

To Marie-Alix

"Le plus grand dérèglement de l'esprit, c'est de croire les choses parce qu'on veut qu'elles soient, et non parce qu'on a vu qu'elles sont en effet."

J. B. Bossuet

PREFACE

This thesis presents some contributions to the synthetic chemistry of nitrogenous carbohydrates.

In the Introduction, the significance of rare amino sugars and aminocyclitols is outlined. Some general reactions of nitro sugars which are frequently used in syntheses of amino sugars, are then briefly described, and a review of the methods available for the synthesis of diamino sugars is given. This is followed by a statement of the specific goals of this thesis, 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 diamino and triamino sugars. In Part II, the nucleophilic addition of anthranilic acid to a nitroolefinic sugar is studied, and the synthesis of bisglycosidylamines, a new class of amino sugar derivatives, is reported. Part III is concerned with the synthesis of inosatriamines and also presents a novel synthesis of 2,5-dinitroaniline.

ACKNOWLEDGMENTS

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ABSTRACTS*

Part I.

The synthesis of 2,3-diamino-2,3-dideoxy- and 2,3,4-triamino-2,3,4-trideoxy-D-glucose derivatives is described. Addition of ammonia to methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-hex-2-enopyranoside (I) furnished methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside (III) in high yield. Alternatively, III was obtained by an elimination-addition reaction from methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro- α -D-glucopyranoside (II); in this case, small proportions of by-products were isolated. One of the by-products was identified as methyl 4,6-O-benzylidene-3-deoxy-3-nitro- α -D-glucopyranoside (V) and the other was a nitroamine, presumably the D-manno isomer (VI) of III. The N-acetyl derivative (IV) of III was debenzylidenated to give methyl 2-acetamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside (VIII). Catalytic hydrogenation of VIII afforded the amine hydrochloride X, which was converted into the diacetamido compound XI and the fully acetylated derivative XII. Acid hydrolysis of X produced 2,3-diamino-2,3-dideoxy- α -D-glucose dihydrochloride (XIII).

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

ABSTRACTS*

Part I.

The synthesis of 2,3-diamino-2,3-dideoxy- and 2,3,4-triamino-2,3,4-trideoxy-D-glucose derivatives is described. Addition of ammonia to methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-hex-2-enopyranoside (I) furnished methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside (III) in high yield. Alternatively, III was obtained by an elimination-addition reaction from methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro- α -D-glucopyranoside (II); in this case, small proportions of by-products were isolated. One of the by-products was identified as methyl 4,6-O-benzylidene-3-deoxy-3-nitro- α -D-glucopyranoside (V) and the other was a nitroamine, presumably the D-manno isomer (VI) of III. The N-acetyl derivative (IV) of III was debenzylidenated to give methyl 2-acetamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside (VIII). Catalytic hydrogenation of VIII afforded the amine hydrochloride X, which was converted into the diacetamido compound XI and the fully acetylated derivative XII. Acid hydrolysis of X produced 2,3-diamino-2,3-dideoxy- α -D-glucose dihydrochloride (XIII).

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

The 4,6-diacetate (IX) of the acetamidonitro glycoside VIII reacted with ammonia at room temperature to give methyl 2,4-diacetamido-2,3,4-trideoxy-3-nitro- α -D-glucopyranoside (XV) in 57% yield. Acetylation of XV provided its 6-acetate (XVI), whereas catalytic hydrogenation furnished methyl 2,4-diacetamido-3-amino-2,3,4-trideoxy- α -D-glucopyranoside hydrochloride (XVII). From XVII, the corresponding 2,3,4-triacetamido compound (XVIII) and its 6-acetate (XIX) were prepared.

Part II.

Nucleophilic addition of anthranilic acid to methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-hex-2-enopyranoside (I) afforded the 2,3-diequatorially substituted product, namely, methyl 4,6-O-benzylidene-2-(2-carboxyphenyl)amino-2,3-dideoxy-3-nitro- α -D-glucopyranoside (II), which was quantitatively converted by diazomethane to the methyl ester (III). Compounds II and III were debenzylidenated to IV and VI, respectively, and these products were acetylated to V and VII, respectively. Catalytic hydrogenation of the debenzylidenated acid (IV) afforded methyl 2,3-diamino-2,3-dideoxy- α -D-glucopyranoside dihydrochloride (VIII) which was characterized as the free base (IX) and as the di-N-acetyl derivative (X).

Nucleophilic addition of methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside (XII) to the nitroolefin I furnished bis(methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranosid-2-yl)amine (XIII). Its debenzylidenated derivative (XIV) gave a tetraacetate (XV), and catalytic hydrogenation of XIV produced bis(methyl 3-amino-2,3-dideoxy- α -D-glucopyranosid-2-yl)amine which crystallized as the trihydrochloride (XVI). Acetylation of XVI afforded a di-N-acetyltetra-O-acetyl derivative (XVII), the secondary amino group remaining free presumably owing to steric hindrance.

Part III.

Treatment of penta-O-acetyl-deoxy-nitro-scyllo-inositol (I) afforded 1,3-diacetamido-1,2,3-trideoxy-2-nitro-scyllo-inositol (IV) and a stereoisomer (II) possessing most probably the muco configuration. The latter was further characterized as its tri-O-acetyl derivative (III), and it gave, on catalytic hydrogenation, 1,3-diacetamido-2-amino-1,2,3-trideoxy-muco-inositol hydrochloride (V). Selective N-acetylation of V provided the triacetamido derivative VI, whereas complete acetylation furnished the triacetamido-tri-O-acetyl derivative VII. Similarly, catalytic hydrogenation of the scyllo compound IV afforded the corresponding amine (VIII), which was further characterized as the fully acetylated derivative IX.

with ammonia, followed by N-acetylation

Treatment of 2,3,5,6-tetra-o-acetyl-1,4-dideoxy-1,4-dinitro-neo-inositol (XVI) with ammonia led to aromatization and 2,5-dinitroaniline (XVII) was obtained in high yield. Treatment of XVI with sodium bicarbonate in refluxing benzene also effected aromatization, the product being 2,5-dinitrophenyl acetate (XIX).

Addendum

Nitration of trans,trans-2-nitro-1,3-cyclohexanediol (I) with sodium nitrite and silver nitrate in the presence of sodium hydroxide afforded 2,2-dinitrocyclohexane-cis-1,3-diol (II), and subsequent acetylation gave the corresponding diacetate (III).

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

A. The Significance of Rare Amino Sugars and Aminocyclitols

The advent of the era of antibiotics some thirty years ago has provided the medical world with a powerful weapon in its fight against disease and human suffering. On the other hand, the discovery and characterization of these antibiotics have revealed some unique and hitherto unknown chemical structures.

Of obvious interest to the carbohydrate chemist are those antibiotics which are partially or totally comprised of carbohydrate components. These components are often unusual amino sugars (1), some of which also occur in certain bacterial polysaccharides (2). In contrast to the more common 2-amino-2-deoxyhexoses, especially D-glucosamine and D-galactosamine, which are abundant in the animal kingdom (3) where they exist as components of mucopolysaccharides, glycoproteins and gangliosides, many of the unusual amino sugars produced by microorganisms carry an amino function on carbon atoms other than C-2. Some diamino sugars, which are not found in higher organisms, have been discovered as components of antibiotics (4) and as building units in a bacterial polysaccharide (5). Various amino sugars that possess configurations which are uncommon in plant and animal carbohydrates, such as the

L-gluco, D-gulo, L-ido and L-altro configurations, have been encountered in products of microbial origin. Finally, a number of aminocyclitols form components of antibiotics elaborated by fungi, whereas higher plants and animals apparently can synthesize non-nitrogenous cyclitols (inositols) only (6). Tables I and II list a few examples of these unusual amino sugars and aminocyclitols together with the sources from which they were obtained, to illustrate the variety of structures encountered.

The diversity of structure and configuration in these novel amino sugars and aminocyclitols presents a challenge to carbohydrate chemists, who have invested considerable time and energy, during the past two decades, in devising chemical syntheses for these natural products and for many stereoisomers and structural analogs. Such research may contribute to the chemistry of antibiotics mainly in three ways:

1. It provides model compounds which can be used for purposes of comparison and identification, in degradation studies undertaken to elucidate newly discovered carbohydrate antibiotics.
2. Synthetic amino sugars and aminocyclitols could serve as key intermediates in eventual, total chemical syntheses of natural antibiotics.
3. Synthetic amino sugars and aminocyclitols might be used in the synthesis of structurally or configura-

tionally modified antibiotics that have not yet been discovered or that do not exist in nature. Such synthetic analogs could be of value in the combat of strains of microorganisms which are resistant to the antibiotics presently available. Chemical modification might also reduce medicinally undesirable side effects that are shown by many existing drugs. For example, 3-amino-3-deoxy-D-glucose has been suspected (53a) of being responsible for the considerable ototoxicity of kanamycin, and it would be interesting to see whether this effect could be diminished by substituting a different amino sugar for that moiety.

Table I

SOME UNUSUAL AMINO SUGARS OCCURRING IN NATURE

<u>Amino Sugar</u>	<u>Structure</u>	<u>Source</u>	<u>Reference</u>
3-Amino-3-deoxy- D-glucose (Kanosamine)		Kanamycins A, B, C	7, 8
4,6-dideoxy-4- dimethylamino- D-glucose (Amosamine)		Amicetin	9, 10, 11
5-Amino-5-deoxy- D-glucose		Nojirimycin	12 - 15
6-Amino-6-deoxy- D-glucose		Kanamycin A	7, 8

Table I (continued)

<u>Amino Sugar</u>	<u>Structure</u>	<u>Source</u>	<u>Reference</u>
Desosamine		Erythromycin	16
		Narbomycin	17
		Picromycin	18
		Methymycin	19
2-Amino-2-deoxy-D-gulose		Streptothricin	20, 21
2-Methylamino-2-deoxy-L-glucose	<p>R=CH₃</p>	Streptomycin	22
2,6-Diamino-2,6-dideoxy-L-idose (Neosamine B)		Neomycin B	23 - 30
		Paromomycin I	31 - 34

Table I (continued)

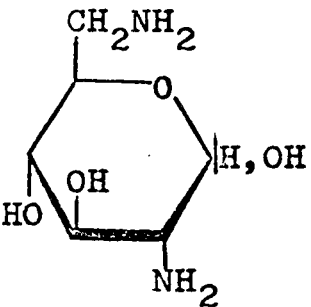
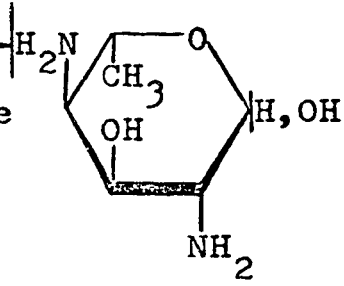
<u>Amino Sugar</u>	<u>Structure</u>	<u>Source</u>	<u>Reference</u>
2,6-Diamino-2,6-dideoxy-D-glucose (Neosamine C)		Neomycin C Paromomycin II	26, 29, 30 31 - 34
2,4-Diamino-2,4,6-trideoxy-L-altrose (Bacillosamine)		<u>Bacillus subtilis</u> polysaccharide	5 35 - 37

Table II

SOME AMINOCYCLITOLS OCCURRING IN ANTIBIOTICS

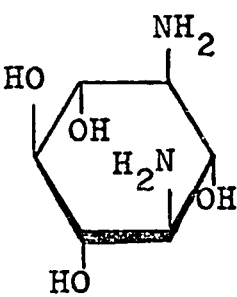
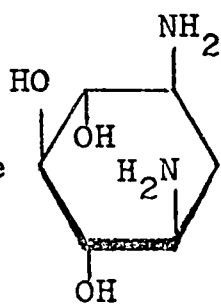
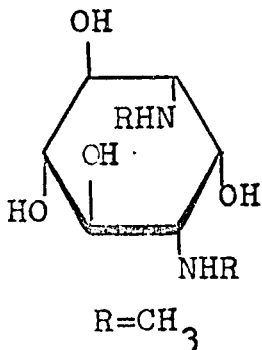
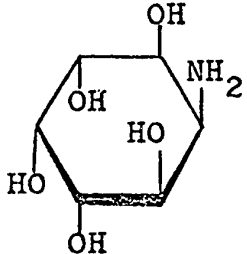
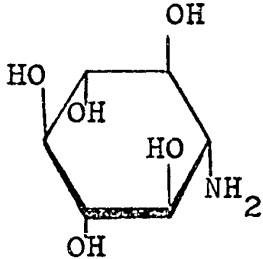
<u>Aminocyclitol</u>	<u>Structure</u>	<u>Antibiotic</u>	<u>Reference</u>
Streptamine		Streptomycin	38 - 40
		Dihydrostreptomycin	
		Mannosidostreptomycin (Streptomycin B)	
		Hydroxystreptomycin	
2-Deoxystreptamine		Neomycins	24, 41
		Paromomycins	42
		Kanamycins	43
		Gentamycins	44
		Hygromycin B	45
Actinamine	 <p>R=CH₃</p>	Actinospectatine	46 - 49

Table II (continued)

<u>Aminocyclitol</u>	<u>Structure</u>	<u>Antibiotic</u>	<u>Reference</u>
<u>neo</u> -Inosamine-2		Hygromycin Antibiotic 1703 - 18B	50 - 51 52
<u>scyllo</u> -Inosamine		Bluensomycin	53

B. Nitro Sugars as Precursors of Amino Sugars

Although there exist several different possibilities of introducing nitrogen into a carbohydrate molecule, one of the more versatile and convenient approaches to amino sugars is by way of the corresponding nitro sugars. This route is especially useful for 3-amino sugars because their 3-nitro precursors can be easily obtained by cyclization of "sugar dialdehydes" with nitromethane. The resulting mixtures of stereoisomeric nitro sugars can sometimes be separated and the individual isomers catalytically hydrogenated to the corresponding amino derivatives; or alternatively, the mixture may be hydrogenated and isolation of individual isomers may then be achieved at the amino stage.

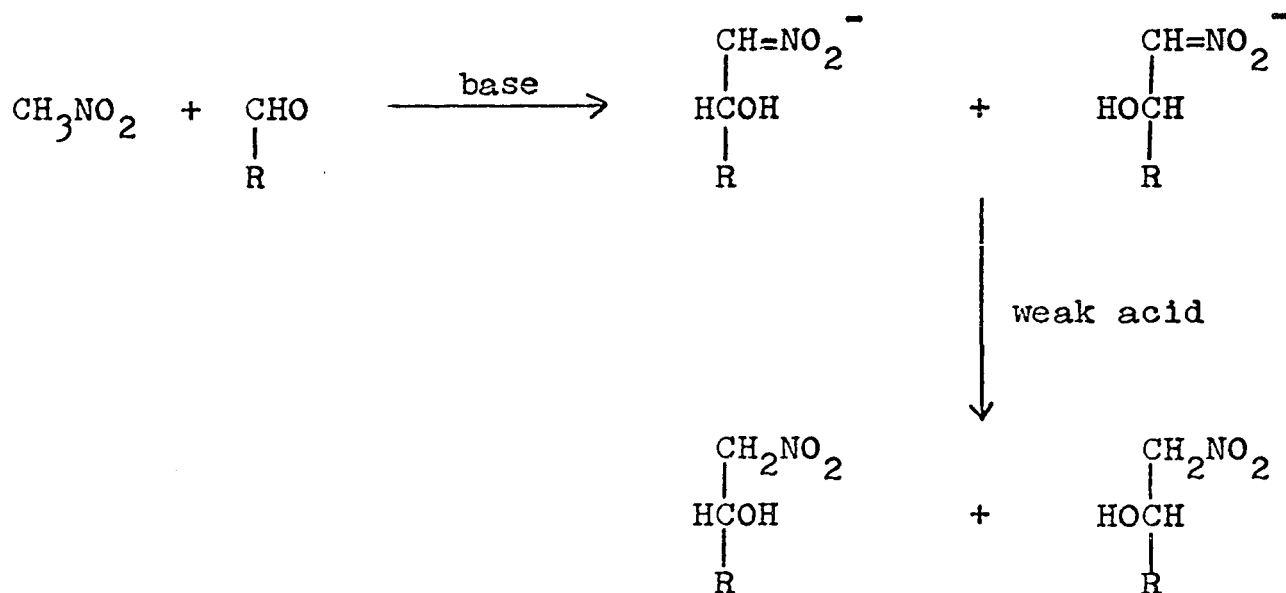
These approaches have been successful in multifarious cases and have furnished, among others, the D- and L- enantiomers of 3-amino-3-deoxy-ribose (54), 3-amino-3-deoxy-xylose (as methyl pyranosides) (54) and 3-amino-3-deoxy-arabinose (55); 3-amino-3-deoxy-D-glucose, -D-mannose, -D-talose, and -D-galactose (56-58); 3-amino-2,3-dideoxy-D-arabino-hexose (59); 3-amino-2,3-dideoxy-D-lyxo-hexose (60); 3-amino-1,6-anhydro-3-deoxy- β -D-gulose, - β -D-altrose, and - β -D-idose (61); 3-amino-3,6-dideoxy-L-glucose (62), -L-mannose, -L-galactose, and -L-talose (63); 4-amino-2,7-anhydro-4-deoxy- β -D-gulo-, - β -D-altro-, and - β -D-allo-heptulopyranose (64,65); and 4-amino-4-deoxy- α -L-sorbose and - β -D-tagatose (66).

C. Some Aspects of Nitro Sugar Chemistry

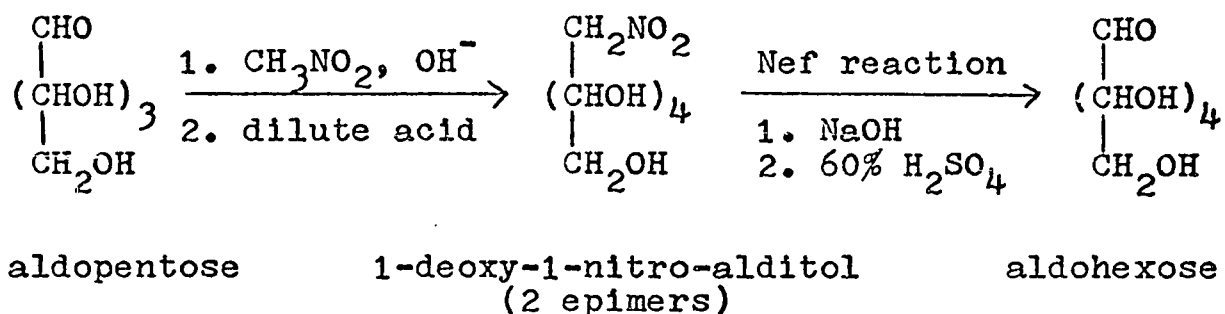
Since the present thesis elaborates on reactions of nitro sugars and nitrocyclitols, two aspects of nitro sugar chemistry which are involved in the synthetic schemes to be presented will be briefly reviewed: the addition of nitromethane to aldehydes and the synthesis of nitroolefinic sugars.

1. The Nitromethane-Aldehyde Addition Reaction

In 1895, in a paper entitled "Formation synthétique d'alcools nitrés", L. Henry (67) first described the base-catalyzed addition of nitromethane to aldehydes, which yields nitro alcohols:

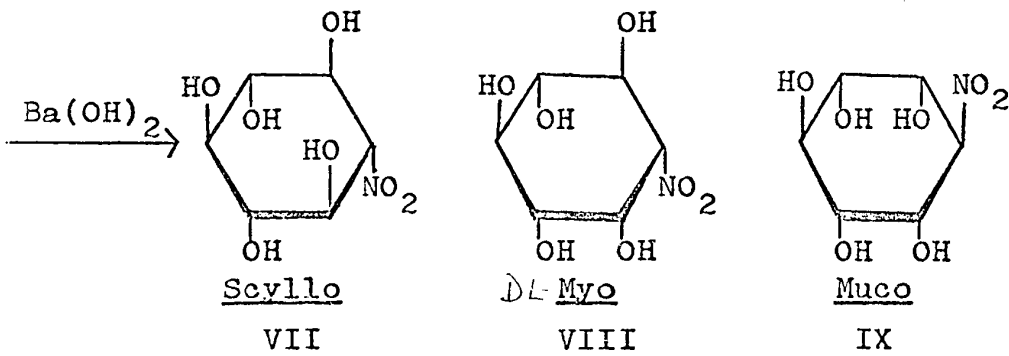
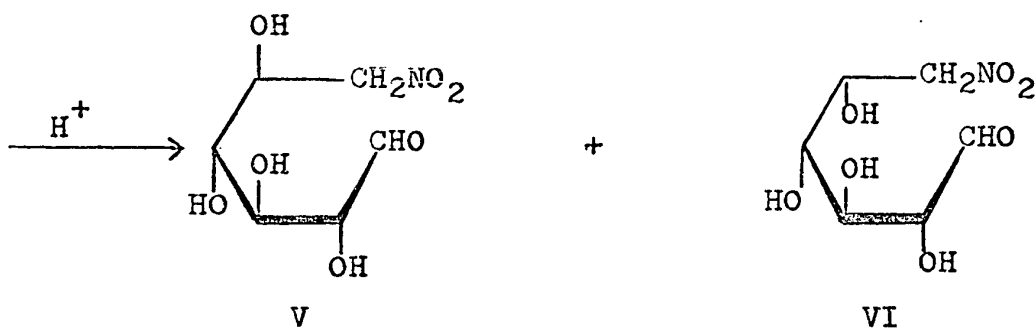
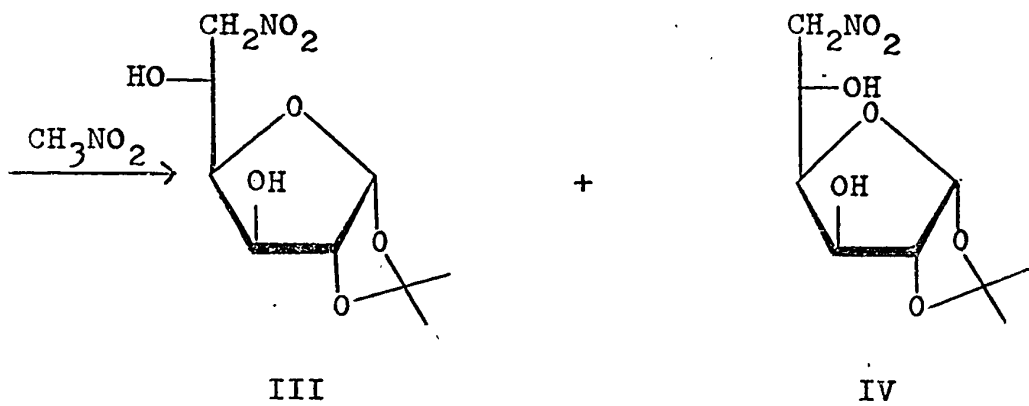
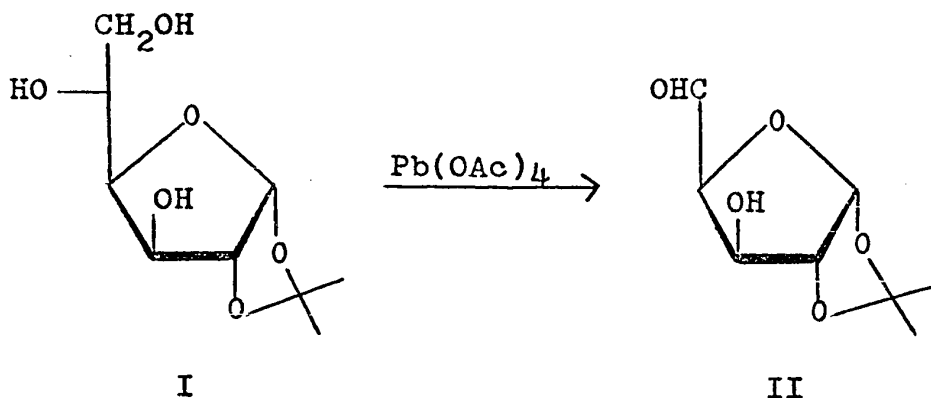


The reaction has found widespread application in aliphatic and aromatic chemistry and has been reviewed in detail (68-72). It was successfully introduced into the carbohydrate field in 1944 by Sowden and Fischer (73), who prepared deoxynitroalditols from aldoses and nitromethane, and then submitted the adducts to the Nef reaction to obtain the corresponding aldoses:



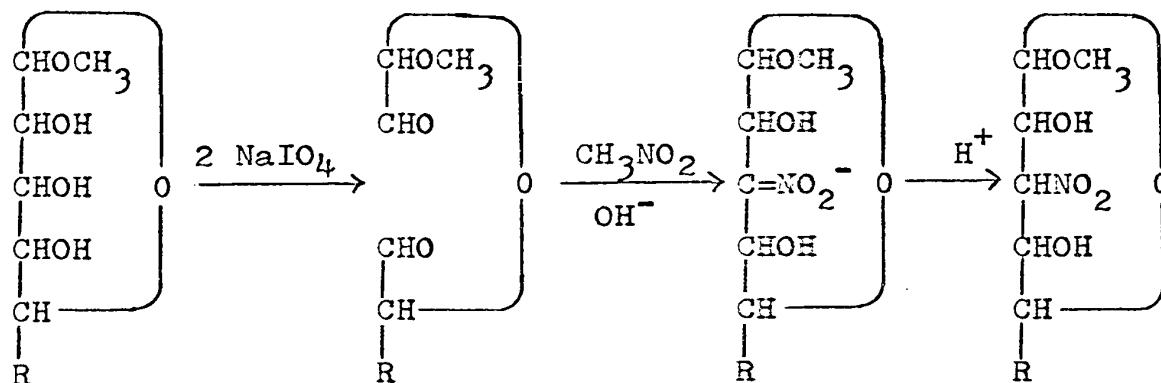
The Sowden-Fischer synthesis has become one of the most reliable methods for lengthening the carbon chain of carbohydrates (74).

Applying the above principle, Grosheintz and Fischer (75) condensed with nitromethane the 1,2-O-isopropylidene- α -D-xylo-pentodialdo-1,4-furanose (II) that can be prepared by lead tetraacetate oxidation of 1,2-O-isopropylidene- α -D-glucofuranose (I), and they obtained a mixture of 6-deoxy-1,2-O-isopropylidene-6-nitro-D-glucofuranose (III) and its L-idofuranose isomer (IV). Deacetonation of these products provided the free



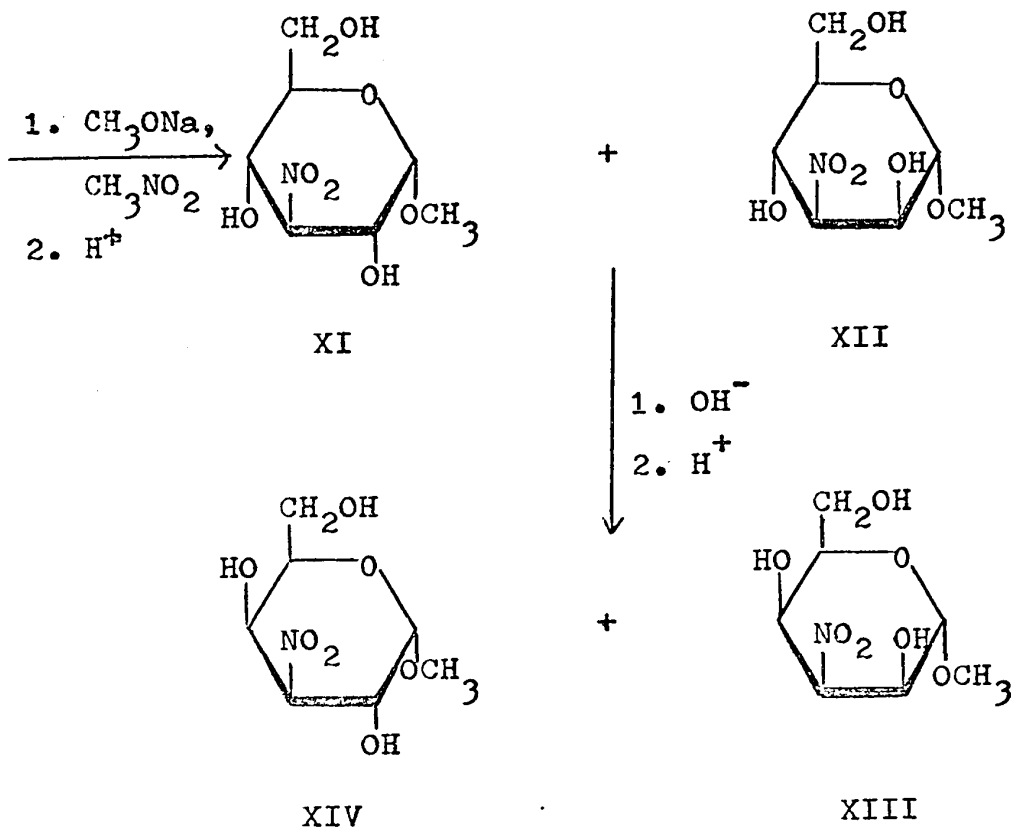
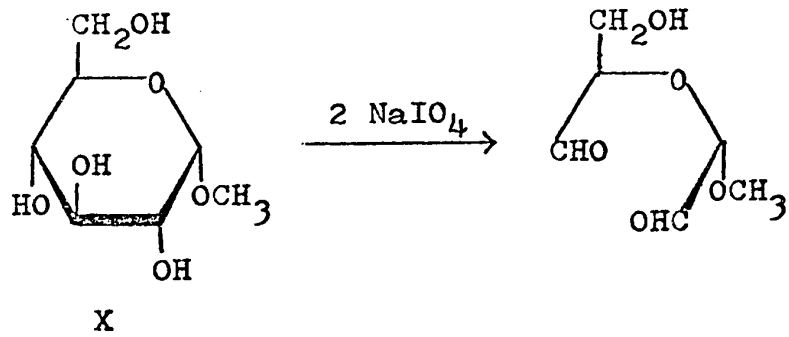
6-nitro-6-deoxy-D-glucose (V) and 6-nitro-6-deoxy-L-idose (VI). Under the influence of barium hydroxide, these free nitro sugars underwent an internal Henry reaction to give a mixture of stereoisomeric deoxynitroinositols having the scyllo (VII), myo-1 (VIII) and muco-3 (IX) configurations. When the internal Henry condensation was performed in the presence of sodium hydroxide, only the myo-1 and scyllo-nitroinositols were formed (75-77). This particular example of the nitroalkane-aldehyde reaction is mentioned at this point because the cyclization products have served as starting materials for the synthesis of diamino and triamino inositols, as will be outlined subsequently in this thesis.

A new class of nitro sugars was rendered accessible by Baer and Fischer (78), who condensed nitromethane with periodate-oxidized glycosides ("sugar dialdehydes"). The latter undergo a double Henry addition to yield nitropyranosides:

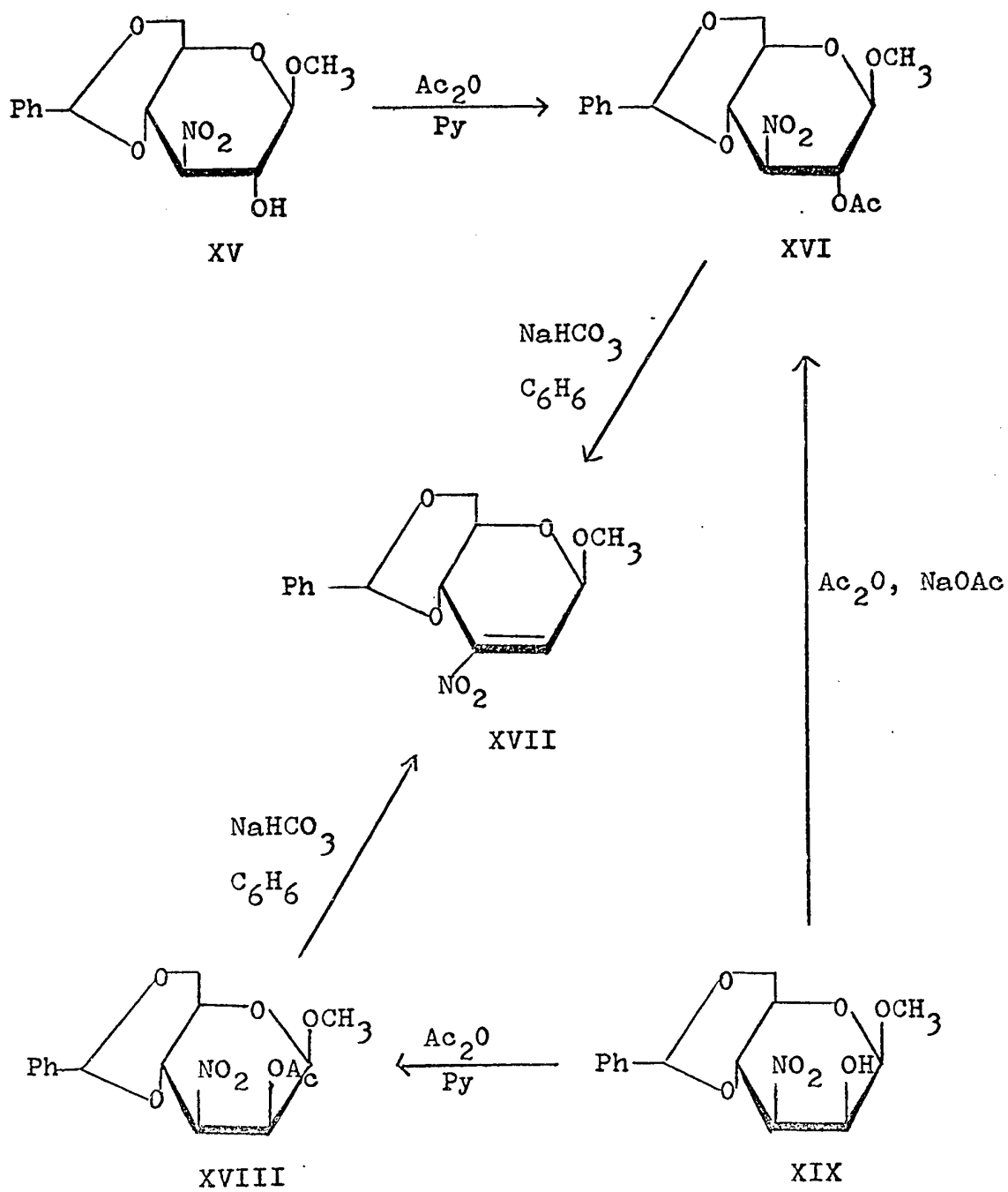


R = H, CH₂OH, CH₃

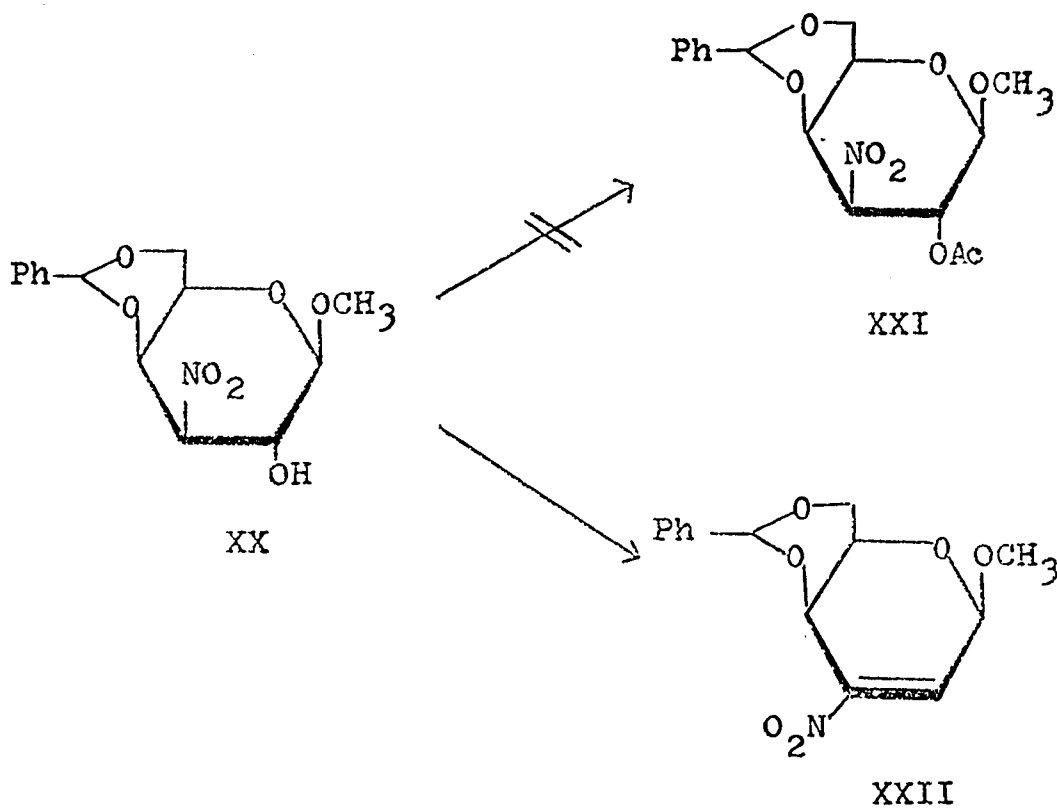
In this cyclization, two new asymmetric centers are generated during the formation of the nitronate, and a third one, on acidification of the nitronate: thus eight stereoisomers are theoretically possible. However, the reaction normally proceeds with a marked stereoselectivity, so that one or two of the isomers are obtained as main products and one or two others may be obtained in small proportions, while the remaining ones are not formed in isolable quantities. The isomeric-product composition seems to depend on whether the reaction is performed under conditions of kinetic control or whether thermodynamic equilibration is allowed. For example, the dialdehyde made from methyl- α -D-glucopyranoside (X) gives, under kinetic control, chiefly the methyl 3-deoxy-3-nitro- α -D-hexopyranosides having the gluco (XI) and manno (XII) configurations, while those having the talo (XIII) and galacto (XIV) configurations arise upon subsequent, slow epimerization of the nitronates in alkaline solution (57,58). A common configurational feature of these nitro sugars is the equatorial orientation of the C-3 nitro group (if the compounds are depicted in the C1 chair conformation). Similar results are obtained in the analogous series of β -D-glycopyranosides where the cyclization products (gluco, galacto and manno stereoisomers) also have the C-3 nitro group oriented equatorially (56,80,81).



The reaction has found manifold applications in the synthesis of open-chain, nitroolefinic derivatives of sugar alcohols (88,90-92). Baer and coworkers (59,93,94) have applied it in the synthesis of the first sugar derivatives possessing a nitroolefinic grouping as part of the glycosidic ring. Thus, the nitroolefin XVII (methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- β -D-erythro-hex-2-enopyranoside) was obtained both from the D-gluco nitroacetate XVI and from its D-manno isomer XVIII. The requisite acetates (XVI and XVIII) were prepared from their alcohol precursors (XV and XIX) by acetylation with acetic anhydride in cold pyridine. However, when the mannoside (XIX) was acetylated with hot acetic anhydride and sodium acetate, the product was the gluco acetate (XVI) and not the manno acetate (XVIII). Evidence was adduced that this epimerization proceeded via intermediate olefin (XVII). Reactions will be described later in this thesis, in which similar α -nitroolefins are assumed to arise, by elimination processes from β -nitroacetates, and then to undergo nucleophilic additions producing new, β -substituted nitro compounds. It is of interest that in reactions such as those just mentioned, the stereochemical configuration of the molecule even at a site not directly involved in the transformation may govern the result. For example, the D-galacto isomer (XX) of XV and XIX failed to become acetylated with acetic anhydride and pyridine in the cold. When acetylation



was attempted under forcing conditions with hot acetic anhydride and sodium acetate, there was obtained neither the corresponding 2-acetate (XXI) nor an epimer thereof, but solely the nitroolefin (XXII).



Although many carbohydrate nitroacetates have been successfully dehydroacetylated under standard conditions, i.e. by refluxing in benzene with dry sodium bicarbonate, the reaction has occasionally been found to be sluggish, and the reflux times required and yields obtained have not always been accurately reproducible. Also, cer-

tain by-products have been encountered in varying proportions (95). Recently Jones and coworkers (86) were able to overcome such difficulties by substituting triethylamine for sodium bicarbonate, thus performing the reaction in homogeneous medium.

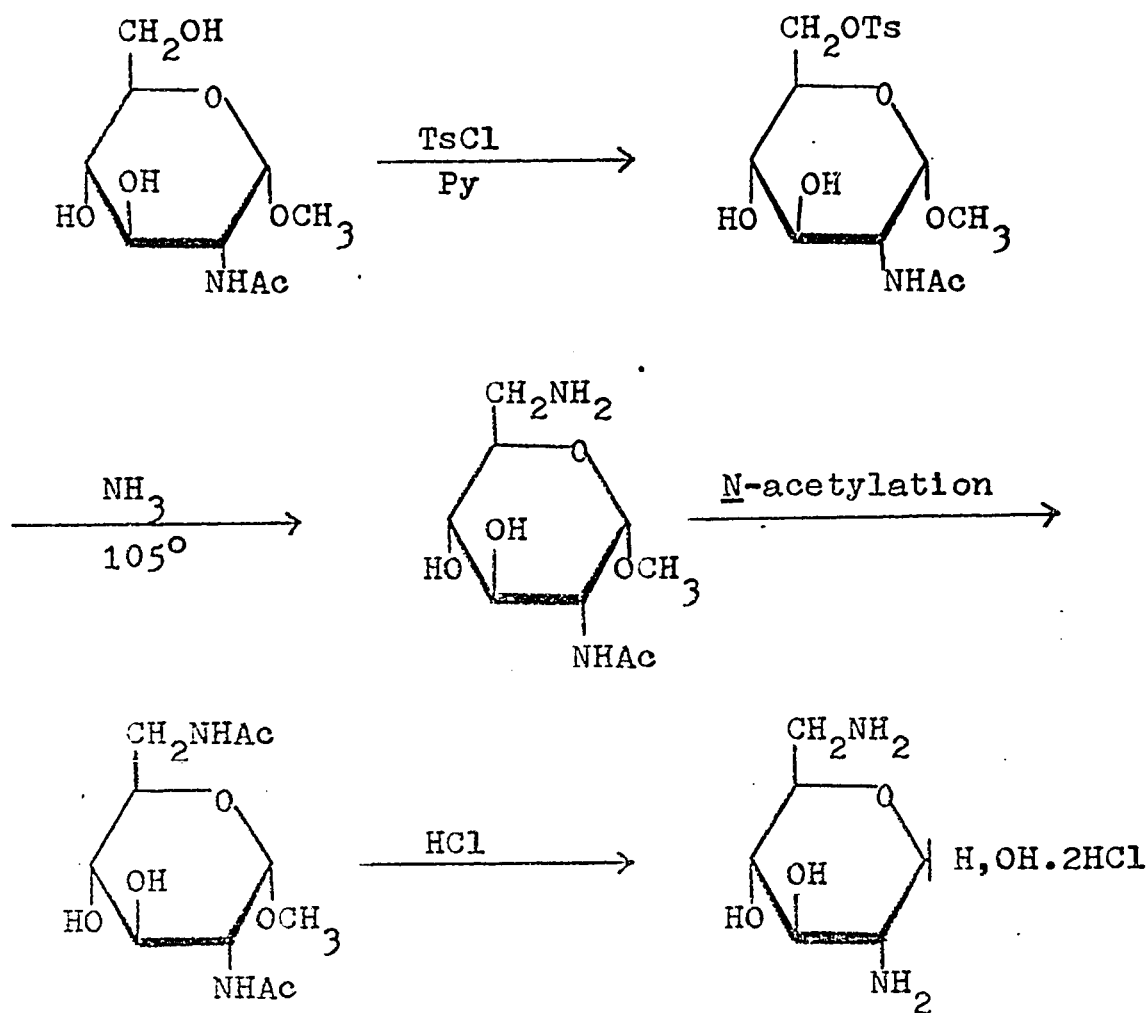
D. Methods for the Synthesis of Diamino Sugars

Since a significant portion of this thesis deals with the synthesis of diamino sugars, a brief review of the synthetic methods presently available for such sugars will be given:

1. Direct Nucleophilic Displacement Reactions

This method has found almost universal application for such syntheses. The displacements are carried out on suitably blocked carbohydrates. Common leaving groups are the *p*-toluenesulfonyloxy (tosyloxy) and methanesulfonyloxy (mesyloxy) groups, and convenient nucleophiles are ammonia, hydrazine and azide. In the last two cases, the resulting hydrazino and azido products are subsequently reduced to the amino stage.

