyl-α-L-glucopyranoside Hydrochloride (IV)

The fully methylated compound III (150 mg) in ethanol (1 ml) was introduced into a mixture of pre-reduced platinum dioxide (100 mg) and 0.1 N HCl (6.4 ml).

The mixture was hydrogenated at room temperature and atmospheric pressure. After two weeks, the solution was filtered and evaporated to give a white solid. The solid was washed by trituration with ethyl acetate and it weighed 95 mg (61.6%) after drying. It decomposed at 263-265° and showed $[\alpha]_D$ -133° (c, 1, in chloroform).

Anal. Calcd for $C_9H_{20}O_4NCl$ (241.7): C, 44.72; H, 8.34; Cl, 14.67. Found: C, 44.87; H, 8.11; Cl, 14.88.

Infrared bands (cm^{-1}) were at 3200-3000w, b, (NH); 2800-2500m (several bands); 1600s, 1500s (NH_3^+); 1195m; 1170m; 1100s; 1050s; 1000s; 975w; 910w; 880w; 840w; 740w.

A 60-MHz NMR spectrum taken in deuterium oxide with acetone as internal standard showed the expected substituent resonances, namely, a doublet (splitting, 6 Hz) for C-CH_3 at 0.87 ppm upfield from the acetone signal, and three singlets for OCH_3 in the region about 1.20-1.30 ppm downfield from the acetone signal.

Methyl 3-Acetamido-3,6-dideoxy-2,4-di-O-methyl-α-L-glucopyranoside (V)

The hydrochloride IV (30 mg) in a mixture of water (3 ml) and methanol (1 ml) was cooled in an ice bath. With stirring of the solution, Dowex 1x8 ($CO_3^=$ form,

1 ml) and acetic anhydride (0.5 ml) were added. After 90 minutes the anion-exchange resin was filtered off, and the filtrate was passed through a small column containing cation-exchange resin Amberlite IR-120(H^+) (10 ml). The column was washed twice with water, the combined solution was heated on a steam bath for 15 minutes and was then evaporated to dryness at a bath temperature of 45°. Crystallization of the residue from ethyl acetate afforded long needles (26 mg, 85%), m.p. 210-211°; $[\alpha]_D$ -128.4° (c, 0.69, in methanol).

Anal. Calcd for $C_{11}H_{21}O_5N$ (247.3): C, 53.42; H, 8.56; N, 5.66. Found: C, 53.28; H, 8.49; N, 5.75.

The product exhibited typical infrared bands (cm^{-1}) at 3290s, 3100m, (NH); 1650s (amide I); 1560s (amide II). Other bands occurred at 1320m; 1160m; 1100s; 1050s; 990m; 960m. NH_3^+ bands were absent.

NMR data ($CDCl_3$): τ 5.22 (1H, d, $J_{1,2}$= 4Hz, H-1); τ 6.08 (1H, m, H-3); τ 6.22-6.92 (3H, m, H-2, H-4, and H-5); τ 6.54, 6.60 (9H, 3s, OCH_3); τ 8.01 (3H, s, N-acetyl); τ 8.74 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

Methyl 4-O-Acetyl-3,6-dideoxy-2-O-methyl-3-nitro-α-L-glucopyranoside (VI)

1) By acetylation of the 2-O-methyl ether II.

The 2-O-methyl ether II (350 mg) in acetic anhydride (5 ml) was stirred in a dry-ice bath. Boron trifluoride etherate (3 drops) was added. After ten minutes the mixture was poured into ice water with vigorous stirring. The mixture was evaporated, and several portions of added ethanol were evaporated from the residue. Trituration of the residue with water and filtration yielded the product (433 mg, 99.5%) that was dried and recrystallized from ether-petroleum ether to furnish nice, long needles, m.p. 78.5-79.5°; $[\alpha]_D$ -149.5° (c, 0.95, in chloroform).

Anal. Calcd for $C_{10}H_{17}O_7N$ (263.2): C, 45.62; H, 6.51; N, 5.32. Found: C, 45.55; H, 6.55; N, 5.14.

Characteristic infrared absorptions (cm^{-1}) occurred at 1747s (ester carbonyl); 1550s (NO_2); 1220s; 1190m; 1060w; 1045s; 953w; 882w; 782w. There was no hydroxyl peak.

NMR data ($CDCl_3$): τ 4.82 (1H, t, $J_{3,4}$= $J_{4,5}$ = 10Hz, H-4); τ 5.07 (1H, d, $J_{1,2}$= 3.5Hz, H-1); τ 5.15 (1H, t, $J_{2,3}$= $J_{3,4}$=10Hz, H-3); τ 6.08 (1H, q, $J_{1,2}$= 3.5Hz, $J_{2,3}$= 10Hz, H-2); τ 6.19 (1H, m, H-5); τ 6.55

6.59 (6H, 2s, OCH_3); τ7.97 (3H, s, O-acetyl); τ 8.82 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

The results of several exploratory acetylations suggested that exceeding the reaction time and amount of catalyst specified above tend to cause partial acetolysis at the glycosidic center, to give a mixture of compounds VI and VII.

2) By methylation of the 4-O-acetyl derivative XIII

The monoacetate XIII (described on p.149) in anhydrous ether (3 ml) was methylated with ethereal diazomethane solution (generated from 2 g of N-nitroso-methylurea) and boron trifluoride etherate according to the procedure described (p. 121) for the methylation of I. After work-up, a pale yellow syrup was obtained and dissolved in the minimum amount of carbon tetrachloride. Cautious addition of petroleum ether and scratching with a glass rod produced colorless crystals (35 mg, 83%). The product was identical with that obtained under 1) according to IR and NMR spectra.

1,4-Di-O-acetyl-3,6-dideoxy-2-O-methyl-3-nitro-α-L-glucopyranose (VII)

A solution of compound II (310 mg) in acetic anhydride (6 ml) was stirred magnetically in an ice bath

for ten minutes. Now, boron trifluoride etherate was added dropwise (10 drops). After one hour the solution was evaporated several times with added portions of toluene to give a yellow syrup. The syrup was dissolved in ethyl acetate and treated with activated charcoal. After filtration and evaporation a light-brown solid was obtained. Crystallization from ethyl acetate-petroleum ether afforded white crystals of VII (90 mg). T.l.c. of the mother liquor using benzene-ethyl acetate (9:1) revealed the presence of additional VII and of two minor components. Column chromatography of the mother liquor on a silica gel column, with the solvent system just mentioned, furnished 196 mg of VII, which raised the total yield to 86%; m.p. 108-109°; $[\alpha]_D$ -123.2° (c, 1.1, in chloroform).

Anal. Calcd for $C_{11}H_{17}O_8N$ (291.2): C, 45.39; H, 5.84; N, 4.81. Found: C, 45.20; H, 5.74; N, 4.81.

Characteristic infrared bands (cm^{-1}): 1745s (ester carbonyl); 1550s (nitroalkane). Other bands occurred at 1220s; 1140m; 1110m; 1045m; 1015m; 935m; 900w and 845w. Hydroxyl absorption was absent.

NMR data ($CDCl_3$): τ 3.54 (1H, d, $J_{1,2}$= 3.5Hz, H-1); τ 4.76 (1H, t, $J_{4,5}$= $J_{3,4}$= 10Hz, H-4); τ 5.17 (1H, t, $J_{2,3}$= $J_{3,4}$= 10Hz, H-3); τ 5.98 (1H, q, $J_{1,2}$= 3.5Hz,

τ 6.61 (3H, s, 2-OCH_3); $J_{2,3}$= 10Hz, H-2); τ 6.03 (1H, m, H-5); τ 7.84 (3H,s, 1-O-acetyl); τ 7.94 (3H, s, 4-O-acetyl); τ 8.79 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

In a similar but small-scale experiment the reaction mixture (from 15 mg of II, 1 ml of acetic anhydride, and 1 drop of boron trifluoride etherate) was poured into ice and the product was extracted with chloroform. Evaporation followed by crystallization from ethanol-petroleum ether gave 18 mg (91%) of VII.

Methyl 3,4,6-Trideoxy-2-O-methyl-3-nitro-α-L-erythro-hex-3-enopyranoside (IX)

A. From the 2-O-methyl ether II by the action of triphenylphosphine and carbon tetrachloride

1) Methyl 4-chloro-3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-galactopyranoside (VIII)

A mixture of compound II (700 mg), triphenyphosphine (2.1 g), and Drierite (1 g) in carbon tetrachloride (40 ml) was heated under reflux with vigorous stirring. After twelve hours the mixture was filtered and the solution evaporated. The resulting yellow syrup was placed on a silica gel (12 g) column and

eluted with ethyl acetate - carbon tetrachloride (2:8,v/v). Appropriate fraction (as indicated by t.l.c.) were pooled and evaporated to give a white, solid residue. Recrystallization from cold ether-petroleum ether mixture furnished the pure chloronitro compound VIII (326 mg, 44.3%). Evaporation of the mother liquor gave a colorless syrup (164 mg). An NMR spectrum indicated that this syrup was composed of chloronitro sugar VIII and nitroolefin IX, in a ratio of about 1:2, corresponding to about 55 mg of VIII and 109 mg of IX. Pure VIII melted at 100-101° and exhibited $[\alpha]_D$ -180.2° (c, 1.34, in chloroform).

Anal. Calcd for $C_8H_{14}ClO_5N$ (239.7): C, 40.09; H, 5.89; Cl, 14.79. Found: C, 40.23; H, 5.96; Cl, 14.61.

Prominent infrared frequencies (cm^{-1}) occurred at 1560s, doublet; 1200m; 1160m; 1120s; 1090ms; 1048s, shoulder; 980m; 930m; 790w. Hydroxyl absorption was absent.

NMR data ($CDCl_3$): τ 5.05 (2H, superimposed quartet and doublet assigned to H-3 and H-1 respectively, with $J_{1,2}$= 3.5Hz, $J_{2,3}$= 10Hz, $J_{3,4}$= 3.5Hz; τ 5.46 (1H, q, $J_{3,4}$= 3.5Hz, $J_{4,5}$= 1.5Hz, H-4); τ 5.77 (1H, octet; $J_{4,5}$= 1.5Hz, $J_{5,6}$= 6-6.5Hz, H-5); τ 5.86 (1H, q, $J_{1,2}$= 3.5Hz, $J_{2,3}$= 10Hz, H-2); τ 6.52, 6.58

(6H, 2s, OCH_3); τ 8.68 (3H, d, $J_{5,6}$= 6-6.5Hz, $\underline{C}$-CH_3). Spin decoupling by double irradiation at τ 5.46 (H-4) changed the H-3 signal at τ5.05 to a doublet ($J_{2,3}$= 10Hz) while the H-1 doublet at the same position remained unchanged. Similarly the H-5 octet in the τ 5.8 region collapsed to a quartet while the H-2 quartet remained unchanged.

2) Nitroolefin IX

The reaction of compound II described under 1) was modified as follows. A solution of II (22 mg) and triphenylphosphine (22 mg) in carbon tetrachloride (about 4 ml) was refluxed for 20 hours, with vigorous stirring. Fresh triphenylphosphine (22 mg) in carbon tetrachloride (2 ml) was then added, and refluxing was continued for another 26 hours. The reaction mixture was allowed to cool, filtered, and passed through a small silica gel column. Elution with benzene removed the remaining triphenylphosphine. The column was then eluted with benzene-ethyl acetate (9:1,v/v), the appropriate fractions were collected and evaporated to give a pale yellow, crystalline product (14.5 mg, 72%) which was sufficiently pure for elemental analysis. Recrystallization from ether-petroleum ether yielded long flaky crystal of IX, m.p. 103-105°;

$[\alpha]_D$ -205.6° (c, 0.9, in chloroform).

