Syntheses of Nitrogen-containing Sugars

by

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PREFACE

This thesis presents some contributions to the synthetic chemistry of branched-chain and nitrogenous carbohydrates. In the Introduction, the significance of branched-chain sugars and diamino sugars as constituents of microbial metabolites is outlined, and synthetic methods available in this field are reviewed. The experimental work undertaken for the thesis is then described and the results are discussed. The investigation is divided in two main parts: syntheses of novel, nitrogen-containing branched-chain sugars, and a synthetic approach to hitherto unknown 2,3-diamino-2,3-dideoxy-D-galactose.

ACKNOWLEDGMENTS

I am deeply indebted to my research supervisor, Prof. Hans H. Baer, for his guidance, instructions and patience throughout the course of this research work and preparation of this thesis.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACTS

PART I

Approaches to the synthesis of nitrogen-containing, branched-chain sugars were investigated. The Michael reaction of methyl 2-O-acetyl-4,6-O-benzylidene-3-nitro-β-D-glucopyranoside (I) or of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (II) with nitroalkanes led to branched-chain dinitro sugar derivatives, namely, methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-nitroalkyl-β-D-glucopyranosides (III-VI). The nitroalkanes employed included nitromethane, nitroethane, 1-nitropropane and 2-nitropropane. The three primary nitroalkanes mentioned were added in a similar manner to methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-*threo*-hex-2-enopyranoside (VIII) to furnish methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-nitroalkyl-β-D-galactopyranosides (IX-XI), while addition of 2-nitropropane did not succeed in this case. Analogous Michael reactions of I and VIII with diethyl malonate gave the corresponding branched-chain mononitro glycosides XIII and XIV. Another approach to the synthesis of branched-chain nitro glycosides involved nitroethane cyclization of the dialdehyde (XVI) obtained from periodate-oxidized

methyl β-D-xylopyranoside (XV). The reaction gave a methyl 3-deoxy-3-C-methyl-3-nitro-pentopyranoside which was subsequently converted into amino sugar derivatives (XVIII and XIX).

PART II

A synthesis of derivatives of hitherto unknown 2,3-diamino-2,3-dideoxy-D-galactose was undertaken. The introduction of an amino function in position 2 of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-threo-hex-2-enopyranoside (VIII) by the action of aqueous ammonia or of molten ammonium acetate led to methyl 4,6-O-benzylidene-2-benzylideneamino-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXI) which could be converted into the corresponding 2-acetamido derivative (XXII). De-O-benzylidenation of XXII gave methyl 2-acetamido-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXIII). Acetylation of XXIII with acetic anhydride catalyzed by boron trifluoride furnished the corresponding 4,6-di-O-acetate (XXIV). Catalytic hydrogenation of XXIII gave the amine hydrochloride XXV, which was N-acetylated to methyl 2,3-diacetamido-2,3-dideoxy-β-D-galactopyranoside (XXVI), or fully acetylated to the 4,6-di-O-acetate (XXVII) of XXVI.

INTRODUCTION

I. On Antibiotics and Carbohydrates

Antibiotics are defined, in a broad sense, as chemical substances which are produced by microorganisms and which possess inhibitory activities against the growth of other microorganisms. Microorganisms that produce antibiotics are actinomycetes, fungi and bacteria, although antibiotic substances have been encountered also in some algae, lichens, insects and higher plants. The antibiotics in present-day clinical use number less than thirty, even though in the past two decades several thousand new antibiotics have been recorded, with some six hundred of them well characterized (1).

Many important antibiotics contain carbohydrate moieties and some are known to consist entirely of carbohydrate components (2). The carbohydrate components are branched-chain sugars, amino sugars, diamino sugars and aminocyclitols, the majority of them being found in antibiotics from Streptomyces and Actinomyces species. Much attention had been focused on the chemistry of these carbohydrates and their synthesis. Although considerable progress has been made in this field in recent years, the synthesis of branched-chain sugars and diamino sugars is still an area that merits further study. The present

thesis is aimed at making a contribution to the synthesis of these two classes of sugars. Some aspects of the chemistry of the unusual branched-chain and diamino sugars (Tables I and II) found in antibiotics and bacteria will be reviewed in the following sections as a background to the experimental work undertaken for this thesis.