A straightforward application of the above principle is exemplified in the synthesis of 2,6-diamino-2,6-dideoxy-D-glucose by Rinehart and coworkers (96).



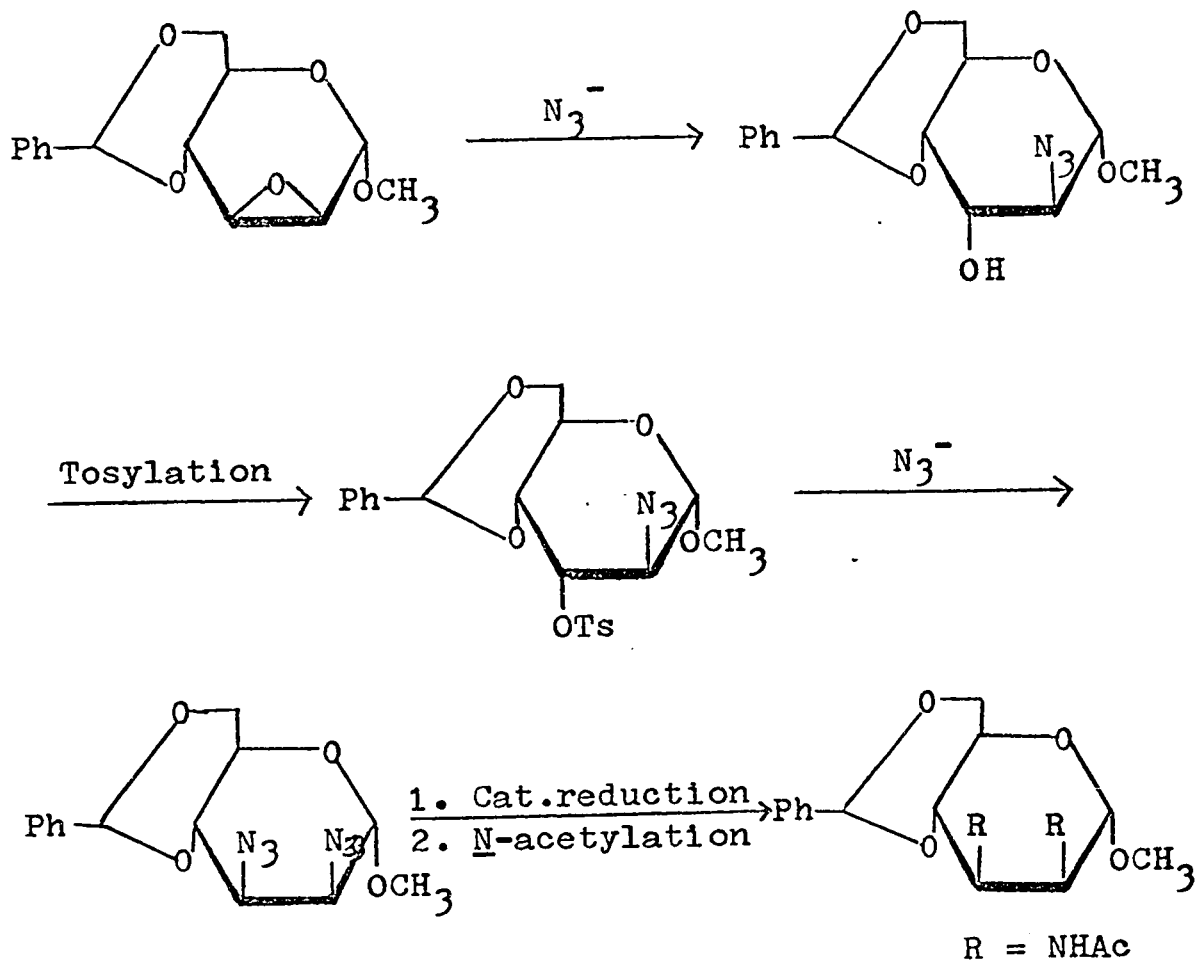
Diamino sugars synthesized in this way include 2,3-diamino-2,3-dideoxy-D-glucose and -D-allose (97); 3,6-diamino-3,6-dideoxy-D-altrose (98) and -D-glucose (99); 2,6-diamino-2,6-dideoxy-D-allose (100), -D-galactose (101), -D-mannose (102,103), -D-glucose (104), and -L-idose (105).

2. Nucleophilic Displacements with Neighboring Group Participation

It is often possible to synthesize carbohydrates that contain within the same molecule a good leaving group and a neighboring substituent which can act as a nucleophile. The latter, under suitable conditions, can be made to effect an intramolecular S_N2 displacement that leads to a cyclic intermediate such as an epoxide, aziridine (epimine) or oxazoline. These cyclic intermediates can then be subjected to ring opening with nucleophiles such as azide, ammonia or hydrazine - and nitrogenous functions may thus be introduced into the molecule. This approach has been used in the synthesis of certain diamino sugars and will be exemplified below:

a) Via Epoxides:

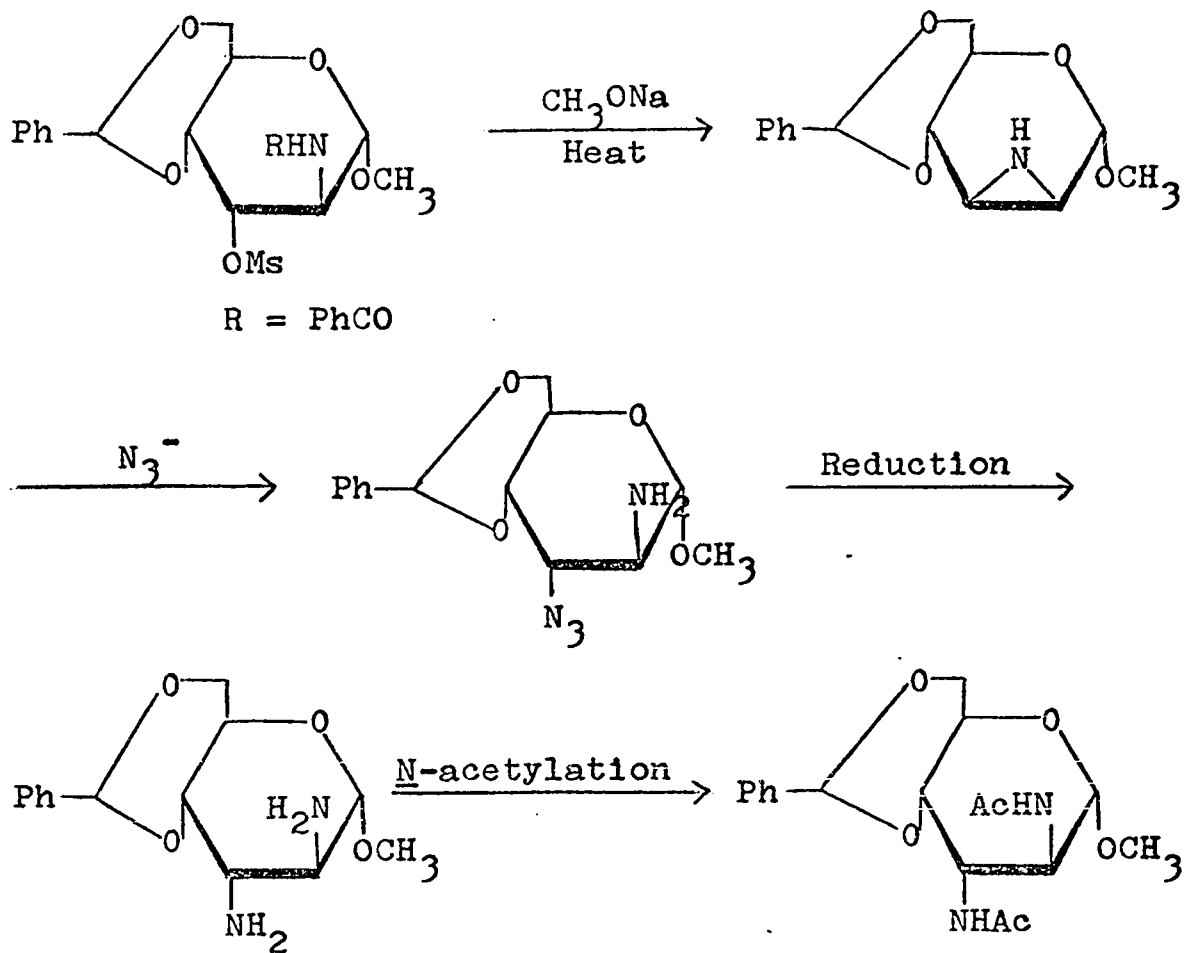
Nucleophilic attack on the epoxide proceeds according to the Fürst-Plattner rule (106), especially if the carbohydrate molecule is not very mobile conformationally. This is illustrated in the synthesis of a 2,3-diamino-D-mannose derivative by Guthrie and Murphy (107):



The principle has been applied in the synthesis of 2,3-diamino-2,3-dideoxy-D-mannose (108); 2,6-diamino-2,6-dideoxy-D-altrose (109); 3,6-diacetamido-3,6-dideoxy-D-gulose and -D-idose (110); 3,6-diamino-3,6-dideoxy-D-allose (111), -D-idose (112, 113) and -L-talose (114).

b) Via Aziridines (epimines)

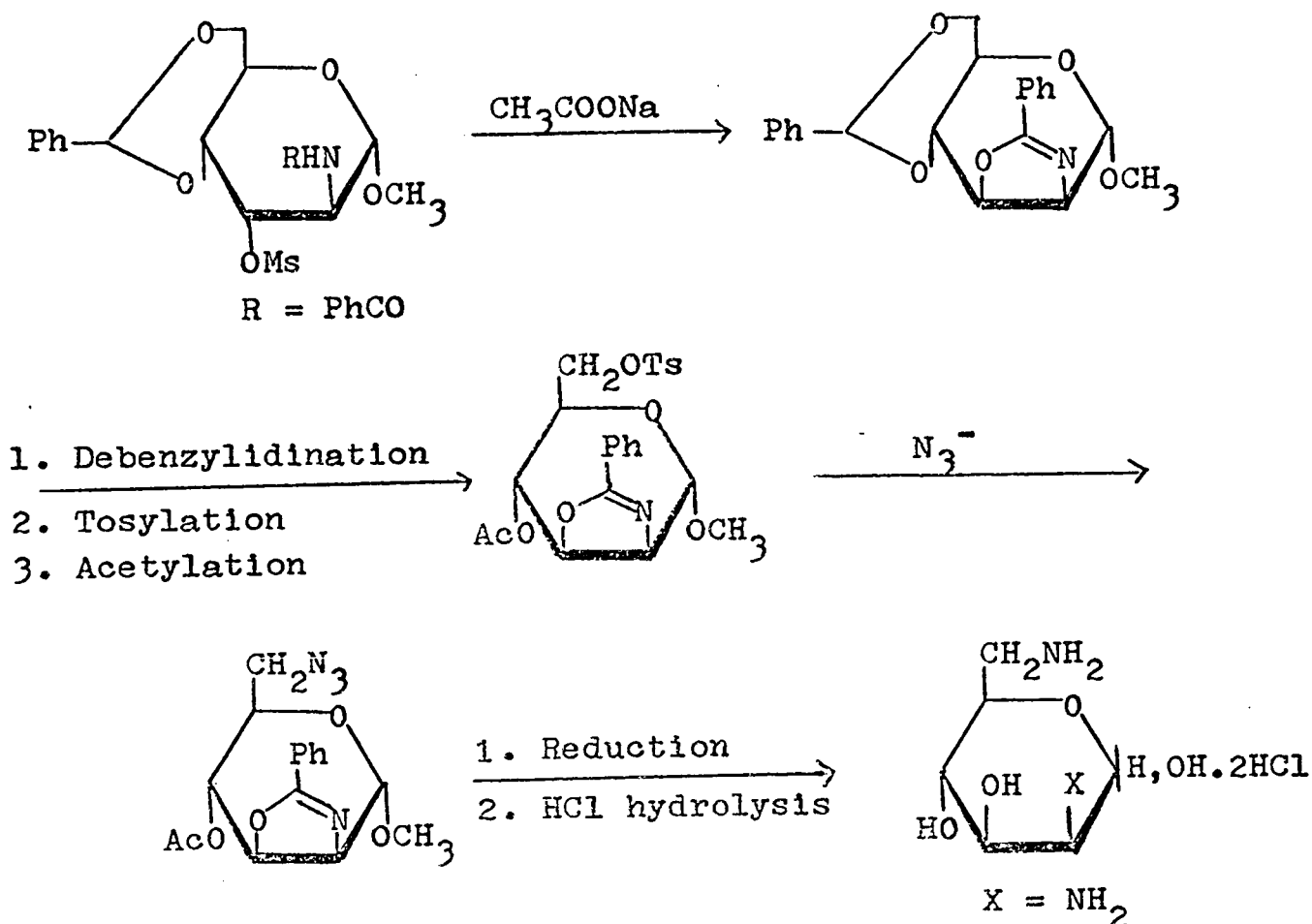
Guthrie and coworkers (115) used this approach to synthesize derivatives of 2,3-diamino-2,3-dideoxy-D-altrose:



The epimine rings - like their epoxide counterparts - are opened in accordance with the Fürst-Plattner rule, although exceptions have been encountered (116,117).

c) Via Oxazolines:

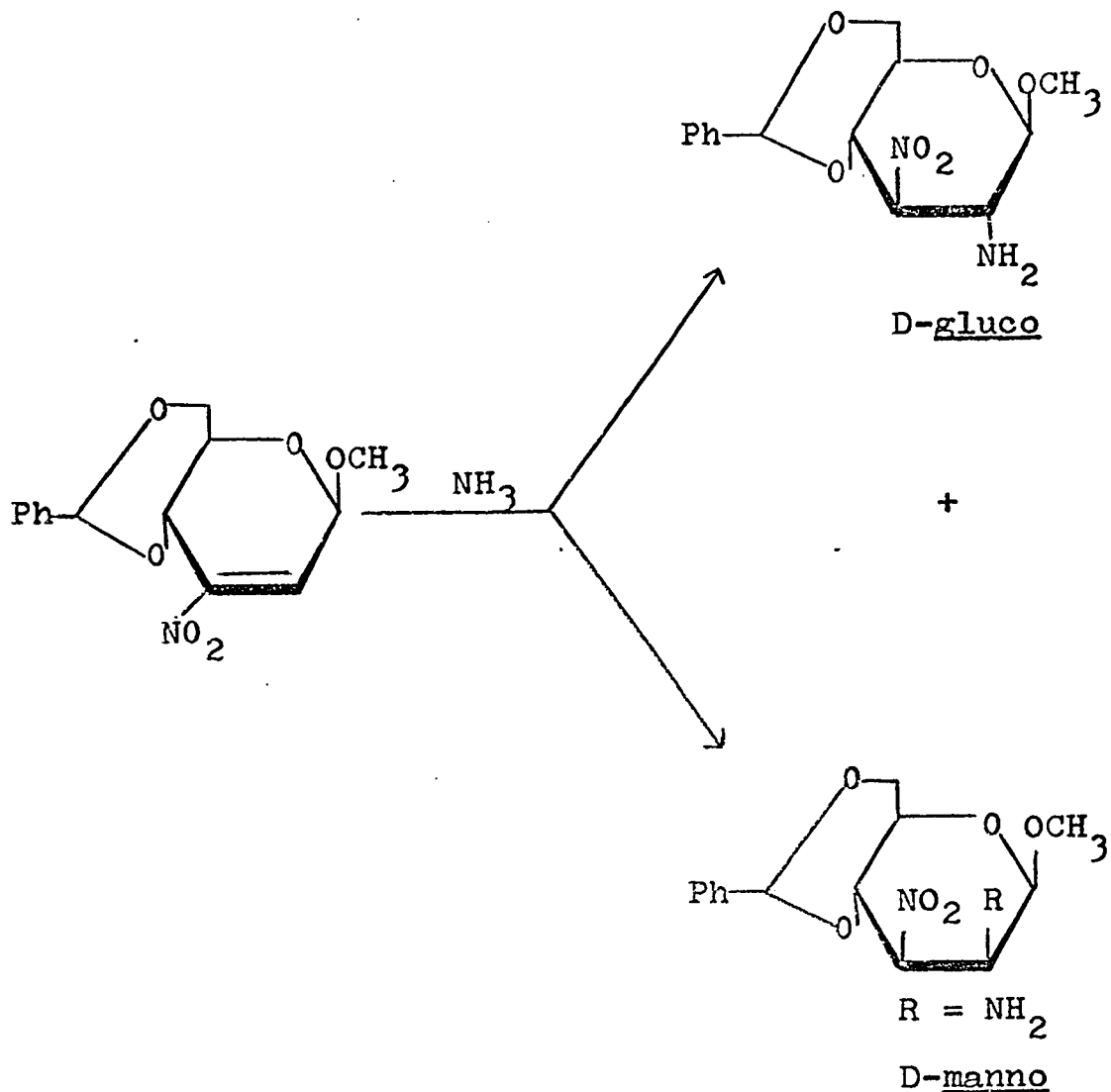
2,6-Diamino-2,6-dideoxy-D-mannose has been prepared (118) by this method:



Other diamino sugars synthesized via this route include 2,6-diamino-2,6-dideoxy-D-allose (97) and -D-galactose (119).

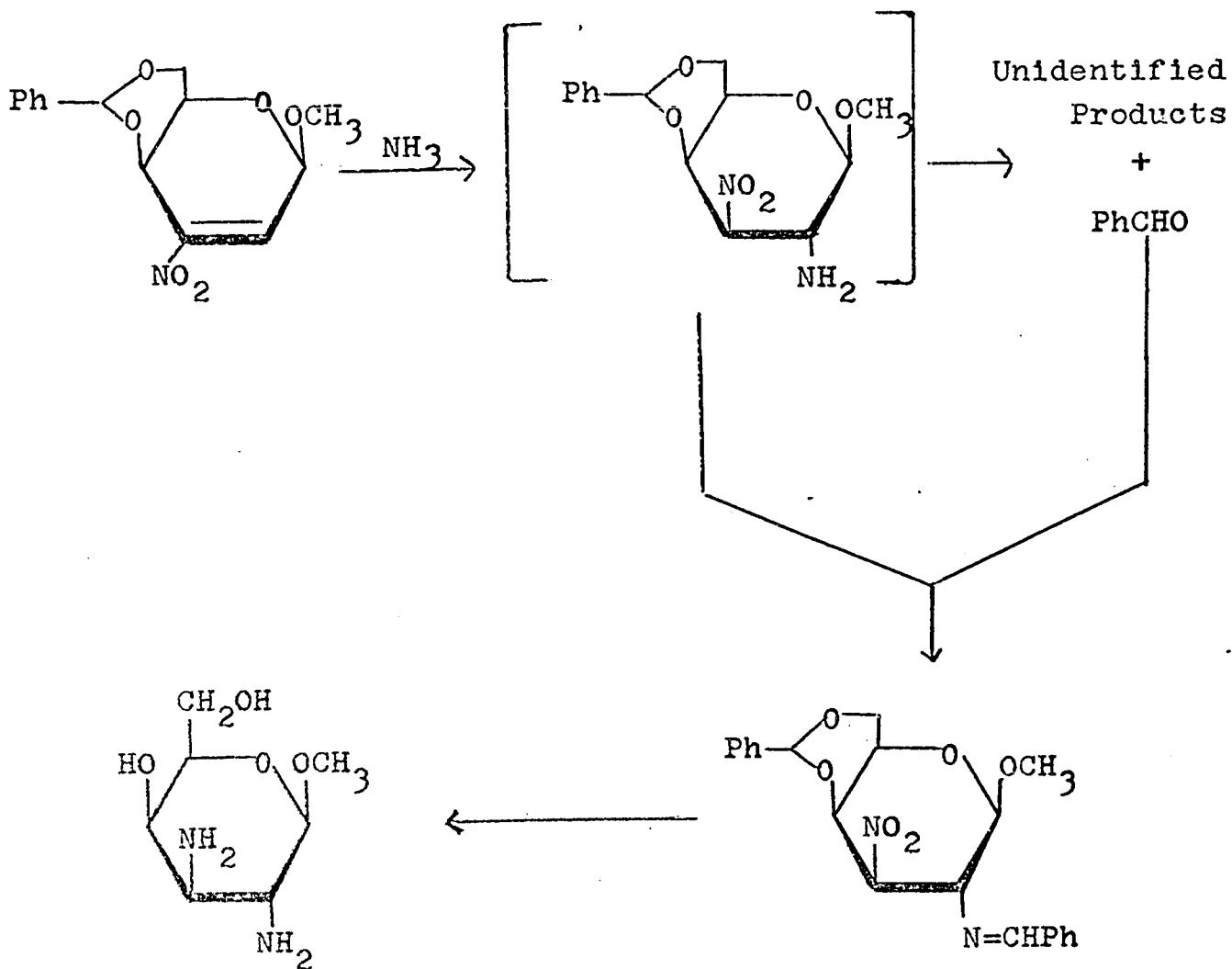
3. Synthesis via Nitro Sugars:

Baer and Neilson (120) made use of the activating effect of the nitro group to introduce an amino group in vicinal position:



The addition gave predominantly the D-gluco nitroamine derivative, which after N-acetylation, debenzylidenation, reduction of the nitro group and final acid hydrolysis gave 2,3-diamino-2,3-dideoxy-D-glucose. The minor addition product furnished 2,3-diamino-2,3-dideoxy-D-mannose (121) in a similar sequence of steps.

The synthesis of 2,3-diamino-2,3-dideoxy-D-galactose (122) was achieved in an analogous fashion.



However, the nitroamine engendered in this case turned out to be less stable than its gluco isomer. Under the conditions of the reaction it suffered, in part, a base-catalyzed elimination of the 4,6-O-benzylidene blocking group followed by transformations of undetermined nature; the benzaldehyde so liberated formed a Schiff base with surviving nitroamine, and this Schiff base could be isolated and utilized for the further steps of the synthesis.

E. Specification of the Aims of this Thesis

As could be gauged from the previous paragraphs in which a few aspects of the chemistry of nitro sugars were briefly presented, these compounds are endowed with interesting properties which merit further studies. Since our knowledge of these sugars is still rather limited, it was deemed worthwhile to investigate the following problems that bear on their utilization in the synthesis of amino sugars:

1. The nitro group in 3-deoxy-3-nitro-sugars exerts an activating effect which has been utilized for the introduction of substituents on the vicinal carbon atom, C-2. However, previous and concurrent work has been directed mainly towards the study of β -glycosidic nitro sugars, and it was therefore interesting to see whether reactions involving C-2 are influenced by the anomeric configuration of the glycoside. In particular, the introduction of an amino group on C-2 was to be studied in the α -glycoside series; this could lead to an alternative, and perhaps improved, synthesis of 2,3-diamino-2,3-dideoxy sugars. Further, it was to be investigated whether an amino group could be introduced on C-2 and an additional one on C-4, so that an avenue would be opened to 2,3,4-triamino-2,3,4-trideoxy sugars.

2. The study of 3-deoxy-3-nitro- α -glycosides could then be extended to include the introduction, at C-2, of other substituents. Of special interest in this regard would be the behavior of anthranilic acid, an addend which had exhibited an unusual behavior in the β -glycosidic series (121,135). Also, it was to be investigated whether two nitro sugar molecules could be linked together by an amine bridge. Such a synthesis would provide a novel type of nitrogenous "disaccharides".

3. Finally, similar amination reactions were to be performed with compounds that are closely related to nitro sugars, namely, mononitro and dinitro inositols. Work in this area would contribute to the chemistry of inosdiamines and related derivatives, which are of current interest in the realm of antibiotics.

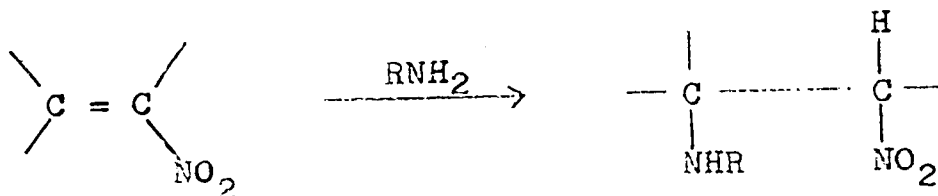
PART I

THE REACTION OF NITRO SUGARS WITH AMMONIA

DISCUSSION*

A. Synthesis of Derivatives of 2,3-Diamino-2,3-dideoxy-
D-glucose

As already outlined in the introduction, most of the diamino sugars described so far in the literature have been synthesized by nucleophilic displacement reactions - with or without neighboring group participation - on suitably blocked carbohydrates. A different approach was taken in the present synthesis. Use was made of the activating effect of the nitro group in nitroolefins, which enables ammonia and amines to be added so as to furnish vicinal aminonitro compounds as precursors for vicinal diamines.

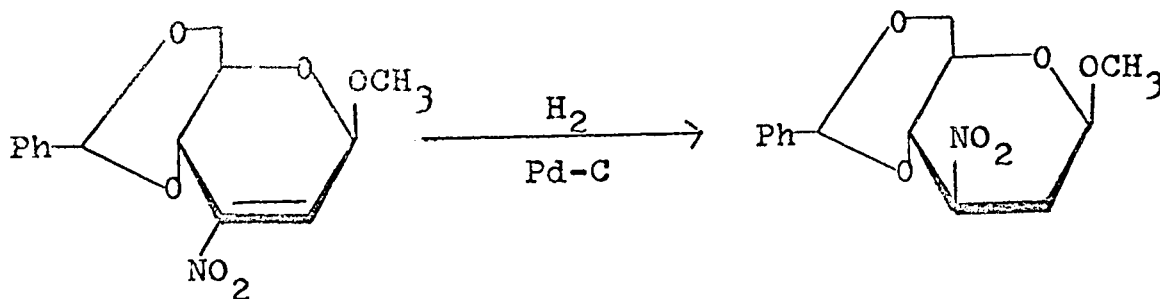


Although this reaction had been known for many decades and had been widely employed in general aliphatic chemistry (123), it found a first application in carbohydrate chemistry (124) only as late as 1959. At the outset

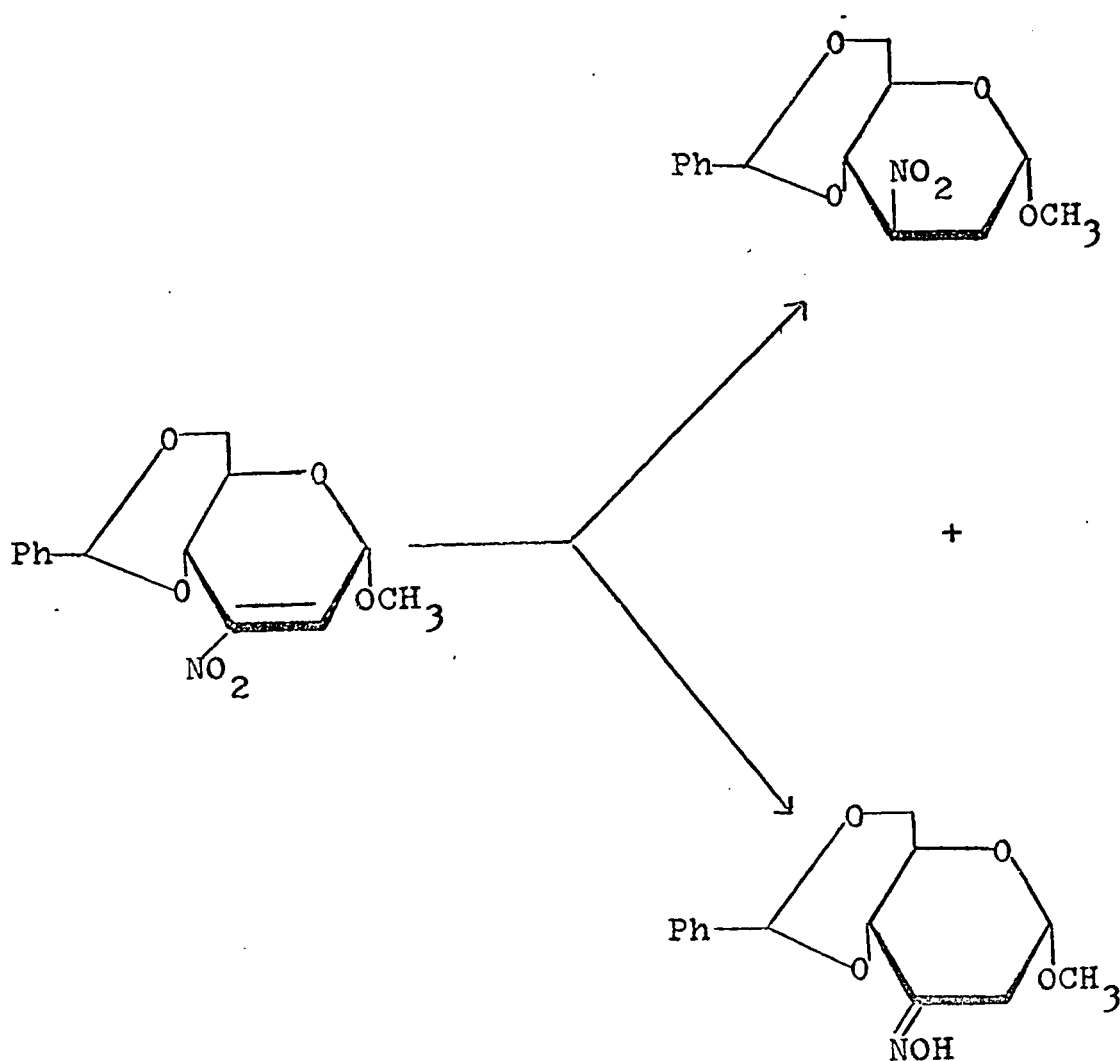
* For convenience, compounds in this chapter are numbered using a new set of Roman numerals.

of the work for this thesis, the reaction had been studied with a number of sugar alcohols (alditols) (124-128) and with one blocked sugar (129) which all possessed a terminal nitroalkene grouping; a few additional examples of this kind have been reported in the meantime (130,131). Baer and coworkers (120,122) applied the principle to sugars that contained a nitroalkene grouping as part of the ring. Thus, 2,3-unsaturated 3-nitro glycosides were aminated in position 2, and this approach led ultimately to the synthesis of derivatives of 2,3-diamino-2,3-dideoxy-D-glucose (120) and -D-galactose (122).

The unsaturated nitro glycosides used in the work just mentioned (120,122) were of the β -type. Previous experience with such 3-nitro hexosides and their α -anomers has shown that the anomeric configuration may influence the course of certain reactions. For example, selective catalytic hydrogenation of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- β -D-erythro-hex-2-enopyranoside gave the saturated nitro glycoside (with β -D-arabino configuration) in 87% yield, as the sole product (59):



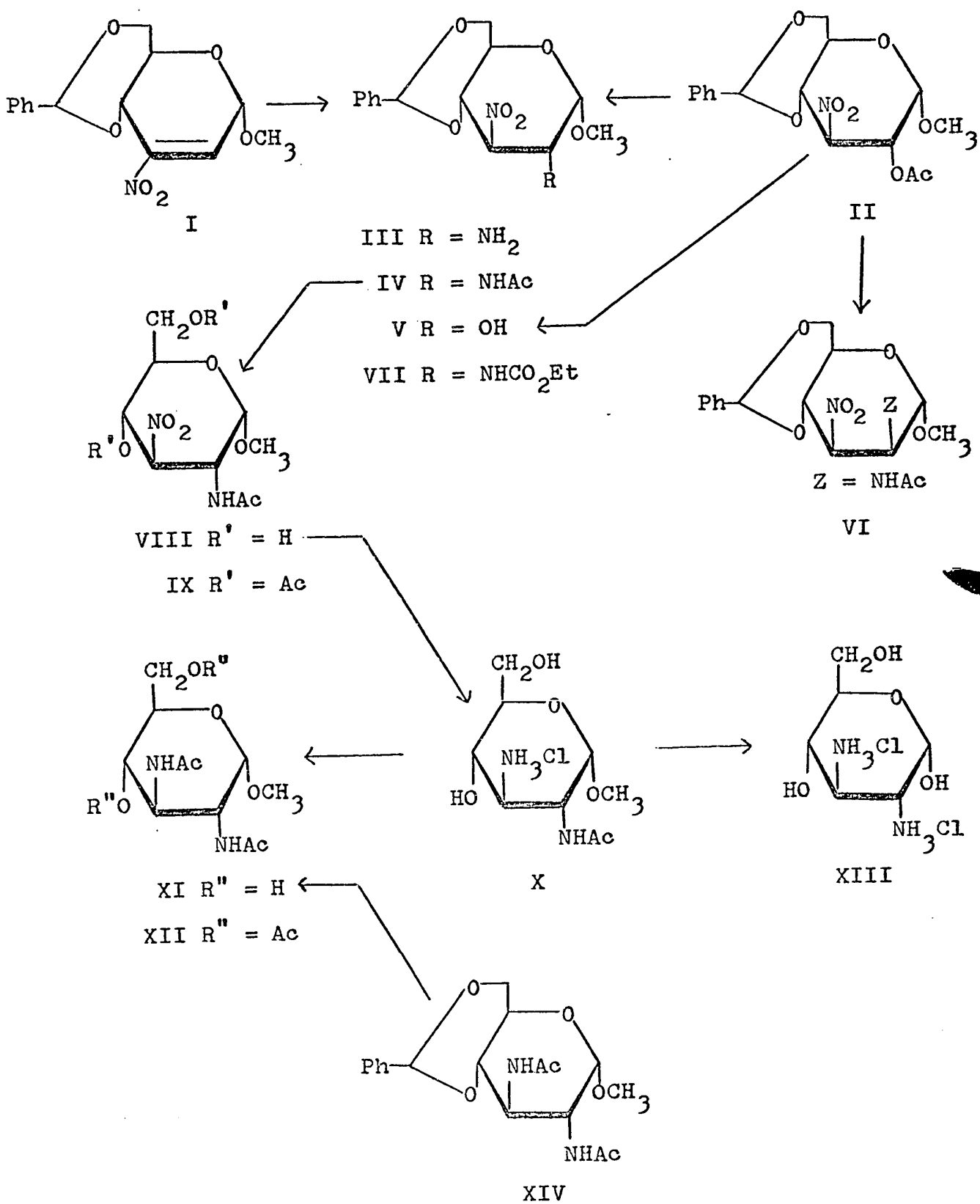
However, when the same reaction was applied to the corresponding α -anomeric nitroolefin, the saturated 3-nitro derivative was isolated in smaller yield (43.5%), but in addition a 3-oximino derivative was formed in a large proportion (49%) (94):



In view of these results it was deemed worthwhile to study the reaction of ammonia with nitro glycosides of the α -series. It was hoped that such investigations would contribute to a better understanding of stereochemical effects in this area and at the same time lead to the synthesis of some hitherto inaccessible aminonitro and diamino sugars.

An initial difficulty in applying the reactions described by Baer and coworkers (120,122) to the α -series stemmed partly from the fact that the α -anomeric nitroolefin I (Scheme I) was not as readily available as its β -anomer. It was reported (94) that the dehydroacetylation [Schmidt-Rutz reaction (87)] of the nitroacetate II to the nitroolefin I required at least nine days for completion, in contrast to only about two days for the analogous conversion of the β -anomer (59). The authors attributed this difference in reactivity to a steric influence of the anomeric methoxyl group. It was found, however, during the course of the present work, that the reaction time for this dehydroacetylation in the α -series could be reduced from nine to two days when absolutely anhydrous conditions were observed. Yields in the order of 80% or more of the nitroolefin I were eventually obtained.

Reaction of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-hex-2-enopyranoside (I) in a mixture of gently refluxing benzene and aqueous 15N ammonia afforded

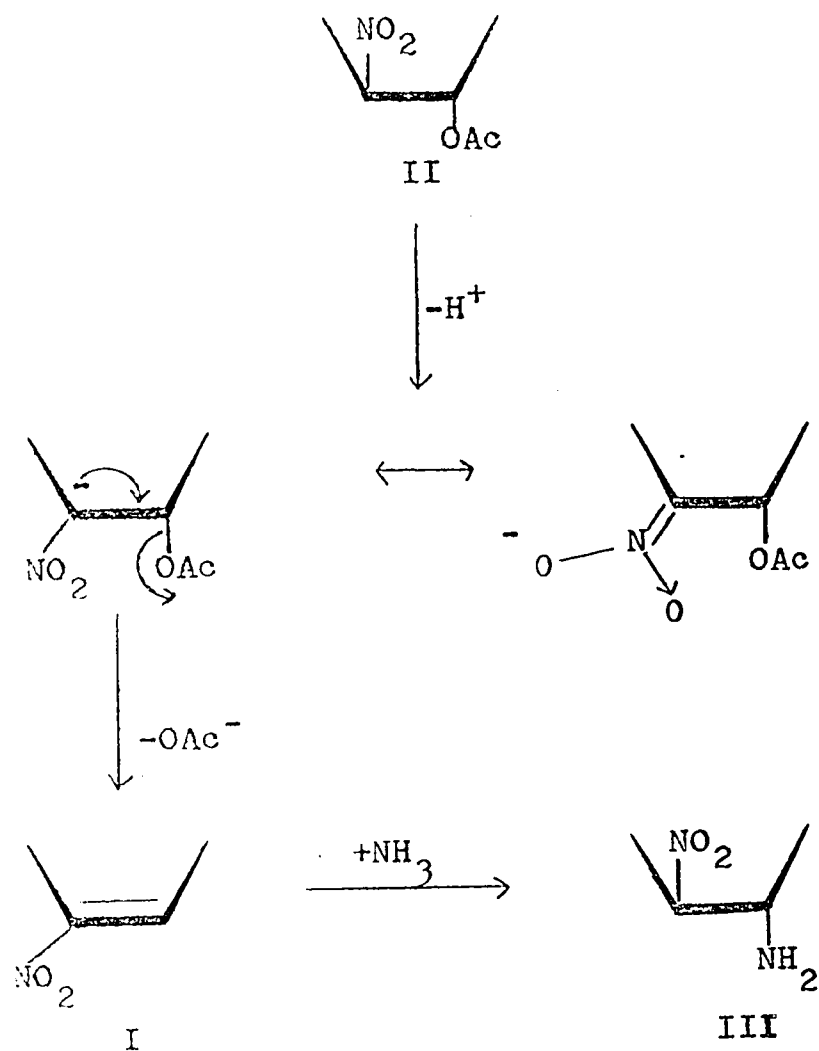


Scheme I. Diamino sugars from nitro sugars.

a single product, methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside (III), in 95% yield. The addition, monitored by thin layer chromatography, was relatively facile, proceeding to completion within one hour. It could also be carried out conveniently at room temperature, in benzene or in tetrahydrofuran, to give the same product III in 81 to 87% yield within one hour.

The nitroamine III was also formed when the more readily accessible precursor of I, namely methyl 4,6-O-benzylidene-2-O-acetyl-~~2,3-dideoxy~~-3-nitro- α -D-glucopyranoside (II), was treated with 15N aqueous ammonia, at room temperature for forty minutes. Thin layer chromatography revealed that the nitroamine III, which was the preponderant product, was accompanied in this case by two by-products. These were difficult to remove by fractional crystallization, although in one experiment pure III could be isolated in moderate yield (30%). A more satisfactory separation was finally achieved by column chromatography on silica gel, which furnished III in 79% yield. The nature of the two minor products will be discussed further below:

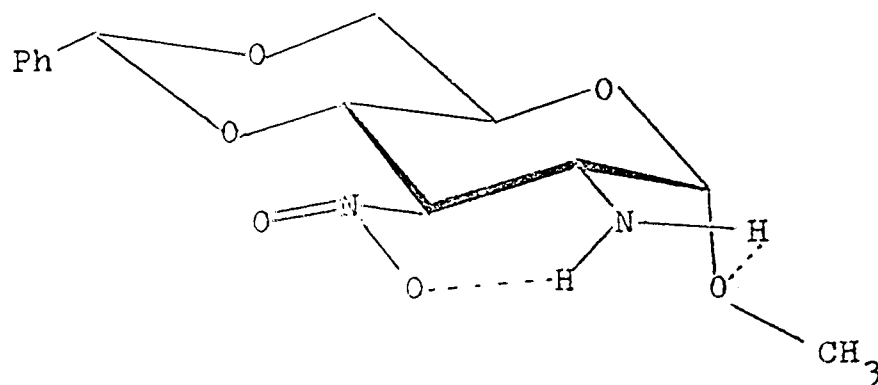
The formation of III from the nitroacetate II may be visualized as proceeding via the nitroolefin I, which was generated in situ under the reaction conditions:



Ammonia abstracts the acidic C-3 proton of II to form the nitronate, which then eliminates the C-2 acetoxy group to give intermediate nitroolefin I, and the latter then adds ammonia to give III. This type of elimination-addition reaction in β -nitro acetates was first discovered in 1936 by Chattaway (132), who observed that the action of ammonia (or *p*-toluidine or phenylhydrazine) upon such acetates did

not produce alcohols by ammonolysis but led to the formation of vic-nitroamines. This was confirmed by Irving and Fuller (133,134), who offered the aforementioned mechanism.

It is interesting that in the infrared spectrum of the nitroamine III (Fig.I) the NH_2 stretching bands, which occur at 3420 and 3356 cm^{-1} , are very weak. The typical NH_2 bending and rocking absorptions near 1600 and 830 cm^{-1} , respectively, are also very weak. This may perhaps be rationalized in terms of hydrogen-bonding as shown below:



III

One of the amino hydrogen atoms could participate in hydrogen-bonding with one oxygen atom of the nitro group, giving rise to a six-membered ring. The second amino hydrogen atom could simultaneously engage in hydrogen-bonding with

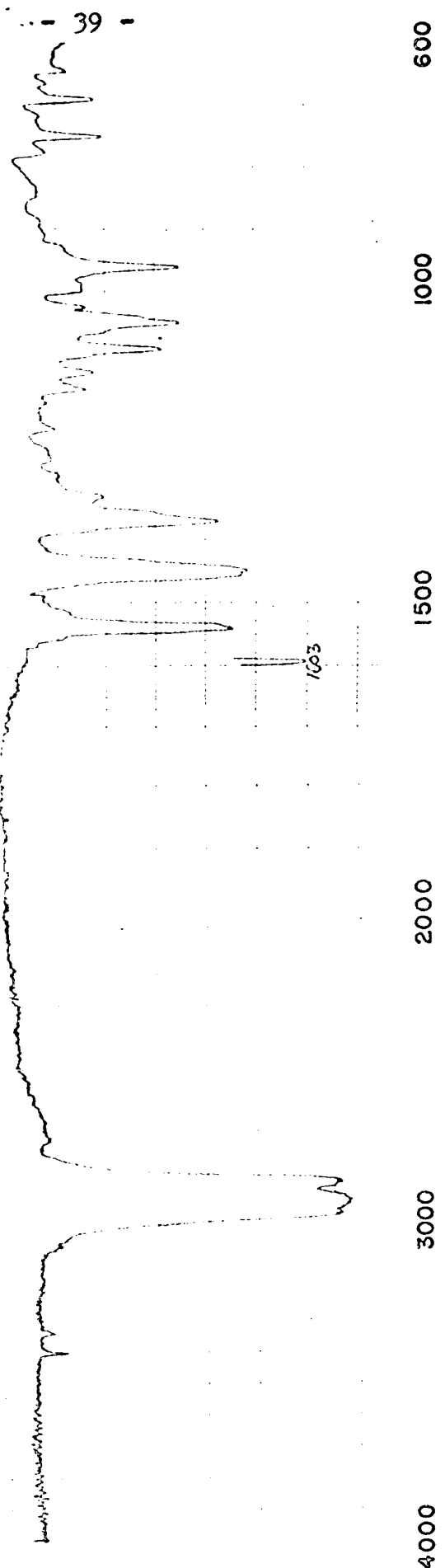


Fig. I. Infrared spectrum of compound III in Nujol mull.

the oxygen of the glycosydic methoxyl group. With both hydrogens being tied up in this way, a considerable weakening of the NH vibrations would appear reasonable. This view is supported by the fact that the β -anomer of III exhibits (120) a single sharp NH stretching band at 3390 cm^{-1} . In this case only one hydrogen atom of the amino group might be bonded (with the oxygen of the nitro group); the second amino hydrogen atom would appear less likely to bond, as the glycosidic methoxyl group of the β -anomer is in trans-position to ^{H_a} amino group. The β -manno isomer of III shows (121,135) NH₂ stretching bands of medium intensity at 3320 and 3385 cm^{-1} . Apparently, intramolecular hydrogen bonding is not favored in this isomer.