Anal. Calcd for $C_8H_{13}O_5N$ (203.2): C, 47.29; H, 6.45; N, 6.89. Found: C, 47.43; H, 6.60; N, 7.02.

The infrared spectrum of the product showed absorptions (cm^{-1}) at 1670w (C=C); 1515s (nitroalkene); 1350s (shoulder); 1185m; 1150m; 1110s; 1070m; 970m; 890m; 800m (shoulder).

NMR data ($CDCl_3$): τ 2.94 (1H, d, $J_{4,5}$= 2.0Hz, H-4); τ 5.08 (1H, d, $J_{1,2}$= 3Hz, H-1); τ 5.35 (1H, q, b, $J_{5,6}$= 7Hz, H-5); τ 5.59 (1H, q, $J_{1,2}$= 3Hz, $J_{2,5}$= 2.0Hz, H-2); τ 6.43, 6.46 (6H, 2s, OCH_3); τ 8.62 (3H, d, $J_{5,6}$= 7Hz, C-CH_3).

An ultraviolet spectrum in chloroform showed λ_{max} 245 nm (ε, 5300).

Alternatively, 30 mg of chloronitro compound VIII was put on a column containing 10 g of silica gel. The column was eluted slowly with a mixture of benzene-ethyl acetate (9:1,v/v). The eluate was collected and evaporated to dryness. Crystalline product IX was obtained (21 mg, 82.5%). It melted at 102-104° and IR and NMR spectra were identical with those obtained from nitroolefin IX described in the previous paragraph.

B. By methylation of methyl 3,4,6-trideoxy-3-nitro-α-L-erythro-hex-3-enopyranoside (XIV)

To a cooled solution of nitroolefin XIV (see p.151) (20 mg) in anhydrous ether (2 ml) was added 1 drop of boron trifluoride etherate. Ethereal diazomethane solution generated from 2 g N-nitroso-methylurea was then cautiously added, with stirring, at such a rate that no excess of diazomethane was building up during the reaction. Methylation was completed within 10 minutes as shown by t.l.c. (solvent system, 20% ethyl acetate in benzene). A white flocculent precipitate of polymethylene was removed by filtration, and the solution was evaporated to give a colorless, crystalline product (20 mg, 93%). It melted at 102-103° and exhibited $[\alpha]_D$ -204.5° (c, 1, in chloroform), and its infrared spectrum was identical with that of IX described in section A.

Methyl 3-Amino-3,4,6-trideoxy-2-O-methyl-α-L-xylo-hexopyranoside Hydrochloride (XI)

Nitroolefin IX (60 mg) in ethanol (8 ml) was reduced with sodium borohydride (60 mg) at 0°. After fifteen minutes about 5 ml of methanol was added, and the solution was neutralized with Amberlite IR-120

(H^+). The filtered solution was evaporated to give an oil from which several portions of added methanol were successively evaporated. The resultant, colorless syrup of the saturated nitro compound X ($[\alpha]_D$ -195°, c, 0.55, in chloroform) was chromatographically homogeneous (t.l.c.).

The syrup was hydrogenated over prereduced platinum dioxide (60 mg) in the presence of an equivalent amount of dilute hydrochloric acid. After four hours of hydrogenating, the solution was filtered and evaporated to give white, crystalline XI (57 mg, 95%), which melted with decomposition at 206-208° and exhibited $[\alpha]_D$ -144.6° (c, 0.65, in methanol).

Anal. Calcd for $C_8H_{18}O_3NCl$ (211.7): C, 45.39; H, 8.57; Cl, 16.75. Found: C, 45.27; H, 8.52; Cl, 16.92.

Methyl 3-Acetamido-3,4,6-trideoxy-2-O-methyl-α-L-xylo-hexopyranoside (XII)

The amine hydrochloride XI (22 mg) was N-acetylated (2h, at 0°) using a mixture of water (10 ml), methanol (1 ml), acetic anhydride (1 ml), and Dowex 1x8 ($CO_3^=$ form, 3 ml). After work-up, the N-acetylated product was obtained in a yield of 19 mg (84%). It melted at 178-179° and showed $[\alpha]_D$ -160.5° (c, 0.87, in chloroform).

Anal. Calcd for $C_{10}H_{19}O_4N$ (217.3): C, 55.28; H, 8.82; N, 6.45. Found: C, 55.45; H, 8.74; N, 6.44.

NMR data ($CDCl_3$): τ 5.12 (1H, d, $J_{1,2}$ = 3Hz, H-1); τ 5.82-6.14 (2H, m, b, H-3 and H-5); τ 6.59 (6H, s, OCH_3); τ 6.76 (1H, q, $J_{1,2}$= 3Hz, $J_{2,3}$= 10Hz, H-2); τ 7.71 (1H, octet, H-4_e); τ 7.95 (1H, m, H-4_a); τ 8.04 (3H, s, N-acetyl); τ 8.83 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

B. SYNTHESIS OF DIAMINO SUGARS

Methyl 4-Amino-3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-glucopyranoside Hydrochloride (XV)

The monoacetate VI (200 mg) in anhydrous ether (30 ml) was added dropwise to liquid ammonia (10 ml), and the mixture was stirred in a dry-ice bath for 6 hours during which time some ammonium acetate was observed to precipitate. The crystals were filtered off and excess ammonia was removed by evaporating several times with ether. The colorless syrup so obtained was dissolved in anhydrous ether and titrated with ethereal hydrogen chloride in the presence of Tashiro indicator. A slightly pink, crystalline precipitate occurred which was collected, redissolved in anhydrous methanol, and decolorized with activated charcoal. Upon evaporation of the solvent, the hydrochloride XV was obtained as a white solid. Crystallization from a mixture of methanol,

ethyl acetate and petroleum ether furnished flaky crystals (189 mg, 96.5%) which melted with decomposition at 156-157°. Recrystallization from methanol-ethyl acetate raised the decomposition point to 161-163°; $[\alpha]_D$ -130.6° (c, 0.79, in methanol). R_{GN} = 2.81.

Anal. Calcd for $C_8H_{17}O_5N_2Cl$ (256.7): C, 37.43; H, 6.68; Cl, 13.81. Found: C, 37.31; H, 6.59; Cl, 13.73.

Infrared frequencies (cm^{-1}) were at 3120 (broad); 2800-2400m, broad; 1590s, 1505s (NH_3^+); 1550s (nitroalkane); 1355s; 1195m; 1115s; 1055s; 940m. Ester carbonyl absorption was absent.

Methyl 4-Acetamido-3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-glucopyranoside (XVI)

1) Directly from the 4-acetate VI.

Compound VI (35 mg) was dissolved in anhydrous ether (20 ml). The solution was cooled in a dry-ice bath and dry ammonia gas was bubbled through for about five hours. The mixture was then allowed to stand at room temperature overnight. Ammonium acetate was filtered off, and the solution was evaporated to give a glassy syrup. Acetic anhydride (2 ml) was added and then evaporated from the product at a bath temperature of 40°. This

procedure was repeated several times, and finally a slightly yellow solid was obtained. Crystallization from ethyl acetate -petroleum ether afforded fine needles of XVI (28 mg, 80%); m.p. 206-208°; $[\alpha]_D$ -134.6° (c, 1.57, in chloroform).

Anal. Calcd for $C_{10}H_{18}O_6N_2$ (262.3): C, 45.79; H, 6.92; N, 10.68. Found: C, 45.69; H, 6.73; N, 10.56.

Prominent infrared bands (cm^{-1}) occurred at 3310s (NH); 1660s (amide I); 1560-1540s (nitroalkane and amide II). Ester carbonyl absorption was absent.

NMR data ($CDCl_3$): τ 4.03 (1H, d, b, NH); τ 5.09 (1H, d, $J_{1,2}$= 3.5-4Hz, H-1); τ 5.18 (1H, t, $J_{2,3}$=$J_{3,4}$ 10Hz, H-3); τ 5.75 (1H, q, $J_{3,4}$= $J_{4,5}$= $J_{4,NH}$= 10Hz, H-4); τ 6.10 (1H, q, $J_{1,2}$= 3.5-4Hz, $J_{2,3}$= 10Hz, H-2); τ 6.20 (1H, m, b, H-5); τ 6.50, 6.61 (6H, 2s, OCH_3); τ 8.05 (3H, s, N-acetyl); τ 8.77 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

2) From the amine hydrochloride XV

Compound XV (100 mg) in a mixture of water (10 ml) and methanol (2 ml) was stirred in an ice bath for 15 minutes. Anion exchange resin Dowex 1x8 ($CO_3^=$ form, 2 ml) and acetic anhydride (2 ml) were added. After two hours the solution was filtered, and the filtrate was passed through a column of cation exchange resin Amberlite IR-120 (H^+) (10 ml). The column was washed twice with

5-ml portions of methanol. The combined effluents were boiled on a steam bath for fifteen minutes and evaporated to give a yellow syrup. The syrup was dissolved in a small amount of absolute ethanol, and petroleum ether was carefully added to incipient turbidity. Beautiful, long needles crystallized in a yield of 97 mg (95%). This product was identical in all respects with compound XVI described in the preceding subsection.

Methyl 3,4-Diamino-3,4,6-trideoxy-2-O-methyl-α-L-gluco-pyranoside Dihydrochloride (XVII)

The aminonitro compound XV (100 mg) was hydrogenated in water (10 ml) in the presence of pre-reduced platinum dioxide and 0.1 N hydrochloric acid (3.9 ml). The hydrogenation was conducted at ordinary temperature and pressure for four hours. Evaporation then gave a white, solid residue which was crystallized from ethanol-ethyl acetate to yield the diamino sugar XVII (95 mg, 93%). The compound began to turn brown at 150° and melted with decomposition at 188-190°; $[\alpha]_D$ -110.9° (c, 0.68, in methanol). R_{GN} = 1.57.

Anal. Calcd for $C_8H_{18}O_3N_2$ (263.2): C, 36.51; H, 7.66; Cl, 26.95. Found: C, 36.77; H, 7.84; Cl, 26.90.

Infrared bands (cm^{-1}) were recorded at 3400m, broad (NH); 2800-2400m, broad (NH_3^+); 1595s, 1505s (NH_3^+); 1200m; 1170m; 1110s; 1050s; 950w.

Methyl 3,4-Diacetamido-3,4,6-trideoxy-2-O-methyl-α-L-glucopyranoside (XVIII)

The diamino sugar dihydrochloride XVII (60 mg) was N-acetylated at 0° in a magnetically stirred mixture of water (4 ml), methanol (1 ml), acetic anhydride (2 ml), and Dowex 1x8 ($CO_3^=$ form, 2 ml). After a reaction time of two hours the resin was filtered off and the filtrate was passed through a cation exchange column containing 10 ml of Amberlite IR-120 (H^+). The eluates were collected and boiled for fifteen minutes on a steam bath. Evaporation of the solution gave a solid residue which was crystallized from ethanol and ethyl acetate to furnish the diacetamido compound XVIII (55 mg, 88%). It sublimed at a temperature of 298-300° and exhibited $[\alpha]_D$ -201° (c, 0.6, in methanol).

Anal. Calcd for $C_{12}H_{22}O_5N_2$ (274.3): C, 52.54; H, 8.08; N, 10.21. Found: C, 52.35; H, 7.97; N, 10.21.

Characteristic infrared frequencies (cm^{-1}) occurred at 3300s, 3100m (NH); 1640s (amide I); 1560s, 1540s (amide II). Other bands were at 1300m; 1160m;

1115m; 1090s; 1040s; 1030s; 960m; 900m.

NMR data ($CDCl_3$ + 3 drops MeOH): τ 2.92 (1H, b, NH); τ 5.17 (1H, d, $J_{1,2}$= 3-4Hz, H-1); τ 5.79 (1H, q, $J_{3,4}$= $J_{4,5}$= $J_{4,4NH}$= 10Hz, H-4); τ 6.23-6.89 (3H, m, H-2, H-3, and H-5); τ 6.58, 6.60 (6H, 2s, OCH_3); τ 8.08 (6H, 2s, N-acetyl); τ 8.85 (3H, d, $J_{5,6}$= 5-6Hz, C-CH_3).