Table I

Nonnitrogenous and Nitrogenous Branched-chain Sugars Found in Antibiotics

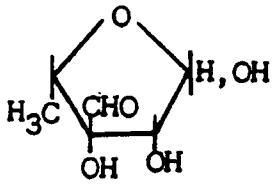
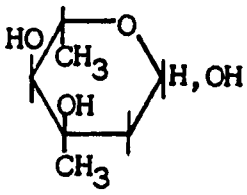
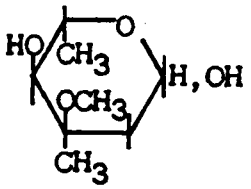
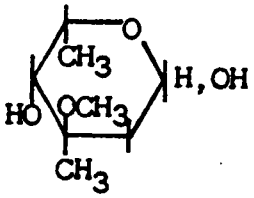
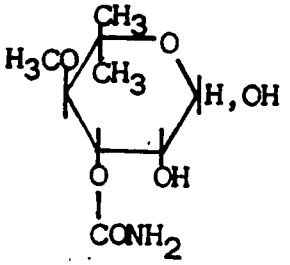
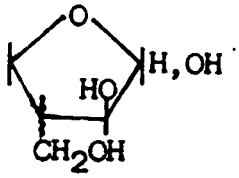
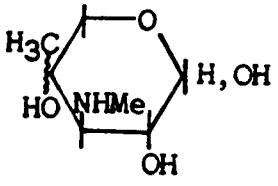
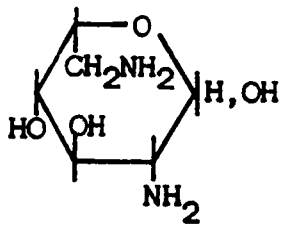
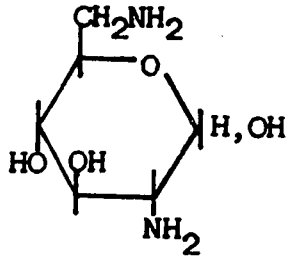
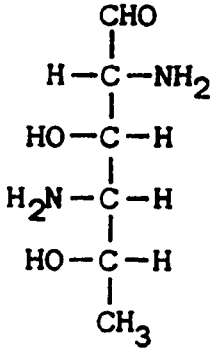
Sugars	Structure	Antibiotic	References
Streptose		Streptomycin	3
Mycarose		Carbomycin	16,17
Cladinose		Erythromycin	18
Arcanose		Lankamycin	32,33
Noviose		Novobiocin	35,36,37
Cordycepose		Cordycepin	43,44
Garosamine		Gentamicin C	49,50

Table II

Diamino Sugars Found in Antibiotics and in a Bacterial Polysaccharide

Diamino Sugars	Structure	Source	References
Neosamine B		Neomycin B	52-58
		Paromomycin I	63-66
Neosamine C		Neomycin C	55,57,58
		Paromomycin II	63-66
Bacillosamine		Bacterial polysaccharide from Bacillus subtilis	67-70