Although the amino group in III could not be readily detected in the infrared, chemical proof of its presence was provided by N-ethoxycarbonylation and N-acetylation (Scheme I): Reaction of III with ethyl chloroformate in pyridine afforded in 81% yield the urethan VII, methyl 4,6-O-benzylidene-2-ethoxycarbonamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside; and reaction with acetic anhydride in tetrahydrofuran at room temperature gave in 90% yield the acetamido derivative IV, methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside. Both VII and IV exhibited characteristic NH stretching bonds near 3300 cm^{-1} (of medium

strong intensity) and intense amide I bands in the 1660 - 1695 cm^{-1} region. The amide II bands of medium intensity partially overlapped with the nitro absorptions in the 1550 - 1530 cm^{-1} region.

As has been mentioned above, the reaction of ammonia with the nitro ester II gave the nitroamine III admixed with two by-products, and purification of III so prepared was cumbersome. It proved advantageous to N-acetylate the crude mixture, whereby it became possible to isolate the main product as the N-acetyl derivative (IV) in 76% yield, and to isolate also the two minor products. One of the latter was found to be an acetamidonitro glycoside isomeric with IV (Fig. II and III); in the original reaction mixture it had no doubt existed as a free amine isomeric with III. The isolated amount of isomeric acetamidonitro glycoside corresponded to a yield of 5%. Arguments to be subsequently presented allow a tentative assignment to it of the D-manno configuration (VI).*

The other by-product did not contain an amino function

* Interestingly, VI crystallized from chloroform-n:pentane as platelets that contained tightly-bound chloroform of crystallization. The presence of the latter was suggested by analytical data and verified by mass spectroscopy (see Experimental). Removal of the chloroform required heating at 100° and 1 mm for five days.

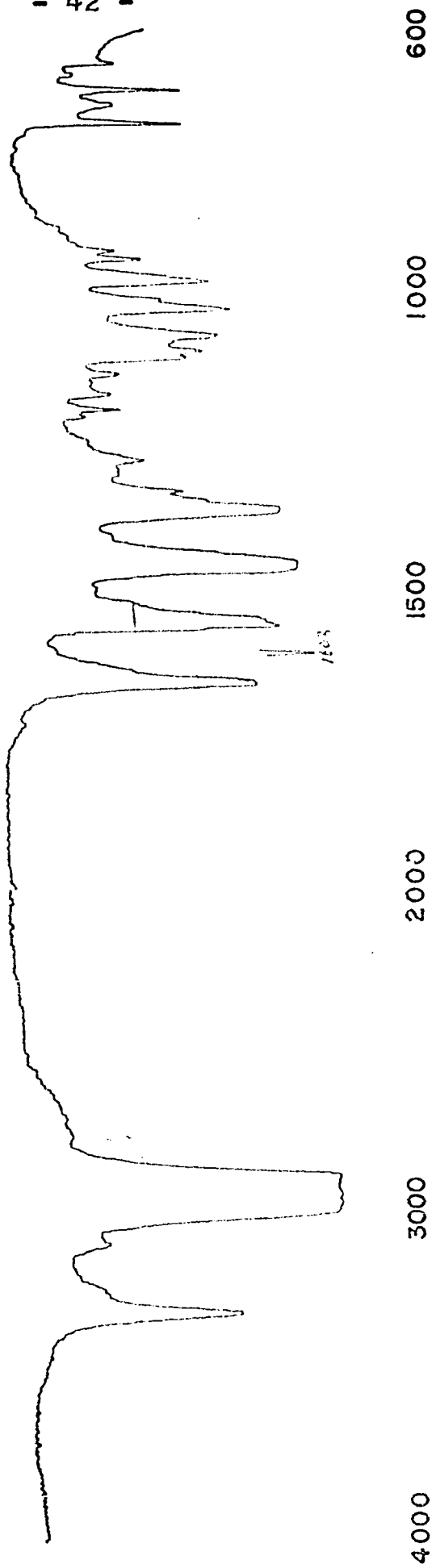


Fig.II. Infrared spectrum of compound IV in Nujol mull.

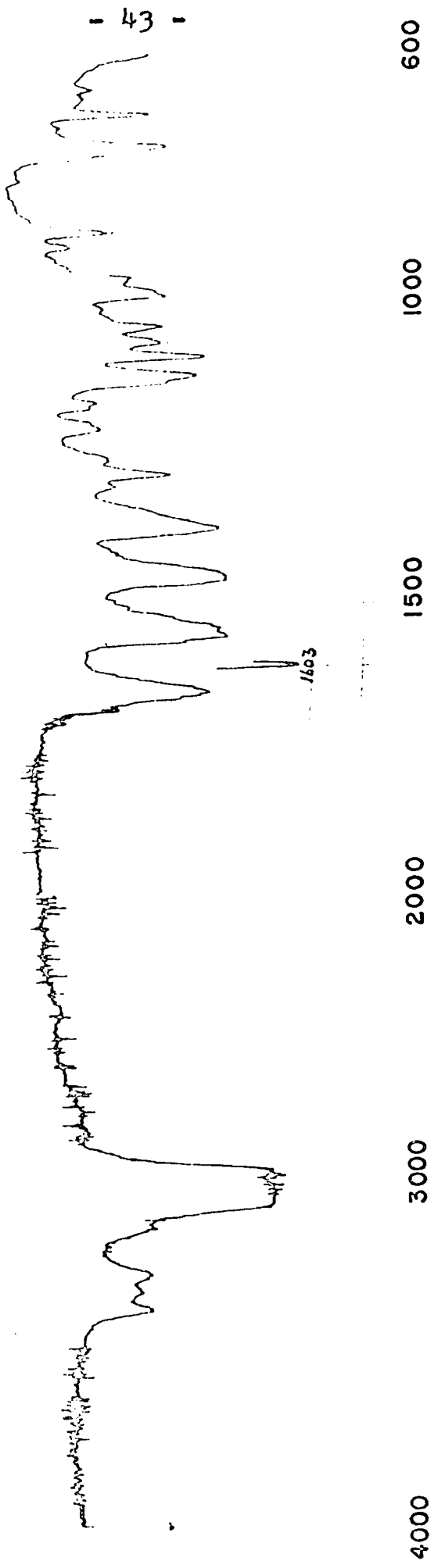


Fig.III. Infrared spectrum of compound VI in Nujol mull.

and hence was unaffected by the N-acetylation procedure. By comparison with an authentic sample (93) it was identified as a known compound, namely methyl 4,6-O-benzylidene-3-deoxy-3-nitro- α -D-glucopyranoside (V), and its yield amounted to 3%. It is interesting to note that an analogously performed amination of the β -anomer of II had yielded (120), just as in the present reaction, chiefly the D-gluco nitroamine (β -anomer of III) along with a small proportion of what later (135) transpired to be the corresponding β -D-manno nitroamine. However, the product analogous to V was not encountered in the β -series.

Two pathways may be considered for the formation of V from II:

- (a) Ammonolysis of the 2-O-acetyl group in II, competing with β -elimination;
- (b) Base-catalyzed hydration of the intermediary nitroolefin I, competing with amination.

The fact that V arose in the reaction of aqueous ammonia with the ester (II) but not with the olefin (I) apparently renders the second mechanism (b) unlikely. However, the two reactions as originally performed were not strictly comparable inasmuch as different solvents had been employed - benzene for I and tetrahydrofuran for II. In order to eliminate this ambiguity the amination of I was repeated using tetrahydrofuran as the solvent. Thin layer chromatography indicated that the reaction proceeded well

at room temperature within one hour. Only III was isolated and no V was detected. It is therefore concluded that I is not an intermediate in the formation of V from II, and the pathway (a) is preferred. One may speculate as to why such ammonolytic deacetylation does occur in the α -series (to however slight an extent), whereas it was not observed in the β -series. The main reaction which the 2-acetates of both anomeric series incur evidently is dehydroacetylation followed immediately by ammonia addition. The dehydroacetylation is initiated by abstraction of the activated proton from C-3, and since this proton is attached axially, the abstracting base will have to approach from an axial direction. In the α -glycoside II, this approach could be slightly hindered, sterically and electronically, by the axial methoxyl group so that the β -elimination is somewhat retarded and ester ammonolysis gains in competition. Considering the small proportion of V that was formed, the effect must be rather insignificant, however.

Next, the acetamidonitro derivative IV was smoothly debenzylidenated in 70% acetic acid at 100°. The reaction, which was monitored by thin layer chromatography, was complete after forty minutes and afforded methyl 2-acetamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside (VIII) in 86% yield. The compound is readily distinguishable from its precursor IV by a broad infrared band of medium-strong

intensity at 3500 - 3200 cm^{-1} , with peaks at 3420 and 3320 cm^{-1} (OH, NH), and also by the absence of the typical phenyl bands 755 and 703 cm^{-1} which are present in the spectrum of IV. Acetylation of VIII with acetic anhydride, using boron trifluoride catalysis (136), afforded methyl 2-acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-nitro- α -D-glucopyranoside (IX) in 80% yield. This diacetate was required for the synthesis described in Part I, Section B.

The next step in the present synthesis was platinum-catalyzed hydrogenation of the acetamidonitro derivative VIII, which was performed at room temperature and atmospheric pressure in the presence of hydrochloric acid. The calculated volume of hydrogen (3 mole-equivalents) was absorbed within twenty-four hours, and crystalline, ninhydrin-positive methyl 2-acetamido-3-amino-2,3-dideoxy- α -D-glucopyranoside hydrochloride (X) was obtained in 96% yield. It is noteworthy that the β -anomer of X, obtained in a similar reaction, was amorphous (120).

Selective acetylation of X at 0° with acetic anhydride in methanol-water, in the presence of an anion exchange resin, afforded the diacetamido derivative XI, methyl 2,3-diacetamido-2,3-dideoxy- α -D-glucopyranoside, in 82% yield. Complete acetylation of X was effected in refluxing acetic anhydride in the presence of anhydrous sodium acetate, and this procedure furnished methyl 2,3-

diacetamido-4,6-di-O-acetyl-2,3-dideoxy- α -D-glucopyranoside (XII) in 90% yield. The compound was obtained as a white solid which tended to form gels and resisted all attempts at crystallization from common solvents. However, the compound melted sharply at 275 - 276° (dec) and gave a correct elemental analysis, as well as infrared and NMR spectra consistent with its structure.

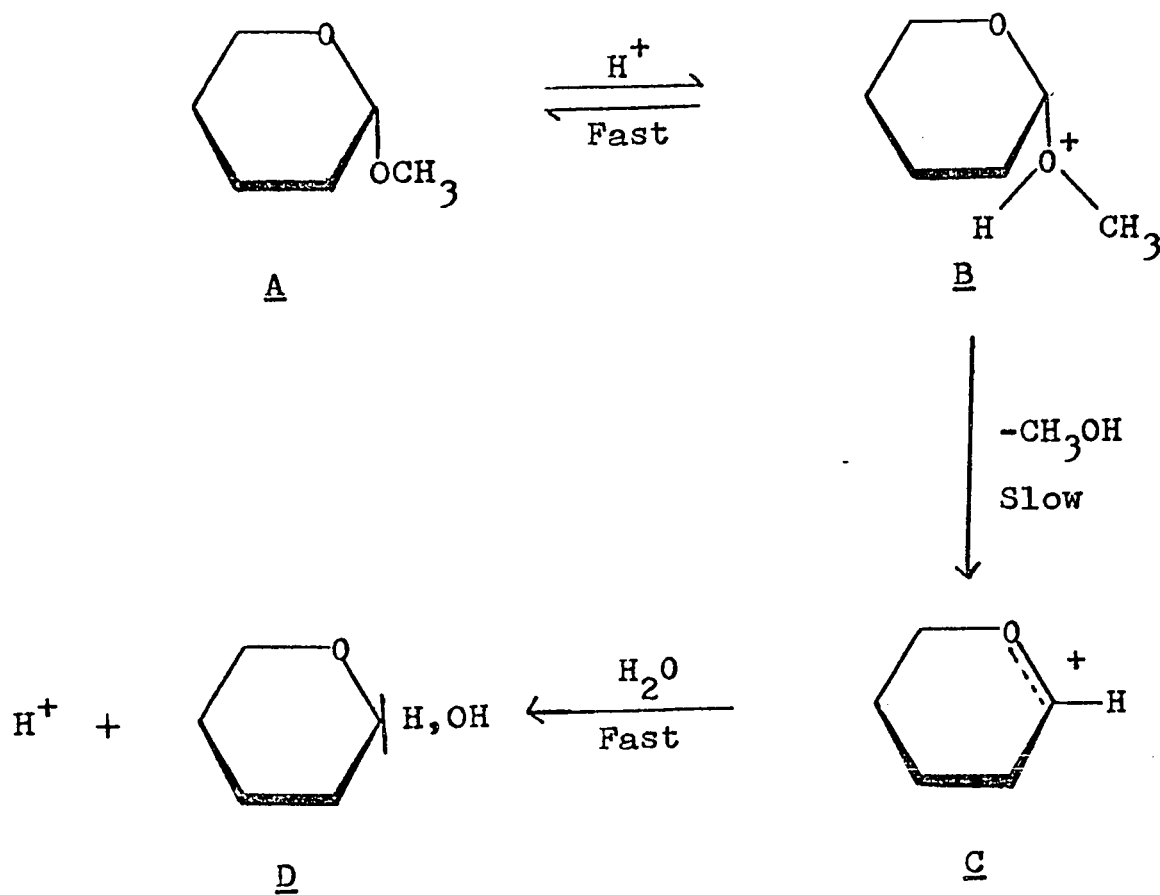
Hydrolysis of the glucoside X in refluxing 6N hydrochloric acid for eighteen hours gave the free diamino sugar, methyl 2,3-diamino-2,3-dideoxy- α -D-glucose dihydrochloride (XIII), in 30% yield. The sugar was identified by comparison with an authentic sample (120). In addition to superimposable infrared spectra, the two samples had similar decomposition ranges, chromatographic mobility, and mutarotations, as follows:

	<u>XIII</u>	<u>Authentic Sample</u>
1. Decomposition range	180 - 188°	180 - 185°
2. R_{GN}^*	0.83	0.83
3. $[\alpha]_D^{23}$		
a) Initial, extrapolated	+ 62°	+ 66°
b) Final (2 hours)	+ 49.7°	+ 46.8°
	(<u>c</u> 1.1, H ₂ O)	(<u>c</u> 0.98, H ₂ O)

* Speed relative to glucosamine hydrochloride

The conditions which had to be used in the present hydrolysis were more drastic than those used (120) for the hydrolysis of the β -anomer of X, where refluxing with 4N hydrochloric acid for ninety minutes gave XIII in 71% yield. It had also been found that hydrolysis of the β -anomer of the diacetamido compound XI could even be done with 1N hydrochloric acid in two hours and gave an equally good yield of XIII. Such was not the case in the α -series. Preliminary experiments indicated that hydrolysis of XI with 1N hydrochloric acid was sluggish and gave, after sixteen hours, two ninhydrin-positive sugar derivatives (R_{GN} 0.83 and 1.30, respectively) in an approximate ratio of 1:1. Similarly, refluxing with 6N hydrochloric acid for fifteen hours produced the same two substances, although the slower-moving one then predominated. The faster-moving spot probably represented methyl 2,3-diamino-2,3-dideoxy- α -D-glucopyranoside dihydrochloride, formed by initial hydrolysis of the N-acetyl groups.

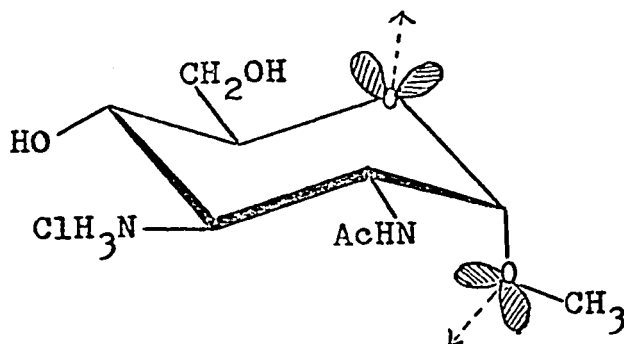
The greater resistance of the α -glucosides X and XI to acid hydrolysis, in comparison to their β -anomers, was to be expected. The mechanism now generally accepted for the acid-catalysed hydrolysis of glycosides is the cyclic carbonium ion mechanism first postulated by Edward (137) and illustrated below:



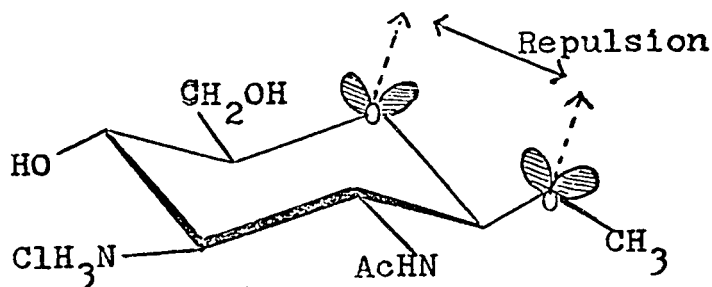
It involves a fast protonation of the anomeric oxygen in the glycoside (A) to form the conjugate acid (B). This is then followed by the slow heterolysis of the exocyclic O-C-1 bond to form a cyclic carbonium-oxonium ion C, which then reacts with water to give the free sugar D.

In the C chair form, the resultant dipole due to the unshared orbitals of the ring oxygen is closer to the equatorial, glycosidic oxygen of the β -anomer than it is to axial, glycosidic oxygen of the α -anomer. The

situation for X and its β -anomer X(a) may be illustrated as follows:



X. α -Glucoside



X(a). β -Glucoside

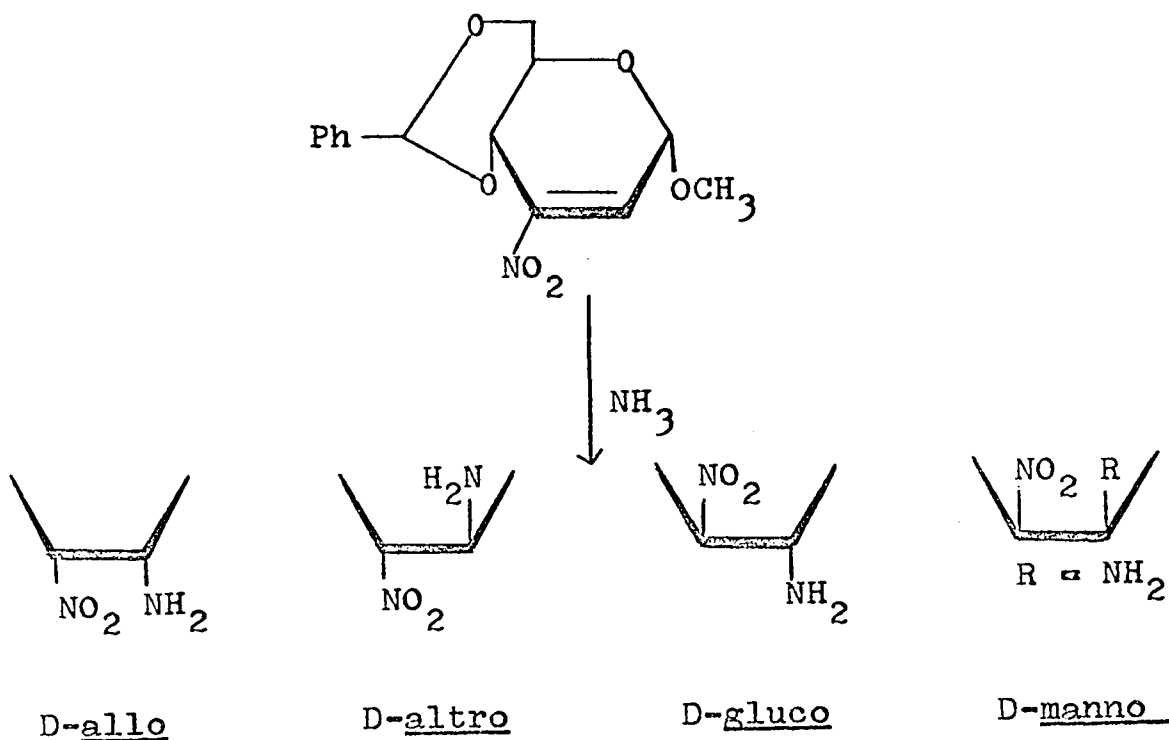
In the β -anomer X(a), the repulsion between the unshared orbitals on the geminal oxygen atoms at C-1 will be greater than in the α -anomer, and hence the free energy in the ground state will be greater in X(a) than in X. Since the free energy for the transition state is the same for both glucosides, it follows that the activation energy for the hydrolysis of the α -glucoside X is greater than that for its β -anomer X(a). Hence the former under-

goes hydrolysis less readily. Moreover, one has to consider that hydrolysis of the C-2 acetamido group takes place concurrently with hydrolysis of the glycosidic methoxyl, giving rise to a positively charged ammonium group. If in a given molecule the amide hydrolysis precedes the glycoside hydrolysis, the latter is seriously impeded due to the ionic charge generated in the vicinity (138). Hence, in 2-acetamido- α -glycosides which hydrolyze at C-1 more slowly to start with, the competing C-2 amide hydrolysis becomes a severer impediment than in 2-acetamido- β -glycosides. These are probably the factors responsible for the difficulties in preparing the free diamino sugar XIII from its glycosides X or XI.

Nevertheless, the work described above has demonstrated that 2,3-diamino-2,3-dideoxy-D-glucose can well be synthesized, on a preparative scale, starting from the α -glycosides I or II, the moderate yield (30%) in the final step notwithstanding. This result is of special significance because methyl α -D-glucopyranoside, which is used as a point of departure for making I and II, is an inexpensive industrial product (\$5.40 per kilogram), which renders the process rather more attractive economically than that in the β -series, starting from methyl β -D-glucopyranoside (\$300 per kilogram).

Proof of Configuration

In the foregoing discussion it has been tacitly assumed that all the derivatives listed in Scheme I (except VI) possess the D-gluco configuration. Only the configuration of the by-product V had been ascertained immediately, as this happened to be a known compound and an authentic sample was at hand for comparison. However, since the addition of ammonia to the nitroolefin I generates two asymmetric centers, four possible stereoisomeric nitroamines could theoretically be formed, namely those with the D-allo-, D-altro-, D-gluco- and D-manno- configurations, respectively:



Of course, at the end of the synthetic sequence when the diamino sugar dihydrochloride XIII had been identified as the known D-gluco isomer, the nitroamine III and the intermediates derived therefrom (IV and VII to XII) could in retrospect be assigned the same configuration: all of the steps that were involved, including the catalytic hydrogenation of the nitro compound VIII in acid medium (139,140), were expected to proceed without configurational change. Nevertheless, it was desirable to adduce confirmatory evidence along the way, and this was achieved by an independent synthesis of the diacetamido glycoside XI and by gathering some nuclear magnetic resonance (NMR) data.

Recently, Ali and Richardson (141) obtained methyl 2,3-diacetamido-4,6-O-benzylidene-2,3-dideoxy- α -D-glucopyranoside (XIV) by borohydride reduction and subsequent N-acetylation of the corresponding 3-azido derivative, which they had synthesized in a stereochemically unambiguous manner. The authors kindly provided a sample of XIV, and its debenzylidenation by 90% trifluoroacetic acid (142) yielded a substance identical with XI according to infrared spectra, mixed melting point, and thin layer chromatogram.

The NMR spectrum, in deuterated chloroform, of the fully acetylated nitro derivative IX (Fig. IV) was characterized by the presence of three sharp singlets,

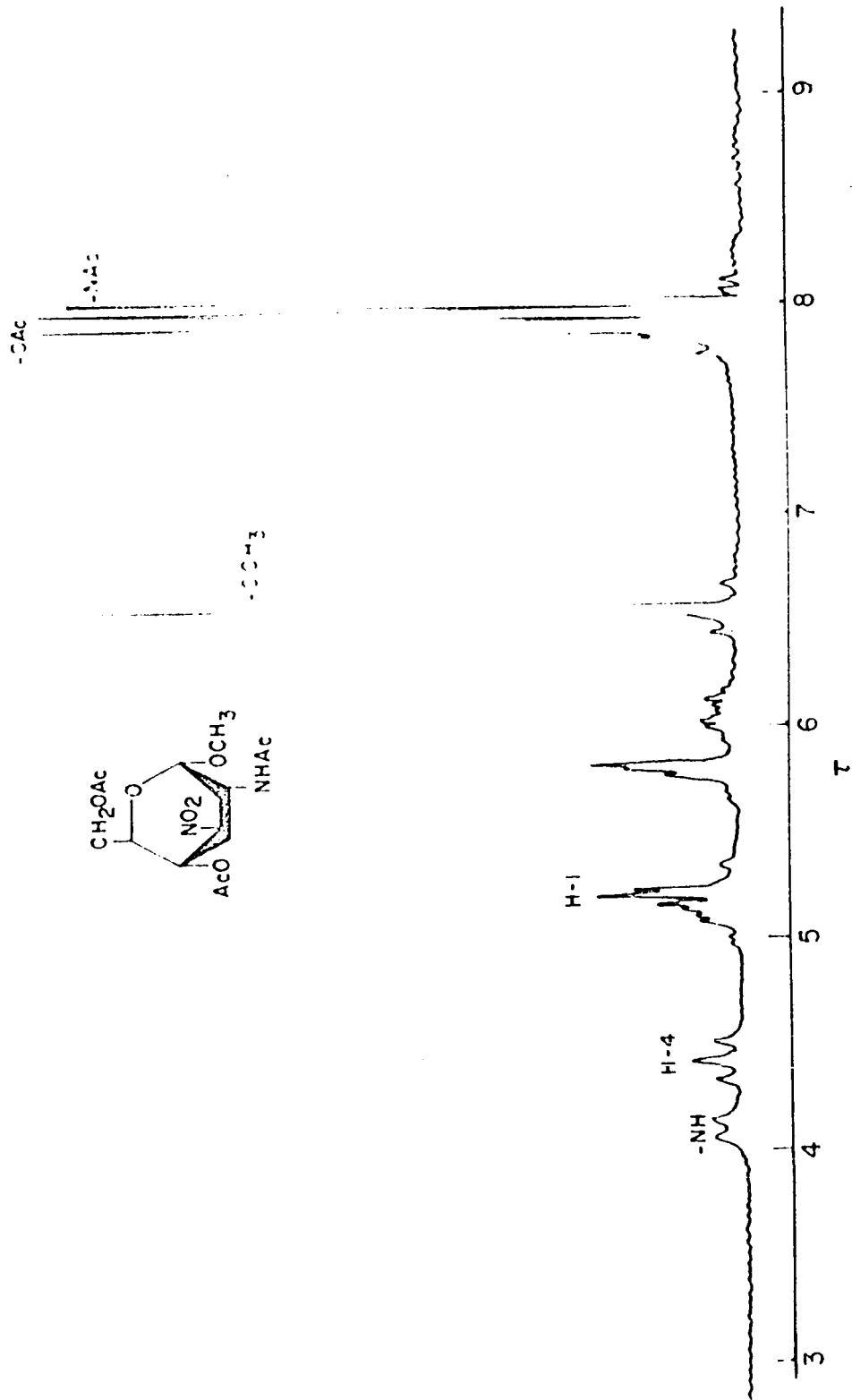


Fig. IV. NMR spectrum of compound IX in deuterated chloroform.

each integrating for three protons, at 8.03, 7.98 and 7.90 τ . These can be assigned to the methyl protons of an equatorial C-2 acetamido group and equatorial acetoxy groups at C-6 and C-4, respectively, on the basis of abundant chemical shifts data for acetylated pyranose sugars and cyclitols (62, 65, 120, 143-146). Although the chemical shift ranges recorded in the literature for axial and equatorial acetamido and acetoxy groups in such compounds are quite useful (see also the more detailed discussion in Part I, Section B), and few misassignments seem to have been made, there is nevertheless an element of uncertainty because of the closeness of the ranges. More reliable information can be obtained from the coupling constants of the ring protons, if the corresponding signals are sufficiently resolved.

The anomeric proton of IX gave a well-resolved doublet at 5.24 τ with a spacing of 3 Hz. The magnitude of the latter suggested axial-equatorial coupling. Since the anomeric proton was known to be equatorial (i.e., IX was an α -D-hexopyranoside) the signal was consistent with an axial proton (and hence an equatorial acetamido substituent as postulated above) at C-2. A one-proton signal attributable to H-4 appeared as a symmetrical triplet that was centered at 4.43 τ and exhibited a large spacing (9 Hz) which proved axial-axial coupling with both H-3 and H-5. Hence, the nitro group at C-3 must be equa-

torially oriented. Finally, the glycosidic methoxyl protons gave a sharp singlet at 6.58τ , the chemical shift being in accord (143a) with the known stereochemistry (axial methoxyl) at the anomeric center. If the substituents at C-2 and C-3 in IX were indeed oriented equatorially as suggested by the above data, this should be verified by the occurrence of two equatorial acetamido signals in the acetylated reduction product XII. The signals (Fig.V) were found as sharp three-proton singlets at 8.04 and 8.10τ , in line with expectations. The C-4 and C-6 acetoxy signals likewise were in the expected region, at 7.93 and 7.97τ .

It must be emphasized that the NMR data that could be evaluated did not in themselves provide absolute proof of configuration, but they strongly suggested the D-gluco configuration for the compounds in question, in full agreement with the chemical results. There remains to be discussed the minor by-product VI, which was isomeric with the acetamidonitro compound IV and probably had the D-manno configuration. This tentative configurational assignment suggested itself on the grounds that the analogous reaction in the β -series (120,135) had given a D-manno by-product. The assumption received support from the NMR spectrum of VI in deuterated chloroform, which exhibited a very small splitting (ca. 1 Hz) of the anomeric proton signal, in line with 1,2-diequatorial coupling, and

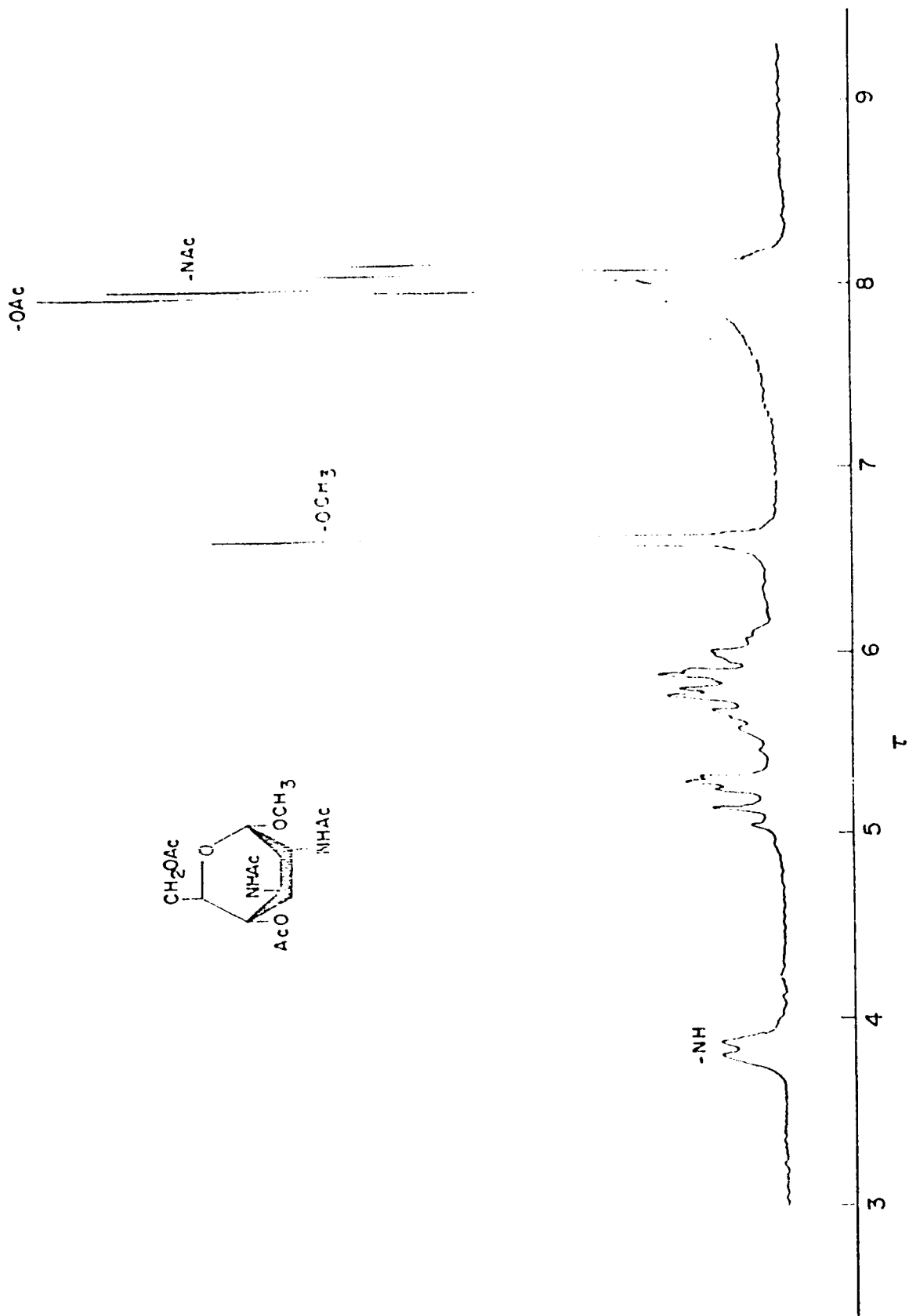


Fig.V. NMR spectrum of compound XII in deuterated chloroform.

a chemical shift of 7.96 τ for the N-acetyl protons in agreement with an axial acetamido group (143,144).

B. Synthesis of Derivatives of 2,3,4-Triamino-2,3,4-trideoxy-D-glucose

Much attention has been focused^s during the past two or three decades on the synthesis of monoamino and diamino sugars. Interest in these compounds has been sparked by the great and long-known biological significance of monoamino sugars in the animal kingdom and by the more recent discoveries of structurally unusual mono- and diamino sugars in microorganisms and their metabolites. Monosaccharides that carry more than two amino functions, however, have not yet been discovered in nature. This partially explains the only moderate interest in triamino sugars shown so far by synthetic chemists. However, the chemical synthesis of this class of compounds deserves attention in view of their possible biological activity and in anticipation of their eventual discovery in nature. It is known that in many antibiotics, e.g. the neomycins, amino groups are located on the sugar as well as the cyclitol components of the molecule. It would be interesting to synthesize model compounds in which all the amino groups are present on the sugar component, and test them for biological activity. In this context, therefore, the synthesis of triamino (and polyamino) sugars deserves attention.

Only a few derivatives of triamino sugars have so far been synthesized. These are methyl 2,3,6-tribenzamido-

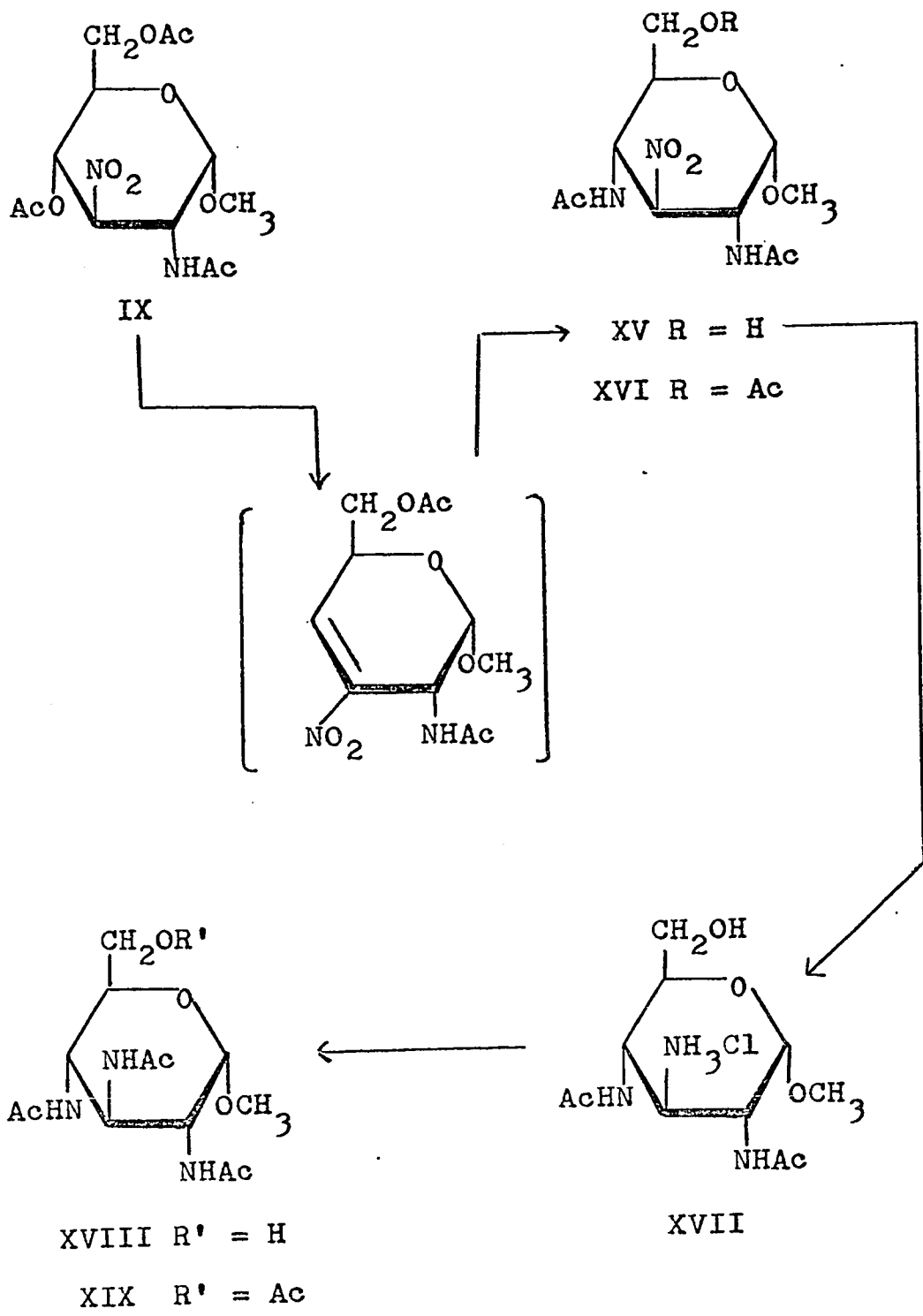
2,3,6-trideoxy- β -D-allopyranoside (97); methyl 2,3,6-triacetamido-2,3,6-trideoxy-4-O-methylsulfonyl- α -D-glucopyranoside (79); methyl 2,3,5-triamino-2,3,5-trideoxy- β -D-arabinoside and -xyloside (147) and 2,3,4-triamino-1,6-anhydro-2,3,4-trideoxy- β -D-idopyranose (obtained as trihydrochloride and tri-N-acetyl derivative) (148). In the syntheses of the first four compounds, nitrogen functions were introduced in part by displacement of sulfonate ester groups with azide, whereas the D-idose derivative arose from an anhydrosugar dialdehyde in a nitromethane cyclization performed in the presence of benzylamine, followed by catalytic hydrogenation.

In principle, the activating effect of the nitro group in a suitable nitro sugar could be used to introduce two vicinal amino groups. This has been demonstrated in a model reaction by Baer and Wang (149) who synthesized trans,trans-1,3-diacetamido-2-nitrocyclohexane by the action of ammonia upon trans,trans-2-nitro-1,3-cyclohexanediol diacetate, followed by N-acetylation. The product was subsequently reduced to the 1,2,3-triamino stage. Kienzle (135) tried to apply this reaction to methyl 2,4,6-tri-O-acetyl-3-deoxy-3-nitro- β -D-glucopyranoside (136), but he could isolate a methyl diacetamidonitrotrideoxy hexoside in 2-4% yield only, and therefore abandoned this approach without having completely characterized his product. In view of Kienzle's apparent difficulties in the

direct diamination of an acetylated nitro glycoside, it was felt that a stepwise introduction of two amino groups flanking the nitro group might be more promising*. It was therefore decided to use as starting material a nitro sugar into which one amino group had already been introduced, as described in the preceding section.

The precursor chosen was methyl 2-acetamido-4,6-di-O-acetyl-3-deoxy-3-nitro- α -D-glucopyranoside (IX). Preliminary considerations would suggest that the C-4 acetoxy group in IX, being activated by the C-3 vicinal nitro group, should easily undergo base-catalyzed elimination to generate a very reactive 3,4-nitroolefin. If the elimination occurred in the presence of ammonia, an amino function would probably enter at C-4 in a reaction analogous to the conversion of nitroolefin I to nitroamino derivative III. The 6-Oacetyl group, not being activated,

* At the time of this writing (May 1969) the March 21 issue of *Angewandte Chemie* was received, in which F. W. Lichtenthaler, P. Voss and N. Majer (150) reported in a preliminary communication to have successfully applied the direct diamination (149) to our methyl 2,4,6-tri-O-acetyl-3-deoxy-3-nitro- β -D-glucopyranoside (136). It is to be noted that these studies refer to the β -series, whereas the present thesis is concerned with α -glycosides.