C. SYNTHESIS OF TRIAMINO SUGARS

Methyl 2,4-Diacetamido-2,3,4,6-tetradeoxy-3-nitro-α-L-glucopyranoside (XX)

Dry ammonia gas was passed at -70° through an ethereal solution of diacetate XIX (250 mg) obtained as described on p.144 . The reaction was complete after a period of 5 h as shown by the disappearance of starting material (t.l.c.). Ammonium acetate deposited during the reaction was filtered off, and the solution was concentrated at room temperature. The resulting syrup was evaporated several times with added acetic anhydride and then with toluene, at a bath temperature of about 50°, to give a slightly yellow, solid residue. The solid was dried in vacuo and triturated with hot ethyl acetate.

Colorless crystals of XX (149 mg, 60%) were collected by filtration and shown to be pure by t.l.c. (methanol-chloroform, 1:4). The compound melted with decomposition at 331° and exhibited $[\alpha]_D$ -108.8° (c, 1, in methanol). [Reported value: m.p. 309° (dec.), $[\alpha]_D$ -133° (c, 0.5, in methanol) (125)].

The mother liquor was revealed by t.l.c. to contain at least two additional compounds.

Anal. Calcd for $C_{11}H_{19}O_6N_3$ (289.3): C, 45.67; H, 6.62; N, 14.53. Found: C, 45.60; H, 6.39; N, 14.68.

Infrared absorptions (cm^{-1}) were: A doublet at 3340s and 3310s (NH); 1660s (amide I); 1552s, 1535s (nitro and amide II); 1300m; 1270m; 1192w; 1133m (shoulder); 1090m; 1030ms.

The NMR spectrum (in DMSO-d_6) is shown in Fig. 9. Assignments were made as follows: τ 1.54-1.82 (2H, b, 4 peaks, NH); τ 5.13 (1H, t, $J_{2,3}$= $J_{3,4}$= 11Hz, H-3); τ 5.36 (1H, d, $J_{1,2}$= 3-3.5Hz, H-1); τ 5.28-6.46 (3H, m, H-2, H-4, H-5); τ 6.68 (3H, s, OCH_3); τ8.22 (6H, s, N-acetyl); τ 8.89 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

Methyl 2,4-Diacetamido-3-amino-2,3,4,6-tetradeoxy-α-L-glucopyranoside Hydrochloride (XXI)

The nitroacetamido compound XX (60 mg) was

suspended in dilute hydrochloric acid (50 ml of water plus 3.5 ml of 0.1 N HCl), and hydrogenated with pre-reduced platinum dioxide catalyst for three days at ordinary temperature and pressure. The filtered solution was evaporated several times with ethanol to give a white solid (60 mg, 97.5%). A test sample did not show nitronate absorption in the ultraviolet when dissolved in 0.1 N sodium hydroxide solution, indicating complete reduction. The solid was recrystallized from ethanol-ethyl acetate and then melted with decomposition at 259-260°; $[\alpha]_D$ -103.2° (c, 0.5, in water).

Anal. Calcd for $C_{11}H_{22}O_4N_3Cl$ (295.8): C, 44.67; H, 7.50; Cl, 11.95. Found: C, 44.55; H, 7.50; Cl, 11.86.

Characteristic infrared frequencies (cm^{-1}) occurred at : 3270s, b; 3070m, b, (NH); 2800-2400m, b; 1660s (amide I); 1590m. 1505m (NH_3^+); 1545s (amide II). Other bands were at 1305m; 1278m; 1235w; 1200m; 1176m; 1132s; 1105m; 1070s; 1055s; 1000, several peaks; 962m; 946m; 882w; 840w.

Methyl 2,3,4-Triacetamido-2,3,4,6-tetradeoxy-α-L-gluco-pyranoside (XXII)

The amine hydrochloride XXI (76 mg) was

N-acetylated with acetic anhydride (0.5 ml) and Dowex 1x8 ($CO_3^=$ form) in a mixture of methanol (3 ml) and water (5 ml). The mixture was stirred for 90 minutes at 0°, and the filtered solution was evaporated to give a pale yellow solid. The solid was dissolved in methanol and upon standing in the open air afforded fine needles of XXII (63 mg, 81%); m.p. 360°; $[\alpha]_D$ -135° (c, 0.7, in methanol). The reported physical constants (125) were: m.p. 320°; $[\alpha]_D$ -124° (c, 0.5, in acetic acid).

Compound XXII was sparingly soluble in methanol and hardly soluble in water and other common organic solvents.

The infrared spectrum showed characteristic absorptions at 3300s (shoulder), 3100w, b (NH); 1650s (amide I); 1550s (amide II). Other bands were at 1220-1210m, doublet; 1200-1120m, several peaks; 1096m (shoulder); 1050m; 923w (shoulder).

Part II

A. SYNTHESIS OF NITROOLEFIN SUGARS FROM METHYL 3,6-DI-DEOXY-3-NITRO-α-L-HEXOPYRANOSIDES

Methyl 2,4-Di-O-acetyl-3,6-dideoxy-3-nitro-α-L-gluco-pyranoside (II)

Dihydroxy compound I (1 g) (84) was dissolved in acetic anhydride (5 ml), and the solution was cooled in an ice-bath. Boron trifluoride etherate (3 drops) was added with stirring. After 15 minutes the solution was poured into ice water with vigorous stirring. A white solid was formed and collected by filtration (1.345 g, 95%). It melted at 109-111° and was recrystallized from methanol to yield colorless plates; m.p. 113-113.5°; $[\alpha]_D$ -155.3° (c, 1.3, in chloroform).

Anal. Calcd for $C_{11}H_{17}O_8N$ (291.2): C, 45.36; H, 5.88; N, 4.81. Found: C, 45.39; H, 5.80; N, 4.83.

Infrared bands (cm^{-1}) were at 1740s (ester carbonyl); 1546s (NO_2); 1335m; 1220s; 1187ms; 1165m; 1139m; 1100m 1088m; 1025s; 950m; 923m; 890m; 833w; 780w.

NMR data ($CDCl_3$): τ 4.74 (1H, q, $J_{1,2}$= 3.5Hz, $J_{2,3}$= 10Hz, H-2); τ 4.81 (1H, t, $J_{3,4}$= $J_{4,5}$= 10Hz, H-4);

τ 5.01 (1H, d, $J_{1,2}$= 3.5Hz, H-1); τ 5.07 (1H, t, $J_{2,3}$= $J_{3,4}$= 10Hz, H-3); τ 6.16 (1H, octet, $J_{4,5}$= 10Hz, $J_{5,6}$= 6Hz, H-5); τ 6.62 (3H, s, OCH_3); τ 8.98 (6H, s, O-acetyl); τ 8.79 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

This compound was recently reported by Lichtenthaler et al. (125) to have m.p. 109-110° and $[\alpha]_D$ -154° (c, 1.0, in chloroform).

Schmidt-Rutz Reaction of Diacetate II:

Methyl 2-O-Acetyl-3,4,6-trideoxy-3-nitro-α-L-erythro-hex-3-enopyranoside (III) and Methyl 2-O-Acetyl-3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (IV)

Diacetate II (950 mg), sodium bicarbonate (4.75 g, dried at 120°) and Drierite powder (500 mg) were refluxed with magnetic stirring in benzene (50 ml, dried over sodium wire). After 40 h the reaction mixture was filtered and the filtrate was evaporated to give a yellow syrup (810 mg). The NMR spectrum of the syrup suggested that it was a mixture of olefin III and starting diacetate II in a ratio of 3:2. The syrup was dried in vacuo, dissolved in dry benzene (50 ml), and again refluxed in the presence of fresh sodium bicarbonate (4 g) and Drierite (400 mg). The progress of the reaction

was monitored by infrared spectroscopy. The reaction was stopped when the nitroalkane peak at 1560 cm^{-1} had disappeared completely, after about 16h. Filtration and evaporation gave a brownish-yellow syrup (500 mg). Thin layer chromatography with benzene containing 10% of ethyl acetate showed at least four spots. The syrup was chromatographed on a column containing 30 g of silica gel, by use of the solvent mixture just mentioned. Fractions of 5 ml were collected, inspected by t.l.c., appropriately pooled, and evaporated to dryness.

The first few fractions yielded a brownish-yellow solid material (14 mg) which was not identified.

The material corresponding to the second-fastest t.l.c. spot was collected as a slightly yellow, crystalline product (160 mg, 21.2%). Recrystallization from ether-petroleum ether furnished the olefin IV as small, cube-like crystals; m.p. 81-81.5°; $[\alpha]_D$ -165° (c, 0.8, in chloroform).

Anal. Calcd for $C_9H_{13}O_6N$ (231.2): C, 46.75; H, 5.67; N, 6.06. Found: C, 46.73; H, 5.84; N, 6.22.

Characteristic infrared absorptions (cm^{-1}, in chloroform) occurred at: 1735s (ester carbonyl); 1675w (C=C); 1520s (nitroalkene). Other bands were at:

1425m, b; 1368ms; 1343s; 1195s, b; 1153ms; 1120ms; 1080s; 1028ms; 1000w; 980w; 913m.

UV data (in chloroform): λ_{max} 247 nm; $\underline{\varepsilon}$, 5700.

NMR spectrum (Fig.10)in deuterated chloroform showed: τ 2.56 (1H, d, $J_{4,5}$= 2Hz, H-4); τ 4.28 (1H, q, $J_{1,2}$= 1Hz, $J_{2,5}$= 2Hz, H-2); τ 5.12 (1H, d, $J_{1,2}$= 1Hz, H-1); τ 5.46 (1H, 12 peaks, $J_{2,5}$= $J_{4,5}$= 2Hz, $J_{5,6}$= 7.5Hz, H-5); τ 6.57 (3H, s, OCH_3); τ 7.93 (3H, s, O-acetyl); τ 8.55 (3H, d, $J_{5,6}$= 7.5Hz, C-CH_3).

The material corresponding to the third t.l.c. spot was eluted from the column as a yellow syrup (30 mg, 4%). It was dissolved in a small amount of ether to which petroleum ether was added to incipient turbidity. After cooling overnight in the refrigerator, small colorless crystals of olefin III were obtained. They melted at 98-99° and exhibited $[\alpha]_D$ -258.5° (c, 0.84, in chloroform).

Anal. Calcd for $C_9H_{13}O_6N$ (231.2): C, 46.75; H, 5.67; N, 6.06. Found: C, 46.58; H, 5.69; N, 6.21.

Characteristic infrared absorptions (cm^{-1} in chloroform) occurred at : 1745s (ester carbonyl); 1680w (C=C); 1522s (nitroalkene). Other bands were at: 1442m, b; 1370s; 1340s; 1200s; 1152ms; 1128s; 1050s; 985m; 956m; 938w; 910m; 890m; 860w.

UV data (in chloroform): λ_{max} 247 nm; $\underline{\varepsilon}$, 5250.

NMR data (Fig.11, in $CDCl_3$): τ 2.73 (1H, q, $J_{2,4}$= 1Hz, $J_{4,5}$= 1.5-2Hz, H-4); τ 4.08 (1H, m, H-2); τ 4.98 (1H, d, $J_{1,2}$= 4Hz, H-1); τ 5.36 (1H, m, $J_{5,6}$= 7Hz, H-5); τ 6.54 (3H, s, OCH_3); τ 7.91 (3H, s, O-acetyl); τ 8.59 (3H, d, $J_{5,6}$= 7Hz, C-CH_3). Spin decoupling by double irradiation at 4.08τ (H-2) changed the H-1 signal at 4.89τ to a singlet while the quartet (H-4) at 2.73τ became a doublet with a coupling constant $J_{4,5}$= 1.5-2Hz. In addition, the H-5 signal (12 peaks) in the 5.3 region collapsed to an octet showing $J_{4,5}$= 2Hz and $J_{5,6}$= 7Hz.