II. Unusual Sugars as Components of Antibiotics and Bacterial Polysaccharide

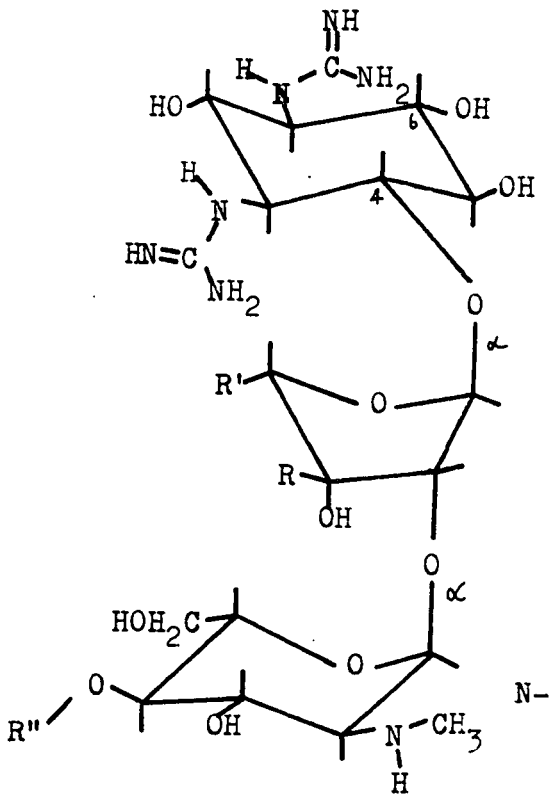
A. Nonnitrogenous branched-chain sugars

1. Streptose in the Streptomycins

In 1944 Waksman, Schatz and Bugie (3) isolated from cultures of Streptomyces griseus the important antibiotic, streptomycin, a drug useful in the treatment of many infections which are resistant to penicillin. The evidence leading to the elucidation of its structure was accumulated by four groups of workers led by Folkers (4), Wintersteiner (5), Carter (6) and Wolfrom (7).

The complete structure of streptomycin is depicted in Fig. I. All the configurational details, except that of the attachment of streptose to C-4 or C-6 of the streptamine molecule (8), have been established. The glycosidic linkages have been shown, partly by n.n.r. spectroscopy, to be of the α-type (8). The other known Streptomyces metabolites of the streptomycin family are hydroxystreptomycin, dihydrostreptomycin and mannosidostreptomycin (Fig. I) (9).

The structure of streptose (5-deoxy-3-C-formyl-L-lyxose, I), was established by identifying its oxidation and reduction products (10,11,12,13,14). Owing to its instability, the sugar could not be



Streptidine

Streptose

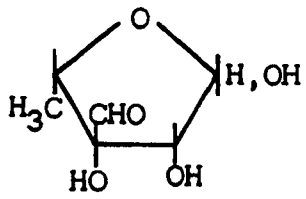
N-Methyl-L-Glucosamine

	R	R'	R"
Streptomycin	CHO	CH_3	H
Dihydrostreptomycin	CH_2OH	CH_3	H
Hydroxystreptomycin	CHO	CH_2CH	H
Mannosidostreptomycin	CHO	CH_3	$C_6H_{11}O_5$ (*)

(*) α-D-mannopyranosyl

Fig. I. Streptomycins

isolated upon hydrolysis of streptobiosamine or streptomycin, and its molecular formula, $C_6H_{10}O_5$, was originally calculated from the known formulas of streptomycin, streptidine and N-methyl-L-glucosamine. However, the chemical synthesis of streptose, achieved as late as 1965 (15), confirmed the assigned structure.