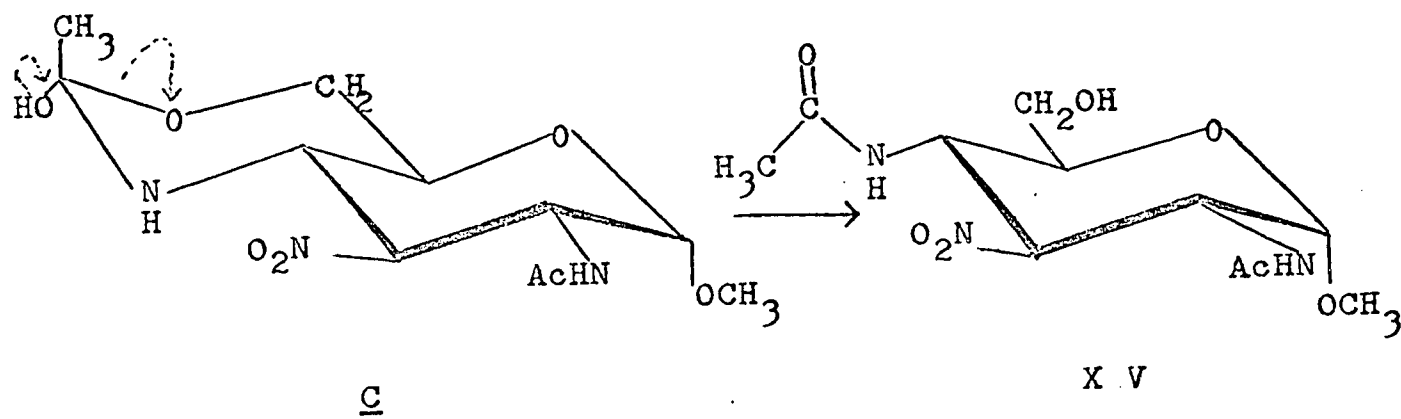
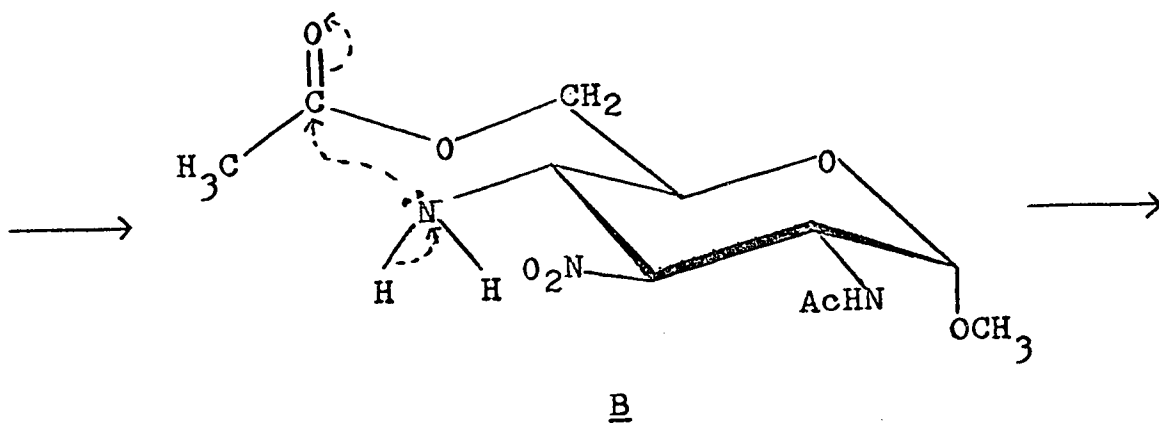
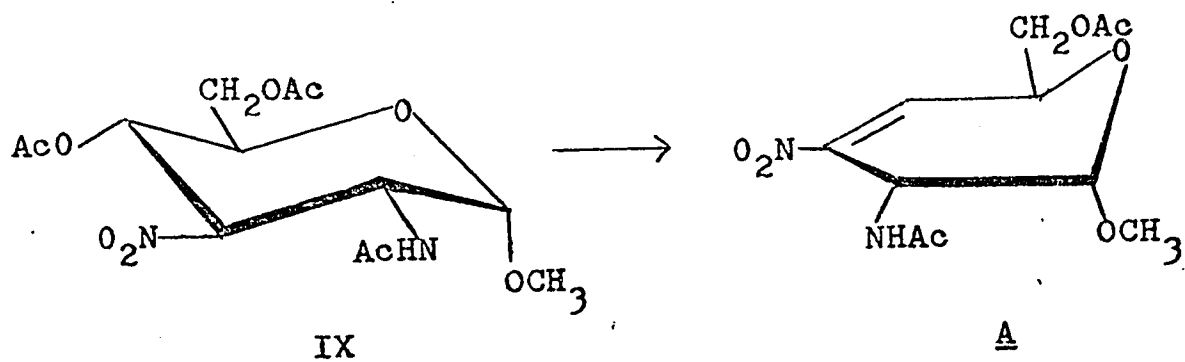


Scheme II. Triamino sugars from nitro sugars.

would simply undergo ammonolysis, or alternatively it could migrate to the new amino group at C-4, so that the resulting compound would be a 2,4-diacetamido-3-nitro derivative, a potential triamino sugar. Experiment confirmed this prediction.

Reaction of the nitroacetamido derivative IX (Scheme II) with 15 N aqueous ammonia in tetrahydrofuran was completed within twenty-five minutes as indicated by thin layer chromatography. Work-up afforded methyl 2,4-diacetamido-2,3,4-trideoxy-3-nitro- α -D-glucopyranoside (XV) in 57% yield. The fact that the amino group which had entered at C-4 had become acetylated by acyl migration was evident from the results of elemental analysis and from the NMR spectrum (in deuterated dimethylsulfoxide) that showed two separate acetamido methyl signals.

Such acyl migrations have been previously observed in aminations of acetylated nitroalditols (See for instance reference 124). In the present case XV is probably formed from IX by the following mechanism:



The initial step involves the formation of a nitroolefin (A) in a manner analogous to the generation in situ of the 2,3-nitroolefin I by ammonia from the nitroacetate II (See page 37). The olefin then adds ammonia, giving rise to the 4-amino derivative (B) in which the 6-O-acetyl group is favorably oriented for migration to the 4-amino function. The migration is assumed to proceed through a cyclic intermediate (C) (89), which then rearranges to the 2,4-diacetamido-3-nitro derivative XV.

Compound XV was acetylated with acetic anhydride and boron trifluoride (136) to give methyl 2,⁴~~3~~-diacetamido-6-O-acetyl-2,3,4-trideoxy-3-nitro- α -D-glucopyranoside (XVI) in 80% yield.

Hydrogenation of XV over Adams catalyst was performed in acid medium at room temperature and atmospheric pressure, and was completed in two days when the calculated amount (3 mole-equivalents) of hydrogen had been absorbed. The colorless reaction product was difficult to crystallize as it tended to form gels with common solvents. Crystallization was finally achieved from absolute ethanol-ethyl acetate at 70°: methyl 2,4-diacetamido-3-amino-2,3,4-trideoxy- α -D-glucopyranoside hydrochloride (XVII) was thus obtained in 94% yield as white needles. The infrared spectrum of crystalline XVII showed an unexpected, weak absorption band at 1740 cm^{-1} , due probably to a small

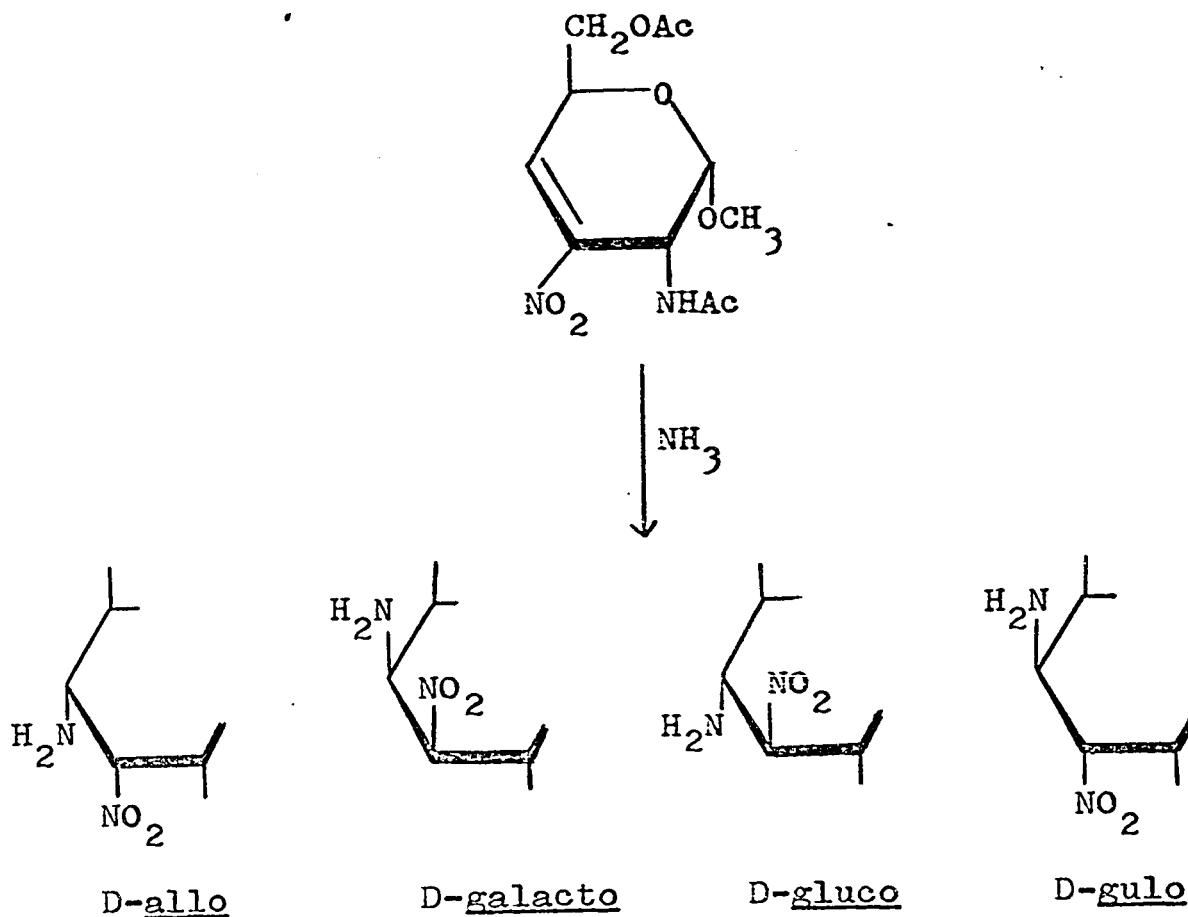
proportion of ethyl acetate of crystallization. The latter could not be removed by drying the sample for seventy-two hours at 100° and 1 mm, but it disappeared by several co-evaporations of the sample with water. However, the compound thereafter could not be crystallized from various common solvents except again from absolute ethanol-ethyl acetate. It would thus appear that some ethyl acetate was necessary for crystallization although the amount incorporated was so small that it was not reflected in the elemental analysis.

N-Acetylation of XVII with acetic anhydride in methanol-water at 0°, in the presence of anion exchange resin, furnished methyl 2,3,4-triacetamido-2,3,4-trideoxy- α -D-glucopyranoside (XVIII) in 50% yield, whereas complete acetylation with acetic anhydride-pyridine afforded methyl 2,3,4-triacetamido-6-O-acetyl-2,3,4-trideoxy- α -D-glucopyranoside (XIX) in 60% yield. The yields of XVIII and XIX were rather low because both compounds tended to give gels and had to be crystallized meticulously: The yields reported are those of the crystalline products isolated, and do not necessarily reflect the total amount of product formed in each reaction.

Proof of Configuration

Since the formation of XV from IX must be assumed to proceed via a 3,4-nitroolefin intermediate as already

discussed, four stereoisomers could theoretically have arisen, and consequently, proof of configuration was needed. The four possible configurations are D-allo, D-galacto, D-gluco, and D-gulo.



It could a priori be regarded as fairly probable that the amination would lead to a product having the most stable, equatorial disposition of the C-3 and C-4 substituents, and consequently, the D-gluco configuration. This was ascertained by NMR spectroscopy.

The NMR spectrum of XV (Fig.VI) in deuterated dimethyl sulfoxide (DMSO-d_6) exhibited two acetamido

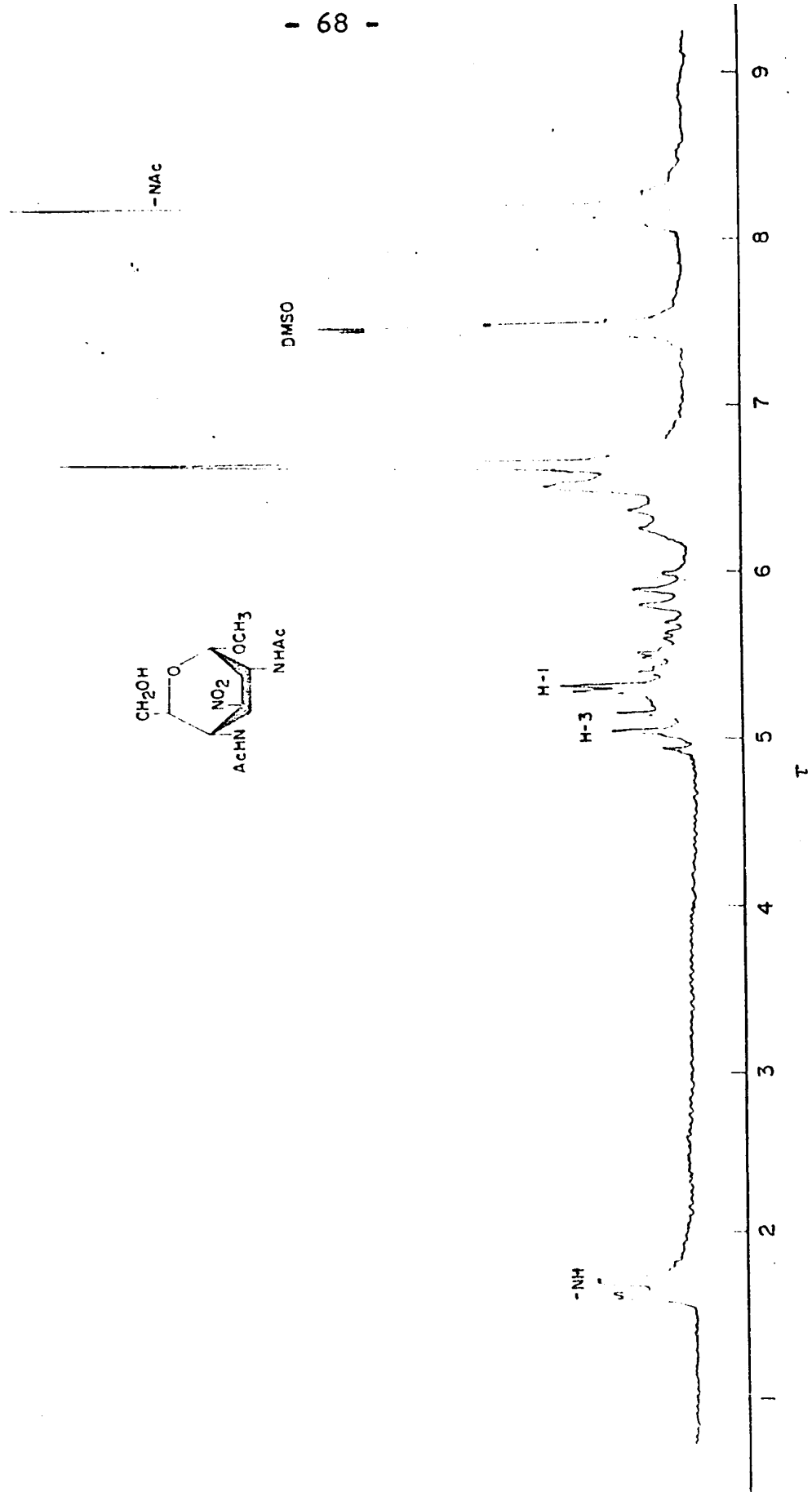


Fig.VI. NMR spectrum of compound XV in deuterated dimethyl sulfoxide.

signals at 8.22 and 8.23 τ , respectively, within the range (8.21 - 8.27 τ) cited by Lichtenthaler and coworkers (143d) for equatorial orientation in a large number of acetylated amino sugars in that solvent. For axial acetamido groups, these authors have compiled values of 7.95 - 8.10 τ (in DMSO-d₆). Corresponding values given for deuterium oxide solutions (143c) are 8.05 - 8.08 τ (equatorial) and 7.90 τ (axial). Compound XV gave two coinciding acetamido signals at 8.04 τ in deuterium oxide, again suggesting equatorial orientation for these groups. Although most of the individual ring protons in XV were difficult to analyze in DMSO-d₆, there was a clearly resolved, symmetrical triplet at 5.07 τ , assignable to H-3. Its splitting ($J_{2,3} = J_{3,4} = 11.3$ Hz) required axial arrangement of H-2, H-3 and H-4 and thus confirmed the D-gluco configuration. Finally, the anomeric proton gave a doublet at 5.30 τ with $J_{1,2} = 3$ Hz (i.e. axial-equatorial coupling), in line with the known stereochemistry at these centers.

The above assignment was confirmed by the NMR spectrum of XIX in DMSO-d₆ (Fig.VII). Especially prominent were a 6-proton singlet at 8.27 τ and a 3-proton singlet at 8.20 τ for the three equatorial acetamido groups, and a 3-proton singlet at 8.08 τ for the equatorial acetoxy group. The ring proton signal at lowest field was the anomeric doublet at 5.34 τ ($J_{1,2} = 3$ Hz). In methanol solution,

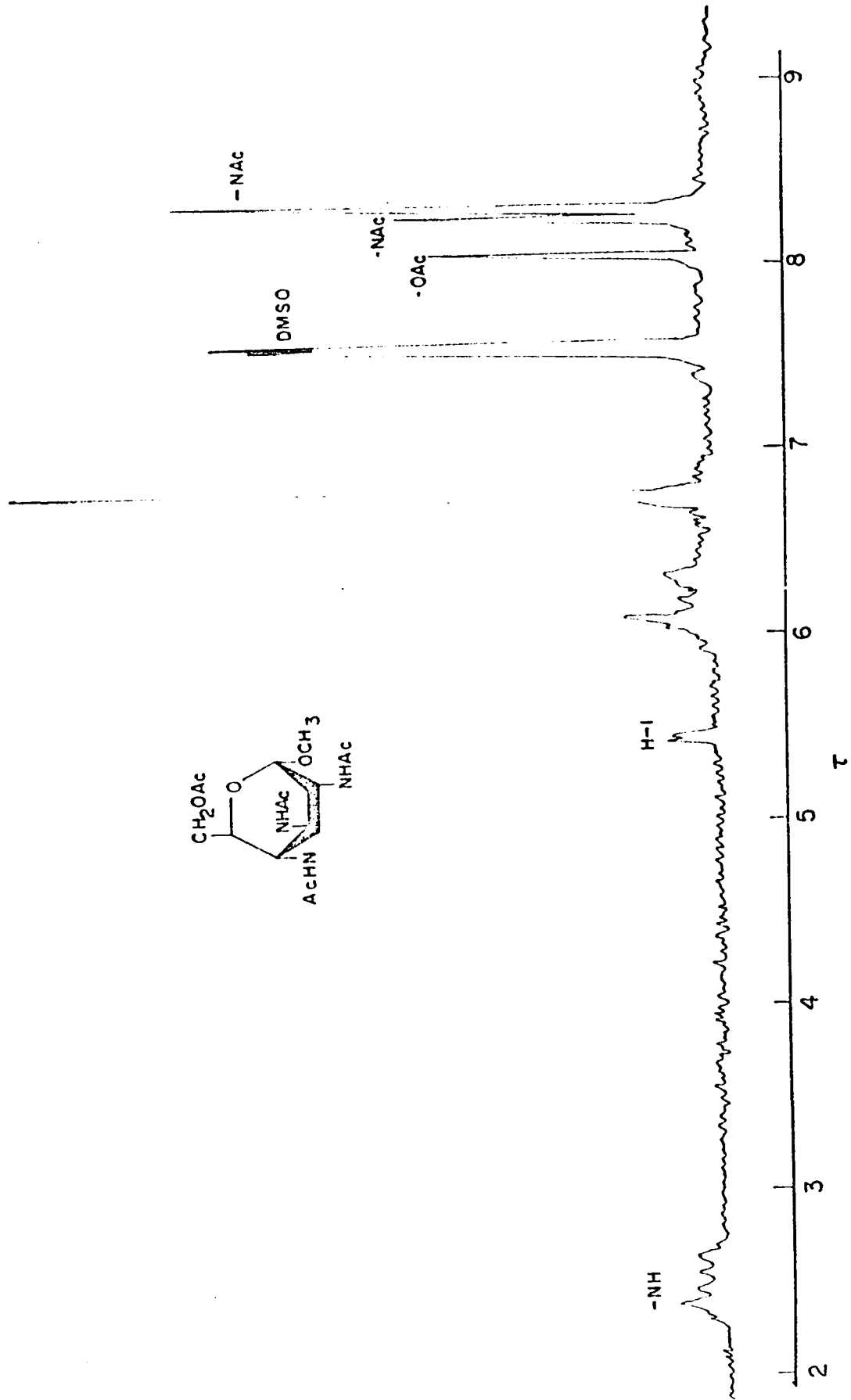


Fig.VII. NMR spectrum of compound XIX in deuterated dimethyl sulfoxide.

XIX exhibited a sharp acetoxy resonance at 7.97 τ , and the acetamido groups resonated at 8.08 (3H) and 8.12 τ (6H) in the range accepted for equatorial orientation in chloroform solution. This agrees with the results of detailed studies by Hasagawa and Sable (151) and with previous observations made in our laboratory (135,149), according to which methanol and chloroform appear to be comparable solvents as far as chemical shifts of acetyl resonance in sugars are concerned. In the absence of special structural features that may cause abnormal shielding or deshielding, equatorial acetamido groups resonate in deuteriochloroform at 8.05 - 8.10 τ in inosamines [19 examples compiled by Lichtenthaler and Emig (143c)] and in about the same range in pyranoid amino sugars (143d, 144-146, 152).

Table III

CHEMICAL SHIFTS (τ) DATA FOR EQUATORIAL ACETYL PROTONS
OF NEW GLYCOSIDES DESCRIBED IN PART I

<u>Compd.</u>	<u>Solvent</u>	<u>2-NHAc</u>	<u>3-NHAc</u>	<u>4-NHAc</u>	<u>4-OAc</u>	<u>6-OAc</u>
IX	CDCl ₃	8.03			7.90	7.98
XII	CDCl ₃	8.04	8.10		7.92	7.97
XV	DMSO-d ₆	8.22		8.23		
	D ₂ O	8.04		8.04		
XIX	DMSO-d ₆	8.27	8.20	8.27		8.00
	CH ₃ OH	8.12	8.08	8.12		7.97

Table IV

CHARACTERISTIC INFRARED ABSORPTION FREQUENCIES (cm^{-1}),
IN NUJOL MULL, OF NEW GLYCOSIDES DESCRIBED IN PART I*

<u>Compd.</u>	<u>OH</u>	<u>NH</u>	<u>Ester C=O</u>	<u>Amide I</u>	<u>NO₂, Amide II</u>	<u>Phenyl</u>
III		3420w 3356w			1550s	762m 701m
IV		3300ms		1660s	1550-1540s	753m 700m
VI		3315m 3260w 3200m		1650s	1555-1535s	755ms 704ms
VII		3325ms		1695s	1550-1540s	755m 703m
VIII	3420m 3500-3200	3320ms		1650s	1555-1530s	
IX	3340m		1735s	1650s	1552s, 1530ms	
X	3420m 3230m	3320ms 2800-2400 1585mw 1520ms		1658s	1542ms	

* Designations are strong (s), medium-strong (ms), medium (m), medium-weak (mw) and weak (w).

Table IV (continued)

<u>Compd.</u>	<u>OH</u>	<u>NH</u>	<u>Ester C=O</u>	<u>Amide I</u>	<u>NO₂, Amide II</u>	<u>Phenyl</u>
XI	3460m 3425m 3120m	3290ms		1645s	1560-1545ms	
XII		3315m	1743s	1650s	1548ms	
XV	3500-3200m 3410m	3345ms 3315ms		1660s	1552s 1550-1530ms	
XVI		3345ms 3310ms	1735s	1670-1650s	1555-1530ms	
XVII	3500-3200	3280ms 3080w 2700-2500w 1588w 1510w		1658s	1550ms	
XVIII	3470w 3225w	3330ms 3300s		1643s 1620ms	1568ms 1550s	
XIX		3340ms 3300ms 3230m	1735ms	1640s	1533ms	

PART II

NUCLEOPHILIC ADDITIONS TO
METHYL 4,6-O-BENZYLIDENE-2,3-DIDEOXY-3-NITRO-
 α -D-ERYTHRO-HEX-2-ENOPYRANOSIDE

D I S C U S S I O N *

A. Synthesis of Carbohydrate Derivatives of Anthranilic Acid

Certain compounds containing anthranilic acid and sugars exist in nature as bacterial metabolites. Thus 1-(2-carboxyphenyl)amino-1-deoxy-D-ribulose has been detected in cultures of Aerobacter aerogenes (153) and Escherichia coli (154), and 1-(2-carboxyphenyl)amino-1-deoxy-D-fructose is produced by Salmonella typhimurium (155), Neurospora crassa (156) and the tryptophan-deficient mutant of Saccharomyces cerevisiae (157). These compounds, which are supposed to be intermediates in the bacterial biosynthesis of tryptophan, have also been synthesized chemically (158) by use of the Amadori rearrangement of anthranilic acid aldosylamines.

Although no sugars that carry an o-carboxyphenyl-amino group on carbon atoms other than C-1 have yet been discovered in nature, the synthesis of certain methyl β -glycosides substituted at C-2 by that group has recently been achieved in this laboratory (135). Thus, it was found that the stereochemical course of the nucleophilic addition of anthranilic acid to methyl 4,6-O-benzylidene-2,3-dideoxy-

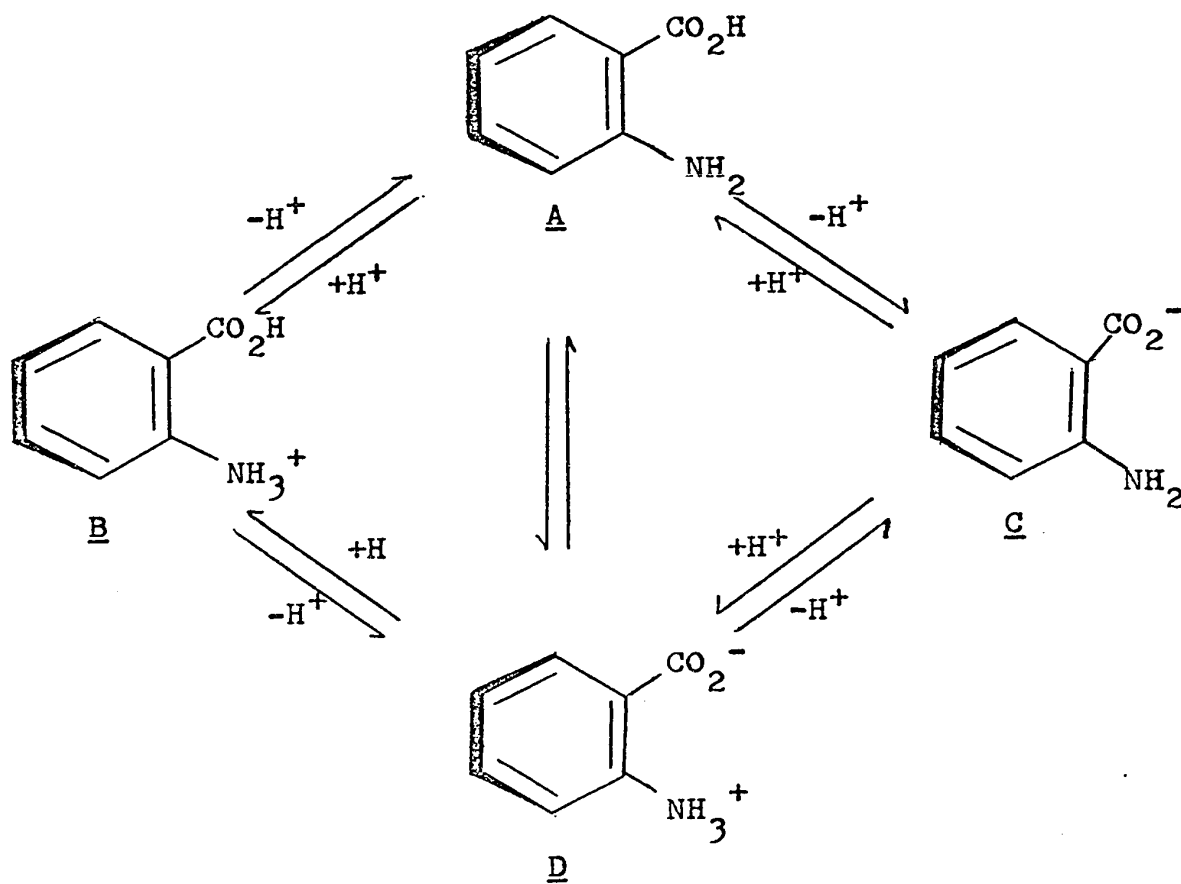
* For convenience, compounds in this chapter are numbered using a new set of Roman numerals.

3-nitro- β -D-erythro-hex-2-enopyranoside (the β -anomer of I) in benzene solution depended in a characteristic and yet unexplained manner on the reaction conditions: When the addend was employed in excess and a catalytic amount of solid potassium hydroxide was present, the adduct assumed 2,3-diequatorial substituent orientation (i.e., the D-gluco configuration). On the other hand, when anthranilic acid and the β -nitroolefin were used in equimolar proportions in the absence of catalyst, the addend entered axially and the product, isolated in 56% yield, assumed the D-manno configuration*. In view of these differences, the behavior of configurationally different, though closely related, systems commanded interest. In particular, it seemed worthwhile to investigate whether the anomeric configuration of the sugar exerts a directive influence on the course of such additions. It was therefore decided to study the addition of anthranilic acid to the α -glycoside I, methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-hex-2-enopyranoside.

In a reaction of anthranilic acid with the nitroolefin I, due consideration must be given to the possibility that either the carboxylate anion or the amino group of the anthranilic acid could act as nucleophile, for it has

* Additions of the meta and para isomers of anthranilic acid led to D-gluco adducts only, regardless of the conditions (135).

been shown by Bjerrum (159), in 1923, that anthranilic acid can exist in solution in the following acid-base equilibria:

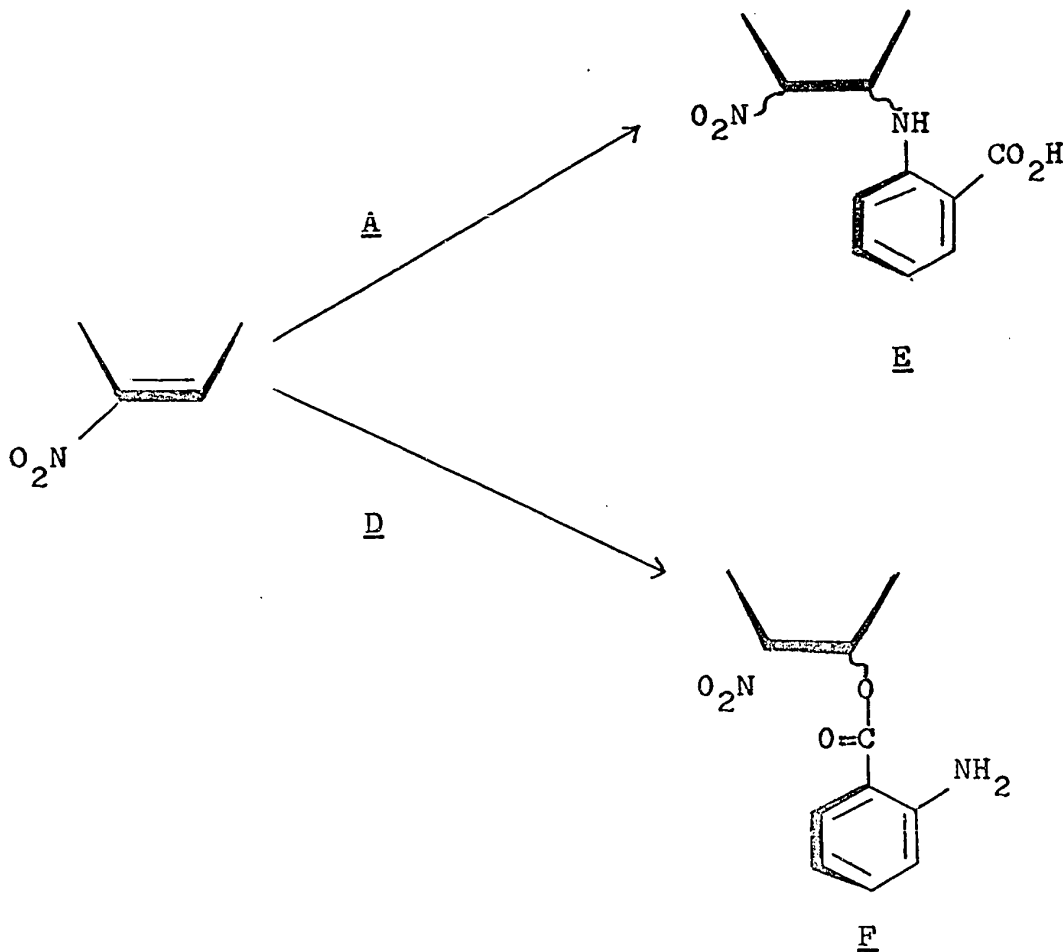


All the additions were performed in anhydrous benzene (which is not a proton donor), and the predominant equilibrium would therefore be expected to be



Consequently, two different adducts could be formed, depending on whether A or D was the nucleophile.

A would react to give a carboxylic acid (E), whereas D would provide a carboxylic ester (F):



As will be shown subsequently, in the present instance the addition reaction gave an adduct of type E, and no evidence for the formation of an adduct of type F was obtained.

The addition of anthranilic acid to methyl 4,6-0-benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-hex-2-enopyranoside (I, Scheme III) was studied under the following conditions:

	<u>Nitroolefin I</u>	<u>Anthranilic Acid</u>	<u>Catalyst</u>
	<u>molar equivalents</u>	<u>molar equivalents</u>	<u> </u>
(a)	1	2	potassium hydroxide
(b)	1	1	potassium hydroxide
(c)	1	1	none
(d)	1	2	triethylamine

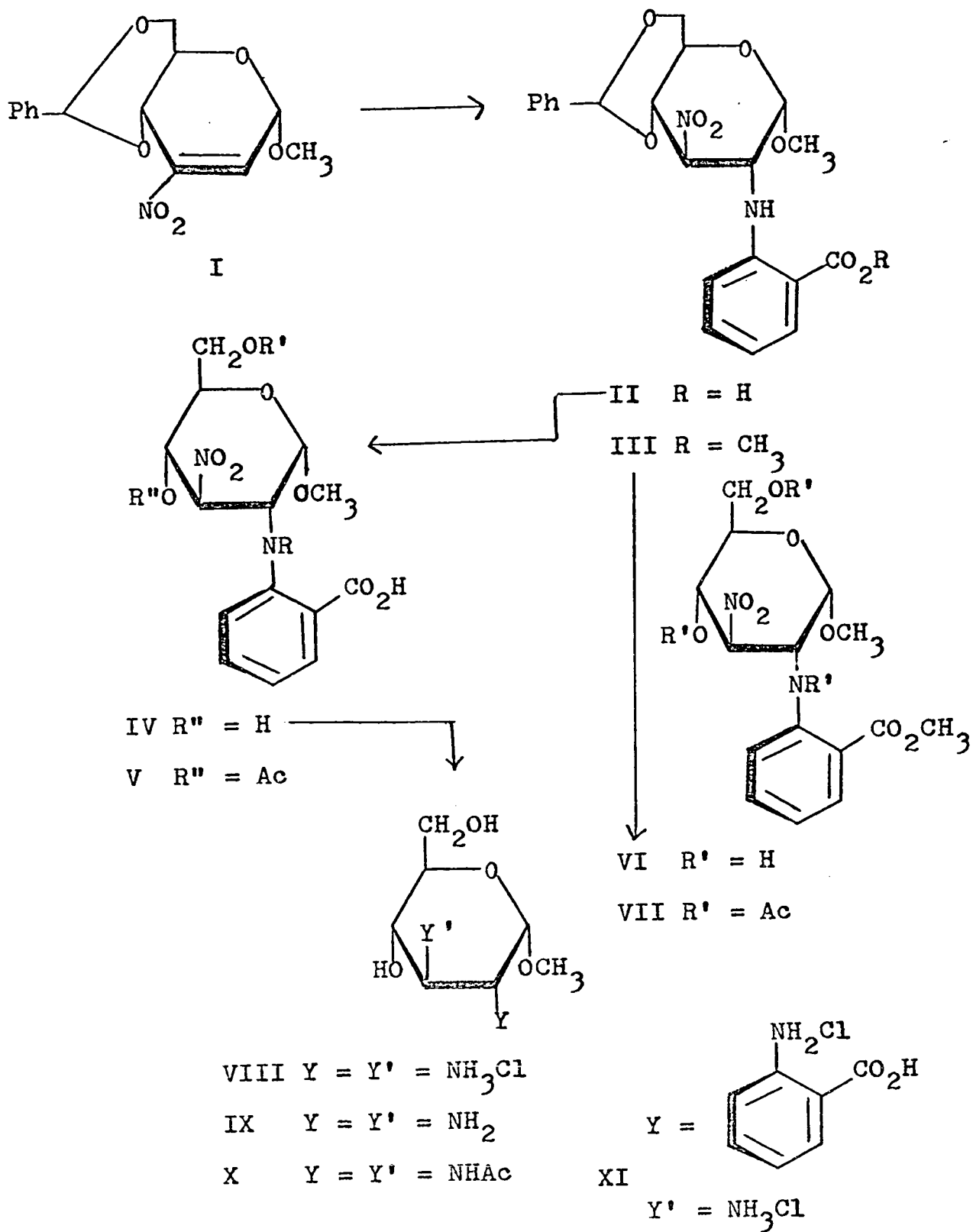
All the additions were performed in refluxing, anhydrous benzene and monitored by thin layer chromatography. The following was then observed:

- (1) Under conditions (a), addition occurred and the reaction was complete within two to three hours. The product precipitated out of the reaction mixture and was obtained as chromatographically uniform, almost colorless needles in 65% yield. It will be shown below that the product was methyl 4,6-0-benzylidene-2-(2-carboxyphenyl)amino-

2,3-dideoxy-3-nitro- α -D-glucofuranoside (II).

Under identical conditions in the β -series (135), the β -gluco anomer of II had been isolated in 83% yield.

- (ii) Under conditions (b), the same reaction product II was formed and could be isolated in yields of only 10 - 15%.
- (iii) When conditions (c) were employed, no reaction appeared to occur: after six days of refluxing, thin layer chromatography did not indicate the formation of any adduct, when "Reagent Grade" benzene (dried by refluxing over sodium wire for twenty-four hours) was used as a solvent. However, when ordinary benzene from the shelf, dried in the same manner, was used, addition took place within thirty hours, and the adduct was identical to that obtained under conditions (a) and (b). It appears possible that the addition had been catalyzed by impurities in the benzene. It is to be recalled the conditions (c) were those under which, in the β -series, addition had taken place and furnished the β -manno isomer of II in 56% yield.
- (iv) Substitution of triethylamine for potassium hydroxide as a catalyst [conditions (d)] again led to the formation II, in improved yield (75%), within three and a half hours.



Scheme III. Synthesis of carbohydrate derivatives of anthranilic acid.

In summary, only one product - namely the gluco adduct II - could be isolated when anthranilic acid reacted with nitroolefin I. Since the crystallization of II was attended with difficulties, mainly owing to gel-formation, the yields of isolated product do not necessarily reflect the total extent to which the additions may have occurred. It must also be emphasized that the yields of isolated adduct do not preclude the formation of additional products, but none could be detected by thin layer chromatography.

The infrared spectrum of II clearly indicated that the product was a carboxylic acid, rather than an ester. Thus, bands associated with the carboxyl group appeared at 3240, 2700 - 2500, and 1668 cm^{-1} , respectively, and no ester carbonyl band was present. There was, furthermore, a single NH stretching vibration (3360 cm^{-1}) as expected for a secondary amine, whereas primary amines are expected to show two bands in that region. Compound II was shown chemically to be an acid by a quantitative esterification with diazomethane, giving methyl 4,6-O-benzylidene-2,3-dideoxy-2-[2-(methoxycarbonyl)phenyl] amino-3-nitro- α -D-glucopyranoside (III). This methyl ester lacked bands at 3240, 2700 - 2500 and 1668 cm^{-1} and showed instead an ester carbonyl band at 1690 cm^{-1} .

The adduct II was further characterized by debenzylidenation in 70% acetic acid at 100°, which

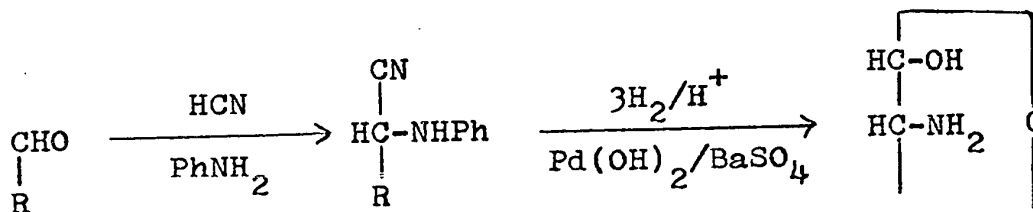
afforded methyl 2-(2-carboxyphenyl)amino-2,3-dideoxy-3-nitro- α -D-glucopyranoside (IV) in 67% yield. Treatment of IV with acetic anhydride-boron trifluoride (136) effected both O- and N-acetylation and provided methyl 4,6-di-O-acetyl-2-[N-(2-carboxyphenyl)]acetamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside (V) in 62% yield.

Similar debenzylidenation of the methyl ester III furnished, in 82% yield, methyl 2,3-dideoxy-2-[2-(methoxycarbonyl)phenyl]amino-3-nitro- α -D-glucopyranoside (VI). Acetylation of the latter with acetic anhydride-boron trifluoride again resulted in O- and N-acetylation to give VII, methyl 4,6-di-O-acetyl-2,3-dideoxy-2-[N-(2-methoxycarbonyl)phenyl]acetamido-3-nitro- α -D-glucopyranoside. This compound crystallized from chloroform with solvent of crystallization, as was evident from the mass spectrum, which exhibited prominent CHCl_2^+ fragments at m/e 83, 85 and 87 in the intensity ratio of 9 : 6 : 1, and from a conspicuous enhancement of the small signal (τ 2.77) normally present in NMR spectra taken in deuterated chloroform. Microanalytical data fitted the presence of 0.75 mole of chloroform. It appears that this solvent was necessary for the crystallization: the compound failed to crystallize when other common solvents were tried.

The debenzylidenated anthranilic acid adduct IV was hydrogenated in acid medium over brown palladium

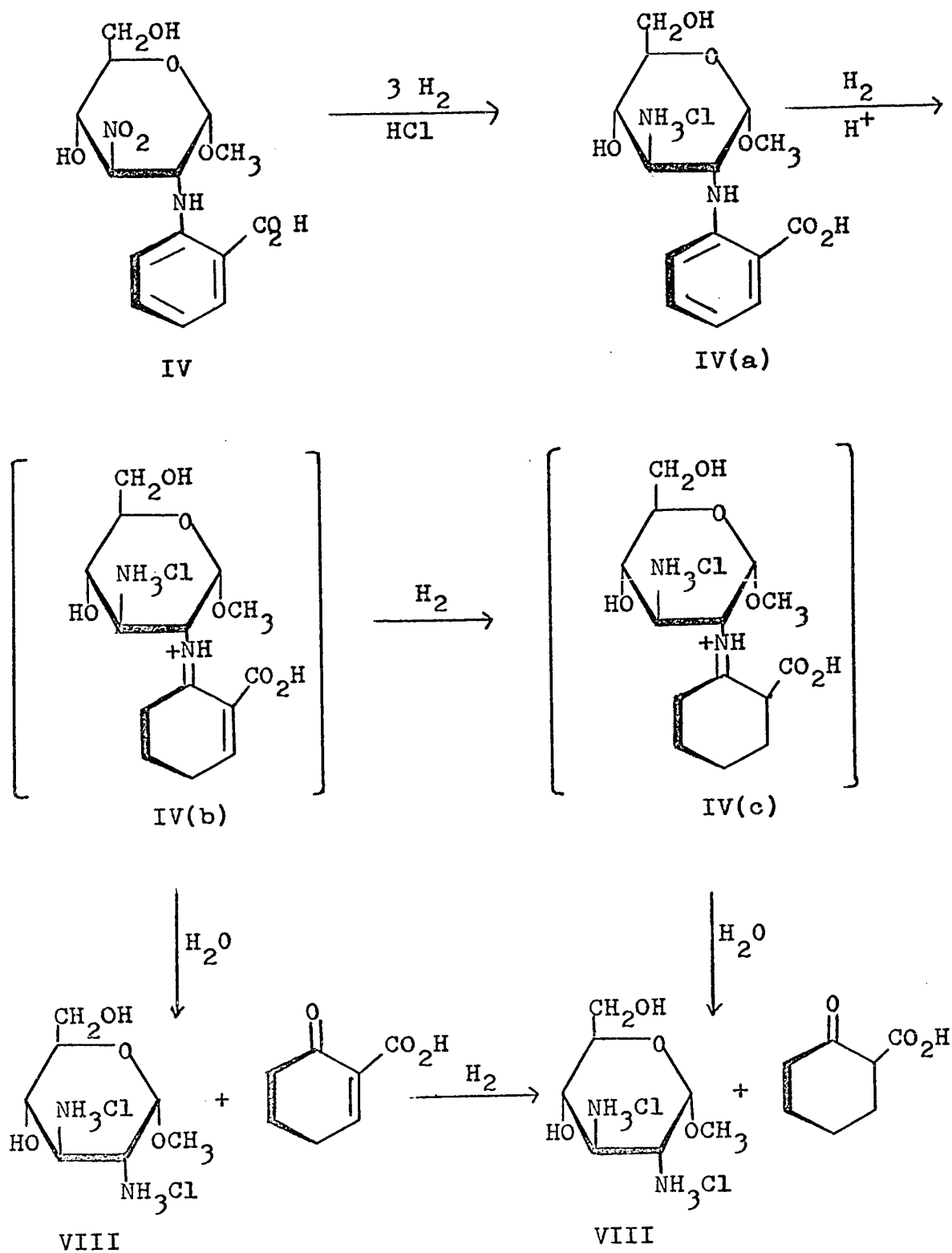
oxyhydrate on barium sulfate (160) (Kuhn's catalyst), at room temperature and atmospheric pressure. Three mole-equivalents of hydrogen was taken up very rapidly and two additional mole-equivalents was consumed in the course of three ^{to five} days. The hydrogenation resulted in reduction of the nitro group to the amino stage and in hydrogenolytic cleavage of the aromatic substituent.