Material corresponding to the fourth spot was obtained from the column as a yellow syrup (30 mg); it was not identified.

It was observed that partial dehydroacetylation occurs in the diacetate II also when it is merely subjected to column chromatography on silica gel. Thus, chromatography of II (500 mg) on 250 g of silica gel column furnished 350 mg of a crystalline material which, although it gave a single spot on t.l.c., appeared to consist of about equal proportions of II and a nitro-olefinic compound. This was suggested by the NMR spectrum

(in $CDCl_3$):there was a signal at 2.70τ attributable to a nitroolefinic proton, and two methoxyl singlets (6.50τ and 6.57τ) as well as two C-methyl doublets (8.58τ and 8.75τ , both sets of equal intensities). The mixture was rechromatographed on a smaller column (30 g of silica gel), 5-ml fractions being collected. Of 18 fractions that contained carbohydrate the first 13 fractions yielded 262 mg of what was a similar mixture as before. The subsequent 5 fractions gave 32 mg of III that was identified by its melting point (97-98.5°) and NMR spectrum.

Methyl 4-O-Acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (VI)

A solution of diacetate II (500 mg) in a mixture of N methanolic hydrochloric acid (9 ml) and acetone (1 ml) was stirred at a temperature of 45-50°. The progress of methanolysis was monitored by t.l.c. (solvent system: 5% methanol in chloroform). It was found that the starting compound had disappeared completely after 2 h. The reaction was stopped and the solution was evaporated without prior neutralization. A yellow syrup (350 mg) was obtained which was chromatographed on

a column containing 20 g of silica gel. Elution was performed with 5% methanol in chloroform and was monitored by t.l.c.. From the fractions containing the monoacetate VI, the latter was obtained as crystals (148 mg, 34.6%) which upon recrystallization from ether and petroleum ether showed m.p. 112-113°; $[\alpha]_D$ -178.5° (c, 1, in chloroform).

Anal. Calcd for $C_9H_{15}O_7N$ (249.2): C, 43.37; H, 6.07; N, 5.62. Found: C, 43.28; H, 5.96; N, 5.70.

The infrared spectrum (cm^{-1}) showed characteristic absorption at: 3460s (OH); 1746s (ester carbonyl); 1555s (nitroalkane). Other bands were at: 1348m (shoulder); 1212s; 1160w; 1140w; 1099m; 1038s; 950w; 928w; 900w; 880w; 840w; 790w.

NMR data (in $CDCl_3$): τ 4.86 (1H, t, $J_{3,4}$= $J_{4,5}$= 10Hz, H-4); τ 5.22 (1H, d, $J_{1,2}$= 4Hz, H-1); τ 5.26 (1H, t, $J_{2,3}$= $J_{3,4}$=10Hz, H-3); τ 5.80 (1H, q, $J_{1,2}$= 4Hz, $J_{2,3}$= 10Hz, H-2); τ 6.20 (1H, octet, $J_{4,5}$= 10Hz, $J_{5,6}$= 6Hz, H-5); τ 6.56 (3H, s, OCH_3); τ 8.00 (3H, s, O-acetyl); τ 8.83 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

Methyl 3,4,6-Trideoxy-3-nitro-α-L-erythro-hex-3-eno-pyranoside (VII)

The diacetate II (2.91 g) was dissolved in a mixture of N methanolic hydrochloric acid (40 ml) and acetone (4 ml), and stirred for 1 h at a temperature of 45-50°. Stirring was then continued at room temperature. The progress of reaction was followed by t.l.c. (solvent system: 20% ethyl acetate in benzene) and when, after 9 h, the starting material had disappeared, the solution was cooled with ice and neutralized with silver carbonate. The filtered solution was evaporated to give a syrup which was chromatographed on silica gel (120 g) column eluted with chloroform containing 5% of methanol. Fractions of 5 ml were collected, inspected by t.l.c., appropriately pooled and evaporated to dryness. A fast-moving and a slow-moving material were thus separated. The former consisted of a colorless syrup (1.275 g). Its infrared spectrum (thin film) showed two nitro absorptions, at 1560 and 1525 cm^{-1}, and the NMR spectrum (in $CDCl_3$) suggested that it was a 3:1 mixture of a monoacetate and a nitroolefin. This mixture was dealt with as described in the next paragraph.

The slow-moving material eluted from the column crystallized and was identified by its melting point (139-141°), and its infrared spectrum to be glycoside I. It amounted to 1 g.

The aforementioned mixture of fast-moving products was treated with 3% hydrogen chloride in anhydrous methanol for 1 h at a temperature of 45-50°. The solution was then neutralized with silver carbonate, filtered, and evaporated to dryness. The resulting syrup was chromatographed on 50 g of silica gel as previously described and yielded two products. Whereas the more slowly moving product (845 mg) was crystalline glycoside I, the faster moving product (200 mg) was the nitroolefin VII. It was obtained as crystals showing m.p. 115-116° and $[\alpha]_D$ -361.7° (c, 0.9, in chloroform).

Anal. Calcd for $C_7H_{11}O_5N$ (189.2): C, 44.44; H, 5.86; N, 7.41. Found: C, 44.58; H, 6.01; N, 7.64.

Characteristic infrared absorptions (cm^{-1}) occurred at 3380s (OH) and 1515s (nitroalkene). Other bands were at: 1300m; 1278m; 1218m; 1198m; 1153ms; 1130ms; 1100ms; 1070s; 1040ms; 985ms; 900m; 860w; 810m; 750m.

Ultraviolet data (in chloroform): λ_{max} 247 nm ($\underline{\varepsilon}$, 4100).

NMR data : τ 2.99 (1H, q, $J_{2,4}$= 1Hz, $J_{4,5}$= 1.5-2Hz, H-4); τ 5.02 (1H, d, $J_{1,2}$= 4.5Hz, H-1); τ 5.22 (1H, m, H-2); τ 5.46 (1H, m, H-5); τ 6.47 (3H, s, OCH_3); τ 7.20 (1H, d, $J_{2,2OH}$= 8Hz, OH; disappeared on deuteration); τ 8.54 (3H, q, $J_{5,6}$= 6Hz, $\underline{C}$-CH_3).

Alternatively, a similar mixture of VI and VII was obtained from pure crystalline monoacetate VI, simply by passing it slowly through a silica gel column.

Acetylation of Nitroolefin VII

A mixture of compound VII (30 mg) and acetic anhydride (1 ml) was cooled in an ice-bath, and boron trifluoride etherate (1 drop) was added. The solution was stirred for 5 minutes and then poured into ice water. Extraction with chloroform (2x20 ml) followed by evaporation of the solvent yielded a pale yellow syrup. Crystallization from ether -petroleum ether furnished small needles (33 mg, 90.2%); m.p. 97-99°; $[\alpha]_D$ -269° ($\underline{c}$, 0.88, in chloroform). The NMR spectrum was identical with that of compound III.

Methyl 2-O-Acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (VIII)

A mixture of dihydroxy compound I (2.92 g), anhydrous ether (30 ml), and acetyl chloride (1 ml) was cooled and stirred in an ice-bath. Triethylamine (1 mole, 1.965 ml) was then added dropwise, and stirring was continued for 1 h at 0° and 4 h at room temperature. A white precipitate was removed by filtration, and the filtrate was evaporated to give a yellow syrup. Thin layer chromatography with 20% ethyl acetate in benzene revealed four spots. They corresponded to unreacted I, 4-acetate VI, 2-acetate VIII, and 2,4-diacetate II (in order of increasing mobility). The syrup was chromatographed on a silica gel column using the t.l.c. solvent system just mentioned.

The diacetate II was isolated as a crystalline product (667 mg, 24%), m.p. 111-113°.

The product of second-highest mobility, VIII, was obtained as a colorless syrup (1.222 g, 51%). Attempts at crystallization did not prove successful. Compound VIII showed $[\alpha]_D$ -133.5° (c, 1, in chloroform).

Anal. Calcd for $C_9H_{15}O_7N$ (249.2): C, 43.37; H, 6.07; N, 5.62. Found: C, 43.38; H, 6.27; N, 5.77.

Infrared bands (cm^{-1} in chloroform) were at: 3600m, 3350m, b, (OH); 1742s (ester carbonyl); 1558s, 1364s (NO_2); 1441m; 1230s, b; 1190s; 1150ms; 1110ms; 1046s; 952w; 904m; 840w.

NMR data (in $CDCl_3$): τ 4.80 (1H, q, $J_{1,2}$= 3.5Hz, $J_{2,3}$= 11Hz, H-2); τ 5.06 (1H, d, $J_{1,2}$= 3.5Hz, H-1); τ 5.14 (1H, q, $J_{2,3}$= 11Hz, $J_{3,4}$= 9Hz, H-3); τ 6.24 (1H, m, H-4); τ 6.31 (1H, m, H-5); τ 6.64 (3H, s, OCH_3); τ 7.98 (3H, s, O-acetyl); τ 8.68 (3H, d, $J_{5,6}$= 6Hz, C-CH_3); τ 6.84 (1H, b, OH; disappeared on deuterium exchange).

The third fraction from the column furnished crystalline compound VI (200 mg, 10%). It melted at 109-111°, and its infrared spectrum was identical with that of VI described earlier.

The most slowly moving material was also obtained in crystalline form (937 mg) and proved to be starting material I.

Methyl 2,4-Di-O-acetyl-3,6-dideoxy-3-nitro-α-L-manno-pyranoside (XI)

To a cooled solution of methyl 3,6-dideoxy-

3-nitro-α-L-mannopyranoside (X)(400 mg) in acetic anhydride (5 ml) was added boron trifluoride etherate (3 drops). After being stirred for 15 min the mixture was poured into and stirred with ice water. A white solid separated and was collected by filtration and dried. It weighed 535 mg (95%) and melted at 140-142°. Recrystallization from methanol raised the melting point to 142-143°. The product (XI) showed $[\alpha]_D$ -8.6° (c, 1.4, in chloroform).

Characteristic infrared absorptions (cm^{-1}): 1750s (ester carbonyl); doublet at 1570s and 1552s (nitroalkane; only a single band was seen at 1560 cm^{-1} in a spectrum in chloroform solution). Other bands were at: 1225s, b; 1170s; 1132s (shoulder); 1080d; 1058d; 1021ms; 990ms; 948m; 937m; 893m; 840w; 810m.

NMR data (in $CDCl_3$): τ 4.41 (1H, t, $J_{3,4}$= 10.5Hz, $J_{4,5}$= 10Hz, H-4); τ 4.49 (1H, q, $J_{1,2}$= 1.5Hz, $J_{2,3}$= 3.5Hz, H-2); τ 5.10 (1H, q, $J_{2,3}$= 3.5Hz, $J_{3,4}$ = 10.5Hz, H-3); τ 5.26 (1H, d, $J_{1,2}$= 1.5Hz, H-1); τ 6.25 (1H, octet, $J_{4,5}$= 10Hz, $J_{5,6}$= 6Hz, H-5); τ 6.62 (3H, s, OCH_3); τ 7.94, 7.97 (6H, 2s, O-acetyl); τ 8.75 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

Compound XI was first prepared in small quantity by Dr. K. Čapek in this laboratory (unpublished

work). The present product was identical with a sample from his preparation according to melting point, optical rotation, and infrared spectrum. Dr. Čapek obtained the following analysis:

Anal. Calcd for $C_{11}H_{17}O_8N$ (291.2): C, 45.36; H, 5.88; N, 4.81. Found: C, 45.37; H, 6.05; N, 4.94. (Data disclosed by permission of Prof. H.H. Baer).