I

2. Mycarose and Cladinose in Macrolides

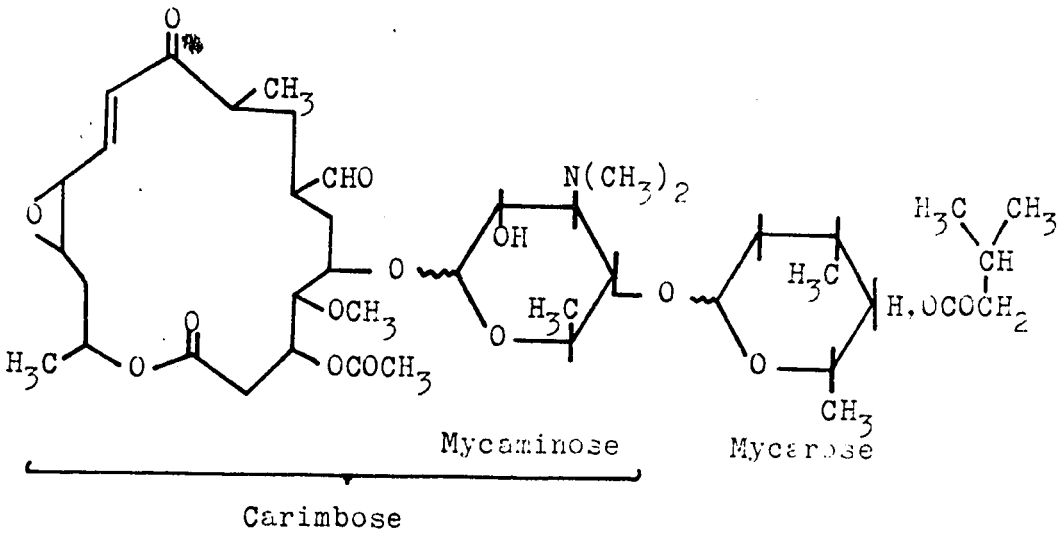
Both cladinose and mycarose occur in the macrolides, a group of antibiotics that possess a macrocyclic lactone moiety and therefore differ very much from streptomycin, although the macrolides are also produced by various strains of Streptomyces in the Actinomycetes family. Carbomycin (16,17), erythromycin (18), oleandomycin (19) and the spiramycins (20,21) are among the members of this group which have gained importance as therapeutic agents. Each of these antibiotics, however different in detailed structure, has an amino sugar joined glycosidically to the macrocyclic lactone ring and a neutral sugar moiety linked either directly to the macrocycle, as in erythromycin and

oleandomycin, or to the amino sugar as in carbomycin and the spiramycins.

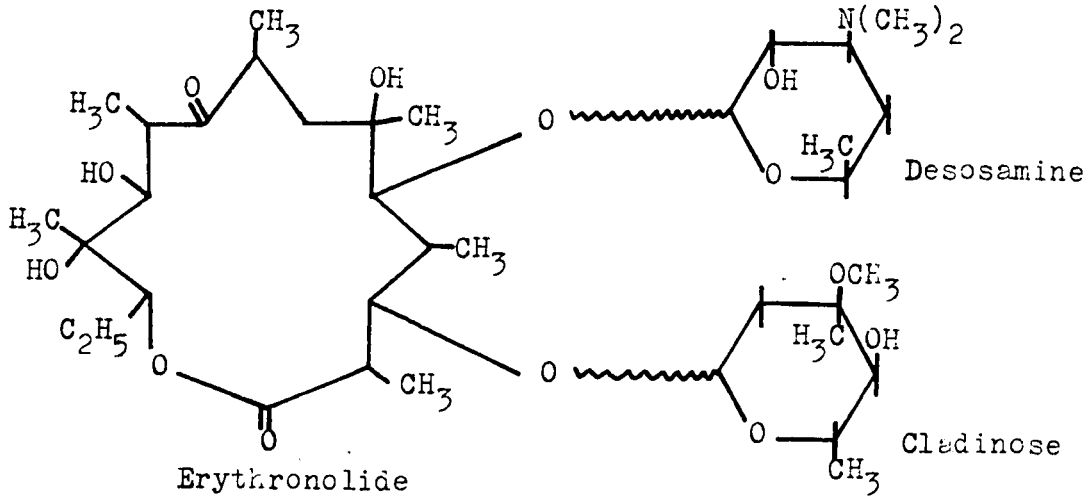
a. Mycarose

Mycarose is the neutral sugar moiety found in carbomycin, also known as magnamycin. Carbomycin was discovered in 1952 by Tanner et al. (16) and also found by Pagano, Weinstein and McKee (17) a year later. It is a metabolic product of strains of S. halstedii. Outstanding achievements in the elucidation of its structure (Fig. II) are due to Woodward and co-workers (22).