The cleavage of arylamino bonds by hydrogenation in acid medium over brown palladium oxyhydrate on barium sulfate had been accidentally discovered by Kuhn and Kirschenlohr (161) while they were reducing arylaminonitriles:



(free aldose)

The mechanism (161,162) proposed for this hydrogenolysis involves the formation of a diene-cation intermediate. In the case of IV, the mechanism would probably be as depicted in Scheme IV.



Scheme IV. Hydrogenolysis with Kuhn's catalyst.

The conversion of compound IV to IV(a) was reflected in the rapid uptake of the first three moles of hydrogen, whereas the hydrogenolysis of IV(a) to VIII was a much slower reaction and required two additional moles of hydrogen. One mole of hydrogen and a proton would first generate from IV(a) the diene-cation IV(b), which could then decompose via two pathways:

- (i) by hydrolysis to give the diamino sugar VIII and a cyclohexenonecarboxylic acid which would then be hydrogenated to a cyclohexanonecarboxylic acid
- or (ii) by the reduction of diene-cation IV(b) to IV(c), followed by cleavage to VIII and the cyclohexanonecarboxylic acid.

In the present instance, the hydrogenation product could not be crystallized as such. Paper chromatography showed an intense, ninhydrin-positive spot (R_{GN} 1.13) and a minor spot (R_{GN} 1.99). The latter was probably due to the presence of XI (Scheme III), resulting from incomplete hydrogenolysis, whereas the major spot corresponded to VIII. The two compounds were separated on an anion-exchange column: elution with water afforded VIII as the free diaminoglucoside IX, whereas XI remained on the column because of its carboxylic acid group. The diamine IX crystallized as hexagonal, white platelets. N-Acetylation afforded crystalline methyl 2,3-diacetamido-2,3-dideoxy-

α -D-glucopyranoside (X). The minor component (R_{GN} 1.99), presumably XI, was eluted from the anion-exchange column with N/10 hydrochloric acid. Although obtained in chromatographically pure form, it failed to crystallize and was not investigated further.

Proof of Configuration

The addition of anthranilic acid to nitroolefin I generates two new asymmetric centers, with the formation of four possible stereoisomers, namely those possessing the D-allo, D-altro, D-gluco, and D-manno configurations. Hence, proof of configuration at C-2 and C-3 was needed. This was provided by NMR spectroscopy and by chemical synthesis.

The NMR signals (in deuterated chloroform) given by the pyranoside ring hydrogens in the acetylated nitro compounds V and VI could be readily analyzed. Thus, V gave a narrow doublet at 4.93 τ for the α -anomeric proton ($J_{1,2} = 3.5$ Hz) and three other clearly separated one-proton signals in the 4.0 - 5.2 τ region (Fig.VIII). The magnitude of $J_{1,2}$ suggested axial-equatorial coupling: since H-1 was known to be equatorial, H-2 must be axial, and the anthranilic acid residue at C-2 must therefore be equatorial. The signal assigned to H-2 was a quartet centered at 4.00 τ with $J_{2,1} = 3.5$ Hz and $J_{2,3} = 11.5$ Hz. The presence of a large coupling in this signal indicated

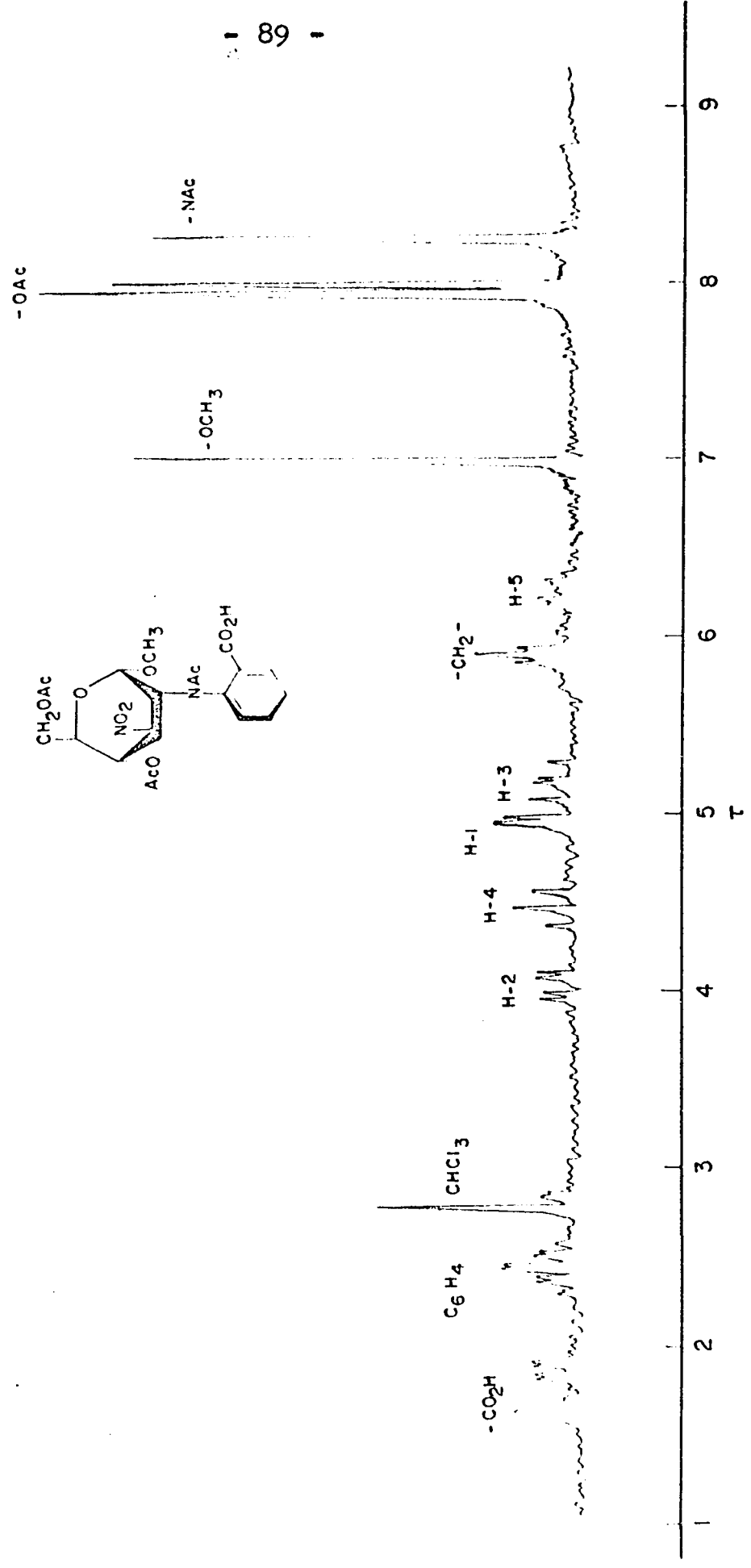


Fig.VIII. NMR spectrum of compound V in deuterated chloroform.

that H-3 was axial. This was confirmed by the occurrence of a quartet at 5.15τ , which was assigned to H-3, and which showed two large splittings ($J_{3,2} = 11.5$ Hz and $J_{3,4} = 10$ Hz), indicating axial disposition of H-2, H-3 and H-4. The H-4 proton gave a symmetrical triplet centered at 4.43τ with $J_{4,3} = J_{4,5} = 10$ Hz, again indicating axial-axial coupling of H-3, H-4 and H-5. Thus all the pyranosidic ring protons except H-1 in V were axial, and this fact established the D-gluco configuration. The spectrum of VII exhibited essentially the same features except that the H-1 doublet partially overlapped the H-3 quartet.

The spectroscopic proof of configuration was confirmed chemically by demonstrating that the diacetamido derivative (X) was identical with independently synthesized methyl 2,3-diacetamido-2,3-dideoxy- α -D-glucopyranoside (compound XI of Part I, Section A; see pages 46 and 53; see also, Experimental, pages 173 and 174).

Table V

CHARACTERISTIC INFRARED ABSORPTION FREQUENCIES (cm^{-1})
OF NEW GLYCOSIDES
DESCRIBED IN PART II (SECTION A)*

Compd.	OH,NH	CO ₂ H	Ester C=O	Amide I	NO ₂	Aromatic
II	3360mw	3240w,b 2700-2500b 1668s			1550s	1578m 1520m 773m 755m 704m
III	3330mw		1690s		1553s	1607m 1585m 1525m 766m 756m 704m
IV	3450-3150b 3350m 3270mw	2700-2500w 1655s			1555s	1580m 1500m 770m

* Designations are broad (b), strong (s), medium-strong (ms), medium (m), medium-weak (mw) and weak (w). The spectra were taken in Nujol mull.

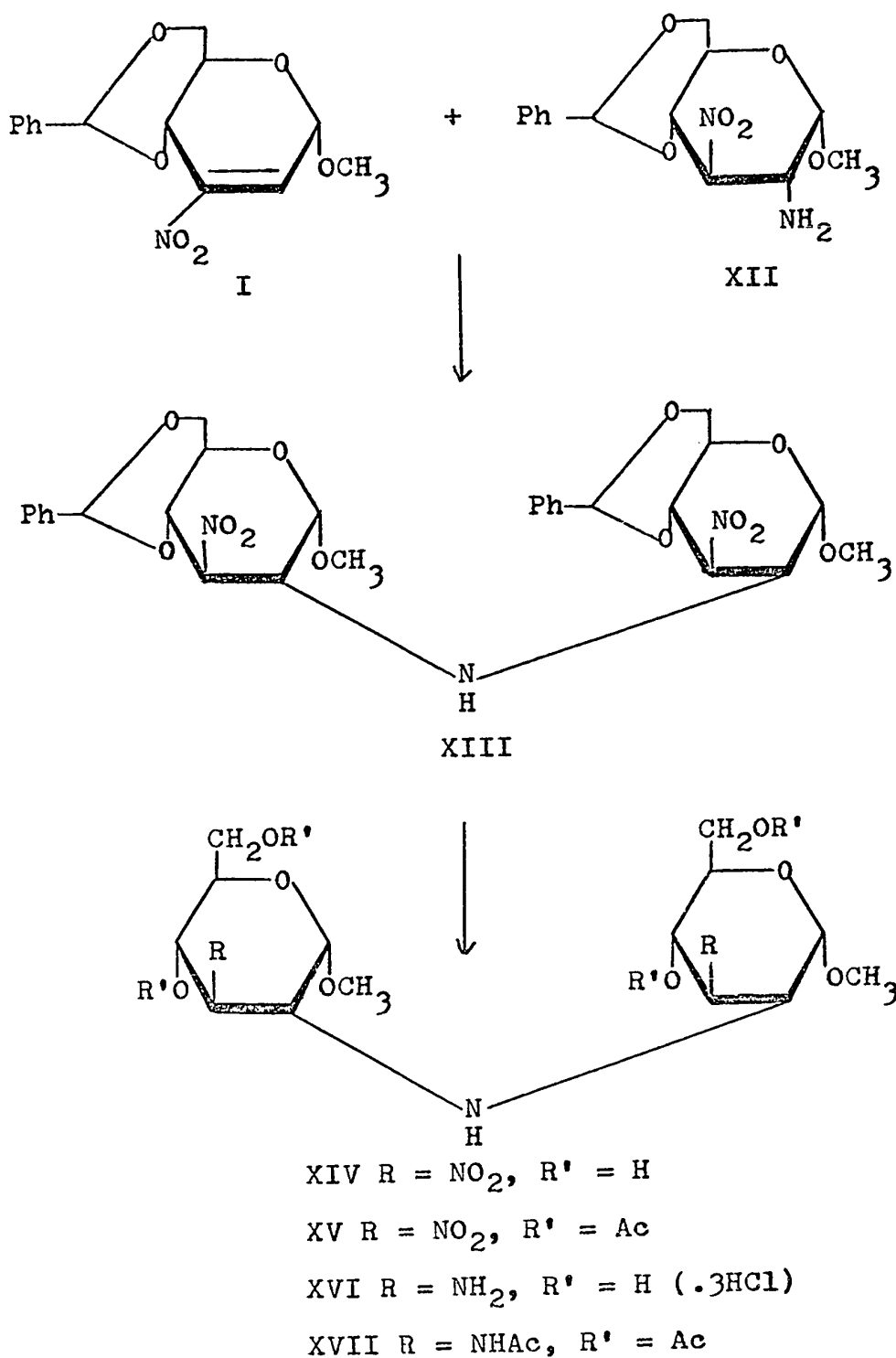
Table V (continued)

<u>Compd.</u>	<u>OH, NH</u>	<u>CO₂H</u>	<u>Ester C=O</u>	<u>Amide I</u>	<u>NO₂</u>	<u>Aromatic</u>
V		2600-2500w 1700s	1766s 1743s	1625s	1562s	1595m 755m
VI	3425m 3200mw 3345ms		1680s		1554s	1600mw 1590m 1528m 760ms
VII			1750s 1722s	1668s	1562ms	762ms
IX	ca.3300b 3375ms 3305ms 1590ms	(3340-3060)				

B. Bisglycosidylamines, a New Class of Amino Sugars

Having observed the relatively facile additions of ammonia and anthranilic acid to the α -nitroolefin I, it was decided to investigate whether the scope of this reaction could be extended to include more complex amines. The addend chosen was the amino sugar XII (Scheme V) that had been synthesized in Part I, Section A (Compound III; see pages 34 to 36). It seemed possible that a reaction between the olefin I and the amine XII would prove more difficult to achieve because of the bulk of XII. On the other hand, the reaction - if feasible - would offer a route to a novel class of amino sugars, namely bisglycosidylamines, which would be amine analogs of disaccharidic ethers.

When the nitroolefin I and the nitroamine XII were allowed to react in a 1 : 1 molar ratio, in refluxing benzene in the presence of a catalytic amount of potassium hydroxide, there was formed the adduct XIII, bis(methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranosid-2-yl)amine, which was isolated in yields of 67 to 78%. No other products could be detected by thin layer chromatography. The rate of addition as well as the yield of adduct seemed to be significantly influenced by the quality of the benzene used as solvent. Thus, in the first run, the reaction was complete in twenty-five hours and afforded



Scheme V. Synthesis of bisglycosidylamines.

a 78% yield of XIII (after recrystallization). However, with a subsequent supply of "Reagent Grade" benzene, longer reaction times (three to three and a half days) were necessary and the yields were somewhat lower. The use of potassium hydroxide as catalyst also deserves comment. It was thought that the nitroamine XII might be sufficiently basic to undergo a Michael addition to nitroolefin I without external catalyst. However, in the absence of potassium hydroxide, the reaction was very sluggish and was not complete after thirteen days.

The formation of XIII was reflected in the infrared spectrum of the reaction product, where the two weak amino absorptions (3420 and 3356 cm^{-1}) present in the starting amine were replaced by a single NH stretching band at 3360 cm^{-1} , and where the nitroalkene band (1535 cm^{-1}) present in the starting olefin was replaced by a nitroalkane band at 1555 cm^{-1} .

Debenzyldination of XIII was attended by difficulties when performed in 70% acetic acid at 100° , as the compound dissolved very slowly in the reaction medium and suffered considerable decomposition. The debenzylidenated product could thus be isolated in a yield of only 37%. A significant improvement was achieved by the use of 90% trifluoroacetic acid at room temperature, according to the method of Christensen and Goodman (142). In this way, bis(methyl 2,3-dideoxy-3-nitro- α -D-glucopyranosid-2-yl)

amine (XIV) was obtained in 60% yield. When recrystallized from ethyl acetate, XIV tenaciously retained some solvent as indicated by infrared spectroscopy. Complete removal of this solvent required drying at 100° and 1 mm for fifty hours.

The compound XIV was smoothly converted by acetic anhydride-boron trifluoride into the tetraacetate XV, bis(methyl 4,6-di-O-acetyl-2,3-dideoxy-3-nitro- α -D-glucopyranosid-2-yl)amine. It is interesting that no acetylation of the secondary amino group in XIV occurred, in contrast to what was observed in similar acetylations of the anthranilic acid adducts IV and VI (page 84). This may be attributed to a reduced accessibility of the secondary amino group in XIV, as compared to such functions in IV and VI.

The dinitroamine XIV was catalytically hydrogenated over platinum to give the triamine, bis(methyl 3-amino-2,3-dideoxy- α -D-glucopyranosid-2-yl)amine. Again, in this compound the secondary amine nitrogen appeared to be severely crowded in by the bulky glycosidyl substituents; for although the compound crystallized as the trihydrochloride (XVI), only two N-acetyl groups were introduced by treatment with acetic anhydride in pyridine, the product being the di-N-acetyltetra-O-acetyl derivative XVII.

Proof of Configuration

The bis- α -D-gluco configuration of the new compounds was ascertained by nuclear magnetic resonance spectroscopy. The 100-MHz spectra of XIII, XV and XVII (Fig. IX, X and XI) clearly indicated that the two glycosidyl moieties in each compound were identical, since each compound gave only one set of substituent resonances. Thus, one sharp methoxyl signal was given by XIII, XV and XVII, and one benzylidene proton singlet was given by XIII; compound XV showed two O-acetyl signals and compound XVII, one N-acetyl and two O-acetyl signals. Inspection of the ring proton resonances (to the extent that they were resolved well enough) likewise revealed equal chemical shifts and spin couplings of corresponding protons in the two glycosidyl moieties of each compound analyzed, proving the glycosidyl moieties to be identical. This fact alone already suggested the bis- α -D-gluco configuration, since it was considered highly unlikely that the α -D-gluco reactant XII should have suffered any stereochemical change during its addition to the α -D-erythro component I.

Direct proof was obtained most conveniently by a more detailed analysis of the spectrum of XV (Fig. X) in deuterated chloroform, in which the ring proton signals were resolved best. In the following discussion, all proton intensities are recorded relative to that of an

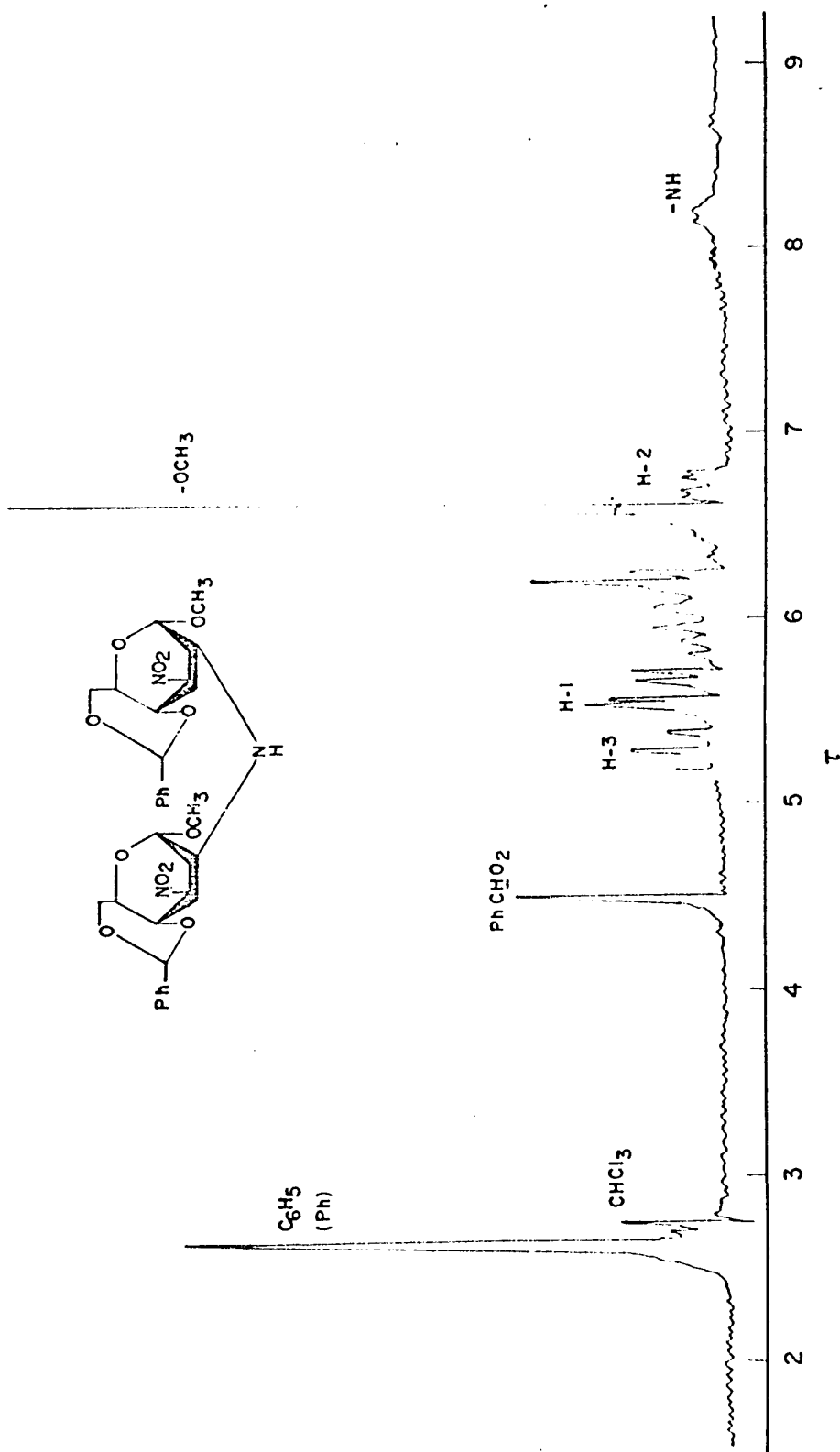


Fig.IX. NMR spectrum of compound XIII in deuterated chloroform.

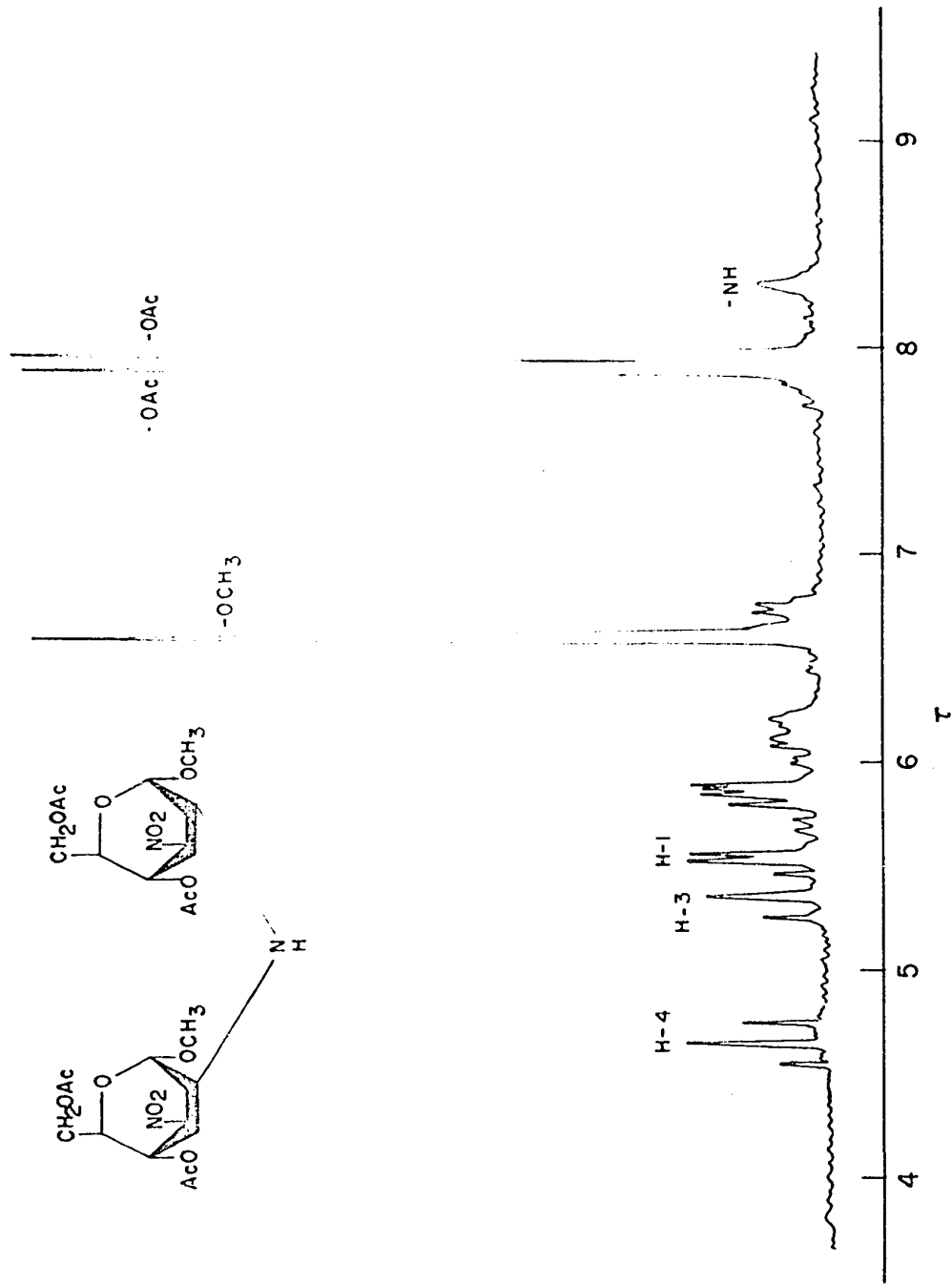


Fig.X. NMR spectrum of compound XV in deuterated chloroform.

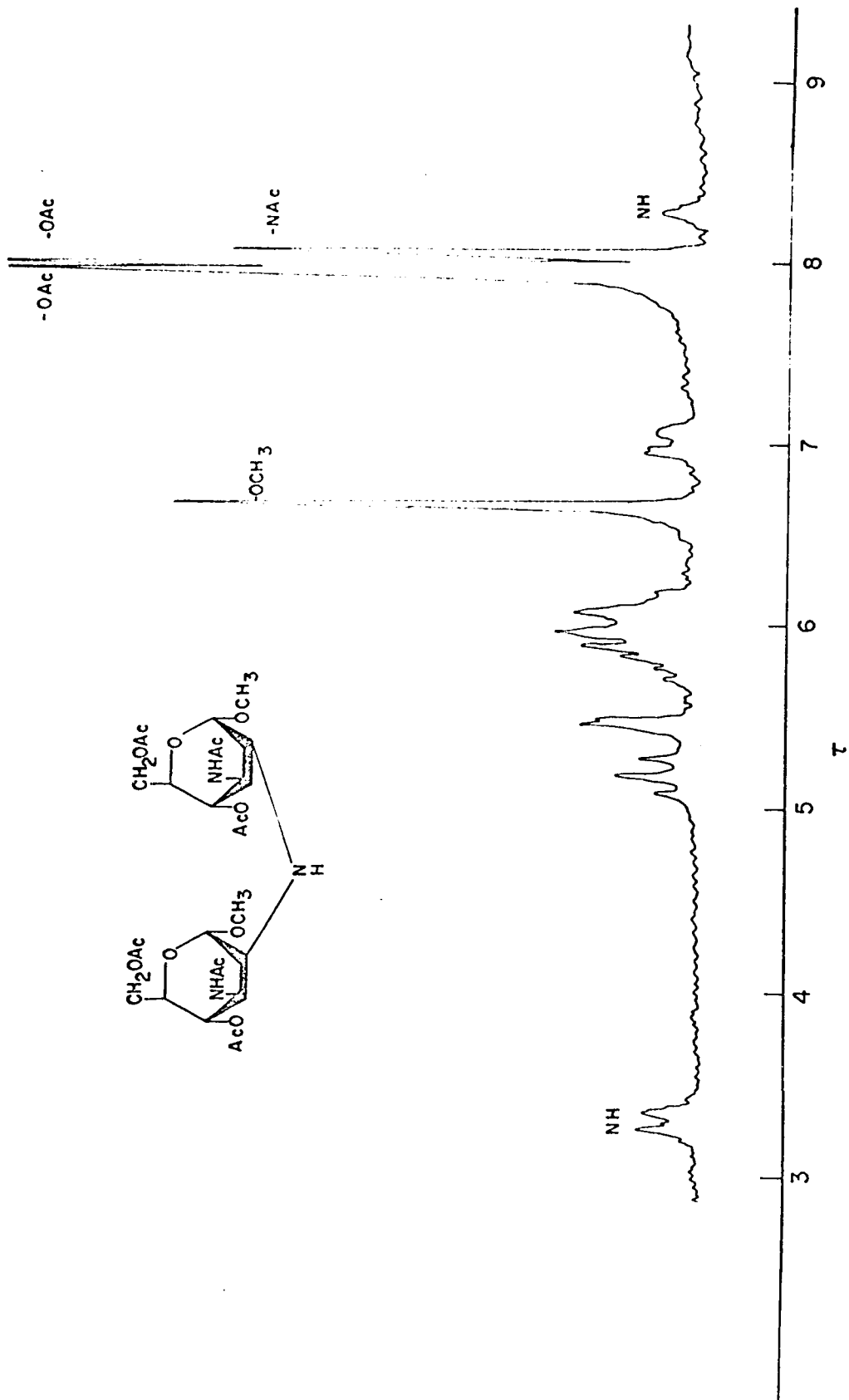


Fig.XI. NMR spectrum of compound XVII in deuterated chloroform.

upfield (8.33 τ) signal attributable to the secondary amine proton, the only proton not duplicated in the molecule. Thus, two symmetrical triplets, each of two-proton intensity, occurred at 4.66 and 5.37 τ , and were assignable to the H-4 and H-3 protons, respectively. Their large splittings of ca. 10 Hz not only confirmed the known, axial orientation of the H-5 and H-4 protons, but also required axial orientation of the H-3 and H-2 protons, thus establishing the gluco configuration. The anomeric protons gave a two-proton doublet at 5.56 τ , which was split by 3 Hz, in accord with 1,2-equatorial-axial coupling. The C-6 methylene groups produced two unsymmetrical quartets integrating to four protons in the region 5.7 - 6.0 τ , and the H-5 protons gave a two-proton octet (width, 18 Hz) centered at 6.18 τ . The methoxyl peak (6H) occurred at 6.64 τ . It partially overlapped a two-proton multiplet which was centered slightly upfield and must belong to the H-2 protons. Despite this overlap a large splitting (by H-3) and a small splitting (by H-1) were recognizable in that signal, which showed additional weak coupling with the vicinal amine hydrogen. Similar multiplets, fortuitously unobserved by the methoxyl absorption, were found in the spectra of XIII and XVII. Finally, the amine hydrogen gave a somewhat broadened signal at 8.33 τ , upfield from the two o-acetyl singlets (7.92, 7.99 τ). The existence

of vicinal coupling between the H-2 protons and the amine hydrogen suggests a retardation of intermolecular exchange of the latter, and this would parallel the observed, low reactivity towards acetic anhydride at that site.

PART III

THE REACTION OF NITRO- AND DINITROINOSITOLS
WITH AMMONIA

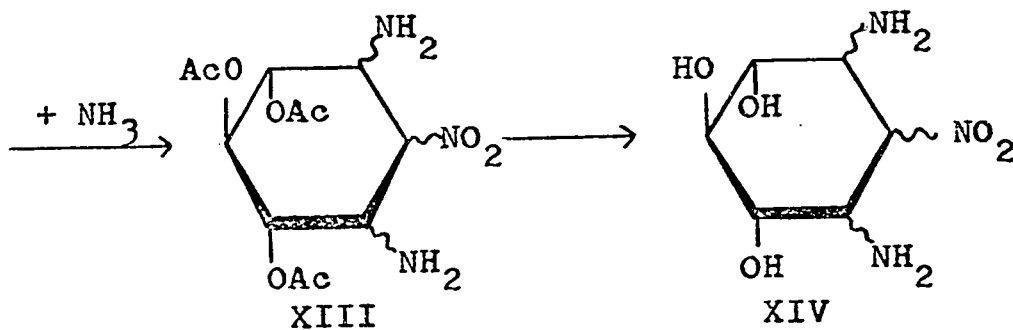
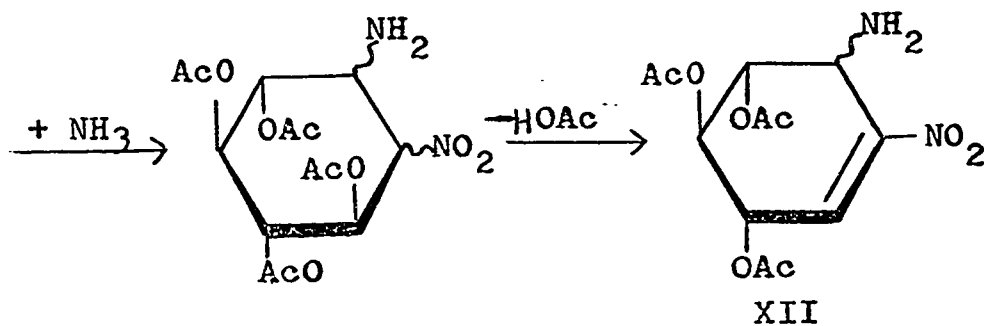
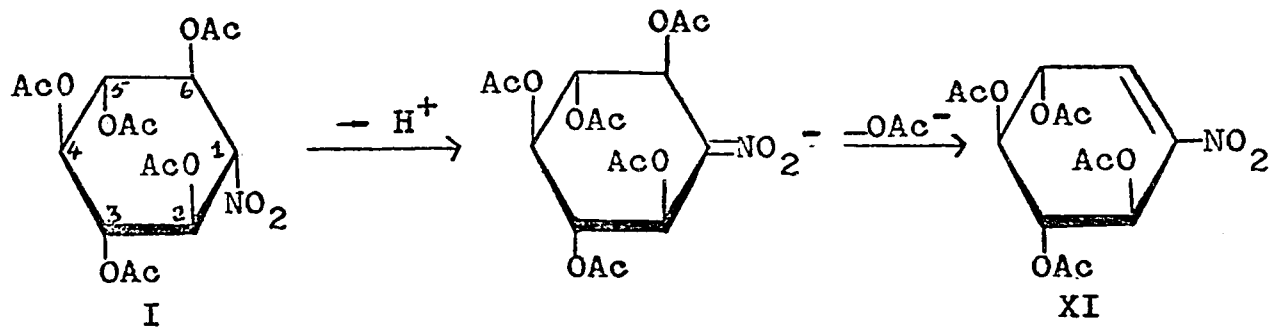
DISCUSSION *

A. Reaction of Deoxynitroinositol Pentaacetates with Ammonia. A Novel Synthesis of Inosatriamines

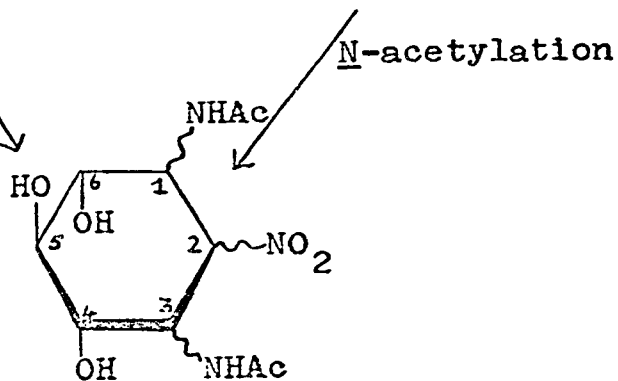
M. C. T. Wang (163) has studied the reaction of deoxynitro-scyllo-inositol pentaacetate (I) with ammonia in aqueous tetrahydrofuran or dioxane at room temperature. After N-acetylation of the reaction mixture, a crude product, thought to be 1,3-diacetamido-1,2,3-trideoxy-2-nitro-scyllo-inositol (IV), was isolated in 69% yield. Recrystallization afforded IV in 32% yield (Scheme VI).

As shown in Scheme VII, the formation of IV from I is thought to involve β -elimination of acetic acid from the nitro compound, which is followed by the addition of ammonia to an intermediate nitroolefin (149), and then, by a second elimination-addition sequence, so that two amino groups are introduced in the positions β and β' to the nitro group. During this process, the three remaining O-acetyl groups are lost, in either one or both of two ways:

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



1. $\underline{O} \rightarrow \underline{N}$ Ac migration
2. Ammonolysis



II: muco

IV: scyllo

Scheme VII. The diamination of nitroinositols.

(a) Ammonolysis of XIII (or partly perhaps of preceding intermediates) to give XIV which is subsequently N-acetylated to IV by the reaction with acetic anhydride.

(b) O → N acetyl migration of two acetyl groups in XIII (or in part at an earlier stage), and ammonolysis of the remaining O-acetyl group.

Since, in the reaction sequence, three asymmetric centers first disappear and are then regenerated, eight stereoisomeric nitrodiamines could theoretically be formed. Wang (163) has isolated only one isomer, namely the scyllo compound (IV), in the relatively moderate yield of 32% (after recrystallization), although the yield of crude product was more than twice as high. The possibility that stereoisomers of IV had been present in the crude reaction product had to be considered. Hence, a reinvestigation of this reaction was undertaken.

The reaction was repeated as described by Wang (163), but its course was monitored by thin layer chromatography. It was found that the reaction mixture gave two spots with R_f 0.6 and 0.4 prior to processing with acetic anhydride. The R_f values of these two products did not change on N-acetylation, and this was taken to indicate that diacetamidonitro derivatives were already formed, at least to some extent, during the interaction of I and ammonia. In preliminary experiments, fractional

crystallization (before N-acetylation) afforded only the fast-moving product, in poor yield (15%), whereas the slow-moving component could not be isolated. However, N-acetylation greatly facilitated the process of isolation, and the two acetamidonitro derivatives could be isolated in pure form in yields of 22 and 37%, respectively, by fractional crystallization. The separation was tedious, and the sum of the yields does not necessarily reflect the total amount of reaction product. However, thin layer chromatography gave no indication for the presence of additional isomers. The slow-moving component was identical with the 1,3-diacetamido-1,2,3-trideoxy-2-nitro-scyllo-inositol (IV) of Wang (163). The fast-moving component, which is readily distinguishable from IV by its melting point and also by spectroscopy (Fig. XII and XIII), will be shown to be a stereoisomer and to possess, most likely, the muco configuration.

The proposed mechanism of diamination (Scheme VII) implies that any deoxynitroinositol pentaacetate that is stereoisomeric with I at C-1, C-2 or C-6 should, on similar treatment with ammonia, furnish the same products as did I, although the speeds of reaction might differ. When deoxynitro-myo-inositol pentaacetate (X) was treated with aqueous ammonia in tetrahydrofuran at room temperature, the diamination reaction did indeed occur and appeared, qualitatively, to be somewhat faster than that of the

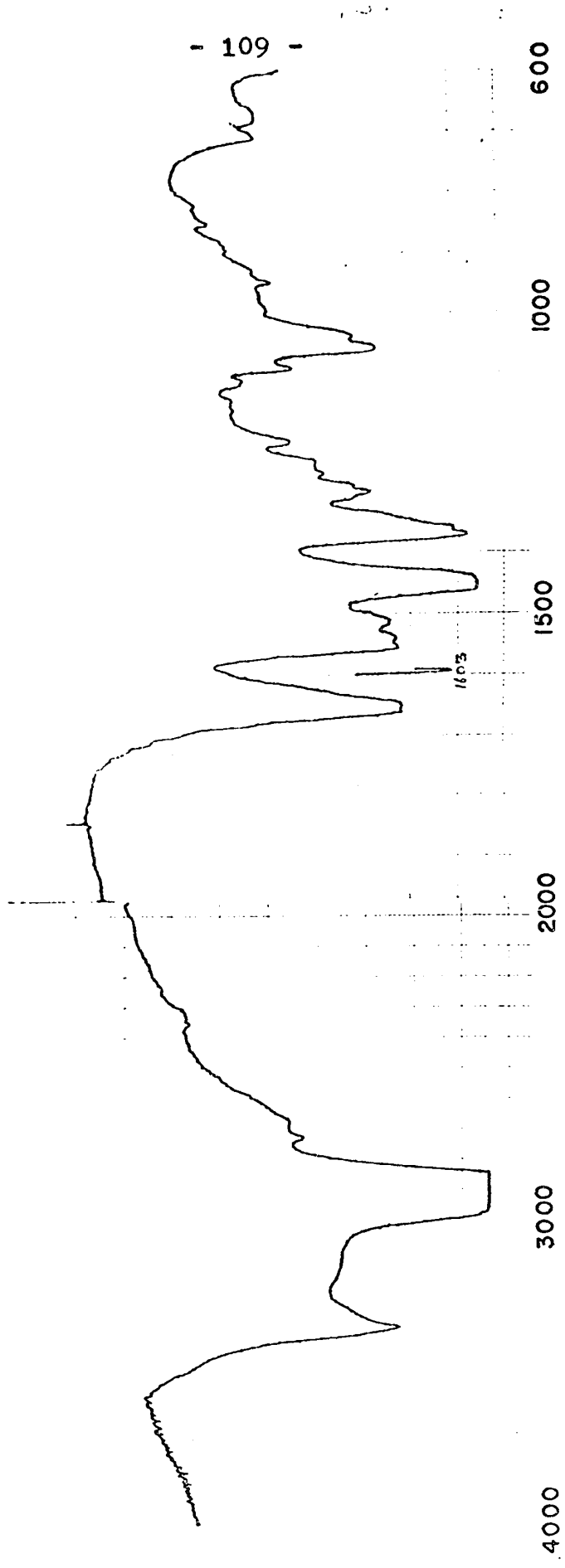


Fig.XII. Infrared spectrum of compound II in Nujol mull.