Methyl 4-O-Acetyl-3,6-dideoxy-3-nitro-α-L-mannopyranoside (XII)

The diacetate XI (1 g) was dissolved in 3% methanolic hydrogen chloride (25 ml), and the solution was kept at a temperature of 45-50°. The methanolysis was monitored by t.l.c. (solvent system, 20% ethyl acetate in benzene), and the reaction was stopped as soon as the starting material had disappeared (90 min). The reaction mixture, without neutralization, was evaporated at room temperature to give a syrup which was dissolved in a small amount of the chromatographic solvent mixture just mentioned and passed over a silica gel column (25 g), by elution with the same solvent system. Fractions of 5 ml were collected, inspected by t.l.c., appropriately pooled, and evaporated to dryness.

The fast-moving material obtained from the column was the monoacetate XII. It was isolated as white crystals (652 mg, 76%) that melted at 159-160° and had $[\alpha]_D$ -37.5° (c, 0.93, in chloroform).

Anal. Calcd for $C_9H_{15}O_7N$ (249.2): C, 43.37; H, 6.07; N, 6.62. Found: C, 43.34; H, 6.17; N, 5.77.

Characteristic infrared frequencies (cm^{-1}) occurred at : 3500s (OH); 1720s (ester carbonyl) and 1550s (nitroalkane).

NMR data (in $CDCl_3$): τ 4.41 (1H, t, $J_{3,4}$= 10.5Hz, $J_{4,5}$= 10Hz, H-4); τ 5.21 (1H, q, $J_{2,3}$= 3Hz, $J_{3,4}$= 10.5Hz, H-3); τ 5.27 (1H, d, $J_{1,2}$= 2Hz, H-1); τ 5.54 (1H, m, H-2; after deuterium exchange the multiplet became a quartet, with $J_{1,2}$= 2Hz, $J_{2,3}$= 3Hz); τ 6.26 (1H, octet, $J_{4,5}$= 10Hz, $J_{5,6}$= 6.5Hz, H-5); τ 6.61 (3H, s, OCH_3); τ 7.11 (1H, d, $J_{2,2OH}$ = 7Hz, OH ; this doublet disappeared on deuteration); τ 7.98 (3H, s, O-acetyl); τ 8.76 (3H, d, $J_{5,6}$= 6.5Hz, C-CH_3).

From subsequent fractions of the column, 150 mg (21%) of dihydroxy compound X was collected.

Methyl 3,4,6-Trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (XIII)

1) From Methyl 4-O- Acetyl-3,6-dideoxy-3-nitro-α-L-mannopyranoside (XII)

Monoacetate XII (50 mg) was placed on a column of silica gel (10 g) and eluted slowly with a 9:1 mixture of benzene and ethyl acetate. The eluate was evaporated to give a colorless syrup (33 mg, 87%) of XIII which exhibited $[\alpha]_D$ -198° (c, 1, in chloroform).

Characteristic infrared bands (cm^{-1} in chloroform) were recorded at 3600m (OH); 1675w (C=C); 1522s (nitroalkene). Other absorptions were at: 1348s; 1198s, b; 1158ms; 1122ms; 1078s; 1050ms; 1010m; 998m; 972m; 925w; 890w.

NMR data (in $CDCl_3$): τ 2.72 (1H, s, H-4); τ 5.08 (1H, s, H-1); 5.46 (1H, s, H-2); τ 5.51 (1H, m, H-5); τ 6.58 (3H, s, OCH_3); τ 7.08 (1H, b, OH; disappeared on deuterium exchange); τ 8.57 (3H, d, $J_{5,6}$= 7Hz, C-CH_3).

Ultraviolet data (in chloroform): λ_{max} 251 nm (ε, 5000).

2) From Methyl 2-O-Acetyl-3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (IV)

Compound IV (40 mg) was treated with 3%

methanolic hydrogen chloride (10 ml) at room temperature for 48 h. The solution was then evaporated to yield a slightly yellow syrup which was purified by column chromatography on silica gel (solvent system, 10% ethyl acetate in benzene). A colorless syrup (21 mg, 65%) was obtained. It showed $[\alpha]_D$ -195° (c, 0.8, in chloroform) and its NMR spectrum was identical with that of compound XIII described in the preceding section 1).

Methyl 2,3,6-Trideoxy-3-nitro-α- L- erythro-hex-2-eno-pyranoside (IX)

The crystalline hydrate of the glycoside X (1.37 g) was dried in an oil-pump vacuum at about 80° for 4 h. The resulting syrup of anhydrous X was dissolved in anhydrous ether, and acetyl chloride (1.02 mole, 0.44 ml) was added. The mixture was magnetically stirred in an ice-bath, and triethylamine (1 mole, 0.85 ml) was slowly added. The reaction was allowed to proceed for 1 h at 0° and for another 2 h at room temperature. The white precipitate of triethylammonium chloride was removed and the filtered solution was evaporated to give a syrup. Thin layer chromatography (solvent system: 20% ethyl acetate in benzene) showed four spots. Separation

by column chromatography (100 g silica gel) using the same solvent system yielded four components (a-d):

a) The fastest-moving material was isolated as crystals (88 mg) which melted at 142-144°, and were identified by an NMR spectrum as diacetate XI.

b) The second-fastest component was colorless, crystalline nitroolefin IX (227 mg). Recrystallization from ether-petroleum ether furnished long prisms; m.p. 124-125°; $[\alpha]_D$ +162.6 (c, 1, in chloroform).

Anal. Calcd for $C_7H_{11}O_5N$ (189.2): C, 44.44; H, 5.86; N, 7.41. Found: C, 44.58; H, 6.01; N, 7.64.

The infrared spectrum (cm^{-1}, in chloroform) showed typical absorption at 3600s (OH); 1523s (nitroalkene). Other bands were at: 1470w; 1338s; 1285w; 1190ms, b; 1131s; 1088s; 1070s; 1050s; 972ms; 915w,b; 870w.

UV absorption (in chloroform) showed λ_{max} 247 nm (ε, 3662).

NMR data (in $CDCl_3$): τ 2.97 (1H, q, $J_{1,2}$= 3.5Hz, $J_{2,4}$= 1Hz, H-2); τ 4.88 (1H, q, $J_{1,2}$= 3.5Hz, $J_{1,4}$= 1Hz, H-1); τ 5.60 (1H, 12 peaks, $J_{1,4}$= $J_{2,4}$= 1Hz, $J_{4,4OH}$= 3.8Hz, $J_{4,5}$= 8.5Hz, H-4); τ 6.00 (1H, octet, $J_{4,5}$= 8.5Hz, $J_{5,6}$= 6Hz, H-5); τ 6.55 (3H, s, OCH_3); τ 6.95 (1H, d, $J_{4,4OH}$= 3.8Hz, OH; disappeared on deuteration); τ 8.62 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

C) A small amount of material (25 mg) corresponding to the third spot was collected as a syrup. The NMR spectrum was identical with that of the nitroolefin XIII.

d) The most slowly moving material obtained from the column proved to be unreacted starting material X. It amounted to 800 mg.

Based on the amount of X that had actually reacted, the yields of XI, IX, and XIII were 14, 54 and 6%, respectively.

Methyl 4-O-Acetyl-2,3,6-trideoxy-3-nitro-α-L-erythro-hex-2-enopyranoside (V)

To an ice-cooled solution of nitroolefin IX (30 mg) in acetic anhydride (0.5 ml) was added a droplet of boron trifluoride etherate, and the solution was stirred for 2 min. The mixture then was poured into ice water which was extracted with chloroform (2x20 ml). The chloroform layer was evaporated with added portions of toluene to give a syrup. Crystallization from ether-petroleum ether afforded crystalline compound V (25 mg, 68%). It melted at 81-81.5° and exhibited $[\alpha]_D$ + 99.3° (c, 1.1, in chloroform)

Anal. Calcd for $C_9H_{13}O_6N$ (231.2): C, 46.75; H, 5.67; N, 6.06. Found: C, 46.77; H, 5.51; N, 6.25.

NMR data (Fig.13, in $CDCl_3$): τ 2.90 (1H, q, $J_{1,2}$= 3.5Hz, $J_{2,4}$= 1.3Hz, H-2); τ 4.18 (1H, sextet, $J_{1,4}$= 1Hz, $J_{2,4}$= 1.3Hz, $J_{4,5}$= 8.3Hz, H-4); τ 4.83 (1H, q, $J_{1,2}$= 3.5Hz, $J_{1,4}$= 1Hz, H-1); τ 5.93 (1H, octet, $J_{4,5}$= 8.3Hz, $J_{5,6}$= 6.5Hz, H-5); τ 6.54 (3H, s, OCH_3); τ 7.97 (3H, s, O-acetyl); τ 8.71 (3H, d, $J_{5,6}$= 6.5Hz, C-CH_3).

The ultraviolet spectrum in chloroform showed λ_{max} at 247 nm (ε, 3620).

Dehydroacetylation of Diacetate XI by the Action of Silica Gel

The diacetate XI (100 mg) was put on a 10-g silica gel column. The column was eluted slowly with benzene containing 2% of ethyl acetate. The eluate was evaporated to furnish a crystalline material (70 mg). A 60-MHz NMR spectrum suggested the product to consist of two nitroolefinic components, presumable IV and V with the former preponderating strongly. Crystallization from ether-petroleum ether afforded small crystals which melted at 78-80° and whose NMR spectrum was identical with that of compound IV obtained previously from II.

Methyl 2,4-Di-O-acetyl-3,6-dideoxy-3-nitro-α-L-galacto-pyranoside (XVI)

Methyl 3,6-dideoxy-3-nitro-α-L-galacto-pyranoside XV (200 mg) was dissolved in acetic anhydride (3 ml) and cooled in an ice-bath. Three drops of boron trifluoride etherate were added with stirring. After 5 min the mixture was poured into vigorously stirred ice water which caused a white solid to separate. Filtration and drying in vacuo yielded 260 mg (92.5%) of product. Recrystallization from ethyl acetate and petroleum ether furnished fine needles of the diacetate XVI; m.p. 122-123°; $[\alpha]_D$ -171° (c, 1.2, in chloroform). The data were in agreement with those found by Dr. K. Čapek who first prepared this compound in preliminary, unpublished experiments in this laboratory. His sample gave the following elemental analysis:

Anal. Calcd for $C_{11}H_{17}O_8N$ (291.2): C, 45.36; H, 5.88; N, 4.81. Found: C, 45.52; H, 6.00; N, 4.67. (Data disclosed by permission of Prof. H. H. Baer).

Infrared absorptions (cm^{-1}) were at: 1742s (ester carbonyl); 1558s (nitroalkane); 1220s; 1195ms; 1152m; 1130m; 1110m; 1071s; 1050s; 1025s; 972m; 960m; 896w; 875w; 820w; 780w.

NMR data (in $CDCl_3$): τ 4.31 (1H, q, $J_{3,4}$= 3.5 Hz, $J_{4,5}$= 1Hz, H-4); τ 4.40 (1H, q, $J_{1,2}$= 3.5Hz, $J_{2,3}$=

11Hz, H-2); τ 4.96 (2H, superimposed quartet and doublet assigned to H-3 and H-1, respectively, with $J_{1,2}$= 3.5Hz, $J_{2,3}$= 11Hz, $J_{3,4}$= 3.5Hz); τ 5.88 (1H, q, b, $J_{4,5}$= 1Hz, $J_{5,6}$= 6.5Hz, H-5); τ 6.63 (3H, s, OCH_3); τ 7.96, 7.98 (6H, 2s, O-acetyl); τ 8.84 (3H, d, $J_{5,6}$= 6.5Hz, C-CH_3).