Methanolysis of the antibiotic yielded a crystalline base, called carimbose, $C_{30}H_{47}NO_{12}$, and an oily neutral substance, $C_{13}H_{24}O_5$, which is the 4-isovaleryl methyl glycoside of a branched-chain sugar (22). Alkaline hydrolysis of the neutral cleavage product gave isovaleric acid and anomeric methyl glycosides of which one was isolated in crystalline form. From this isomer, the crystalline reducing sugar, mycarose (II), was obtained. From the nature of oxidative degradation products and other analytical evidence, mycarose was shown to be a 2,6-dideoxy-3-C-methyl hexose, and on the basis of further degradation studies, it was assigned the L-xylo configuration (23). But concurrent nuclear magnetic resonance measurements (24) and synthetic studies (25) favoured the L-ribo configuration, and this was confirmed in more recent synthetic work



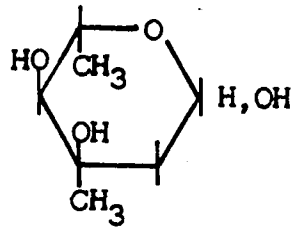
Carbomycin (Magnamycin)



Erythromycin

Fig. II.

by Williams and Overend (26). Mycarose is thus represented by formula II.

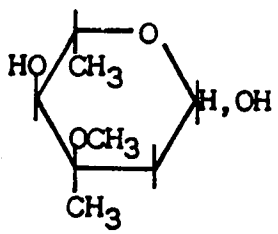


II

b. Cladinose

Erythromycin (Fig. II), isolated in 1952 by McGuire et al. (18) from culture filtrates of Streptomyces erythreus, exhibits similar antibiotic activities as carbomycin. On mild acid hydrolysis, a crystalline base, erythralosamine ($C_{29}H_{49}NO_8$) and a high-boiling liquid, cladinose, were obtained. Drastic hydrolysis of erythromycin or of erythralosamine furnished a complicated mixture of degradation products from which an amino sugar (desosamine, $C_8H_{17}NO_3$) was isolated (27,28,29).

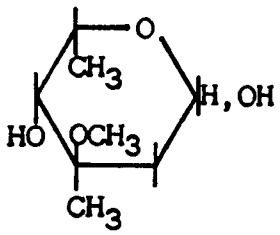
Cladinose has been shown to be 2,6-dideoxy-3-C-methyl-3-O-methyl-L-ribohexose (III) (30,31).



III

3. Arcanose in Lankamycin

Keller-Schierlein and co-workers reported the discovery of L-arcanose as a component of lankamycin, which was also obtained from Streptomyces (32,33). The structure of L-arcanose was later established and found to be related to cladinose, except that it has the L-xylo configuration. This was shown by n.m.r. studies of its di-O-acetyl derivative and by its chemical transformation into cladinose (34). Arcanose is 2,6-dideoxy-3-C-methyl-3-O-methyl-L-xylo-hexose (IV).



IV

4. Noviose in Novobiocin

The three antibiotics streptonivicin, cathomycin and cardelmycin, produced by Streptomyces niveus (35), Streptomyces sheroides (36) and a non-specified Streptomyces, respectively, were proved to be identical (37) and the antibiotic was later renamed as novobiocin. Novobiocin is active against many Gram-positive bacteria and inhibits a limited range of Gram-negative organism (38).