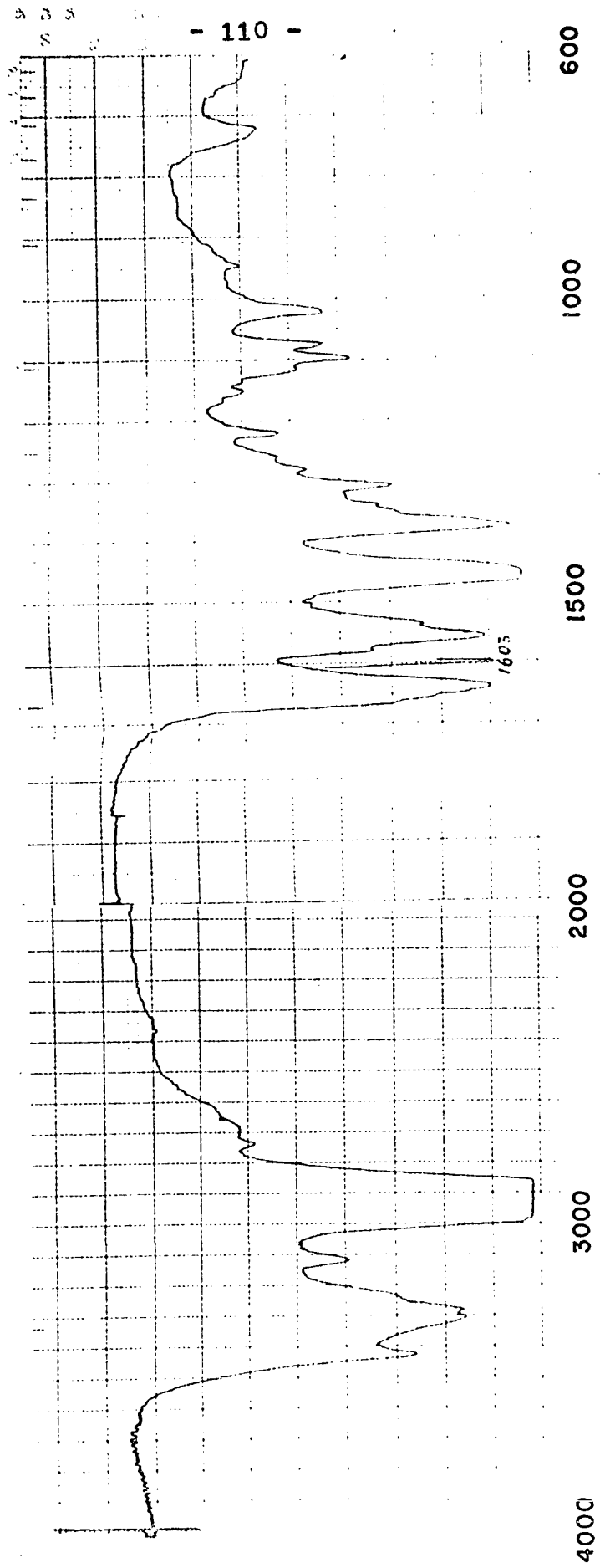


Fig. XIII. Infrared spectrum of compound IV in Nujol mull.

scyllo isomer (I). The crude reaction product, which was crystalline and which was obtained in yields of 66 - 73%, showed, on thin layer chromatography, two spots whose mobilities were identical with those of II and IV, respectively. Work-up without preceding N-acetylation afforded one of the components in pure form, in 38% yield, whereas the other component could not be separated from the mixture. The isolated material proved identical with the muco isomer II.

The new isomer II was readily O-acetylated, in almost quantitative yield, by the use of acetic anhydride-boron trifluoride, to give 1,3-diacetamido-4,5,6-tri-O-acetyl-1,2,3-trideoxy-2-nitro-muco-inositol (III). Hydrogenation of II over Adams catalyst afforded the 1,2,3-inosatriamine derivative V, which was N-acetylated to give 1,2,3-triacetamido-1,2,3-trideoxy-muco-inositol (VI)*. Peracetylation furnished the hexaacetyl derivative (VII).

The scyllo isomer IV furnished on catalytic hydrogenation the 1,2,3-inosatriamine derivative VIII.

* VI crystallized with 0.5 mole of ethanol: This was reflected in the microanalytical data, and in the NMR spectrum (in DMSO- d_6), which showed signals attributable to ethanol, namely, a methyl triplet ($J = 7.3$ Hz) at 8.79τ and a methylene quartet in the 6.5τ region.

Although microanalytical data for VIII were not entirely satisfactory (the sample presumably contained ca. 2.5 moles of water of crystallization), complete acetylation provided the corresponding triacetamidi-tri-0-acetyl derivative (IX) which gave a correct elemental analysis and the expected infrared and NMR spectra.

Assignment of Configuration

Since eight stereoisomeric diammononitro inositol derivatives could theoretically be formed by the reaction of I or X with ammonia, proof of configuration at C-1, C-2 and C-3 was required. Compound IV had already been assigned the scyllo configuration (163) on the basis of NMR studies. The configuration of compound II remained to be established, and this was attempted by evaluating the NMR spectra of its derivatives. One of the main difficulties encountered, however, was the poor solubility of II and the compounds derived from it (III, VI and VII) in suitable solvents. The spectra obtained did not permit analysis of the ring proton resonances. Consequently, the assignment had to be based solely on chemical shift data for the acetyl protons.

Subsequent to the studies of Lemieux and coworkers (165), who found that the methyl protons of axially oriented acetoxy substituents in carbohydrates have lower chemical shifts than those of equatorial acetoxy groups,

many confirmatory observations have been reported in the literature and have been reviewed (143a). More recently, very extensive compilations of chemical shift data for O- and N-acetyl groups in polyacetylated pyranose sugars and inositols have been presented by Horton and coworkers (144), Lichtenthaler and Emig (143c), and Hasegawa and Sable (151). These authors have also drawn due attention to abnormal shifts that can be caused by magnetically anisotropic groupings present in the molecule (e.g., keto groups or aromatic substituents), but there is general agreement that, in the absence of such disturbing structural factors, the O- and N-acetyl proton shifts fall into definite ranges indicative of the conformational disposition. In this regard, abnormalities associated with the nitro group have never been encountered, although the spectra of numerous, different nitro derivatives of pyranoses and inositols have been recorded (See, for instance, references 120, 152, 166, 167).

The chemical shifts of the acetyl protons in compounds III, VI and VII are listed in Table VI together with the ranges given by Lichtenthaler and Emig (143b and c) for acetylated inositols and inosamines. The values that were found indicate equatorial orientation of the N-acetyl groups (in III, VI and VII) and axial orientation of the O-acetyl groups (in III and VII).

Table VI

CHEMICAL SHIFTS (τ) OF ACETYL PROTONS
OF INOSITOL DERIVATIVES

<u>Compound</u>	<u>Solvent</u>	<u>N-Acetyl*</u>	<u>O-Acetyl*</u>
III	DMSO-d ₆	8.24 (6)	7.84 (3)
			7.89 (6)
IV	DMSO-d ₆	8.22 (6)	
		8.25 (3)	
VII	DMSO-d ₆	8.24 (9)	7.88 (9)
	CDCl ₃	8.05 (9)	7.85 (9)
IX	DMSO-d ₆	8.30 (9)	8.10 (9)

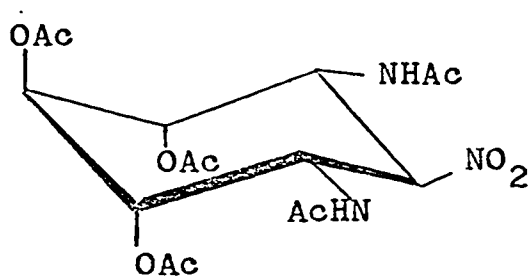
Reported ranges:

	<u>Solvent</u>	
	DMSO-d ₆	CDCl ₃
<u>N-Acetyl</u>		
axial	8.07 - 8.14	7.92 - 7.98
equatorial	8.22 - 8.30	8.05 - 8.10
<u>O-Acetyl</u>		
axial	7.80 - 7.90	7.74 - 7.90
equatorial	7.97 - 8.13	7.93 - 8.03

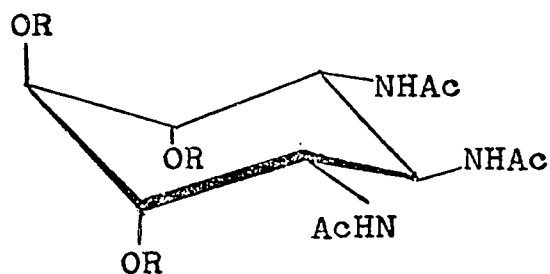
* Number of protons in parentheses.

It is noteworthy that the acetyl resonances of VII in two different solvents are in mutual agreement.

Since the catalytic reduction of the nitro group in acid medium proceeds with retention of configuration (139,140), and since all the N-acetyl signals in the triacetamido derivatives VI and VII are in the equatorial range, it follows that the nitro group in III must also be equatorial. Only the conformational formulas depicted below satisfy the results just described, and these formulas are seen to represent the muco configuration:



III



VI, R = H

VII, R = Ac

It is recognized, however, that a proof of this kind, based on chemical shifts alone, is not an absolute one, and therefore the assignment of the muco configuration to II ought to be confirmed in some other way. For comparison, the NMR spectrum of the hexaacetyl inosatriamine IX (i.e., the scyllo isomer of VII) was taken, in DMSO-d₆.

Two sharp singlets, each corresponding to nine protons, were found at 8.30 and 8.10 τ , respectively, (Table VI), and this was consistent with three equatorial acetamido groups and three equatorial acetoxy groups in this compound*.

It may also be noted that the relative chromatographic mobilities of the isomers II and IV are compatible with the assigned configurations, for it has been observed that inositols having axial hydroxyl groups migrate faster than those having equatorial hydroxyl groups (168).

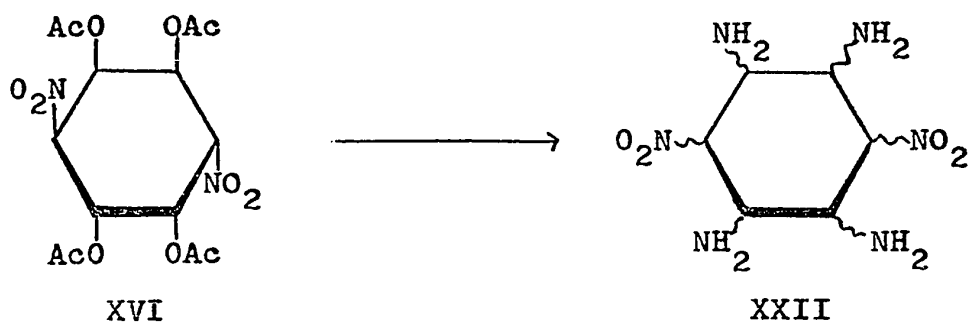
* At the time of this writing (May 1969) the March 21 issue of *Angewandte Chemie* was received, in which F. W. Lichtenthaler, P. Voss and N. Majer (150) reported in a preliminary communication to have applied the diamination reaction to penta-0-acetyl-deoxynitro-scyllo-inositol as first reported by Baer and Wang (149). They isolated only one product and stated that it appeared to be identical with the scyllo derivative IV. Acetylation gave an acetate (scyllo isomer of III) that showed resonances (in DMSO- d_6) at 8.26 τ (6H) and 8.09 τ (9H) for equatorial acetamido and acetoxy groups. The authors also prepared IX and found it to exhibit an N-acetamido signal at 8.28 (9H) and an acetoxy signal at 8.09 τ (9H), in good agreement with our values, but they reported a melting point that was about 20° lower than ours.

To summarize the results of this section, it may be said that the diamination of nitroinositols appears to be a promising route to inosdiamines and inosatriamines. It was shown that, in addition to products having the scyllo configuration (149, 150, 163), products most probably possessing the muco configuration can be obtained. It has been suggested (149) that the method could prove useful for the preparation of intermediates for a novel synthesis of streptomycin; by the same token, stereoisomers of this antibiotic component might become available by this approach. At any rate, it is felt that a contribution has been made to the chemistry of inosatriamines, a class of compounds of which, at the inception of the diamination reaction, only two representatives were known, namely, 1,3,5-cis-inosatriamine (169,170) and its 1,3,5-scyllo isomer (171).

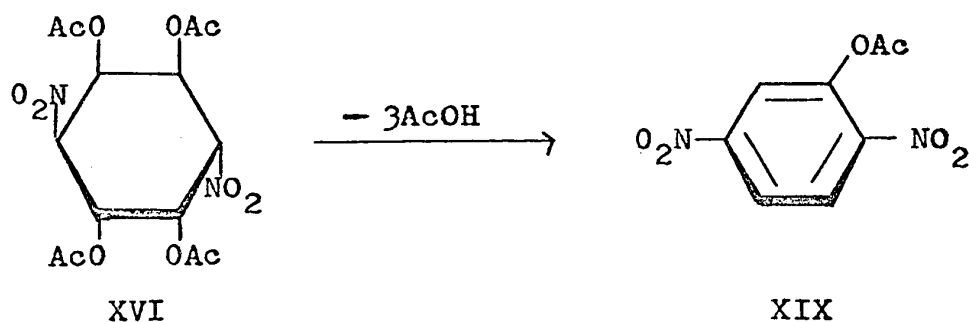
B. Reaction of 2,3,5,6-Tetra-O-acetyl-1,4-dideoxy-1,4-dinitro-neo-inositol with Ammonia. A Novel Synthesis of 2,5-Dinitroaniline

In continuation of the studies undertaken to explore the scope of the diamination of nitro cyclitol acetates (see the preceding Section), the reaction of 2,3,5,6-tetra-O-acetyl-1,4-dideoxy-1,4-dinitro-neo-inositol (XVI) with ammonia was investigated. Several possibilities could a priori be envisaged for the course that this reaction might take, for example:

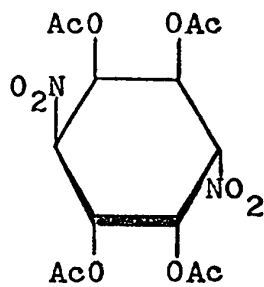
1. Complete amination:



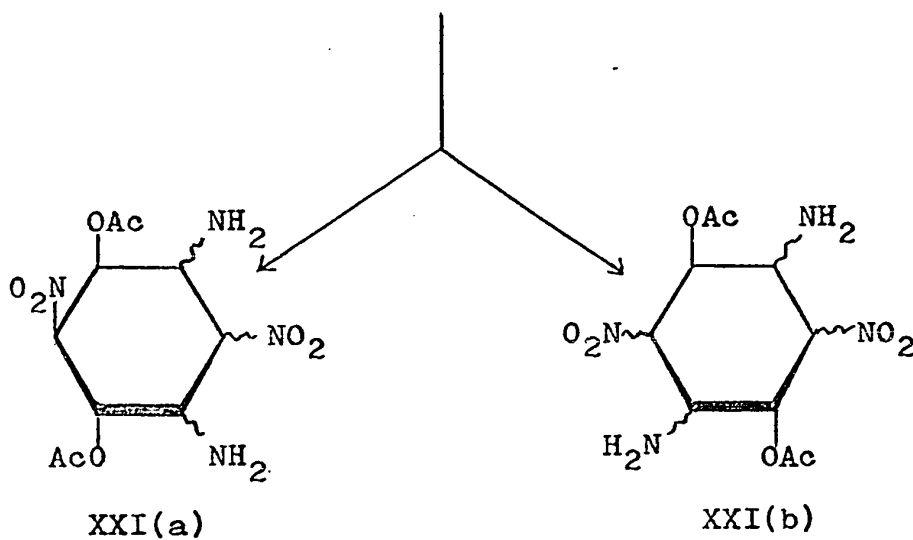
2. Aromatization to 2,5-dinitrophenyl acetate:



3. Diamination, followed by O \longrightarrow N acetyl migration:

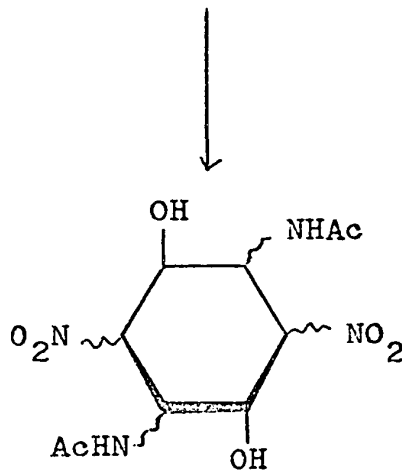
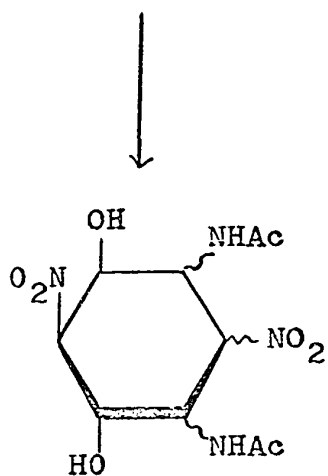


XVI

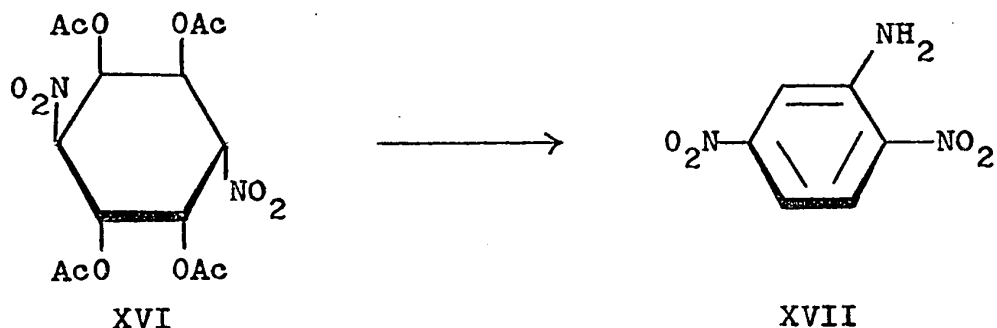


XXI(a)

XXI(b)

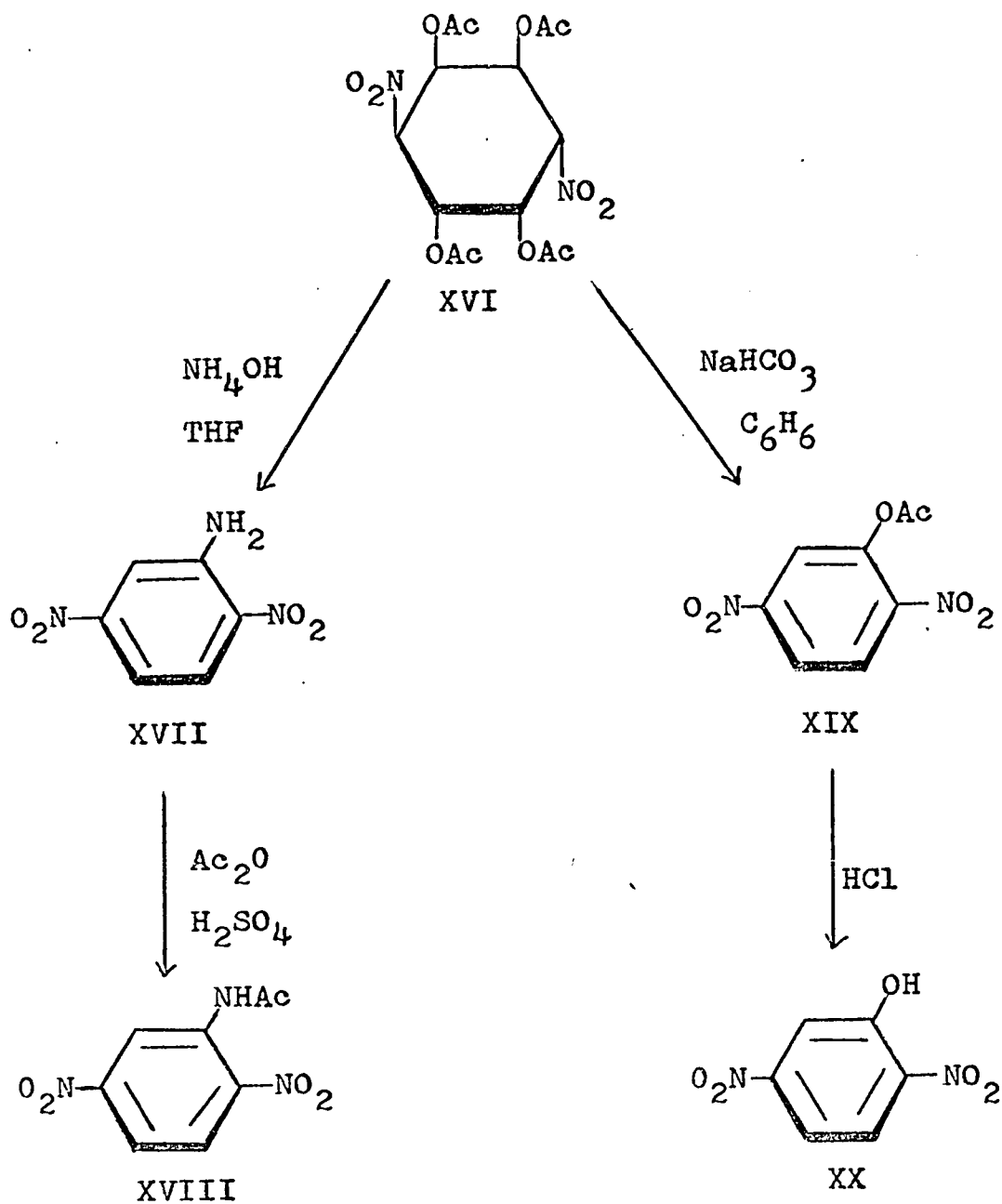


4. Introduction of an amino group followed by aromatization to 2,5-dinitroaniline:



The possibility of aromatization had to be considered because it was known that the dinitroinositol tetraacetate readily gives 2,5-dinitrophenyl acetate (XIX) on heating with pyridine (172). In the course of the present work it was shown, moreover, that the same aromatization to XIX occurs quantitatively when XVI is heated in benzene solution in the presence of sodium bicarbonate. (Acid hydrolysis of XIX produced 2,5-dinitrophenol in 93% yield). On the other hand, if a molecule of ammonia were first introduced and aromatization followed, the formation of 2,5-dinitroaniline (XVII) would be expected. This proved indeed to be the case.

The reaction of 2,3,5,6-tetra-O-acetyl-1,4-dideoxy-1,4-dinitro-neo-inositol (XVI) with aqueous ammonia at room temperature (Scheme VIII) afforded in 76% yield a yellow compound (XVII) that melted at 137 - 138° and gave analytical



Scheme VIII. The aromatization of a 1,4-dideoxy-1,4-dinitro-inositol.

data corresponding to $C_6H_5N_3O_4$. It exhibited infrared absorptions typical of the amino group (3510, 3398 and 1634 cm^{-1}), of the aromatic ring (1600 and 1500 cm^{-1}), and of an aromatic nitro group (1541 cm^{-1}). These data suggested that XVII was 2,5-dinitroaniline, the reported (173) melting point of which is 137° . This was confirmed by the synthesis of its N-acetyl derivative: Acetylation of XVII afforded in 70% yield 2,5-dinitroacetanilide (XVIII), which showed a melting point of $120 - 121^\circ$ [reported (174,175), mp 121°] and gave an infrared spectrum consistent with the structure.

Undoubtedly, the first step in the formation of XVII is elimination of one molecule of acetic acid, followed by the addition of a molecule of ammonia to the intermediate nitroolefin. Whether this process is then repeated to give intermediary diamines of type XXI(a or b) or possibly even the tetramine (XXII), all of which could aromatize by a series of eliminations activated by the two nitro groups, or whether aromatization takes place immediately when one amino group has entered, cannot be decided without further study.

However, the ease with which XVII is formed in high yield provided a convenient, preparative route to this compound, especially in view of the fact that the starting material, namely the dinitroinositol tetraacetate XVI, is readily available by way of the cyclic addition of

glyoxal and nitromethane (172), followed by acetylation of the resulting dinitroinositol (172,136). 2,5-Dinitroaniline has been prepared previously by nitration of 3-nitroacetanilide (176), by acid-catalyzed rearrangement of 2,3-dinitroacetanilide (177), and by ammonolysis of 2,5-dinitrochlorobenzene (178), but all of these methods were relatively low-yielding, the best yield reported (177) being 47% , and they required tedious purification procedures. It is perhaps significant that XVII and its N-acetate are not listed in the catalogues of the major commercial suppliers of chemicals.

ADDENDUM

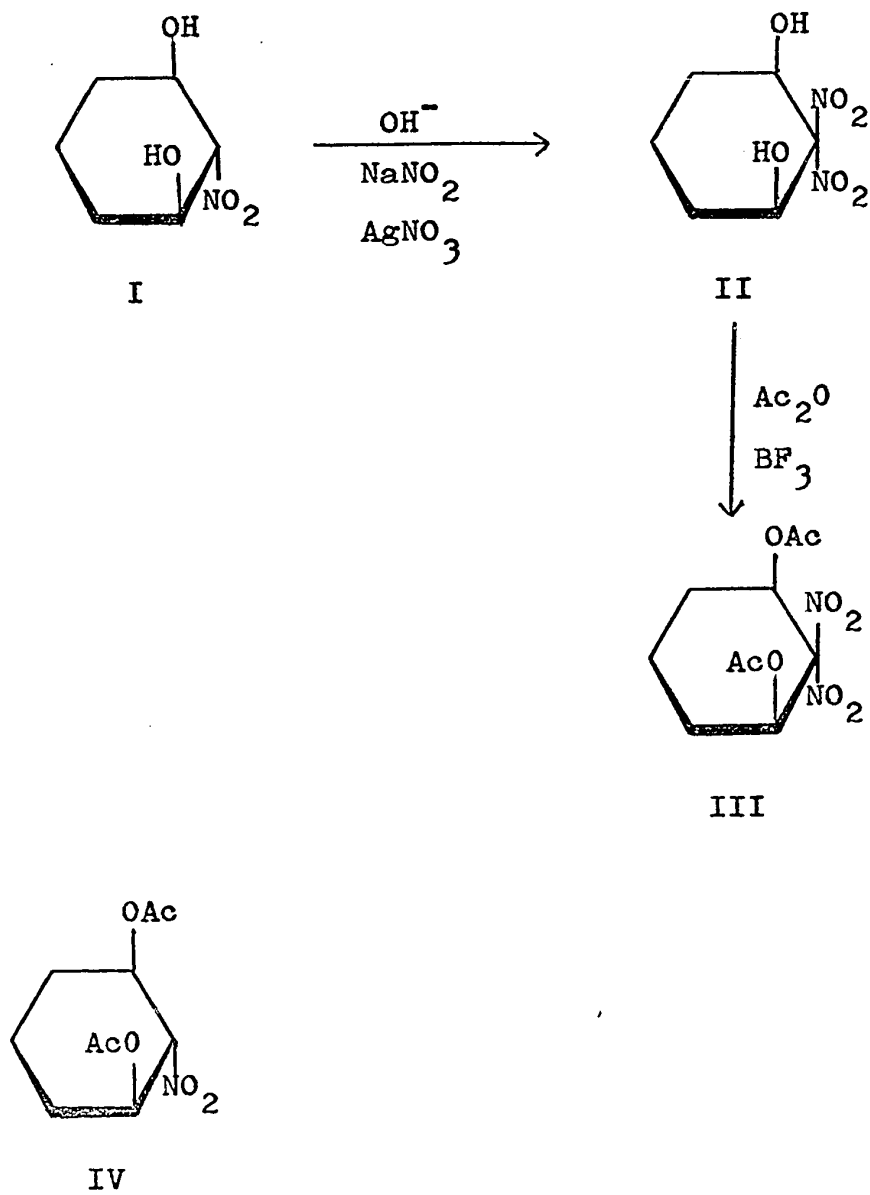
CONCERNING THE SYNTHESIS OF GEMINAL DINITRO COMPOUNDS

DISCUSSION *

In the course of a synthetic program initiated to develop effective methods for the conversion of secondary nitro compounds into the corresponding ketones in carbohydrate chemistry, a route via geminal dinitro compounds was contemplated. It was considered that it should be possible to reduce such a geminal dinitro compound to the (unstable) diamine, which would decompose to give the ketone and ammonia. The oxidative nitration of mononitro compounds, developed by Kaplan and Shechter (179), was to be applied, and it was to be tried first on an alicyclic model compound, namely, trans,trans-2-nitro-1,3-cyclohexanediol (I). The nitrodiol I is readily prepared (180) from glutaraldehyde and nitromethane.

The reaction of I with silver nitrate and sodium nitrite in alkaline medium (Scheme IX) was performed under the conditions specified (179) for other aliphatic nitro compounds and was monitored by thin layer chromatography. The reaction could not, however, be brought to completion. Whereas with several nitroalkanes previously studied (179), the reaction time was only about one hour, in the present case the reaction was incomplete even after five days.

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



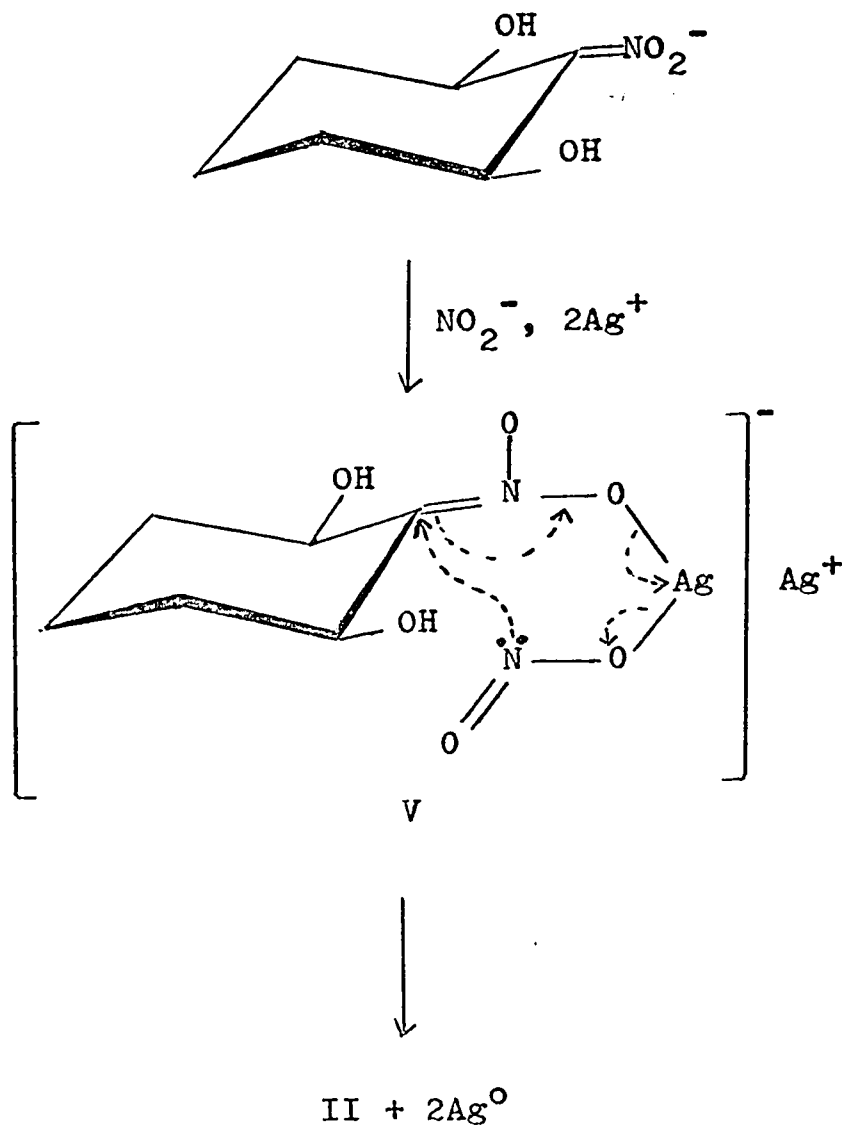
Scheme IX. A synthesis of geminal dinitro compounds.

Work-up afforded a mixture containing the starting diol (I) and a faster-migrating product. Separation could not be achieved by fractional crystallization but only by column chromatography or preparative-scale thin layer chromatography. 2,2-Dinitrocyclohexane-1,3-cis-diol (II) was obtained in 16% yield. Boron trifluoride-catalyzed acetylation of II afforded the corresponding diacetate (III).

Microanalytical data indicated the presence of two nitro groups in each of the products II and III. The geminal disposition of the two nitro groups was suggested by the infrared spectra of II and III, each of which showed two nitro absorption bands at 1590 and 1568 cm^{-1} in the range typical of gem-dinitro compounds (181). (The mononitro derivative I absorbed at 1555 cm^{-1}). This assignment was confirmed by a comparison of the behavior of I and II in the ultraviolet. Neither I nor II showed any high-intensity absorption in the 250- $\text{m}\mu$ region at neutral pH. In alkaline medium, I gave the expected, strong absorption in that region, which is due to the formation of the nitronate chromophore. Compound II, on the other hand, gave no absorption near 250 m in alkaline medium, since it lacks an α -hydrogen and hence does not form a nitronate.

The limited success in the oxidative nitration of I may perhaps be rationalized as follows: Although no

mechanism has unequivocally been proved as yet for this reaction, the one proposed by Kaplan and Shechter (179) may be considered here. It involves an intermediate complex consisting of nitronate, nitrite and silver ions in the ratio of 1 : 1 : 2. Collapse of the complex leads to the products. In the case of I, the complex is presumably to be pictured as V:



It could be that the formation of the complex and/or the approach of the nitrite nitrogen atom to the carbon atom bearing the nitro group is not favored, for steric or electronic reasons, owing to the presence of the vicinal hydroxyl groups. In this connection it is noteworthy that, apart from II, no β,β' -dihydroxy-gem-dinitro compound seems to have been synthesized by this method as yet.

Attempts to introduce a second nitro group at C-3 in methyl 3-deoxy-3-nitro- β -D-ribofuranoside and -glucopyranoside did not meet with success.

EXPERIMENTAL

General Remarks

Melting points were determined in capillaries in an electrically heated aluminum block equipped with a calibrated thermometer.

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

Optical rotations were measured in a Perkin-Elmer automatic polarimeter, model 141, at room temperature ($[\alpha]_D$ means $[\alpha]_D^{23}$).

Unless otherwise specified, infrared spectra were obtained from Nujol mulls on a Beckmann IR-8 instrument, and band intensities are recorded as strong (s), medium-strong (ms), medium (m), medium-weak (mw), and weak (w).

All evaporations were carried out in vacuo at 35 - 40° bath temperature.

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

Thin layer chromatography was performed on silica gel G (E. Merck AG, Darmstadt, Germany). The spots were identified by spraying with a 1% ceric sulfate solution in 10% sulfuric acid.

Column chromatography was performed on silicic acid (Mallinckrodt, 100 Mesh).

Paper chromatography was performed by the descending technique on Whatman N^o 1 paper with acetic acid-ethyl acetate-pyridine-water (1 : 5 : 5 : 3). The spots were identified by spraying with ninhydrin.

R_{GN} means speed relative to D-glucosamine hydrochloride.

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates HA-100 instrument.

Part I

A. SYNTHESIS OF DERIVATIVES OF 2,3-DIAMINO-2,3-DIDEOXY-
D-GLUCOSE

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-
hex-2-enopyranoside (I)

This nitroolefin was prepared by a modification of the method reported in the literature (94). Methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro- α -D-glucopyranoside (3 g, dried at 23° and 1 mm for twenty-four hours), sodium bicarbonate (6 g, oven-dried at 100° for two hours) and a few pieces of Drierite were refluxed with magnetic stirring in dry benzene (150 ml). The progress of the reaction was followed by infrared spectroscopy: Small samples of the reaction mixture were withdrawn occasionally, filtered, and the filtrates were evaporated. The ensuing residues were then examined as Nujol mulls. A gradual disappearance of the peaks at 1745 cm⁻¹ (ester CO) and 1560 cm⁻¹ (nitroalkane) was observed, and a peak at 1535 cm⁻¹ (nitroolefin) appeared concomitantly. Care was taken to add a few fresh pieces of Drierite each time when samples were withdrawn, to ensure anhydrous reaction conditions. Performed in this way, the reaction was complete in two days [reported (94), nine days].

The filtered reaction solution was evaporated to give a white residue (2.3 g, 94%) of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-hex-2-enopyranoside (I), mp 178 - 179°. Recrystallization from ethyl acetate-petroleum ether afforded 1.8 g of stout needles melting at 183 - 184° and showing $[\alpha]_D - 91.7^\circ$ (c 0.9, ethyl acetate). Reported (78), mp 183°, $[\alpha]_D - 93^\circ$ (c 0.9, ethyl acetate).

Methyl 2-Amino-4,6-O-benzylidene-2,3-dideoxy-3-nitro-
 α -D-glucopyranoside (III)

1. By Addition of Ammonia to Nitroolefin I at 80°:

Aqueous 15 N ammonia (40 ml) was added to a solution of compound I (765 mg) in ordinary benzene (40 ml), and the mixture was gently refluxed, with magnetic stirring. The progress of the reaction was followed by thin layer chromatography using chloroform-ethyl acetate (1 : 1) as irrigating system: the fast-moving spot corresponding to the nitroolefin (R_f ca. 0.9) gradually disappeared with the concomitant appearance of a slow-moving spot (R_f ca. 0.4). The reaction was complete within one hour.

The mixture was then concentrated in vacuo, whereupon a fluffy, white solid precipitated. The latter was triturated with cold water, and the suspension was concentrated again for the complete removal of ammonia.

The product was then filtered off, washed several times with cold water, and dried. This crop of methyl 2-amino-4,6-o-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside (III) (771 mg, 95%) melted at 168 - 170°. Recrystallization from ethanol furnished shiny, white needles (697 mg) melting at 170 - 171° and showing $[\alpha]_D + 93.3^\circ$ (c 0.9, dimethylformamide).

Anal. Calcd for $C_{14}H_{18}N_2O_6$ (310.3): C, 54.19; H, 5.85; N, 9.03. Found: C, 54.05; H, 6.08; N, 9.17.

The infrared spectrum of the compound (Fig.I) was characterized by the presence of very weak NH_2 stretching bands at 3420 and 3356 cm^{-1} . The typical NH_2 bending absorptions near 1600 and 830 cm^{-1} were also very weak. Prominent bands were at 1550 cm^{-1} (s), nitroalkane; 1096 (ms) and 1056 cm^{-1} (ms), COC stretching; 762 (m) and 701 cm^{-1} (m), monosubstituted benzene. The amino absorptions were weak also when the spectrum was run in chloroform.

2. By Addition of Ammonia to Nitroolefin I at 23°:

A mixture of compound I (100 mg), dissolved in benzene (10 ml), and 15 N aqueous ammonia (10 ml) was magnetically stirred at 23°. Thin layer chromatography performed as in 1, above, indicated that the reaction was complete within an hour. Work-up as before provided the 2-amino derivative (85 mg, 81%), which was recrystallized from ethanol.

The recrystallized product exhibited $[\alpha]_D + 92.9^\circ$ (c 0.7, dimethylformamide) and melted at $170 - 171^\circ$, undepressed upon admixture of the product from 1. The addition was also performed at 23° in tetrahydrofuran in one hour. Only one product was seen on thin layer chromatography and was isolated in 85 - 87% yield. It melted at $170 - 171^\circ$ and exhibited $[\alpha]_D + 93.8^\circ$ (c 0.8, dimethylformamide), and it gave an undepressed melting point in admixture with III.

3. By Reaction of Ammonia with the Nitroacetate II:

To a solution of methyl 2-0-acetyl-4,6-0-benzylidene-3-deoxy-3-nitro- α -D-glucopyranoside (1 g) ^(30 ml) in tetrahydrofuran (30 ml) was added aqueous 15 N ammonia. ^{^^} The mixture was magnetically stirred at room temperature, and the reaction was monitored by thin layer chromatography, with benzene-ethyl acetate (3 : 2) as irrigating system: two new spots (Rf 0.24 and 0.44) appeared at the expense of the fast-moving spot (Rf 0.91) corresponding to the nitro acetate; in addition a minor, fast-moving spot was sometimes seen. The spot with Rf 0.24 represented the chief product of the reaction. A sample of the 2-amino derivative prepared in 1, above, had the same Rf value in this solvent system.

The reaction was complete within one hour, whereafter the mixture was evaporated. Much foaming

occurred, and a white, fluffy solid precipitated. The solid was triturated with water, and evaporation was repeated to remove residual ammonia and tetrahydrofuran. The crude product was then filtered, washed copiously with cold water and dried. The yield was 803 mg of a crystalline material consisting mainly of the amino derivative III but containing small amounts of other substances.

The amine was very difficult to isolate in pure form from the mixture. Recrystallization from common solvents (ethanol, ethanol-water, ethyl acetate-petroleum ether, chloroform-n-pentane amongst others) failed to effect any reasonable purification of the main product. In one experiment, the crude mixture (100 mg) was dissolved in the minimum amount of hot ethanol and, after filtration, the solution was allowed to cool very slowly and seeded with crystals of III (from 1). Shiny white needles of pure 2-amino compound (48 mg) were deposited within one hour at room temperature. In another, similar experiment the solution was left standing for two hours after seeding: again, beautiful white needles were obtained but they did not prove to be chromatographically uniform.

Eventually, recourse to column chromatography was taken. In a typical run, the crude product (815 mg) was separated on a column (45 cm x 2 cm) by elution with benzene-ethyl acetate mixtures. The chromatographically

pure 2-amino derivative obtained (697 mg, 79%) was recrystallized from ethanol: it melted at 170 - 171° and exhibited $[\alpha]_D + 93.5^\circ$ (c 0.8, dimethylformamide).

However, a much better method of isolating a pure reaction product consisted of N-acetylation, as described below.

Methyl 2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside (IV)

1. By N-Acetylation of the Pure Amino Derivative:

Methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside (III) (100 mg) was dissolved in tetrahydrofuran (10 ml), and a few drops of water were added. The solution was ice-cooled, acetic anhydride (5 ml) was carefully added, and the mixture was kept at room temperature for two hours. Partial evaporation of the tetrahydrofuran initiated precipitation of a white solid. Complete precipitation occurred upon the addition of ice-water, with magnetic stirring. The white precipitate was filtered off and washed several times with cold water until it was free from a pungent smell.

The N-acetyl derivative (102 mg, 90%) was recrystallized from ethyl acetate to give beautiful white needles melting at 277 - 277.5° (with partial sublimation above 240°) and showing $[\alpha]_D + 88.0^\circ$ (c 0.8, dimethylformamide).

Both the crude and recrystallized products gave only one spot (Rf 0.36) on thin layer chromatography with chloroform-ethyl acetate (2 : 3).

Anal. Calcd for $C_{16}H_{20}N_2O_7$ (352.3): C, 54.54; H, 5.72; N, 7.95. Found: C, 54.72; H, 5.88; N, 7.85.

The product exhibited typical infrared bands (Fig.II) at 3300 cm^{-1} (ms), NH; 1660 cm^{-1} (s), amide I; $1550 - 1540\text{ cm}^{-1}$ (s), nitroalkane and amide II bands; and 753 and 700 cm^{-1} (m), monosubstituted benzene.

2. By N-Acetylation without Isolation of the free Amine:

The crude product obtained by the reaction of nitroacetate II (800 mg) with ammonia in tetrahydrofuran, as already described, was N-acetylated as in 1, above.

Thin layer chromatography with chloroform-ethyl acetate (2 : 3) showed three spots having Rf 0.36, 0.26, and ca. 0.9. The major product (Rf 0.36) was obtained in pure form by recrystallization of the crude acetylation-mixture from a small amount of boiling ethyl acetate, which yielded a crop of white needles (325 mg). Concentration of the filtrate and storage at 5° overnight deposited another 135 mg of the pure compound. Evaporation of the filtrate and recrystallization of the residue from a small amount of ethyl acetate yielded a third crop (97 mg) of the pure compound. Finally, column separation of the components of the last mother liquor, by elution with benzene-

ethyl acetate mixtures, resulted in the isolation of a further crop (48 mg), bringing the total yield of pure methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside (IV) to 605 mg (76%, based on II).

The product melted at 277 - 277.5° and exhibited $[\alpha]_D + 87.7^\circ$ (c 0.9, dimethylformamide). Its IR spectrum and chromatographic mobility were identical to those of the compound obtained by N-acetylation of the crystalline amine as described in 1, above. Also, a mixed melting point was undepressed.