Dehydroacetylation of Diacetate XVI by the Action of Silica Gel

The diacetate XVI (110 mg) was passed through a column of silica gel (10 g) by use of benzene containing 2% of ethyl acetate. The flow rate was about 1 drop per 2 seconds. The entire effluent was evaporated to give a syrup. Thin layer chromatography showed two spots (solvent system, 20% ethyl acetate in carbon tetrachloride). An NMR spectrum of this mixture indicated a ratio of 1.3:1 for compound III and XVII.

The syrupy mixture was passed through another column containing 10 g of fresh silica gel, this time by use of ethyl acetate - carbon tetrachloride (1:4,v/v). The column yielded a fraction corresponding to the faster t.l.c. spot and one corresponding to the slower spot. The former afforded crystals of XVII(32 mg)of m.p. 88-89°; $[\alpha]_D$ +27.5° (c, 0.75, in chloroform).

Anal. Calcd for $C_9H_{13}O_6N$ (231.2): C, 46.75; H, 5.67; N, 6.06. Found: C, 46.88; H, 5.81; N, 6.18.

The ultraviolet spectrum showed λ_{max} 247 nm with ε, 3700 (in chloroform).

Infrared bands (cm^{-1}) were at 1750s (ester carbonyl); 1530s (nitroalkene); 1445m; 1390m; 1372s; 1200s, b; 1160m; 1131s; 1090s; 1050s; 1000s; 976s; 928m; 912m; 892m; 870w.

NMR data (Fig.14, in $CDCl_3$): τ 2.73 (1H, d, $J_{1,2}$= 3,5Hz, H-2); τ 4.11 (1H, d, $J_{4,5}$= 2.5Hz, H-4); τ 4.76 (1H, d, $J_{1,2}$= 3.5Hz, H-1); τ 5.77 (1H, octet, $J_{4,5}$= 2.5Hz, $J_{5,6}$= 6.5Hz); τ 6.55 (3H, s, OCH_3); τ 7.92 (3H, s, O-acetyl); τ 8.75 (3H, d, $J_{5,6}$= 6.5Hz, C-CH_3).

The slow-moving fraction gave crystals (37 mg) of m.p. 97-99° that were in the same manner identified as III.

Alternatively, nitroolefin XVII was prepared from methyl 3,6-dideoxy-3-nitro-α-L-talopyranoside (XVIII). Thus, to an ice-cooled solution of nitro glycoside XVIII (100 mg) in anhydrous ether (5 ml) was added acetyl chloride (1 ml). Now triethylamine (1 ml) was added dropwise and with stirring. The reaction mixture was kept at 0° for 5 min and then stirred at room

temperature for another 30 min. Thereafter, 20 ml of ether was added and the mixture was extracted twice with water (40 ml). The ether layer was evaporated to give a colorless syrup. Crystallization from ether-petroleum ether afforded nitroolefin XVII (10 mg, 9%); m.p. 89.5-90°. The NMR spectrum was identical with that of the compound XVII described above.

Acetylation of Methyl 3,6-Dideoxy-3-nitro-α-L-talopyranoside (XVIII) Catalyzed by Boron Trifluoride

1) Methyl 2,4-Di-O-acetyl-3,6-dideoxy-3-nitro-α-L-talopyranoside (XIX)

Methyl 3,6-dideoxy-3-nitro-α-L-talopyranoside (XVIII) (300 mg) in acetic anhydride (10 ml) was cooled an ice-bath for 15 min. One small drop of boron trifluoride etherate was added. The solution was stirred for 2 min, and was then poured into ice water. Extraction with chloroform (2x20 ml) and evaporation of the extract gave a colorless syrup. The syrup was dissolved in ethanol (5 ml), and petroleum ether was added to incipient turbidity. On standing overnight in the refrigerator the solution deposited colorless prisms which analyzed correctly

for the structure of diacetate XIX.

Anal. Calcd for $C_{11}H_{17}O_8N$ (291.2): C, 45.36; H, 5.88; N, 4.81. Found: C, 45.34; H, 5.70; N, 4.93.

Infrared spectrum (cm^{-1}, in chloroform) showed characteristic absorptions at 1745s (ester carbonyl) and 1558s (nitroalkane). Other bands occurred at 1440m; 1365s; 1250-1190s (broad); 1150m; 1125s; 1100s; 1070s; 1020s; 980m; 950m; 890m.

NMR data (in $CDCl_3$): τ 4.19 (1H, q, $J_{3,4}$= 3.5Hz, $J_{4,5}$= 1.5Hz, H-4); τ 4.41 (1H, q, $J_{1,2}$= 1.5Hz, $J_{2,3}$= 3.5Hz, H-2); τ 5.10 (1H, d, $J_{1,2}$= 1.5Hz, H-1); τ 5.15 (1H, t, $J_{2,3}$= $J_{3,4}$= 3.5Hz, H-3); τ 5.95 (1H, octet, $J_{4,5}$= 1.5Hz, $J_{5,6}$= 6.5Hz, H-5); τ 6.61 (3H, s, OCH_3); τ 7.92, 7.94 (6H, 2s, O-acetyl); τ 8.78 (3H, d, $J_{5,6}$= 6.5Hz, C-CH_3).

Unfortunately, in subsequent experiments the compound could not be obtained in crystalline condition again, and no record of melting point and specific rotation for the crystals is available.

2) Methyl 4-O-Acetyl-2,3,6-trideoxy-3-nitro-α-L-threo-hex-2-enopyranoside (XVII) and Methyl 2-O-Acetyl-3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (IV)

In the experiments aimed at preparing the

diacetate XIX it was found that nitroolefinic products tend to arise if a larger proportion of catalyst is employed. Thus, 100 mg of XVIII in acetic anhydride (2 ml) was allowed to react as described under 1) but for 5 min and with addition of 3 drops of boron trifluoride etherate. Work-up as above furnished a pale yellow syrup (110 mg, 99%) whose NMR spectrum (Fig.15) suggested that it was a mixture of about equal proportions of the nitroolefins IV and XVII.

A similar mixture of nitroolefins could be prepared from the diacetate XIX. Thus, the diacetate (120 mg) was placed on a column of silica gel (10 g), and eluted at a slow rate with benzene containing 2% ethyl acetate. The eluate was evaporated to give a colorless syrup (91 mg, 95%) whose NMR spectrum was identical with that of the mixture obtained by the acetylation process.

In one case, such a mixture (100 mg)was dissolved in ether (1 ml), petroleum ether (10 ml) was added, and cooling overnight in the refrigerator produced white crystals (18 mg) melting at 79-80° and exhibiting $[\alpha]_D$ -166° (c, 1, in chloroform). An NMR spectrum identified the product as IV.

3) 1,4-Di-O-acetyl-2,3,6-trideoxy-3-nitro-α-L-threo-hex-2-enopyranose (XX) and Methyl 2-O-Acetyl-3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (IV)

A mixture of glycoside XVIII (1 g), acetic anhydride (10 ml) and boron trifluoride etherate (30 drops) was kept overnight in the refrigerator. The solution was poured into ice water and extracted with chloroform (3x50 ml). The extract was evaporated several times with added portions of toluene to give a slightly yellow syrup. The syrup was dissolved in a minimum amount of ethanol, petroleum ether was added to incipient turbidity, and the solution was stored overnight in a refrigerator. Crystalline XX (341 mg) was collected by filtration. It melted at 140-141° and showed $[\alpha]_D$ +149° (c, 0.8, in chloroform).

Anal. Calcd for $C_{10}H_{13}O_7N$ (259.2): C, 46.33; H, 5.06; N, 5.40. Found: C, 46.13; H, 5.10; N, 5.33.

Characteristic infrared frequencies (cm^{-1}) occurred at 1760s, 1738s (ester carbonyl) and 1540s, 1358s (NO_2). Other bands were at : 1340m; 1316m; 1215s; 1146s; 1120m; 1073m; 1038m; 992s; 948s (shoulder); 910m; 880w; 800m; 680m.

NMR data (Fig.16, in $CDCl_3$): τ 2.65 (1H, d,

$J_{1,2}$= 3,5Hz, H-2); τ 3.33 (1H, d, $J_{1,2}$= 3,5Hz, H-1); τ 4.13 (1H, d, $J_{4,5}$= 2.5Hz, H-4); τ 5.72 (1H, octet, $J_{4,5}$= 2.5Hz, $J_{5,6}$= 6.5Hz, H-5); τ 7.92 (6Hz, s, O-acetyl); τ 8.75 (3H, d, $J_{5,6}$= 6.5Hz, C-CH_3).

The UV spectrum (in chloroform) showed λ_{max} 245 nm (ε, 5500).

The mother liquor yielded upon evaporation a yellow syrup (450 mg) which was put onto a silica gel column. Elution of the column with 2% methanol in chloroform yielded from the first six fractions (5 ml each) a crystalline product. Recrystallization from ether-petroleum ether afforded white crystals (62 mg, 11.2%) which melted at 80-82° and showed $[\alpha]_D$-163° (c,1, in chloroform). The product was identical with methyl 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (IV) obtained by Schmidt-Rutz reaction described previously.

The remaining fractions gave a syrupy mixture of IV and XVII according to the NMR spectrum.

Methyl 3,4,6-Trideoxy-2-O-methyl-3-nitro-α-L-threo-hex-3-enopyranoside (XXI)

A. By methanolysis of a mixture of acetates XVII and IV

A 1:1 mixture of XVII and IV (90 mg, obtained as described on p.168) was stirred in 3% anhydrous, methanolic hydrogen chloride (15 ml) at room temperature for two days. Evaporation of the reaction mixture at room temperature gave a yellow syrup which was chromatographed with benzene containing 10% of ethyl acetate on a small silica gel column. The 2-O-methyl derivative XXI was obtained from the column as colorless oil (38 mg). It exhibited $[\alpha]_D$ -113.3° (c, 1.1, in chloroform).

UV data (in chloroform): λ_{max} 247 nm (ε,4860).

Infrared frequencies (cm^{-1}, in chloroform) were recorded at : 1670w (C=C); 1520s (nitroalkene); 1445m, b; 1346s (shoulder); 1188m; 1155m; 1100s; 1070s; 1052s; 1028m; 998m (shoulder); 900m. There was no hydroxyl absorption in the region above 3000 cm^{-1}.

NMR data (in $CDCl_3$): τ 2.72 (1H, s, H-4); τ 5.18 (1H, s, H-1); τ 5.53 (1H, m, H-5); τ 5.79 (1H, s, H-2); τ 6.51, 6.58 (6H, 2s, OCH_3); τ 8.57 (3H, d, $J_{5,6}$ = 7Hz, C-CH_3). Detailed spectrum (S.W. = 250 c.p.s.) showed: H-4, d, $J_{4,5}$= 1.8Hz; H-1, d, $J_{1,2}$= 1Hz; H-5, 12 peaks, $J_{2,5}$= 1.8Hz, $J_{4,5}$= 1.8Hz, $J_{5,6}$= 7Hz; H-2, q, $J_{1,2}$= 1Hz, $J_{2,5}$= 1. Hz.

Further elution of the column gave 14 mg of a colorless syrup that was shown to be identical with the

hydroxy nitroolefin V by comparing their NMR spectra and mobility on t.l.c..

B. By methylation of nitroolefin XIII

A cooled solution of nitroolefin XIII (30 mg) in anhydrous ether (2 ml) was methylated with an ethereal solution of diazomethane (generated from 4 g of N-nitroso-methylurea) and boron trifluoride etherate (0.5 ml). The addition of diazomethane solution was regulated at such a rate that no excess of it was building up during the reaction. After 1.5 h a flocculent precipitate of polymethylene was removed by filtration and the solution was evaporated to give an oily product. Thin layer chromatography (solvent system, 20% ethyl acetate in carbon tetrachloride) revealed the presence of starting material and a new, fast-moving product. The oil was chromatographed on a silica gel column by use of the above solvent mixture. The fast-moving compound (17 mg) was isolated and shown to be identical with XXI by comparison of NMR and IR spectra.

Twelve milligrams of starting compound XIII was recovered by continued elution of the column.

B. SYNTHESIS OF L-DESOSAMINE

Methyl 3,4,6-Trideoxy-3-nitro-α-L-xylo-hexopyranoside (XXII)

A solution of nitroolefin VII (130 mg, obtained as described on p. 151) in ethanol (10 ml) was cooled in an ice-bath for 15 min. Sodium borohydride (52 mg) was added in small portions to the magnetically stirred solution and allowed to react for another 10 to 15 min. Then, methanol (20 ml) was added and the mixture was treated with cation-exchange resin, Amberlite IR-120 (H^+) (4 ml). The solution was filtered and then evaporated several times with methanol to give a colorless syrup (128 mg, 99%). Crystallization from ether, with addition of petroleum ether to incipient turbidity, yielded small flaky crystals of compound XXII; m.p. 56-57°; $[\alpha]_D$ -198° (c, 1, in chloroform).

Anal. Calcd for $C_7H_{13}O_5N$ (191.2): C, 43.97; H, 6.85; N, 7.33. Found: C, 43.95; H, 6.87; N, 7.50.

Characteristic infrared absorptions occurred at 3440 cm^{-1} (broad, shoulder) (OH), and 1545 cm^{-1} (strong, NO_2).

NMR data (in $CDCl_3$): τ 5.20 (1H, d, $J_{1,2}$= 3-4Hz, H-1); τ 5.25 (1H, m, H-3); τ 5.90 (1H, m, H-2;

the multiplet became a quartet after deuterium exchange, with $J_{1,2}$= 3.5Hz, $J_{2,3}$= 10Hz); τ 6.07 (1H, m, H-5); τ 6.59 (3H, s, OCH_3); τ 7.75 (1H, octet, $J_{3,4e}$= 4Hz, $J_{4a,4e}$= 12Hz, $J_{4e,5}$= 2Hz, H-4e); τ 8.12 (1H, q, $J_{3,4a}$= $J_{4a,4e}$= $J_{4a,5}$= 12Hz, H-4a); τ 8.77 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

Methyl 2-O-Acetyl-3,4,6-trideoxy-3-nitro-α-L-xylo-hexopyranoside (XXIII)

A mixture of nitro alcohol XXII (20 mg) and acetic anhydride (1 ml) was cooled in an ice-bath, and boron trifluoride etherate (1 drop) was added. After 5 min the reaction mixture was poured into ice water which was extracted twice with chloroform (20 ml). Removal of solvent furnished a slightly yellow liquid (24 mg, 95%). Bulb-to bulb distillation in vacuo (1 mm, 120°) gave an analytical sample showing $[\alpha]_D$ -173° (c, 1.3, in chloroform).

Anal. Calcd for $C_9H_{15}O_6N$ (233.2): C, 46.35, H, 6.48; N, 6.01. Found: C, 46.51; H, 6.55; N, 6.13.

Infrared absorptions were recorded from a liquid film (cm^{-1}): 1745s (ester carbonyl); 1550s (nitro-alkane); 1445ms; 1370s (shoulder); 1225s; 1190ms; 1115s (shoulder); 1073s; 1045s; 960m; 926m; 892m; 870m; 770m.

NMR data (in $CDCl_3$): τ 4.74 (1H, q, $J_{1,2}$= 3.5Hz, $J_{2,3}$= 11-11.5Hz, H-2); τ 5.01 (2H, superimposed sextet and doublet assigned to H-3 and H-1, respectively with $J_{1,2}$= 3.5Hz, $J_{2,3}$=$J_{3,4a}$= 11Hz, $J_{3,4e}$= 4.5Hz); τ 6.03 (1H, m, H-5); τ 7.64 (1H, octet, $J_{3,4e}$= 4.5Hz, $J_{4a,4e}$= 11-11.5Hz, $J_{4e,5}$= 2Hz, H-4_e); τ 7.99 (3H, s, O-acetyl); τ 8.09 (1H, q, $J_{3,4a}$= $J_{4a,4e}$= $J_{4a,5}$= 11-11.5Hz, H-4a); τ 8.80 (3H, d, $J_{5,6}$= 6Hz, C-CH_3).

Methyl 3-Amino-3,4,6-trideoxy-α-L-xylo-hexopyranoside (XXIV)

The nitro compound XXII (282 mg) was hydrogenated in a mixture of ethanol (4 ml) and water (16 ml) in the presence of prereduced platinum dioxide and N hydrochloric acid (1.5 ml). The solution was filtered after 4 h of hydrogenating, and it was evaporated to give a stiff syrup (292 mg, 100%) which solidified when dried in vacuo. The white, hygroscopic solid was dissolved in a mixture of water (10 ml) and methanol (10 ml), and Dowex 1x8 ($CO_3^=$ form, 5 ml) was added. The mixture was stirred at room temperature for 3 h. After filtration and evaporation of the solution a colorless, crystalline product was obtained (240 mg, 96.5%). Recrystallization from methanol yielded compound XXIV exhibiting m.p. 138-

139° and $[\alpha]_D$ -178.7° (c, 0.87, in methanol).

Anal. Calcd for $C_7H_{15}O_3N$ (161.2): C, 52.15; H, 9.38; N, 8.69. Found: C, 52.31; H, 9.23; N, 8.79.

Infrared frequencies (cm^{-1}) were at: 3360s, 3290s, 3260-3020s, b (NH and OH); 1597m (NH_2); 1342ms (shoulder); 1300m; 1225m; 1208m; 1182s; 1140m; 1125-1098s, several peaks; 1070s; 1050s; 1030s (shoulder); 995ms; 970ms; 920ms; 843ms; 790ms; 660w.

A 60-MHz NMR spectrum in deuterium oxide gave the following data (τ values expressed with reference to the DOH signal for which τ = 5.28 was assumed): τ 5.83-6.33 (1H, m, b, H-5); τ 6.73 (3H, s, OCH_3); τ 6.78 (1H, q, $J_{1,2}$= 4Hz, $J_{2,3}$= 10Hz, H-2); τ 7.17 (1H, sextet, $J_{2,3}$= $J_{3,4a}$= 10Hz, $J_{3,4e}$= 4Hz, H-3); τ 8.24 (1H, octet, $J_{3,4e}$ = 4Hz, $J_{4a,4e}$= 13Hz, $J_{4a,5}$= 10Hz, H-4e); τ 8.93 (1H, sextet, $J_{3,4a}$= $J_{4a,5}$= 10Hz, $J_{4a,4e}$= 13Hz, H-4a); τ 8.95 (3H, d, $J_{5,6}$= 6Hz, C-CH_3). The DOH peak occurred at 5.28τ , obscuring the anomeric proton. A spectrum in acetone-d_6 showed H-1 at 5.40τ , with $J_{1,2}$= 3.5Hz.

A small portion of the hygroscopic hydrochloride of XXIV was N-acetylated with acetic anhydride in the presence of Dowex 1x8 ($CO_3^=$ form) in a mixture of methanol and water according to the previous procedure. A 60-MHz NMR spectrum (in $CDCl_3$) of the N-acetylated

derivative XXV so obtained showed the expected substituent resonances, namely, a broad N-H peak at τ 4.61, a singlet for OCH_3 at τ 6.59, a singlet at τ 8.02 for N-Ac and a doublet at τ 8.84 for C-CH_3. The anomeric proton gave a doublet at τ 5.39 ($J_{1,2}$= 3.5Hz) whereas the other ring proton signals could not be analyzed.

Methyl 3-Dimethylamino-3,4,6-trideoxy-α-L-xylo-hexopyranoside (XXVI)

The amino sugar XXIV (230 mg) was refluxed for 4 h in a mixture of 98-100% formic acid (2 ml) and 37-41% formaldehyde (1 ml). The reaction mixture was then evaporated several times with added N hydrochloric acid and ethanol at a temperature of about 50°, to give a yellow syrup. The syrup was dissolved in methanol (10 ml) and water (10 ml) and was stirred with Dowex 1x8 ($CO_3^=$ form, 4 ml) for 2 h at room temperature. The filtered solution was evaporated and the syrup obtained was put on a silica gel column. Elution with methanol-chloroform (6:4,v/v) yielded XXVI as a pale yellow syrup. A 60-MHz NMR spectrum in deuterated chloroform showed the expected resonances for H-1 at τ 4.87 (doublet, with splitting $J_{1,2}$= 3-4Hz); a three-proton singlet at τ 6.53 (OCH_3); a six-proton

singlet at τ 7.70 (NMe_2); and a three-proton doublet at τ 8.78 ($\underline{C}$-CH_3), with $J_{5,6}$= 6Hz.

The oily compound XXVI was not further purified and characterized, but subjected to hydrolysis as described below.

3-Dimethylamino-3,4,6-trideoxy-L-xylo-hexopyranose (XXVII, L-desosamine) and its Hydrochloride

The oily glycoside XXVI was refluxed in 6 $\underline{N}$ hydrochloric acid (5 ml) for 4 h. The hydrolyzate was evaporated several times with water and ethanol and then treated with Dowex 1x8 (OH^- form, 5 ml) in a mixture of methanol and water (1:1, 30 ml). The mixture was stirred for 3 h at room temperature. The filtered solution was evaporated to give a syrup which was purified by passage through a silica gel column, the eluent being methanol-chloroform (4:6,v/v). There was obtained 165 mg (66%) of L-desosamine (XXVII) as a colorless syrup which exhibited $[\alpha]_D$ -42.4°; $[\alpha]_{578}$ -42.9°; $[\alpha]_{546}$ -46.8°; $[\alpha]_{436}$ -76.5° ($\underline{c}$, 0.85, in water). These values remained unchanged for a period of 24 h. The solution turned brown on further standing at room temperature and the rotation began to decrease.

The NMR spectrum (60-MHz) of the syrup in deuterium oxide is shown in Fig.17. It is identical with the spectrum published for the D-enantiomer(138).

To obtain L-desosamine hydrochloride, L-desosamine (50 mg) was treated with N hydrochloric acid (2 ml). The solution was evaporated several times with water and ethanol to yield a glassy syrup. The syrup was dissolved in a minimum amount of absolute ethanol, and petroleum ether was added to incipient turbidity. A white, crystalline product (80 mg, 97%) was collected, m.p. 173-175° (decomposition). The crystals were recrystallized twice from the same solvent system and the melting point was raised to 183-184° (see Table VIII on p.105 for literature values for the D-enantiomer). The product exhibited mutarotation (c, 0.75, in water):

$[\alpha]_D$: -64.0°(2')→ -50.2°(16 h)→ -52.5°(24 h)→ -52.0°(48 h).

$[\alpha]_{578}$: -64.2°(2')→ -52.8°(16 h)→ -54.7°(24 h)→ -54.4°(48 h).

$[\alpha]_{546}$: -73.5°(2')→ -60.0°(16 h)→ -61.5°(24 h)→ -62.1°(48 h).

$[\alpha]_{436}$:-121.5°(2')→ -100° (16 h)→ -101° (24 h)→ -106° (48 h).

See Table VIII on p.105 for reported end rotations of the D-enantiomer.

The IR spectrum (Fig.18) of L-desosamine hydrochloride (in KBr) is identical with the spectrum published for the D-enantiomer.

Methyl 3,6-Dideoxy-4-O-methyl-3-nitro-α-L-glucopyranoside (XXVIII)

A solution of nitroolefin VII (100 mg) in anhydrous methanol (20 ml) was gently refluxed overnight. Removal of the solvent furnished a white solid. Recrystallization from ether-petroleum ether yielded fine, long needles of XXVIII (108 mg, 92.5%) which melted at 113-113.5° and exhibited $[\alpha]_D$ -183.5° (c, 0.83, in chloroform).