In variation of the procedure, the 2-O-acetyl derivative (II) was treated with ammonium hydroxide in tetrahydrofuran as before, but the reaction mixture was extracted with tetrahydrofuran and the tetrahydrofuran layer washed with water (to remove residual ammonia) and subsequently N-acetylated. Yields were of the same order as before, and an equally pure product was obtained after recrystallization from ethyl acetate.

Isolation of By-products V and VI

The two other components (Rf ca. 0.9 and 0.26) mentioned in the preceding section, were isolated during the column chromatography there described. After evaporation of the corresponding eluate, the fast-moving component (Rf ca. 0.9) was obtained as a syrup that crystal-

lized from chloroform-n:pentane as rectangular, oblong white platelets (22 mg). The product melted at 154 - 155° and displayed $[\alpha]_D + 95.3^\circ$ (\underline{c} 0.7, chloroform). It was methyl 4,6-0-benzylidene-3-deoxy-3-nitro- α -D-glucopyranoside (V). An authentic sample (93) of V, crystallized from chloroform-n:pentane, melted at 154 - 155° and exhibited $[\alpha]_D + 95.5^\circ$ (\underline{c} 1, chloroform). The authentic sample and the isolated product had identical infrared spectra and gave an undepressed mixed melting point.

The component of Rf 0.26, also obtained as a syrup from the column, was crystallized from chloroform-n:pentane, and gave beautiful, hexagonal white platelets. This substance, which was presumably methyl 2-acetamido-4,6-0-benzylidene-3-deoxy-3-nitro- α -D-mannopyranoside (VI), (40 mg) sublimed gradually above 115° and melted at 123 - 125° with much foaming. It displayed $[\alpha]_D + 16.0^\circ$ (\underline{c} 0.8, chloroform) and gave an infrared spectrum distinctly different from that of the gluco isomer IV. It contained chloroform of crystallization.

Anal. Calcd for $C_{16}H_{20}N_2O_7$ (352.3): C, 54.54; H, 5.72; N, 7.95. Calcd for $C_{16}H_{20}N_2O_7 \cdot 1/3CHCl_3$: C, 50.00; H, 5.20; N, 7.15. Found: C, 50.60; H, 5.26; N, 6.59.

The chloroform of crystallization was readily seen in the mass spectrum of the compound, especially at low ionization potential (15 eV), when the peaks characteristic of the $CHCl_2^+$ fragments from chloroform appeared

as follows:

<u>m/e</u>	<u>relative intensity</u>	
83	9	} These two peaks were especially prominent
85	6	
87	1	

The chloroform was removed (as verified by a mass spectrum) by drying the sample at 100° and 1 mm for five days. The melting point of the compound now was 186 - 187° without prior sublimation. The compound now gave an analysis as follows: C, 54.73; H, 5.50; N, 8.13.

Infrared data (Fig.III): 3315 (m), 3260 (w) and 3200 cm⁻¹ (m), NH; 1650 cm⁻¹ (s), amide I; 1555 - 1535 cm⁻¹ (s), NO₂ and amide II; 755 and 704 cm⁻¹ (ms), phenyl. The following peaks were present in VI, but absent in IV: 3315, 3260 and 3200 cm⁻¹ (all medium), 1075 and 900 cm⁻¹ (m).

Methyl 4,6-O-Benzylidene-2-ethoxycarbonamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside (VII)

The amino derivative III (650 mg) was dissolved in ice-cooled pyridine (20 ml). Ethyl chloroformate (7 ml) was then added dropwise at 0°. A vigorous reaction occurred, with the evolution of white fumes. The reaction mixture turned pink, then purple after a few hours. It was left

at room temperature for sixteen hours, during which time it turned pale yellow. Addition of ice-water, with magnetic stirring, resulted in a copious precipitation of a white solid which was filtered, washed several times with cold water, and dried.

The crude, acylated product (647 mg, 81%) melted at 209 - 211°. Recrystallization from ethanol gave fine colorless needles (576 mg), mp 213 - 214°, $[\alpha]_D + 83.5^\circ$ (c 1.5, dimethylformamide).

Anal. Calcd for $C_{17}H_{22}N_2O_8$ (382.4): C, 53.40; H, 5.80; N, 7.33. Found: C, 53.21; H, 5.90; N, 7.31.

Characteristic infrared bands occurred at 3325 cm^{-1} (ms), NH; 1695 cm^{-1} (s), amide I; 1550 - 1540 cm^{-1} (s), nitroalkane and amide II; and 755 (m) and 703 cm^{-1} (m), monosubstituted benzene.

Methyl 2-Acetamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside (VIII)

The benzylidene derivative IV (273 mg) was suspended in 70% acetic acid (30 ml) and heated on a steam bath for forty-five minutes. Thin layer chromatography of the reaction mixture, using chloroform-ethyl acetate (2 : 3) as irrigating system, then indicated complete absence of the starting compound (Rf 0.36) and the formation of a non-migrating spot corresponding to the debenzylidenated product (VIII).

The yellowish reaction mixture was evaporated to a syrup that smelled strongly of acetic acid and benzaldehyde. The syrup was co-evaporated four times with water (to remove benzaldehyde), then four times with ethanol (to remove acetic acid). It was then dissolved in boiling ethyl acetate and treated with activated charcoal to give, after removal of the solvent, a colorless syrup. The latter was dissolved in the minimum amount of ethyl acetate, and petroleum ether was carefully added to incipient turbidity: beautiful white prisms of methyl 2-acetamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside (VIII) crystallized in a yield of 175 mg (86%). The product melted with decomposition at 162 - 163 $^{\circ}$ and exhibited $[\alpha]_D + 114.2^{\circ}$ (c 0.8, water).

Anal. Calcd for $C_9H_{16}N_2O_7$ (264.2): C, 40.91; H, 6.10; N, 10.60. Found: C, 41.04; H, 6.05; N, 10.46.

Prominent infrared bands occurred at 3500 - 3200 cm^{-1} (broad with peaks at 3420 and 3320 cm^{-1}), OH, NH; 1650 cm^{-1} (s), amide I; 1555 - 1530 cm^{-1} (s), nitroalkane and amide II.

Methyl 2-Acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-nitro-
 α -D-glucopyranoside (IX)

Methyl 2-acetamido-2,3-dideoxy-3-nitro-
 α -D-glucopyranoside (VIII) (740 mg) was suspended in acetic anhydride (11 ml). Boron trifluoride etherate (5 drops) was cautiously added, whereupon the glucoside started to dissolve in a moderately exothermic reaction. Dissolution was completed by warming the flask slightly. The mixture was kept at room temperature for one hour, and was then co-evaporated with excess ethanol (four times) until no smell of acetic anhydride was perceptible: a yellowish-brown, solid residue was thus obtained. The latter was treated with activated charcoal in boiling ethyl acetate, then recrystallized from ethyl acetate-petroleum ether. Beautiful, colorless needles of the acetylated product were obtained (779 mg, 80%). The crystals melted at 177 - 178° and displayed $[\alpha]_D + 101.4^\circ$ (c 1.03, chloroform).

Anal. Calcd for $C_{13}H_{20}N_2O_9$ (348.3): C, 44.83; H, 5.79; N, 8.05. Found: C, 44.68; H, 5.74; N, 8.20.

Characteristic infrared absorptions occurred at 3340 cm^{-1} (m), NH; 1735 cm^{-1} (s), ester carbonyl; 1650 cm^{-1} (s), amide I; 1552 cm^{-1} (s), nitroalkane; 1530 cm^{-1} (ms), amide II; 1260 cm^{-1} (ms), acetate C-O-C.

The NMR spectrum of compound IX is shown in Fig.IV.

Methyl 2-Acetamido-3-amino-2,3-dideoxy- α -D-glucopyranoside
Hydrochloride (X)

Platinum dioxide (350 mg) was prehydrogenated in 0.1 N hydrochloric acid (35 ml). The acetamidonitro derivative VIII (893 mg), dissolved in water (75 ml), was then added and hydrogenation allowed to proceed with efficient shaking at room temperature and atmospheric pressure. The hydrogen uptake was very rapid initially: the first mole-equivalent was absorbed within one hour, the second within three hours. After ten hours, the calculated amount of hydrogen (3 mole-equivalents) was almost completely absorbed. However, the reaction was allowed to proceed for twelve additional hours to ensure complete hydrogenation. Filtration of the catalyst and evaporation of the solvent resulted in a white, semi-solid residue which was crystallized from ethanol-ethyl acetate to give needles of methyl 2-acetamido-3-amino-2,3-dideoxy- α -D-glucopyranoside hydrochloride (880 mg, 96%).

The hydrochloride (X) gradually turned brown above 250° and melted with decomposition at 257 - 258°. It exhibited $[\alpha]_D + 101.2^\circ$ (c 1.1, methanol) and gave one spot on paper chromatography, $R_{GN} = 1.50$.

Anal. Calcd for $C_9H_{19}N_2O_5Cl$ (270.7): C, 39.93; H, 7.07; Cl, 13.10. Found: C, 40.03; H, 7.26; Cl 13.02.

Characteristic infrared absorptions occurred at 3420 (m) and 3230 cm^{-1} (m, broad), OH; 3320 cm^{-1} (ms), NH; 2800 - 2400 (m/w, broad band), 1585 (mw) and 1520 cm^{-1} (ms), NH_3^+ ; 1658 cm^{-1} (s), amide I; 1542 cm^{-1} (ms), amide II.

Methyl 2,3-Diacetamido-2,3-dideoxy- α -D-glucopyranoside (XI)

A solution of the hydrochloride X (310 mg) in water (15 ml) and methanol (1 ml) was cooled in an ice-water bath and stirred with Dowex 1 x 2 (CO_3^- form; 6 ml). Acetic anhydride (0.7 ml) was added, and stirring was maintained for two and a half hours. The anion-exchange resin was then filtered off and the filtrate was briefly stirred at 0° with Rexyn 101 (H^+) cation-exchanger. The filtered solution was evaporated to yield a white residue which was co-evaporated with ethanol (three times) in order to remove all traces of unreacted acetic anhydride. Recrystallization was performed by dissolving the material in a very small amount of ethanol and carefully adding a relatively large amount of ethyl acetate. The methyl 2,3-diacetamido-2,3-dideoxy- α -D-glucopyranoside (XI) crystallized as short microscopic needles (260 mg, 82%) that melted with decomposition at $245 - 246^\circ$ and exhibited $[\alpha]_D + 60.0^\circ$ (c 0.8, methanol).

Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{N}_2\text{O}_6$ (276.3): C, 47.82; H, 7.30; N, 10.14. Found: C, 47.64; H, 7.46; N, 10.02.

Infrared data: 3460 (m), 3425 (m) and 3120 cm^{-1} (m), OH; 3290 cm^{-1} (ms), NH; 1645 cm^{-1} (s), amide I; 1560 - 1545 cm^{-1} (ms), amide II. No bands attributable to NH_3^+ were present.

A sample was recrystallized from hot, absolute ethanol and an approximately equal amount of ethyl acetate. It then decomposed at 265 - 267° with partial sublimation near 260°. On reheating, the sublimate melted without decomposition at 266 - 267°.

A few milligrams of the benzylidene derivative XIV (141) was dissolved in 0.5 ml of 90% trifluoroacetic acid (142). After thirty minutes the solution was evaporated with several additions of water and then with ethanol, and the residue obtained was recrystallized from absolute ethanol-ethyl acetate. The colorless crystals gave an infrared spectrum superimposable with that of XI, and they exhibited the same behavior on melting, alone and in mixture with XI. The two samples were indistinguishable on thin layer chromatography (chloroform-methanol, 2 : 1).

Methyl 2,3-Diacetamido-4,6-di-O-acetyl-2,3-dideoxy-
 α -D-glucopyranoside (XII)

Methyl 2-acetamido-3-amino-2,3-dideoxy-
 α -D-glucopyranoside hydrochloride (79 mg) was refluxed
for thirty minutes in acetic anhydride (5 ml), in the
presence of anhydrous sodium acetate (400 mg). After
cooling, the mixture was poured into ice-water. Magnetic
stirring for fifteen minutes failed to produce any solid
material. The mixture was therefore extracted with
chloroform. The chloroform extract, which was dried
over anhydrous sodium sulfate, furnished on evaporation
a semi-solid residue that was co-evaporated four times
with ethanol in order to remove residual acetic acid. A
dry solid (95 mg, 90%) melting with decomposition at 275 -
276° and showing $[\alpha]_D + 73.5^\circ$ (c 0.9, chloroform) was
finally obtained.

Recrystallization of the crude product was
tried from a number of solvent combinations but proved
exceedingly difficult, chiefly because of gel-formation.
In one instance, attempted recrystallization from
chloroform-n:pentane gave a white fluffy product consisting
of microscopic needles embedded in a gel. However, the
procedure could not be repeated. The crude product never-
theless gave correct analytical data.

Anal. Calcd for $C_{15}H_{24}N_2O_8$ (360.36): C, 49.99; H, 6.71; N, 7.77. Found: C, 50.05; H, 6.57; N, 7.63.

Characteristic infrared absorptions occurred at 3315 cm^{-1} (m), NH; 1743 cm^{-1} (s), ester carbonyl; 1650 cm^{-1} (s), amide I; 1548 cm^{-1} (ms); amide II; 1230 cm^{-1} (ms), acetate C-O-C. Hydroxyl and NH_3^+ bands were absent.

The NMR spectrum of compound XII is shown in Fig.V.

2,3-Diamino-2,3-dideoxy- α -D-glucose Dihydrochloride (XIII)

1. Preliminary Experiments:

(a) Methyl 2,3-diacetamido-2,3-dideoxy- α -D-glucopyranoside (129 mg) was gently refluxed in 1 N hydrochloric acid (20 ml) for sixteen hours. On paper chromatography, the reaction mixture gave two ninhydrin-positive spots of almost equal intensity, R_{GN} 0.83 and 1.30. The more slowly migrating spot had the same R_{GN} value as an authentic sample of 2,3-diamino-2,3-dideoxy- α -D-glucose dihydrochloride (kindly provided by Dr. W. Meyer zu Reckendorf). A few drops of the reaction mixture were neutralized with sodium bicarbonate and found to reduce Fehling solution.

The reaction mixture was further refluxed for another twenty-nine hours. Paper chromatography thereafter indicated little change in the relative

proportions of the two products formed.

(b) Methyl 2,3-diacetamido-2,3-dideoxy- α -D-glucopyranoside (10 mg) was refluxed in a mixture of concentrated hydrochloric acid (1 ml) and water (2 ml) for a total of nine hours. Samples of the solution were withdrawn and investigated by paper chromatography after four, six and nine hours. In all cases two ninhydrin-positive spots (R_{GN} 0.83 and 1.30) were obtained as in (a). Their relative intensities, which were almost equal, changed little after four hours.

(c) Methyl 2-acetamido-3-amino-2,3-dideoxy- α -D-glucopyranoside hydrochloride (20 ml) was refluxed in a mixture of water (5 ml) and concentrated hydrochloric acid (5 ml) for fifteen hours. Paper chromatography again revealed formation of the two products with R_{GN} 0.83 and 1.30, respectively, but this time the slow-moving spot predominated.

2. Acid Hydrolysis of Methyl 2-Acetamido-3-amino-2,3-dideoxy- α -D-glucopyranoside Hydrochloride:

The hydrochloride X (222mg) was refluxed for eighteen hours in a mixture of concentrated hydrochloric acid (15 ml) and water (15 ml). The resulting, brown solution was evaporated to a syrup which was co-evaporated with nine consecutive portions of water (until the smell

of hydrochloric acid was no longer noticeable). The dark syrup was dissolved in water and treated with decolorizing carbon, "Norit A-Neutral", which had been pretreated with boiling, half-concentrated hydrochloric acid and washed neutral.

The colorless filtrate was then evaporated to a syrup that was transferred, with a few milliliters of water, into a Petri dish. Glacial acetic was added dropwise to incipient, but not permanent, turbidity. The solution was then fanned with a stream of hot air and ^{it} slowly deposited beautiful, rhombohedral crystals of 2,3-diamino-2,3-dideoxy-*d*-D-glucose dihydrochloride (XIII). The crystals (25 mg) were filtered off, washed with ice-cold water containing acetic acid, and dried in a vacuum desiccator over potassium hydroxide. Addition of more glacial acetic acid to the filtrate, and continued fanning, furnished another 37 mg of crystalline XIII, bringing the total yield to 62 mg (30%).

The compound had no definite melting point but decomposed gradually between 180° and 188°. Reported (120), dec. 180 - 185°. It exhibited mutarotation in water as follows: $[\alpha]_D + 62^\circ$ (initial, extrapolated) $\longrightarrow + 55.0^\circ$ (13 minutes) $\longrightarrow + 49.7^\circ$ (2 hours, final; c 1.1, water). Reported (120): $[\alpha]_D + 66^\circ$ (initial, extrapolated) $\longrightarrow + 62.1^\circ$ (12 minutes) $\longrightarrow 46.8^\circ$ (2 hours, final; c 0.98). Identity of the compound with an authentic sample was also

supported by paper chromatography (R_{GN} 0.83) and by their infrared spectra, which exhibited characteristic bands at: 3300 cm^{-1} (ms, broad), bonded OH; 3000 - 2200 cm^{-1} (broad band), 1585 cm^{-1} (ms) and 1515 cm^{-1} (ms), NH_3^+ (Amide bands were absent).

B. SYNTHESIS OF DERIVATIVES OF 2,3,4-TRIAMINO-
2,3,4-TRIDEOXY-D-GLUCOSE

Methyl 2,4-Diacetamido-2,3,4-trideoxy-3-nitro-
 α -D-glucopyranoside (XV)

Methyl 2-acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-nitro- α -D-glucopyranoside (IX) (2 g) was dissolved in tetrahydrofuran (65 ml), and 15 N aqueous ammonia (39 ml) was added. The mixture was stirred magnetically at room temperature while the progress of the reaction was monitored by thin layer chromatography using chloroform-ethyl acetate (1 : 1). After 25 minutes, the mobile spot corresponding to starting material had vanished and only a non-migrating spot corresponding to reaction products was visible.

The reaction mixture was evaporated to give a yellow, semi-solid residue. The latter was triturated with 99% ethanol, whereby a white, crystalline substance (805 mg) was formed. This was filtered, ^{off} and dried in a high vacuum. The mother liquor was evaporated to a yellow syrup which was dissolved, with gentle warming, in the minimum amount of 99% ethanol. Storage of the solution for two days at 5° yielded a second crop of white crystals (200 mg), thus bringing the total yield of crude methyl 2,4-diacetamido-3-nitro-2,3,4-trideoxy- α -D-glucopyranoside (XV) to 1005 mg (57%). The crude product was chromatographically uniform

(thin layer chromatography with chloroform-methanol (1 : 1) gave a single spot), and was suitable for use in subsequent reactions. It melted at 285 - 286° (dec).

The product was difficult to recrystallize; although soluble in some common solvents (methanol, ethanol) and insoluble in others (chloroform, ethyl acetate, petroleum ether), it tended to precipitate in amorphous form from combinations of these solvents. For analytical purposes, a sample of the crude product (87 mg) was dissolved with gentle warming in a small volume of absolute ethanol, and the filtered solution was allowed to cool very slowly (protected from air-drafts). After three hours at room temperature and twelve hours at 5°, there crystallized microscopic needles (22 mg), melting at 289 - 290° (dec) and showing $[\alpha]_D + 102.1^\circ$ (c 0.79, methanol).

Anal. Calcd for $C_{11}H_{19}N_3O_7$ (305.29): C, 43.27; H, 6.27; N, 13.76. Found: C, 43.44; H, 6.17; N, 13.92.

The infrared spectrum showed broad absorption in the OH and NH stretching region, with peaks at 3410, 3345 and 3315 cm^{-1} . Other characteristic bands occurred at 1660 cm^{-1} (s), amide I; 1552 cm^{-1} (s), nitroalkane; 1550 - 1530 cm^{-1} (ms), amide II. There was no ester carbonyl absorption near 1740 cm^{-1} .

The NMR spectrum of compound XV is shown in Fig.VI.

On thin layer chromatography (chloroform-methanol, 1 : 1), the yellow mother liquor from the crude diacetamido

compound XV gave a spot corresponding to XV and two additional spots, the stronger one migrating more slowly than XV and a minor one remaining at the start. The mother liquor displayed no high-intensity ultraviolet absorption although there was a very weak peak at 253 m which was greatly intensified on addition of sodium hydroxide.

Methyl 2,4-Diacetamido-6-O-acetyl-2,3,4-trideoxy-3-nitro- α -D-glucopyranoside (XVI)

Methyl 2,4-diacetamido-2,3,4-trideoxy-3-nitro- α -D-glucopyranoside (XV) (600 mg) was suspended in acetic anhydride (9 ml). Addition of boron trifluoride etherate (5 drops) caused complete dissolution of the glucoside, in an exothermic reaction. The flask was cooled, and left standing at room temperature for one hour. Co-evaporation of the mixture with ethanol (four times) yielded an almost colorless syrup. The latter was dissolved in absolute ethanol, with gentle warming; petroleum ether was then added dropwise to incipient turbidity, and the 6-O-acetyl derivative (XVI) was soon deposited as colorless crystals (545 mg; 80%) melting at 248 - 249° (dec) and displaying $[\alpha]_D + 90.6^\circ$ (c 0.62, methanol).

Anal. Calcd for $C_{13}H_{21}N_3O_8$ (347.32): C, 44.95; H, 6.09; N, 12.10. Found: C, 44.90; H, 6.07; N, 11.93.

Infrared data: 3345 cm^{-1} (ms) and 3310 cm^{-1} (ms),
NH; 1735 cm^{-1} (s), ester carbonyl; 1670 - 1650 cm^{-1} (s),
amide I; 1555 cm^{-1} (s), nitroalkane; 1530 (ms, broad),
amide II; 1267 cm^{-1} (ms, broad), acetate C-O-C.

Methyl 2,4-Diacetamido-3-amino-2,3,4-trideoxy-
 α -D-glucopyranoside Hydrochloride (XVII)

A solution of the nitroglucoside XV (470 mg) in water (40 ml) was acidified with 1 N hydrochloric acid (2.6 ml) and hydrogenated at room temperature and ordinary pressure over freshly pre-hydrogenated platinum oxide (300 mg). Hydrogenation proceeded at a moderate but steady rate. The uptake of 3 mole-equivalents of hydrogen was completed after forty-eight hours when thin layer chromatography showed the disappearance of the nitroglucoside and its replacement by a more slowly moving compound.

Removal of the catalyst and evaporation of the filtrate yielded a colorless glass which was co-evaporated several times with water in order to remove residual hydrochloric acid. The residue was dissolved in boiling absolute ethanol, and ethyl acetate was cautiously added drop by drop. Soon, there precipitated a copious crop of beautiful, white needles (450 mg, 94%) of the amino sugar hydrochloride, which melted at 234 - 235° (dec) and displayed $[\alpha]_D + 101.5^\circ$ (c 1.11, water). It gave one ninhydrin-positive spot,

R_{GN} 1.35, on paper chromatography.

Anal. Calcd for C₁₁H₂₂N₃O₅Cl (311.77): C, 42.36; H, 7.11; Cl, 11.37. Found: C, 42.57; H, 6.97; Cl, 11.60.

In the infrared, the product exhibited characteristic absorption bands at 3500 - 3200 cm⁻¹ with peak at 3280 cm⁻¹ (OH, NH); 3080, 2700 - 2500, 1588 and 1510 cm⁻¹ (all weak; NH₃⁺Cl⁻); 1658 cm⁻¹ (s), amide I; 1550 cm⁻¹ (ms), amide II. In addition, a weak band at 1740 cm⁻¹ presumably due to a trace of ethyl acetate was present.

The small peak at 1740 cm⁻¹ could not be removed by drying the hydrochloride in vacuo (1 mm) at 100° for seventy-two hours. However, when the compound was dissolved in water and then recovered by evaporation, its infrared spectrum was identical with that of the crystals obtained from ethanol-ethyl acetate, except that the small 1740 cm⁻¹ peak was no longer present. The peak was therefore probably due to ethyl acetate of crystallization.

Methyl 2,3,4-Triacetamido-2,3,4-trideoxy- α -D-glucopyranoside
(XVIII)

The hydrochloride XVII (223 mg) was dissolved in water (10 ml) and methanol (2 ml), and N-acetylated in the presence of Dowex 1 x 2(CO₃⁼) anion exchange resin (4 ml) and acetic anhydride (5 ml). The reaction mixture was stirred at 0° for three hours, the resin was filtered off,

and the filtrate was briefly treated at 0° with a small amount of cation exchange resin, Rexyn 101(H⁺). Evaporation then furnished a white solid residue that was hard to recrystallize as it tended to give gels from the common solvents. Gel formation was avoided by recrystallization from absolute ethanol-ethyl acetate, with scratching of the flask and gentle but continuous warming over the steam-bath; white, microscopic needles of the triacetamido glucoside XVIII were formed (114 mg, 50%).

The compound had no defined melting point; it slowly darkened above 310° and decomposed between 350 - 365°. It exhibited $[\alpha]_D + 135.2^\circ$ (c 0.65, water).

Anal. Calcd for C₁₃H₂₃N₃O₆ (317.34): C, 49.20; H, 7.31; N, 13.24. Found: C, 49.08; H, 7.17; N, 13.13.

Typical infrared absorptions occurred at 3470 cm⁻¹ (w) and 3225 cm⁻¹ (w), OH; 3330 cm⁻¹ (ms) and 3300 cm⁻¹ (s), NH; 1643 (s) and 1620 cm⁻¹ (ms), amide I; 1568 (ms) and 1550 cm⁻¹ (s), amide II.

Methyl 2,3,4-Triacetamido-6-O-acetyl-2,3,4-trideoxy-
α-D-glucofuranoside (XIX)

The hydrochloride (XVII (300mg) was suspended in pyridine (10 ml) and acetic anhydride (5 ml), whereupon the mixture spontaneously turned into a thin gel. The reaction flask was covered with aluminum foil and the gel

was magnetically stirred at room temperature for thirteen hours. The mixture was then co-evaporated twice with methanol and five times with toluene. The resulting, yellowish-white solid residue was dissolved in methanol and treated with Dowex 1 x 2(CO₃⁼) at 0°, whereupon a strong smell of pyridine could be discerned. Evaporation of the methanol and four subsequent co-evaporations with toluene removed all traces of pyridine and left behind the fully acetylated glucoside (208 mg, 60%) as a yellowish residue. The latter melted with decomposition at 335 - 340°, partially subliming above 275°.

Recrystallization was very difficult, as the product easily formed gels. It was almost insoluble in ethyl acetate and chloroform, soluble in hot ethanol, and it formed gels with ethanol-ethyl acetate or ethanol-petroleum ether mixtures. The crude material was best purified by a charcoal treatment in boiling absolute ethanol followed by very slow, draft-free cooling to room temperature and, after nine hours, storage at 5° overnight. The fully acetylated triacetamido glucoside thus crystallized as glittering, white needles (136 mg) melting at 339 - 340° (dec, with partial sublimation above 290°), and displaying $[\alpha]_D + 109.2^\circ$ (c 0.64, methanol).

Anal. Calcd for C₁₅H₂₅N₃O₇ (359.37): C, 50.13; H, 7.01; N, 11.69. Found: C, 49.90; H, 6.87; N, 11.68.

Characteristic infrared bands occurred at 3340 (ms), 3300 (ms) and 3230 cm^{-1} (shoulder), NH; 1735 cm^{-1} (ms), ester carbonyl; 1640 cm^{-1} (s), amide I; 1533 cm^{-1} , amide II; 1248 cm^{-1} (m), acetate C-O-C. Absence of OH and NH_3^+ bands was noted.

The NMR spectrum of compound XIX is shown in Fig.VII.

Part II

A. SYNTHESIS OF CARBOHYDRATE DERIVATIVES OF ANTHRANILIC ACID

Methyl 4,6-O-Benzylidene-2-(2-carboxyphenyl)amino-2,3-dideoxy-3-nitro- α -D-glucopyranoside (II)

1. Preliminary Experiments:

- (a) Addition reaction in the presence of base and a two-molar excess of anthranilic acid:

Methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-hex-2-enopyranoside (147 mg, 0.5 mmole) and anthranilic acid (138 mg, 1mmole) were refluxed in dry benzene (15 ml) with a chip (ca. 100 mg) of potassium hydroxide. The reaction was monitored by thin layer chromatography using chloroform-ethyl acetate (1 : 1) as irrigating system. As anthranilic acid gave considerable "tailing" on the plate, the progress of the reaction was assessed by the gradual disappearance of the fast-moving spot (Rf 0.85) corresponding to nitroolefin, and the concomitant appearance of a non-migrating spot. The reaction was complete within two to three hours. The reaction mixture was then evaporated after removal of the potassium hydroxide chip, and the product was recrystallized from absolute ethanol to give needles that melted at 258 - 259^o (dec) and showed a single spot (Rf 0.7) on thin layer plates irrigated with chloroform-methanol (1 : 1).

(b) Addition reaction in the presence of base and one molar equivalent anthranilic acid:

Experiment (a) was repeated except that only 69 mg (0.5 mmole) of anthranilic acid was used. The reaction was complete in three hours. Recrystallization of the jelly-like, crude product from methanol-water gave, with much difficulty and in much smaller yields (ca. 10 - 15%), needles that melted at 256 - 257° and had the same chromatographic mobility as the product obtained in (a).

(c) Addition reaction with one molar equivalent of anthranilic acid in the absence of base:

Experiment (b) was repeated, except that no potassium hydroxide was added. The reaction was followed chromatographically as before: the intensity of the fast-moving spot corresponding to the nitroolefin appeared to remain constant even after six days of refluxing. Thus, probably no addition occurred under those conditions. The solvent used in this experiment was "Reagent Grade" benzene, dried over sodium wire. However, in another experiment, when ordinary benzene (dried similarly, but presumably of lesser purity) was used, addition occurred within twenty-four to thirty hours of refluxing. The resulting product melted at 259 - 260° and had an infrared spectrum identical with that obtained in (a) and (b).

2. Synthesis:

(a) Catalysis by potassium hydroxide (Yield: 65%):

Methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-hex-2-enopyranoside (733 mg, 2.5 mmole) and anthranilic acid (685 mg, 5 mmole) were refluxed in dry benzene (125 ml) together with a chip (ca. 100 mg) of potassium hydroxide. The reaction was complete within two to three hours as indicated by thin layer chromatography (cf. 1).

The potassium hydroxide chip was removed and the yellow reaction solution was treated with decolorizing carbon. Removal of the solvent by evaporation yielded a yellowish-white residue which was recrystallized from ethanol to give very pale yellow (almost white) needles of methyl 4,6-O-benzylidene-2-(2-carboxyphenyl)amino-2,3-dideoxy-3-nitro- α -D-glucopyranoside (706 mg, 65%). This product melted at 254 - 255° (dec). Recrystallization from ethyl acetate-petroleum ether gave a colorless product and raised the melting point to 260 - 261° (dec, with slight darkening above 255°). $[\alpha]_D + 56.9^\circ$ (c 0.9, dimethylformamide).

(b) Catalysis by triethylamine (Yield: 75%):

The nitroolefin I (733 mg, 2.5 mmole) and anthranilic acid (685 mg, 5 mmole) were refluxed in dry benzene (125 ml) together with triethylamine (2 ml).

The reaction was complete after three and a half hours.

The reaction mixture was co-evaporated twice with toluene (to remove triethylamine), then twice with petroleum ether (b.p. 80 - 100°) and, finally, twice with ethanol. The ensuing, yellowish-white residue was recrystallized from ethanol to give pale yellow needles (715 mg). Concentration of the filtrate and recrystallization from ethanol yielded another batch of needles (80 mg), bringing the total yield to 795 mg (75%). The compound darkened slightly above 230° and melted with decomposition at 252 - 254°.

A recrystallization from boiling ethyl acetate-petroleum ether, which included a treatment with decolorizing carbon, yielded a crop (603 mg) of faintly yellowish (almost white) needles that melted at 261 - 262° with slight darkening above 260°. The recrystallized product exhibited $[\alpha]_D + 57.1^\circ$ (c 0.75, dimethylformamide).

Anal. Calcd for $C_{21}H_{22}N_2O_8$ (430.4): C, 58.60; H, 5.15; N, 6.51. Found: C, 58.74; H, 5.16; N, 6.43.

The infrared spectrum of the present product was identical with that of the product obtained by potassium hydroxide catalysis. Characteristic bands occurred at 3360 cm^{-1} (mw), NH; 3240 cm^{-1} (w, broad), bonded OH; 2700 - 2500 cm^{-1} (w), carboxyl; 1668 cm^{-1} (s), carbonyl of aromatic acid; 1578 cm^{-1} (m), aromatic; 1550 cm^{-1} (s),

nitroalkane; 1520 cm^{-1} (m), aromatic; 773 cm^{-1} (m), 1,2-disubstituted aromatic ring of anthranilic acid residue; 755 (m) and 704 cm^{-1} (m), monosubstituted phenyl of benzylidene group.

Methyl 2-(2-carboxyphenyl)amino-2,3-dideoxy-3-nitro- α -D-glucopyranoside (IV)

Compound II (386 mg) was suspended in 70% acetic acid (40 ml) and heated on a steam-bath. The progress of the debenzylidenation was followed thus: a few drops of the reaction mixture were co-evaporated twice with water, then three times with ethanol, and the resulting syrup was examined by thin layer chromatography using chloroform-methanol (1 : 1). The reaction was characterized by a gradual disappearance of the fast-moving spot (R_f 0.7) corresponding to starting material and a concomitant appearance of a slow (almost non-moving) spot corresponding to the debenzylidenated product. The reaction was complete in forty minutes.

The yellowish reaction mixture was co-evaporated three times with water (to remove benzaldehyde), then four times with ethanol (to remove acetic acid). There was produced a yellowish-white solid (273 mg, 89%). This batch of crude, debenzylidenated product melted at $189 - 190^\circ$, with prior darkening above 170° . Charcoal treatment, followed by recrystallization from ethyl acetate-petroleum

ether furnished a crop (203 mg, 67%) of pure IV as small, stout prisms that melted at 204 - 205°, with slight darkening above 200°, and that displayed $[\alpha]_D + 80.8^\circ$ (c 1, methanol).

Anal. Calcd for $C_{14}H_{18}N_2O_8$ (342.3): C, 49.12; H, 5.30; N, 8.18. Found: C, 49.21; H, 5.46; N, 8.06.

The debenzylidenated product absorbed characteristically in the infrared at 3450 - 3150 cm^{-1} (ms, broad, with maxima at 3350 and 3270 cm^{-1}), NH, bonded OH; 2700 - 2500 cm^{-1} (broad, weak, CO_2H); 1655 cm^{-1} (s), carbonyl of aromatic acid; 1580 and 1500 cm^{-1} (m), aromatic; 1555 cm^{-1} (s), nitroalkane; 770 cm^{-1} (m), 1,2-disubstituted phenyl ring of anthranilic acid residue. Bands at 755 and 704 cm^{-1} corresponding to the benzylidene group in the starting material were absent.

Methyl 4,6-Di-O-acetyl-2-[N-(2-carboxyphenyl)]acetamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside (V)

Compound IV (108 mg) was suspended in acetic anhydride (3 ml). Boron trifluoride etherate (3 drops) was added, whereupon the compound dissolved and heat was evolved. The mixture was kept at room temperature for one hour and then poured over ice-water. Magnetic stirring for fifteen minutes failed to produce any precipitate, even after the addition of a few milliliters of methanol to promote the

decomposition of excess acetic anhydride.

The reaction mixture was therefore extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate, filtered, and evaporated. Three co-evaporations of the residue with ethanol finally afforded a white, crystalline product which on recrystallization from ethyl acetate-petroleum ether gave platelets (91 mg, 62%) melting at 199 - 200° (dec) and exhibiting $[\alpha]_D + 188.9^\circ$ (c 0.9, chloroform).

Anal. Calcd for $C_{20}H_{24}N_2O_{11}$ (468.4): C, 51.29; H, 5.16; N, 5.98. Found: C, 51.51; H, 5.31; N, 5.82.

Typical infrared bands occurred at 2600 - 2500 cm^{-1} (w), CO_2H ; 1766 (s), 1743 cm^{-1} (s), ester carbonyl; 1700 cm^{-1} (s), acid carbonyl of anthranilic acid residue; 1625 cm^{-1} (s), amide I; 1595 cm^{-1} (m), aromatic; 1562 cm^{-1} (s), nitroalkane; 1245 cm^{-1} (s), acetate C-O-C; 755 cm^{-1} (m), 1,2-disubstituted phenyl ring of anthranilic acid moiety; absence of strong absorptions in the 3700 - 3200 cm^{-1} region.

For NMR data, see the Discussion (page 88) and Fig.VIII.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-[2-(methoxycarbonyl)phenyl]amino-3-nitro- α -D-glucopyranoside (III)

To a cooled (0°) solution of II (523 mg) in tetrahydrofuran (20 ml) was added, dropwise and with stirring, a cold solution of diazomethane in ether until a slight yellow tinge persisted. The reaction solution was then slowly brought to room temperature and evaporated (bath temperature not exceeding 40°), whereby a white residue was obtained. Recrystallization from ethyl acetate-petroleum ether gave white, microscopic needles (466 mg). Concentration of the mother liquor and subsequent cooling (at 5°) deposited a further crop of white needles (60 mg), bringing the total yield of III to 526 mg (98%).

The ester had no definite melting point but sublimed gradually between 215° and 223° without decomposition. It displayed $[\alpha]_D + 19.3^\circ$ (c 1, chloroform).

Anal. Calcd for $C_{22}H_{24}N_2O_8$ (444.4): C, 59.45; H, 5.44; N, 6.30. Found: C, 59.66; H, 5.48; N, 6.26.

The infrared spectrum showed typical bands at 3330 cm^{-1} (mw), NH; 1690 cm^{-1} (s), carbonyl of $COOCH_3$; 1607 cm^{-1} (m), aromatic; 1585 cm^{-1} (m) and 1525 cm^{-1} (m), aromatic band, reinforced by NH "bend" absorption; 1553 cm^{-1} (s), nitroalkane; 1270 (ms) and 1253 cm^{-1} (s), acetate C-O-C; 756 cm^{-1} and 704 cm^{-1} (m), monosubstituted phenyl of benzylidene group; 766 cm^{-1} (m), 1,2-disubstituted

phenyl of anthranilic acid ester residue. There was no hydroxyl absorption.

Methyl 2,3-Dideoxy-2-[2-(methoxycarbonyl)phenyl]amino-3-nitro-d-D-glucopyranoside (VI)

The ester III (137 mg) was suspended in 70% acetic acid (20 ml) and heated on a steam-bath. The progress of the reaction, monitored by thin layer chromatography (chloroform-methanol, 3 : 1), was assessed by a gradual conversion of the fast-moving spot corresponding to the starting material to a slow-migrating spot corresponding to the product. The debenzylidenation was complete in forty minutes.

The reaction mixture was co-evaporated twice with water, then twice with ethanol. This treatment resulted in a white residue virtually free from benzaldehyde and acetic acid. Recrystallized from ethyl acetate-petroleum ether, the fine white needles (90 mg, 82%) showed $[\alpha]_D + 68.3^\circ$ (c 0.8, methanol).

The debenzylidenated ester had no definite melting point, but decomposed slowly between 165 and 200°.

Anal. Calcd for $C_{15}H_{20}N_2O_8$ (356.33): C, 50.56; H, 5.66; N, 7.86. Found: C, 50.45; H, 5.79; N, 7.86.

The product absorbed characteristically in the infrared at 3425 (m) and 3200 cm^{-1} (mw), OH; 3345 cm^{-1} (ms),

NH; 1680 cm^{-1} (s), carbonyl of COOCH_3 ; 1600 cm^{-1} (mw), aromatic; 1590 cm^{-1} (s), aromatic band reinforced by NH "bend"; 1528 (m), aromatic; 1554 cm^{-1} (s), nitroalkane; 1255 (s) and 1243 cm^{-1} (s), acetate C-O-C; 760 cm^{-1} (ms), 1,2-disubstituted phenyl of the anthranilic ester moiety.

Methyl 4,6-Di-O-acetyl-2,3-dideoxy-2-[N-(2-methoxycarbonyl)phenyl]acetamido-3-nitro- α -D-glucopyranoside (VII)

The debenzylidenated ester VI (80 mg) was suspended in acetic anhydride (2 ml). Boron trifluoride etherate (3 drops) was added, whereupon the nitro sugar dissolved with evolution of heat. After being kept at room temperature for one hour, the reaction mixture was poured over crushed ice and water. Magnetic stirring for fifteen minutes failed to produce any precipitate.

The mixture was therefore extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to a turbid syrup. Two co-evaporations with ethanol failed to produce any solid residue. The syrup was therefore dissolved in chloroform, treated with charcoal, and recovered by evaporation. The colorless product (VI) then crystallized from a small amount of ethyl acetate, by careful addition of petroleum ether (to incipient, but not permanent, turbidity) and overnight storage of the solution at 2 - 5°. The beautiful, white

platelets (67 mg) melted at 71 - 74° and exhibited $[\alpha]_D + 167.5^\circ$ (c 0.2, chloroform).

Anal. Calcd for $C_{21}H_{26}N_2O_{11}$ (482.43): C, 52.28; H, 5.43; N, 5.81. Calcd for $C_{21}H_{26}N_2O_{11} \cdot 3/4CHCl_3$ (572.1): C, 45.67; H, 4.71; N, 4.90. Found: C, 45.67; H, 4.81; N, 4.71. The analytical data are satisfactory if the presence of 3/4 mole of chloroform of crystallization is assumed. The presence of chloroform was demonstrated by the occurrence, in the mass spectrum (70 eV and 15 eV), of $CHCl_2^+$ fragments at m/e 83, 85 and 87 in the intensity ratio 9 : 6 : 1.

The infrared spectrum of the compound indicated not only that O-acetylation had taken place as expected, but also that acetylation of the secondary amino group at C-2 had occurred. Typical infrared bands were at 1750 cm^{-1} (s) and 1722 cm^{-1} (s), ester carbonyl; 1668 cm^{-1} (s), amide I; 1600 cm^{-1} (mw), aromatic band; 1562 cm^{-1} (ms), nitroalkane; ca. 1250 cm^{-1} (s), broad, acetate C-O-C; 762 cm^{-1} (ms), 1,2-disubstituted phenyl of anthranilic acid residue; no absorptions in the 3700 - 3200 cm^{-1} region.

NMR data ($CDCl_3$): 1.9 - 2.8 τ (complex multiplets, 4 aromatic H); 3.98 τ (quartet, H-2, $J_{2,1} = 3.3$ Hz and $J_{2,3} = 11.5$ Hz); 4.44 τ (triplet, H-4, $J_{4,3} = J_{4,5} = 10$ Hz); 5.12 τ (doublet, H-1, $J_{1,2} = 3.3$ Hz); 5.17 τ (quartet, H-3, $J_{3,2} = 11.5$ and $J_{3,4} = 10$ Hz); 5.88 τ (multiplet, 2H, C-6 methylene); 6.14 τ (singlet, 3H, CO_2CH_3); 6.25 τ (multiplet,

H-5); 7.06 τ (singlet, 3H, OCH₃); 7.93 and 8.00 τ (singlets, 6H, two O-acetyl); 8.31 τ (singlet, 3H, N-acetyl).

The above acetylation was repeated using a modified work-up procedure. Instead of being poured over ice-water, the reaction mixture co-evaporated with ethanol four times to destroy excess acetic anhydride. The resulting syrup, however, failed to crystallize from ethyl acetate-petroleum ether or from ethanol-water, even after charcoal treatment. It would thus appear that the presence of chloroform is essential for the product to crystallize.

Catalytic Hydrogenation of IV

1. Reduction:

A suspension of Pd/BaSO₄.xH₂O catalyst (800 mg) in water (10 ml) was pre-hydrogenated. The nitro sugar IV (838 mg), dissolved in a mixture of ethanol (25 ml) and water (10 ml), was then added together with 1 N hydrochloric acid (6 ml). Hydrogenation was then allowed to proceed at room temperature and atmospheric pressure. The uptake of the first 3 mole-equivalents of hydrogen was very rapid; the next 2 moles was taken up very slowly: uptake ceased after three days.