Anal. Calcd for $C_8H_{15}O_6N$ (221.3): C, 43.43; H, 6.84; N, 6.33. Found: C, 43.58; H, 6.69; N, 6.42.

Infrared absorptions (cm^{-1}) occurred at 3440s (OH); 1550s (NO_2); 1190m; 1130m; 1090s; 1060s; 1028s; 970m.

The NMR spectrum (in $CDCl_3$) showed peaks at τ 5.27 (1H, d, $J_{1,2}$= 3.5-4Hz, H-1); τ 5.89 (1H, t, $J_{2,3}$= $J_{3,4}$= 10Hz, H-3); τ 5.93 (1H, octet, $J_{1,2}$= 3.5-4Hz, $J_{2,3}$= 10Hz, $J_{2,2OH}$= 11.5Hz, H-2; after deuterium exchange the octet became a quartet centered at τ 5.95); τ 5.93-6.77 (2H, m, H-4 and H-5); τ 6.63, 6.59 (6H, 2s, OCH_3); τ 7.68 (1H, d, $J_{2,2OH}$= 11,5Hz, OH; disappeared on deuterium exchange); τ 8.71 (3H, d, $J_{5,6}$= 5.5Hz, C-CH_3).

Part III

Preparation of Compounds:

A. Compounds Ia (146), IIa (147), and IIIa (84) were prepared according to published procedures.

B. Methyl 2,4-Di-O-acetyl-3-deoxy-3-nitro-α-D-arabino-pyranoside (IIb)

Methyl 3-deoxy-3-nitro-α-D-arabinopyranoside (IIa) (50 mg) in acetic anhydride (1 ml) was cooled in an ice bath. Boron trifluoride (1 drop) was then added to the sitrred solution. After 15 min the mixture was poured into well-stirred ice water (20 ml) which was subsequently extracted twice with 20 ml of ether. Evaporation of the solvent gave IIb (65 mg, 90.8%) as a slightly yellow syrup which failed to crystallize. Compound IIb showed $[\alpha]_D$ -194.9° (c, 1.2, in chloroform).

Anal. Calcd for $C_{10}H_{15}O_8N$ (277.2): C, 43.32; H, 5.45; N, 5.05. Found: C, 43.34; H, 5.58; N, 5.20.

The infrared spectrum (liquid film) showed characteristic absorptions at 1750 cm^{-1} (ester carbonyl) and at 1560 and 1370 cm^{-1} (nitro group). Hydroxyl absorption was absent.

The NMR spectrum (in $CDCl_3$) exhibited peaks at: τ 4.37 (1H, q, $J_{1,2}$= 3.5Hz, $J_{2,3}$= 11Hz, H-2); τ 4.43 (1H, m, H-4); τ 4.97 (1H, d, $J_{1,2}$= 3.5Hz, H-1); τ 5.02 (1H, q, $J_{2,3}$= 11Hz, $J_{3,4}$= 3.5Hz, H-3); τ 6.12 (1H, d, $J_{4,5e}$= 1.5Hz, H-5e); τ 6.14 (1H, d, $J_{4,5a}$= 2Hz, H-5a); τ 6.63 (3H, s, OCH_3); τ 7.94 (6H, s, O-acetyl).

C. Methyl 3,4,6-Trideoxy-3-aci-nitro-hex-4-enopyranoside Sodium (VI)

Methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (IIIa)(2.07 g) in 10 ml of N NaOH was diluted with water to a volume of 250 ml and heated on a steam bath for 2 h. The yellow solution was concentrated under diminished pressure at a bath temperature between 30-35°. The resulting syrup was dried in vacuo to yield brownish residue which was taken up in anhydrous methanol (20 ml), and anhydrous ether was added to incipient turbidity. After storage in the refrigerator overnight, 430 mg (20%) of a brownish precipitate was collected. This procedure was repeated several times and the final precipitate showed $[\alpha]_D$ -123.5° (c, 1, in water). The NMR spectrum is shown in Fig.20.

The UV spectrum (in water) showed λ_{max} 295nm (ε, 19200).

Ultraviolet Spectroscopic Studies:

A. Experiments at elevated temperature were performed with solutions of compound IIa, IIb, IIIa and IIIb. Stock solutions were prepared by dissolving 0.05 mmole of compound in 5 ml of water (in case of IIa and IIIa) or in a mixture of 1 ml methanol and 4 ml of water (in case of IIb and IIIb). Aliquots of 0.25 ml were diluted with the corresponding buffer solution (pH 7-12) or 0.1 N NaOH to a volume of 50 ml (c, $5x10^{-5}$ M) and heated on a steam bath. Ultraviolet spectra were recorded on a Perkin-Elmer 202 spectrophotometer from samples withdrawn from time to time from the reaction solution. The samples were cooled down to room temperature by brief immersion in ice water prior to measurement.

B. Room temperature experiments were done on compounds Ia, IIa, IIIa. Each solution had a concentration of 10^{-4} M in 0.1 N NaOH.

The results of the measurements of A and B are shown in Table IX and Fig. 21, respectively.

CLAIMS TO ORIGINAL RESEARCH

Part I

1. The synthesis of methyl ether derivatives of amino sugars via nitro sugars is described for the first time. The first vicinal chloronitro sugar and 3,4-unsaturated nitro sugars are reported. Chemical transformations of the latter led to 3,4-dideoxy-3-amino sugars.
2. Selective introduction of an amino group into the position 4 of 3-nitro glycosides is reported for the first time. Subsequent hydrogenation furnished the hitherto unknown 3,4-diamino derivatives in high yield.
3. One-step introduction of two amino groups into the positions 2 and 4 of a methyl 3,6-dideoxy-3-nitro-hexopyranoside led to the synthesis of methyl 2,3,4-triamino-2,3,4,6-tetradeoxy hexose derivatives.
4. The following new compounds were synthesized:

   Section A

   a. Methyl 3,6-dideoxy-2-O-methyl-3-nitro-α-L-gluco-pyranoside (II)
   b. Methyl 3,6-dideoxy-2,4-di-O-methyl-3-nitro-α-L-glucopyranoside (III)

c. Methyl 3-amino-3,6-dideoxy-2,4-di-O-methyl-α-L-glucopyranoside hydrochloride (IV)

d. Methyl 3-acetamido-3,6-dideoxy-2,4-di-O-methyl-α-L-glycopyranoside (V)

e. Methyl 4-O-acetyl-3,6-dideoxy-2-O-methyl-3-nitro-α-L-glucopyranoside (VI)

f. 1,4-Di-O-acetyl-3,6-dideoxy-2-O-methyl-3-nitro-α-L-glucopyranose (VII)

g. Methyl 4-chloro-3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-galactopyranoside (VIII)

h. Methyl 3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-erythro-hex-3-enopyranoside (IX)

i. Methyl 3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-xylo-hexopyranoside (X)

j. Methyl 3-amino-3,4,6-trideoxy-2-O-methyl-α-L-xylo-hexopyranoside hydrochloride (XI)

k. Methyl 3-acetamido-3,4,6-trideoxy-2-O-methyl-α-L-xylo-hexopyranoside (XII)

Section B

l. Methyl 4-amino-3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-glucopyranoside hydrochloride (XV)

m. Methyl 4-Acetamido-3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-glucopyranoside (XVI)

n. Methyl 3,4-diamino-3,4,6-trideoxy-2-O-methyl-α-L-glucopyranoside dihydrochloride (XVII)

o. Methyl 3,4-diacetamido-3,4,6-trideoxy-2-O-methyl-α-L-glucopyranoside (XVIII)

Section C

p. Methyl 2,4-diacetamido-2,3,4,6-tetradeoxy-3-nitro-α-L-glucopyranoside (XX)*

q. Methyl 3-amino-2,4-diacetamido-2,3,4,6-tetradeoxy-α-L-glucopyranoside hydrochloride (XXI)

r. Methyl 2,3,4-triacetamido-2,3,4,6-tetradeoxy-α-L-glucopyranoside (XXII)*

Part II

5. Acetylation and dehydroacetylation reactions of methyl 3,6-dideoxy-3-nitro-α-L-glycosides were studied under acidic and basic conditions. Controlled methanolysis of fully acetylated derivatives were also performed. These led ot the specific synthesis of 2-O-acetyl or 4-O-acetyl derivatives of methyl 3,6-dideoxy-

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* During the course of this work, a short communication by Lichtenthaler et al. (125) reported the synthesis of the same compound.

3-nitro-glycosides and isomeric nitroolefins having Δ^2-α-L-*erythro*-, Δ^2-α-L-*threo*-, Δ^3-α-L-*erythro* and Δ^3-α-L-*threo*- configuration. The structures of new nitroolefins were established by spectroscopic and chemical means. The use of silica gel (neutral) as dehydroacetylating agent is described for the first time. A first stereospecific synthesis of L-desosamine is reported.

6. The following new compounds are synthesized:

Section A

a. Methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (II)

b. Methyl 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-L-*erythro*-hex-3-enopyranoside (III)

c. Methyl 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-L-*threo*-hex-3-enopyranoside (IV)

d. Methyl 4-O-acetyl-2,3,6-trideoxy-3-nitro-α-L-*erythro*-hex-2-enopyranoside (V)

e. Methyl 4-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (VI)

f. Methyl 3,4,6-trideoxy-3-nitro-α-L-*erythro*-hex-3-enopyranoside (VII)

g. Methyl 2-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (VIII)

h. Methyl 2,3,6-trideoxy-3-nitro-α-L-erythro-hex-2-enopyranoside (IX)

i. Methyl 4-O-acetyl-3,6-dideoxy-3-nitro-α-L-mannopyranoside (XII)

j. Methyl 3,4,6-trideoxy-3-nitro-α-L-threo-hex-3-enopyranoside (XIII)

k. Methyl 4-O-acetyl-2,3,6-trideoxy-3-nitro-α-L-threo-hex-2-enopyranoside (XVII)

l. Methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-L-talopyranoside (XIX)

m. 1,4-Di-O-acetyl-2,3,6-trideoxy-3-nitro-α-L-threo-hex-2-enopyranose (XX)

n. Methyl 3,4,6-trideoxy-2-O-methyl-3-nitro-α-L-threo-hex-3-enopyranoside (XXI)

Section C

o. Methyl 3,4,6-trideoxy-3-nitro-α-L-xylo-hexopyranoside (XXII)

p. Methyl 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-L-xylo-hexopyranoside (XXIII)

q. Methyl 3-amino-3,4,6-trideoxy-α-L-xylo-hexopyranoside (XXIV)

r. Methyl 3-acetamido-3,4,6-trideoxy-α-L-xylo-hexopyranoside (XXV)

s. Methyl 3-dimethylamino-3,4,6-trideoxy-α-L-xylo-hexopyranoside (XXVI)

t. 3-Dimethylamino-3,4,6-trideoxy-L-xylo-hexopyranose (L-desosamine, XXVII)

u. 3-Dimethylamino-3,4,6-trideoxy-L-xylo-hexopyranose hydrochloride (L-desosamine hydrochloride)

v. Methyl 3,6-dideoxy-4-O-methyl-3-nitro-α-L-gluco-pyranoside (XXVIII)

Part III

7. The formation of nitroallylic system in 3-nitrohexo-pyranosides as described by Baer and Kienzle (145) was further investigated. It was studied for the first time in the 3-nitro-3,6-dideoxyhexopyranoside series.

8. The following new compounds were synthesized:

   a. Methyl 2,4-di-O-acetyl-3-deoxy-3-nitro-α-D-arabino-pyranoside (IIb)

   b. Methyl 3,4,6-trideoxy-3-aci-nitro-hex-3-eno-pyranoside sodium (VI) (although the latter was not obtained in analytically pure form).

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