The reaction mixture was filtered through Celite and evaporated to give a jelly-like residue which failed to crystallize from common solvents, even after charcoal

treatment. Paper chromatography of the reaction mixture indicated two ninhydrin-positive spots, R_{GN} 1.13 and 1.99, the faster one being very weak.

2. Separation over anion-exchange resin:

A solution in water (30 ml) of the jelly-like residue obtained in 1, above, was allowed to flow slowly through a column containing 30 ml of Dowex 1 x 2 (OH^-). The column was eluted with water (250 ml), and the eluate was co-evaporated, first with 1 N hydrochloric acid and then several times with water, to yield a foam which failed to crystallize. On paper chromatography, however, it showed only a single ninhydrin-positive spot, R_{GN} 1.13, corresponding to the major hydrogenation product.

3. N-Acetylation. Methyl 2,3-diacetamido-2,3-dideoxy- α -D-glucopyranoside (X):

The foam obtained in 1, above, was N-acetylated at 0° , with magnetic stirring, in a mixture of water (20 ml) and methanol (3 ml) and in the presence of Dowex 1 x 2 (CO_3^-) (7 ml) and acetic anhydride (2 ml). After two hours the resin was filtered off, and the filtrate was briefly treated with Rexyn 101 (H^+), and then evaporated to a syrupy foam. This was dissolved in the minimum amount of 95% ethanol (added dropwise), then a relatively large volume of ethyl acetate was added cautiously, with continual scratching of the flask. Methyl 2,3-diacetamido-2,3-dideoxy- α -D-

glucopyranoside (X) crystallized as white, microscopic needles (125 mg). The yield was 20% (based on IV).

The 2,3-diacetamido derivative melted at 245 - 246° with decomposition and showed $[\alpha]_D + 60.4^\circ$ (c 1, methanol). It was identical with the 2,3-diacetamido glucoside described earlier (page 146), which had the same melting point and exhibited $[\alpha]_D + 60.0^\circ$ (c 0.8, methanol). The compounds had also identical infrared spectra. Furthermore, a mixed melting of the two samples (both crystallized from 95% ethanol-ethyl acetate) was undepressed.

4. Methyl 2,3-diamino-2,3-dideoxy-d-D-glucopyranoside (IX):

Compound IV (900 mg) was hydrogenated over Pd/BaSO₄.xH₂O catalyst (1 g) which had been prehydrogenated in the presence of 1 N hydrochloric acid (7 ml), as described in 1. The reaction required five days for completion. The reaction mixture was worked up and separated over Dowex 1 x 2 (OH⁻) (40 ml) as described in 1 and 2, above, respectively. However, this time the column eluate was not co-evaporated with hydrochloric acid but evaporated alone. The resulting, syrupy residue was co-evaporated with ethanol twice, which gave a white solid. Crystallization from ethanol-ethyl acetate produced colorless hexagonal platelets (227 mg, 45%).

The compound, which gave one ninhydrin-positive spot on a paper chromatogram (R_{GN} 1.15) and a negative

halogen test with acidified silver nitrate, was methyl 2,3-diamino-2,3-dideoxy- α -D-glucopyranoside (IX). It melted at 170 - 171 $^{\circ}$ with prior darkening above 160 $^{\circ}$, and displayed $[\alpha]_D + 147.2^{\circ}$ (c 0.7, water).

Anal. Calcd for $C_7H_{16}N_2O_4$ (192.21): C, 43.74; H, 8.39; N, 14.58. Found: C, 43.82; H, 8.59; N, 14.46.

Infrared bands were at 3375 (ms) and 3305 cm^{-1} (ms), NH_2 ; 3340 - 3060 cm^{-1} (broad), OH; 1590 cm^{-1} (ms), NH.

B. BISGLYCOSIDYLAMINES

Bis(methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranosid-2-yl)amine (XIII)

Methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside (155 mg) and methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-hex-2-enopyranoside (147 mg) were refluxed together in anhydrous benzene (40 ml) with a chip (ca. 100 mg) of potassium hydroxide and a few pieces of Drierite. Thin layer chromatography with chloroform-ethyl acetate (1 : 1) indicated the formation, after about two hours, of a new spot corresponding to the adduct, which migrated faster than either reactant. The reaction was complete in three to three and a half days.

The yellow reaction solution was then treated with decolorizing carbon, filtered, and evaporated. The ensuing white residue was recrystallized from ethyl acetate-petroleum ether to give shiny white needles of XIII in yields of 204 to 228 mg (67 to 75%).

The recrystallized product melted at 284 - 285° (dec) and exhibited $[\alpha]_D + 78.5^\circ$ (c 0.79, dimethylformamide).

Anal. Calcd for $C_{28}H_{33}N_3O_{12}$ (603.57):
C, 55.72; H, 5.51; N, 6.96. Found: C, 55.61; H, 5.38;
N, 6.95.

Typical bands in the infrared spectrum occurred at 3360 cm^{-1} (w), NH; 1555 cm^{-1} (s), nitroalkane, with shoulder at 1565 (NH bending); 765 (ms) and 705 cm^{-1} (ms), monosubstituted benzene.

NMR data (CDCl_3): 2.65τ (narrow multiplet, C_6H_5); 4.50τ (singlet, PhCHO_2 proton); 5.30τ (triplet, H-3, $J_{3,2} = J_{3,4} = 10\text{ Hz}$); 5.56τ (doublet, H-1, $J_{1,2} = 3.5\text{ Hz}$); $5.67 - 6.45\tau$ (overlapping signals ascribable to H-4, H-5, H-6 and H-6'); 6.61τ (singlet, OCH_3); 6.74τ (multiplet, H-2, width ca. 18 Hz); 8.2τ (broad signal, NH). See also Fig.IX.

The reaction time and yield of adduct in this reaction seem to be greatly influenced by the quality of the solvent, benzene. Thus, in the first run, the addition was complete in twenty-five hours and gave a yield of 235 mg (78%) of recrystallized product. However, this could not be repeated in subsequent runs, as a different supply of "Reagent Grade" benzene (dried by refluxing over sodium wire overnight and redistilling, as in the first run) was used. The reaction was very slow when performed in the absence of solid potassium hydroxide. Beginning addition could be detected on thin layer chromatography after at least twenty-four hours; but it remained incomplete after thirteen days of refluxing.

Bis(methyl 2,3-dideoxy-3-nitro- α -D-glucopyranosid-2-yl)
amine (XIV)

1. By debenzylidenation of 90% trifluoroacetic acid:

The benzylidene derivative XIII (517 mg) was taken up in 90% trifluoroacetic acid (6 ml), in which it dissolved in a slightly exothermic reaction. The mixture was allowed to stand at room temperature for ten minutes, and was then evaporated to a yellow syrup that smelled strongly of benzaldehyde and trifluoroacetic acid. Removal of these compounds was achieved by co-evaporation with water (twice), then ethanol (twice). The resulting yellow syrup was then triturated with ether, which caused the debenzylidenated amine (XIV) to crystallize as small, white prisms. This first crop weighed 262 mg after washing with ether.

The mother liquor, which according to thin layer chromatography contained additional XIV but also some starting material, was evaporated to dryness and again treated with 90% trifluoroacetic acid (6 ml), this time for six hours. Work-up as before provided an additional crop (20 mg) of debenzylidenated product, thus bringing the total yield to 282 mg.

The combined crops were recrystallized from ethyl acetate-petroleum ether to give colorless needles. However, the infrared spectrum of these exhibited a band

of medium-strong intensity at 1740 cm^{-1} , which was absent in the spectrum of the crude product. This band, which was probably due to ethyl acetate retained from the recrystallization, was removed by drying the crystals in vacuo (1 mm) at 100° for fifty hours. The yield of ethyl acetate-free, recrystallized XIV was 218 mg (60%).

The product darkened gradually above 205° and melted at $212 - 213^{\circ}$ (dec), with considerable foaming. It exhibited $[\alpha]_{\text{D}} + 161.2^{\circ}$ (c 0.68, water).

Anal. Calcd for $\text{C}_{14}\text{H}_{25}\text{N}_3\text{O}_{12}$ (427.36): C, 39.34; H, 5.89; N, 9.83. Found: C, 39.37; H, 5.75; N, 9.95.

The infrared spectrum displayed characteristic absorption bands at $3500 - 3100\text{ cm}^{-1}$ (ms), OH and NH; 1557 cm^{-1} (s), nitroalkane. Bands near 750 and 690 cm^{-1} characteristic of the benzylidene grouping were absent.

2. By debenzylidenation in 70% acetic acid:

Bis(methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranosid-2-yl)amine (XIII) (90 mg) was suspended in 70% acetic acid (10 ml). The mixture was heated in a steam-bath, and the amine slowly dissolved in the course of one hour, with gradual, brown discoloration of the solution. After sixty-five minutes the mixture was evaporated to a brown syrup which was co-evaporated twice with water and then twice with ethanol. Following decolorization with activated charcoal, the product crystallized from ethyl

acetate-petroleum ether as white needles that were identical (infrared spectrum, thin layer chromatography) with those obtained in 1, above. On drying in vacuo at 100° for fifty hours, the 1740 cm⁻¹ peak was similarly removed and the resulting, ethyl acetate-free debenzylidenated compound (23 mg, 37%) melted at 212 - 213° (dec) and exhibited $[\alpha]_D + 160.8^\circ$ (c 1, water).

Bis(methyl 4,6-di-O-acetyl-2,3-dideoxy-3-nitro- α -D-glucopyranosid-2-yl)amine (XV)

Compound XIV (100 mg) was suspended in acetic anhydride (3 ml). Upon addition of boron trifluoride etherate (3 drops), the amine dissolved after gentle warming on a steam-bath. The reaction mixture was left standing at room temperature for forty minutes, then co-evaporated with ethanol (5 times) to yield a white residue. This was recrystallized from ethyl acetate-petroleum ether to give elongated, hexagonal platelets (85 mg, 61%) of the tetraacetate. The product melted at 208 - 209° and exhibited $[\alpha]_D + 118.5^\circ$ (c 1.05, chloroform).

Anal. Calcd for C₂₂H₃₃N₃O₁₆ (595.51): C, 44.36; H, 5.58; N, 7.05. Found: C, 44.35; H, 5.56; N, 7.15.

Typical infrared bands occurred at 3440 cm⁻¹ (mw), NH; 1740 and 1755 cm⁻¹ (s), ester carbonyl; 1565 cm⁻¹ (w), NH bending; 1552 cm⁻¹ (s), nitroalkane; 1258 cm⁻¹ (s), acetate C-O-C.

For NMR data, see Discussion (page 97) and Fig.X.

Bis(methyl 3-amino-2,3-dideoxy- α -D-glucopyranosid-2-yl)
amine Trihydrochloride (XVI)

In some experiments the benzylidene compound XIII was debenzylidenated as described above and the crude, chromatographically inhomogeneous syrup containing XIV was hydrogenated directly. In a typical run the syrup obtained from 542 mg of XIII was dissolved in water (40 ml), 1 N hydrochloric acid (2.5 ml) and platinum catalyst (200 mg PtO₂, prehydrogenated) were added, and the mixture was hydrogenated for twenty-four hours at ordinary temperature and pressure. The filtered solution was evaporated to give a syrup which was twice co-evaporated with water. The product XVI then crystallized from absolute ethanol as white prisms in a yield of 190 mg (44% based on XIII). It gave a ninhydrin-positive spot on paper chromatography, R_{GN} 1.11, showed $[\alpha]_D + 144.7^\circ$ (c 0.9, water), and decomposed at 245 - 250° with gradual darkening from 200°.

Anal. Calcd for C₁₄H₃₂N₃O₈Cl₃ (476.8):
Cl, 22.31; N, 8.81. Found: Cl, 22.5; N, 8.90.

The infrared spectrum exhibited a sharp band at 3450 cm⁻¹ (m) and broad absorption in the 3300 cm⁻¹ region with maxima at 3340, 3300 and 3250 cm⁻¹ (OH, NH), a band

at 3060 and a broad absorption in the 2700 - 2400 cm^{-1} region, as well as bands at 1640 (mw), 1612 (m), 1598 (ms) and 1520 cm^{-1} (ms) (due to NH_3^+).

A similarly performed hydrogenation of crystalline XIV (300 mg) gave XVI in higher yield (230 mg, 69%). The product had R_{GN} 1.11 and exhibited $[\alpha]_{\text{D}} + 142.9^\circ$ (c 0.7, water); it decomposed slowly above 205° and extensively at 240 - 250°, and its infrared spectrum was identical with that from the preceding preparation.

Bis(methyl 3-acetamido-4,6-di-O-acetyl-2,3-dideoxy- α -D-glucopyranosid-2-yl)amine (XVII)

Compound XVI (121 mg) was suspended in acetic anhydride (3.5 ml) and pyridine (7 ml). The reaction mixture was stirred magnetically for sixteen hours at room temperature in the dark. A homogeneous solution was obtained which was co-evaporated once with excess methanol and several times with toluene until the smell of acetic anhydride and pyridine was no longer discernible. Finally, two additional evaporations with methanol were performed. The resulting brownish syrup was dissolved in chloroform, and the solution was washed several times with water (to remove pyridinium chloride). The chloroform layer was dried over anhydrous sodium sulfate and evaporated to a syrup. Co-evaporation of the latter with absolute ethanol

produced a semi-solid residue which was insoluble in ethyl acetate but soluble in hot absolute ethanol. It was recrystallized from absolute ethanol-petroleum ether to furnish white platelets of the fully acetylated compound (68 mg, 43%). The compound melted at 328° (dec) and exhibited $[\alpha]_D + 123.5^\circ$ (c 0.82, chloroform).

Anal. Calcd for $C_{26}H_{41}N_3O_{14}$ (619.61): C, 50.40; H, 6.67; N, 6.78. Found: C, 50.26; H, 6.48; N, 6.79.

Infrared data: 3310 cm^{-1} (ms), NH; 1740 cm^{-1} (s), ester carbonyl; 1658 cm^{-1} (s), amide I; 1560 cm^{-1} (ms), amide II; 1244 and 1220 cm^{-1} (ms), acetate C-O-C.

NMR data ($CDCl_3$): 3.27 τ (broadened doublet, amide NH); 5.15 τ (triplet, H-4, $J_{4,3} = J_{4,5} = 9.5$ Hz); 5.44 τ (doublet, H-1, $J_{1,2} = 3$ Hz); 5.6 - 6.3 τ (overlapping signals ascribable to H-3, H-5, H-6 and H-6'); 6.64 τ (singlet, OCH_3); 7.00 τ (multiplet, width ca. 18 Hz, H-2); 7.92, 7.95 τ (singlets, equatorial O-acetyl); 8.05 τ (singlet, equatorial N-acetyl); 8.27 τ (broadened signal of secondary amine NH). See also Fig.XI.

Part III

A. SYNTHESIS OF INOSATRIAMINES

1,3-Diacetamido-1,2,3-trideoxy-2-nitro-scyllo-inositol (IV)
and its muco Isomer (II)

1. From deoxynitro-scyllo-inositol pentaacetate:

Deoxynitro-scyllo-inositol pentaacetate (I) (75, 164) (2 g) was dissolved in dioxane (30 ml) and tetrahydrofuran (100 ml). The mixture was cooled in an ice-water bath for five minutes. Aqueous 15 N ammonia (40 ml) was added and the resulting, lightly yellow mixture was stirred at room temperature for one hour. Thin layer chromatography using chloroform-ethyl acetate (2 : 3) thereafter indicated absence of the fast-moving spot that corresponded to starting material and the formation of a non-migrating spot that corresponded to the products. When the irrigating system was changed to chloroform-methanol (1 : 1), the reaction products gave two spots of Rf 0.6 and 0.4, respectively. Cold ethanol was then added and the solution was evaporated to yield a partly crystalline residue. The latter was immediately taken up in methanol (100 ml) and to the cooled (0°) solution, acetic anhydride (6 ml) was added. The mixture was allowed to attain room temperature and was, after one hour, co-evaporated several times with ethanol and then once with benzene. Thin layer chromatography of the crude pro-

duct showed the same two spots that had been seen before the acetylation. The semi-crystalline residue was dried in a high vacuum for two hours at room temperature, and was then recrystallized from ethanol-water. A crop of fine, white needles (261 mg) was deposited after eighteen hours at 5°. This crop melted at 294 - 295° (dec) with prior darkening above 288°. It was 1,3-diacetamido-1,2,3-trideoxy-2-nitro-scyllo-inositol (IV) as described by M. Wang (163) and was the component which had Rf 0.4. Evaporation of the mother liquor and recrystallization of the residue from ethanol-water furnished, first, an additional crop of pure IV, then mixtures of the components with Rf 0.4 and 0.6. These mixtures were again subjected to fractional crystallization. Eventually, a total of 448 mg (32%) of the pure scyllo isomer IV (Rf 0.4) and a total of 304 mg (21.8%) of the pure muco isomer II (Rf 0.6) could be separated.

1,3-Diacetamido-1,2,3-trideoxy-2-nitro-muco-inositol (II) formed large, stout crystals melting at 268 - 269° (dec). It was optically inactive.

Anal. Calcd for $C_{10}H_{17}N_3O_7$ (291.3) (II): C, 41.24; H, 5.88; N, 14.41. Found: C, 41.35; H, 5.85; N, 14.57.

Compound II showed characteristic infrared bands (Fig.XII) at 3370 cm^{-1} (ms), NH; 3300 - 3100 cm^{-1} (broad), OH; 1660 cm^{-1} (s), amide I; 1565 - 1520 cm^{-1} (s to ms), nitroalkane and amide II. The spectrum was readily distinguished from that of IV (Fig.XIII) by the absence of

the following bands which were present in the latter:
3426 cm^{-1} (ms); 3308 and 3280 cm^{-1} (s); 3120 cm^{-1} (w);
1098 cm^{-1} (m); 1073 cm^{-1} (mw) and 1022 cm^{-1} (m). Further-
more, II gave a conspicuous band at 1060 cm^{-1} (ms) with a
shoulder at 1050 cm^{-1} (m), and this band was not given
by IV.

In one experiment, the N-acetylation was omitted.
The muco isomer II (mp 268 - 269°) could nevertheless be
isolated from the reaction mixture by crystallization from
ethanol-water. The yield was 15%. The scyllo isomer could
not be isolated in this instance, although chromatography
indicated its presence in the reaction mixture.

2. From deoxynitro-myo-inositol pentaacetate:

Deoxynitro-myo-inositol pentaacetate X (164)
(300 mg) was dissolved in tetrahydrofuran (20 ml) and
treated with aqueous, 15 N ammonia. Thin layer chromato-
graphy (see under 1) revealed that the reaction was com-
plete after thirty minutes. Work-up as before, afforded a
crystalline solid (137 mg, 66%) which gave two chromato-
graphic spots having Rf 0.4 and 0.6 (i.e., the same two
spots given by the crude product in 1). In the present case,
the crude product was not N-acetylated, but recrystallized
immediately from ethanol-water to furnish crystals of the
muco isomer II (80 mg, 38%) melting at 267 - 268° (dec)
and having an infrared spectrum identical with that of II

obtained in 1. The component having Rf 0.4 (presumably IV) did not crystallize.

When the reaction time was prolonged to one hour, the pentaacetate X (500 mg) afforded the same mixture (257 mg, 73%), with the muco isomer II again being the predominant product, as judged from the intensity of the thin layer spots.

1,3-Diacetamido-4,5,6-tri-O-acetyl-1,2,3-trideoxy-2-nitro-
muco-inositol (III)

Compound II (140 mg) was suspended in acetic anhydride (1.5 ml). Boron trifluoride etherate (6 drops) was added and the mixture warmed gently on a steam-bath for two to three minutes. The starting material dissolved and the acetate III crystallized out immediately. The mixture was cooled at 5° for twenty minutes, and the crystals were then isolated and washed with ether. The crude product was recrystallized from tetrahydrofuran to furnish white needles (190 mg, 95%) of III, melting at 325° (dec) with prior darkening above 320°.

Anal. Calcd for $C_{16}H_{23}N_3O_{10}$ (417.37): C, 46.04; H, 5.55; N, 10.07. Found: C, 46.08; H, 5.38; N, 10.27.

Infrared data: 3316 cm^{-1} (ms), NH; 1766 cm^{-1} (s) with shoulder at 1753 cm^{-1} (ms), ester carbonyl; 1667 cm^{-1} (s), amide I; 1555 cm^{-1} (s) with shoulder at 1542 cm^{-1} (ms),

nitroalkane and amide II; 1245 cm^{-1} (s), acetate C-O-C.

1,3-Diacetamido-2-amino-1,2,3-trideoxy-muco-inositol
Hydrochloride (V)

The diacetamidinitro compound II (291 mg) was dissolved in water (30 ml), acidified with 1 N hydrochloric acid (1.5 ml), and hydrogenated over platinum (120 mg of PtO_2 , prehydrogenated) at normal temperature and pressure for twenty-four hours. Filtration of the catalyst and evaporation of the solution yielded a colorless glass which was repeatedly co-evaporated with water to remove residual acid. Crystallization was then achieved from absolute ethanol, with moderate warming, to furnish the amine hydrochloride V (242 mg, 82%). It melted at $258 - 259^\circ$ (dec), with prior darkening above 253° .

Anal. Calcd for $\text{C}_{10}\text{H}_{20}\text{N}_3\text{O}_5\text{Cl}$ (297.74): C, 40.33; H, 6.77; Cl, 11.91. Found: C, 40.48; H, 6.74; Cl, 11.86.

Infrared data: $3480 - 3100\text{ cm}^{-1}$ (broad) with peaks at 3405 and 3300 cm^{-1} , NH, OH; $2800 - 2300\text{ cm}^{-1}$ (w), NH_3^+ ; 1670 cm^{-1} (s), amide I; 1535 cm^{-1} (ms), amide II.

1,2,3-Triacetamido-1,2,3-trideoxy-muco-inositol (VI)

The hydrochloride V (180 mg), dissolved in water (10 ml) and methanol (2 ml), was N-acetylated at 0° by

magnetic stirring with acetic anhydride (0.5 ml) and Dowex 1 x 2 (CO_3^-), for two hours. Filtration, followed by a brief treatment with a small amount of Rexyn 101(H^+) afforded a colorless liquid which was repeatedly evaporated with methanol. The resulting solid residue failed to crystallize properly. A slightly turbid ethanolic solution of it was clarified with activated charcoal, and a white, solid product (110 mg, 57%) was recovered by evaporation of the solvent. The product decomposed at $300 - 305^\circ$, with very slow darkening above 255° . It appeared to retain ethanol which was not removed by drying in vacuo: The NMR spectrum in DMSO-d_6 exhibited a methyl proton triplet ($J = 7.3 \text{ Hz}$) at 8.79τ and a corresponding methylene proton quartet in the 6.5τ region.

The infrared spectrum of VI showed typical bands at $3500 - 3100 \text{ cm}^{-1}$ (broad) with peaks at 3365 cm^{-1} (m), 3382 cm^{-1} (ms), 3100 cm^{-1} (w), NH, OH; 1663 (s) and 1632 cm^{-1} (s)m amide I; 1545 cm^{-1} (s), amide II.

No satisfactory microanalytical data could be obtained, evidently because of the presence of ethanol in the sample, but possibly also because of other impurities that were not revealed spectroscopically. However, when the presence of 0.5 mole/mole of ethanol was assumed, at least the hydrogen and nitrogen values were correct.

Anal. Calcd for $\text{C}_{12}\text{H}_{21}\text{N}_3\text{O}_6$ (303.31): C, 47.52; H, 6.98; N, 13.36. Calcd for $\text{C}_{12}\text{H}_{21}\text{N}_3\text{O}_6 \cdot \frac{1}{2}\text{C}_2\text{H}_5\text{OH}$ (326.39):

C, 47.82; H, 7.45; N, 12.87. Found: C, 46.51; H, 7.57;
N, 12.84.

1,2,3-Triacetamido-4,5,6-tri-O-acetyl-1,2,3-trideoxy-muco-
inositol (VII)

A suspension of the hydrochloride V (54 mg) in pyridine (2.4 ml) and acetic anhydride (1.2 ml) was stirred for eighteen hours in the absence of light. The resulting pink solution was then repeatedly evaporated with ethanol and then with toluene, to yield a yellow residue. The latter was extracted with chloroform. Evaporation of the extract (which had been dried over sodium sulfate) afforded a white residue which was crystallized from absolute ethanol-petroleum ether to give the hexaacetyl derivative VII (50 mg, 64%). It melted at 320° (dec), with gradual darkening above 310°.

Anal. Calcd for $C_{18}H_{27}N_3O_9$ (429.42): C, 50.34; H, 6.34; N, 9.79. Found: C, 50.14; H, 6.26; N, 9.60.

Infrared data: 3420 (w), 3250 (m), 3200 - 3180 cm^{-1} (m), NH; 1750 cm^{-1} (s), ester carbonyl; 1680 (ms) and 1635 cm^{-1} (s), amide I; 1578 (w) and 1540 cm^{-1} (m), amide II; 1230 (ms) and 1210 cm^{-1} (s), C-O-C.

1,3-Diacetamido-2-amino-1,2,3-trideoxy-scyllo-inositol
Hydrochloride (VIII)

A solution of the diacetamidonitro compound IV (253 mg) in water (30 ml) was hydrogenated for twenty-four hours in the presence of 1 N hydrochloric acid (1.2 ml) and platinum (200 mg of PtO₂, prehydrogenated) as described for the muco isomer II. After identical processing of the reaction mixture, VIII was crystallized (with great difficulty) from ethanol. The hydrochloride (175 mg) melted at 230° with partial sublimation above 210°. The analytical data for carbon and hydrogen are satisfactory if the presence of ca. 2.5 moles/mole of water in the crystals is assumed.

Anal. Calcd for C₁₀H₂₀N₃O₅Cl (297.74): C, 40.33; H, 6.77; Cl, 11.91. Calcd for C₁₀H₂₀N₃O₅Cl·2½H₂O (342.78): C, 35.00; H, 7.31; Cl, 10.35. Found: C, 35.15; H, 6.92; Cl, 11.46.

Infrared bands occurred at 3600 - 3100 cm⁻¹ with peaks at 3506 (mw), 3420 (m), 3330 (m), 3230 cm⁻¹, NH, OH; 2800 - 2300 cm⁻¹ (w), NH₃⁺; 1668 (s) and 1644 cm⁻¹ (ms), amide I; 1565 (ms), 1550 (s), 1522 cm⁻¹ (m), amide II and NH⁺.

1,2,3-Triacetamido-4,5,6-tri-O-acetyl-1,2,3-trideoxy-
scyllo-inositol (IX)

The hydrochloride VIII (125 mg) was acetylated in pyridine (4 ml) and acetic anhydride (2 ml) as described for the muco isomer V. After identical work-up of the reaction mixture, the product was recrystallized from absolute ethanol-petroleum ether, to furnish IX (126 mg), mp 314 - 315°.

Anal. Calcd for $C_{18}H_{27}N_3O_9$ (429.42): C, 50.34; H, 6.34; N, 9.79. Found: C, 50.12; H, 6.11; N, 9.93.

Characteristic infrared bands were at 3408 (m), 3386 cm^{-1} (m), NH; 1738 cm^{-1} (s), ester carbonyl; 1682 (ms) and 1641 cm^{-1} (ms), amide I; 1540 cm^{-1} (ms), amide II; 1270 (ms) and 1235 cm^{-1} (ms), C-O-C.

B. REACTION OF DINITROINOSITOLS WITH AMMONIA

2,5-Dinitroaniline (XVII) from 2,3,5,6-Tetra-O-acetyl-1,4-dideoxy-1,4-dinitro-neo-inositol (XVI)

To a magnetically stirred solution of 2,3,5,6-tetra-O-acetyl-1,4-dideoxy-1,4-dinitro-neo-inositol (136) (XVI, 1 g) in tetrahydrofuran (180 ml) was added dilute ammonium hydroxide (20 ml of 14.8 N NH_4OH plus 160 ml of water). The colorless mixture immediately turned yellow. Stirring was maintained for one hour during which time the mixture became darker in color. Removal of the tetrahydrofuran by evaporation then caused precipitation of an orange-yellow, fluffy solid. The latter was triturated with water, and evaporation was continued to remove most of the tetrahydrofuran and residual ammonia. The solid was then filtered, washed with water, and dried in vacuo to yield 2,5-dinitroaniline (340 mg, 76%) melting at 134 - 135°. Recrystallization from ethanol (with inclusion of a treatment with activated charcoal) raised the melting point to 137 - 138° [reported (173), mp 137°].

Anal. Calcd for $\text{C}_6\text{H}_5\text{N}_3\text{O}_4$ (183.12): C, 39.35; H, 2.75; N, 22.95. Found: C, 39.13; H, 3.01; N, 22.79.

Typical infrared bands occurred at 3510 (m) and 3396 (ms), 1634 cm^{-1} (ms), primary NH_2 ; 1600 (m) and 1500 cm^{-1} (m), aromatic; 873 (mw) and 813 cm^{-1} (mw),

1,2,5-substituted benzene; 1541 cm^{-1} , aromatic NO_2 .

The above aromatization of XVI to 2,5-dinitroaniline could also be carried out with minor variations in procedure, although yields were slightly lower. For instance, the reaction also took place in chloroform or acetone as solvents, at room temperature. The same product was also obtained when a stoichiometric proportion of ammonium hydroxide was used, at room temperature or at -8° .

2,5-Dinitroacetanilide (XVIII)

2,5-Dinitroaniline (100 mg) prepared from XVI was taken up in acetic anhydride (1 ml). Concentrated sulfuric acid (2 drops) was added, whereupon the solution became hot and changed its color from orange-yellow to a pale yellow. The solution was left standing at room temperature for ten minutes, then poured into ice-water. magnetic stirring caused the separation of a pale yellow solid, which was filtered and washed several times with water. Recrystallization from ethanol-water gave 2,5-dinitroacetanilide (86 mg, 70%) as very pale yellow, fine needles melting at $120 - 121^\circ$ [reported (174,175), mp 121°].

Infrared data: 3280 cm^{-1} (m), NH; 1670 cm^{-1} (s), amide I; 1598 cm^{-1} (m), aromatic; 1545 cm^{-1} (s), aromatic

NO_2 : 1515 cm^{-1} (s), amide II; 890 (ms) and 840 cm^{-1} (ms), 1,2,5-substituted benzene.

The NMR spectrum of the compound (in CDCl_3) showed three aromatic protons in the $0.5 - 2.0 \tau$ region. The signal for the N-acetyl protons occurred at 7.67τ .

2,5-Dinitrophenyl Acetate (XIX) from 2,3,5,6-Tetra-
0-acetyl-1,4-dideoxy-1,4-dinitro-neo-inositol (XVI)

The tetraacetate XVI (500 mg) was refluxed in dry benzene (50 ml) together with dry, finely-powdered sodium bicarbonate (2.5 g). Small samples of the solution were withdrawn periodically, filtered, evaporated, and examined by infrared spectroscopy. Progress of the reaction was indicated by the gradual disappearance of the 1753 cm^{-1} (ester carbonyl) and 1570 cm^{-1} (nitroalkane) peaks, with concomitant replacement by peaks at 1775 and 1540 cm^{-1} , respectively, typical of the aromatic product.

Completion of the reaction required ten hours, after which the bicarbonate was filtered off and the benzene evaporated. A pale yellow residue of 2,5-dinitrophenyl acetate (270 mg, 98%) was obtained. On recrystallization from methanol-water, the fluffy, pale yellow needles melted at $94 - 95^\circ$ [repor-

ted* (172), mp 101 - 102.5°].

The infrared spectrum of the product was identical with that synthesized according to Lichtenthaler and Fischer (172). It exhibited characteristic bands at 3122 cm^{-1} (w), aromatic; 1775 cm^{-1} (s), ester carbonyl; 1540 cm^{-1} (s), aromatic NO_2 ; 1175 cm^{-1} (s), acetate C-O-C; 840 (ms) and 900 cm^{-1} (m), 1,2,5-substituted benzene.

2,5-Dinitrophenol (XX)

2,5-Dinitrophenyl acetate (400 mg), obtained as described in the preceding section, was suspended in 2 N hydrochloric acid (20 ml) and hydrolyzed by heating on a steam-bath for thirty minutes. The reaction mixture was then extracted with ether; the ether layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to give a yellow residue. Recrystallization from ethanol-water furnished bright yellow needles of 2,5-dinitrophenol

* A sample of 2,5-dinitrophenol (mp 107-108°) was acetylated with acetic anhydride - boron trifluoride and the product was recrystallized from methanol - water. The 2,5-dinitrophenyl acetate so obtained melted at 94 - 95°.

A sample synthesized according to Lichtenthaler and Fischer (172), i.e., by treatment of XVI with pyridine, likewise showed mp 94 - 95° in our hands.

(300 mg, 93%), mp 107 - 108° [reported (182), mp 108°].

Infrared data: 3280 cm⁻¹ (broad, mw) bonded OH; 3130 (w) and 1633 cm⁻¹ (m), substituted phenyl; 1550 cm⁻¹ (m), NO₂; 1260 cm⁻¹ (ms), phenolic OH; 868 (m) and 832 cm⁻¹ (m), 1,2,5-substituted benzene. The spectrum was superimposable with that of a sample (mp 107 - 108°) prepared in a different manner (172), namely, by the action of pyridine upon 2,3,5,6-tetra-o-acetyl-1,4-dideoxy-1,4-dinitro-neo-inositol, followed by acid hydrolysis.

Addendum

SYNTHESIS OF GEMINAL DINITRO COMPOUNDS

2,2-Dinitrocyclohexane-cis-1,3-diol (II)

An aqueous solution of trans,trans-2-nitro-1,3-cyclohexanediol (I) (180) (500 mg, 3.1 mmole), 1 N sodium hydroxide (3.1 ml, 3.1 mmole), and sodium nitrite (650 mg, 9.3 mmole) was poured into a stirred and chilled (0 - 5°) mixture of aqueous silver nitrate (1070 mg, 6.2 mmole of AgNO₃ in 15 ml of H₂O), sodium hydroxide (2 - 3 drops until Ag₂O appeared) and ether (30 ml). The reaction mixture was protected from light. After ten minutes, it was brought to room temperature, and stirring was continued for several hours. Thin layer chromatography (petroleum ether-ethyl acetate, 3 : 1) indicated, after one hour, the appearance of a new spot (Rf 0.7) that migrated faster than I (Rf 0.3). The reaction did not go to completion even after five days.

Extraction of the reaction mixture with ether, and evaporation of the ethereal layer (which was dried over sodium sulfate) afforded a yellowish syrup that crystallized on repeated evaporation with chloroform. The crystalline, almost colorless, crude product (203 mg) was a mixture of I and II. Attempts at fractional crystallization were unsuccessful, but separation was

finally achieved by column chromatography on silicic acid. Elution with mixtures of petroleum ether and ethyl acetate furnished the pure dinitrodiol II (104 mg, 16%), which crystallized from chloroform as shiny, white platelets melting at 130 - 132°. Small samples of the mixture of I and II were conveniently separated by preparative thin layer chromatography on silica gel plates (20 cm x 20 cm), using petroleum ether-ethyl acetate (3 : 1) as irrigating system.

Anal. Calcd for $C_6H_{10}N_2O_6$ (206.16): C, 34.95; H, 4.89; N, 13.59. Found: C, 34.88; H, 4.88; N, 13.52.

The product II was characterized in the infrared by bands at 3558 (ms), 3500 - 3200 cm^{-1} (broad, with peak at 3400 cm^{-1}), OH; 1590 (m) and 1568 cm^{-1} (s), 1343 (mw) and 1322 cm^{-1} (mw), geminal dinitro. Compound II was readily distinguished from I which gave only a broad hydroxyl peak in the 3500 - 3100 cm^{-1} region, and only one nitro absorption at 1555 (s) and 1338 cm^{-1} (mw).

Unlike I, the dinitro compound II gave no peak in the 250 $m\mu$ ultraviolet region upon addition of aqueous sodium hydroxide.

2,2-Dinitrocyclohexane-cis-1,3-diol Diacetate (III)

A crude mixture (130 mg) of I and II (with the latter preponderating) was suspended in acetic anhydride (2 ml). Addition of boron trifluoride etherate (3 drops) caused complete dissolution in a slightly exothermic reaction. After fifty minutes at room temperature the mixture was poured into ice-water. Magnetic stirring and addition of few milliliters of methanol caused the precipitation of a white solid which was filtered, washed with ice-cold water, and recrystallized from ethanol-water. There was obtained 71 mg of III, mp 73 - 74°.

Compound III gave a single spot (Rf ca. 0.7) on thin layer chromatography (petroleum ether-ethyl acetate, 12 : 5). A sample of the mononitrodiol diacetate (IV) was run for comparison and had Rf ca. 0.6 .

Anal. Calcd for $C_{10}H_{14}N_2O_8$ (290.23): C, 41.38; H, 4.86; N, 9.65. Found: C, 41.58; H, 5.08; N, 9.81.

A pure sample of the dinitrodiol II (80 mg) was acetylated similarly and afforded 81 mg (70%) of recrystallized III, mp 73 - 74° (alone and admixed with the previous sample).

Infrared data: 1755 cm^{-1} (s), ester carbonyl; 1590 (ms) and 1568 cm^{-1} (s), 1332 (w) and 1320 cm^{-1} (w), geminal dinitro; 1215 cm^{-1} (s), acetate C-O-C.

CLAIMS TO ORIGINAL RESEARCH

Part I

1. The introduction of an amino function into the position 2 of derivatives of 3-deoxy-3-nitro-D-glucose was investigated for the first time in the α -glycosidic series. A nitroamine having the α -D-gluco configuration was obtained in high yield, and further chemical transformations led to an economically attractive synthesis of 2,3-diamino-2,3-dideoxy-D-glucose.
2. The synthesis of triamino sugars by a stepwise introduction of two amino groups into the positions 2 and 4 of a 3-deoxy-3-nitro-hexopyranoside is described for the first time. This approach led to the synthesis of various, hitherto unknown α -glycosidic derivatives of 2,3,4-triamino-2,3,4-trideoxy-D-glucose.
3. The following new compounds were synthesized:

Part I, Section A

- (a) Methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside (III)
- (b) Methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranoside (IV)
- (c) A stereoisomer (VI) of IV, probably having the α -D-manno configuration

- (d) Methyl 4,6-O-benzylidene-2-ethoxycarbonamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside (VII)
- (e) Methyl 2-acetamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside (VIII)
- (f) Methyl 2-acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-nitro- α -D-glucopyranoside (IX)
- (g) Methyl 2-acetamido-3-amino-2,3-dideoxy- α -D-glucopyranoside hydrochloride (X)
- (h) Methyl 2,3-diacetamido-2,3-dideoxy- α -D-glucopyranoside (XI)
- (i) Methyl 2,3-diacetamido-4,6-di-O-acetyl-2,3-dideoxy- α -D-glucopyranoside (XII)

Part I, Section B

- (j) Methyl 2,4-diacetamido-2,3,4-trideoxy-3-nitro- α -D-glucopyranoside (XV)
- (k) Methyl 2,4-diacetamido-6-O-acetyl-2,3,4-trideoxy-3-nitro- α -D-glucopyranoside (XVI)
- (l) Methyl 2,4-diacetamido-3-amino-2,3,4-trideoxy- α -D-glucopyranoside hydrochloride (XVII)
- (m) Methyl 2,3,4-triacetamido-2,3,4-trideoxy- α -D-glucopyranoside (XVIII)
- (n) Methyl 2,3,4-triacetamido-6-O-acetyl-2,3,4-trideoxy- α -D-glucopyranoside (XIX)

Part II

4. The nucleophilic addition of anthranilic acid to methyl 4,6-0-benzylidene-2,3-dideoxy-3-nitro- α -D-erythro-hex-2-enopyranoside was studied under a variety of conditions. The reaction appears to give only one adduct, namely that with the 2,3-diequatorial substituent orientation. In this regard, the addition differs from the analogous reaction in the β -glycosidic series.
5. The synthesis of bisglycosidylamines, a novel class of amino sugars, was achieved.
6. The following new compounds were synthesized:

Part II, Section A

- (a) Methyl 4,6-0-benzylidene-2-(2-carboxyphenyl)amino-2,3-dideoxy-3-nitro- α -D-glucopyranoside (II)
- (b) Methyl 4,6-0-benzylidene-2,3-dideoxy-2-[(2-methoxycarbonyl)phenyl] amino-3-nitro- α -D-glucopyranoside (III)
- (c) Methyl 2-(2-carboxyphenyl)amino-2,3-dideoxy-3-nitro- α -D-glucopyranoside (IV)
- (d) Methyl 4,6-di-0-acetyl-2-[N-(2-carboxyphenyl)] acetamido-2,3-dideoxy-3-nitro- α -D-glucopyranoside (V)
- (e) Methyl 2,3-dideoxy-2-[(2-methoxycarbonyl)phenyl] amino-3-nitro- α -D-glucopyranoside (VI)

- (f) Methyl 4,6-di-O-acetyl-2,3-dideoxy-2-[N-(2-methoxycarbonyl)phenyl]acetamido-3-nitro- α -D-glucopyranoside (VII)
- (g) Methyl 2,3-diamino-2,3-dideoxy- α -D-glucopyranoside (IX)

Part II, Section B

- (h) Bis(methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro- α -D-glucopyranosid-2-yl)amine (XIII)
- (i) Bis(methyl 2,3-dideoxy-3-nitro- α -D-glucopyranosid-2-yl)amine (XIV)
- (j) Bis(methyl 4,6-di-O-acetyl-2,3-dideoxy-3-nitro- α -D-glucopyranosid-2-yl)amine (XV)
- (k) Bis(methyl 3-amino-2,3-dideoxy- α -D-glucopyranosid-2-yl)amine trihydrochloride (XVI)
- (l) Bis(methyl 3-acetamido-4,6-di-O-acetyl-2,3-dideoxy- α -D-glucopyranosid-2-yl)amine (XVII)

Part III

7. The diamination of penta-O-acetyl-deoxynitro-scyllo-inositol, followed by N-acetylation, as described by Baer and Wang (149) was further investigated and was found to yield, in addition to 1,3-diacetamido-1,2,3-trideoxy-2-nitro-scyllo-inositol, a stereoisomer to which was tentatively assigned the muco configuration. Further chemical transformations led to the first synthesis of 1,2,3-inosatriamines.

8. A novel and improved synthesis of 2,5-dinitroaniline was achieved by the aromatization, with ammonia, of 2,3,5,6-tetra-0-acetyl-1,4-dideoxy-1,4-dinitro-neo-inositol.

9. The following new compounds* were synthesized:

Part III, Section A

- (a) 1,3-Diacetamido-1,2,3-trideoxy-2-nitro-muco-inositol (II)
 - (b) 1,3-Diacetamido-4,5,6-tri-0-acetyl-1,2,3-trideoxy-2-nitro-muco-inositol (III)
 - (c) 1,3-Diacetamido-2-amino-1,2,3-trideoxy-muco-inositol hydrochloride (V)
 - (d) 1,2,3-Triacetamido-1,2,3-trideoxy-muco-inositol (VI)
 - (e) 1,2,3-Triacetamido-4,5,6-tri-0-acetyl-1,2,3-trideoxy-muco-inositol (VII)
 - (f) 1,3-Diacetamido-2-amino-1,2,3-trideoxy-scyllo-inositol hydrochloride (VIII)
 - (g) 1,2,3-Triacetamido-4,5,6-tri-0-acetyl-1,2,3-trideoxy-scyllo-inositol (IX)
- (See also the footnote on page 116).

* The configuration of the muco compounds was deduced from chemical shift data only. Verification by other means may be required.

Addendum

10. The oxidative nitration of Kaplan and Shechter (179) was applied to a cyclic nitrodiol.

The following new compounds were synthesized:

(a) 2,2-Dinitrocyclohexane-cis-1,3-diol (II)

(b) 2,2-Dinitrocyclohexane-cis-1,3-diol diacetate (III).

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