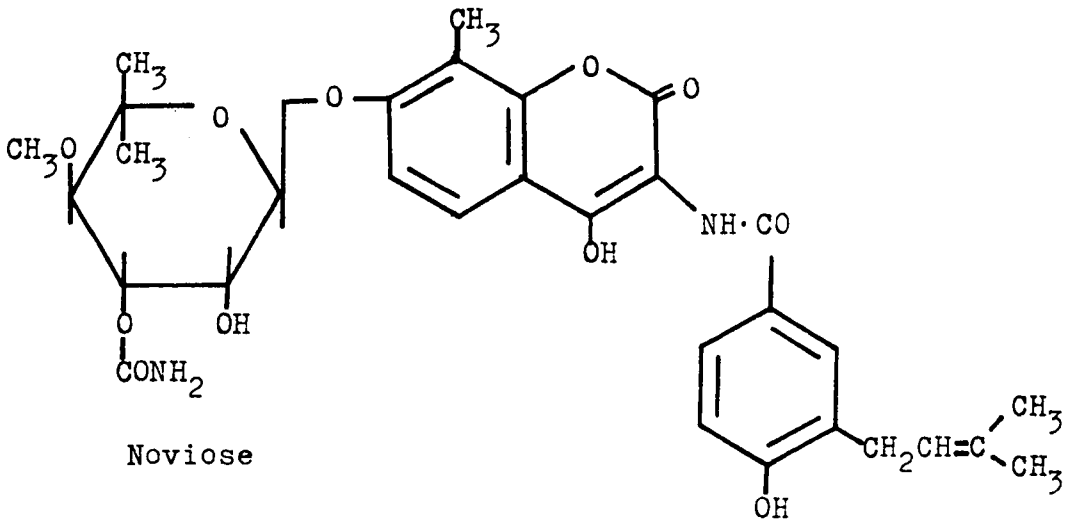
The molecule of novobiocin (Fig. III) is composed of three units, with a central heterocyclic moiety to which a substituted benzoic acid and a branched-chain sugar (noviose) are attached. The structure of the antibiotic was determined independently by Folkers et al. (39) and Hinman (40).

The structural elucidation of noviose, the glycosidic component in novobiocin, was done by degradation studies. The sugar has been shown to be 6-deoxy-5-C-methyl-4-O-methyl-3-O-carbamyl-L-lyxohexose (39,40,41,42).

5. Cordycepose in Cordycepin

Cordycepin is a metabolic product of the fungus Cordyceps militaris, it shows antibacterial activity against Bacterium subtilis strains and mycobacteria (43), and it has been examined for antitumor activity (44). It was shown to be a nucleoside of adenine and the branched-chain sugar named cordycepose. The efforts of Bentley and co-workers (45) led to the establishment of the structure of cordycepin as shown in Fig. IV.

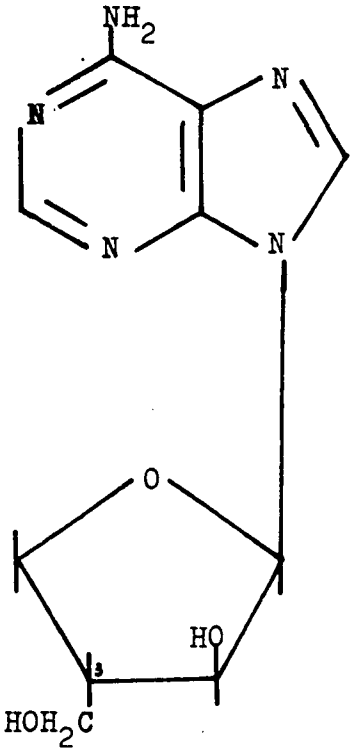
The structure of cordycepose (V) was deduced from acid hydrolysis and periodate oxidation studies of cordycepin as well as from bromine-water oxidation of cordycepose. The configuration of cordycepose at C-3 is still unknown (46,47, 48).



Noviose

Novobiocin

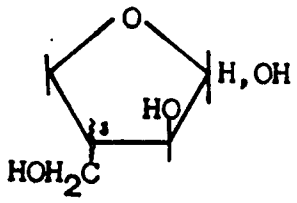
Fig. III.



(Configuration at C-3 unknown)

Cordycepin

Fig. IV



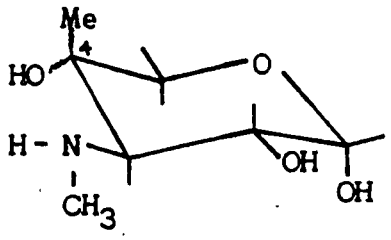
V

B. Nitrogenous branched-chain sugar

Garosamine in Gentamicin

Gentamicin C is a relatively new antibiotic complex which was isolated from fermentation fluid of Micromonospora and is active against gram-negative bacteria (49). The complex has been shown (50) to consist of at least two, closely related, nonreducing pseudotrisaccharides. The total structure is still under extensive study.

Methanolysis of gentamicin C yielded anomeric glycosides of a monosaccharide, methyl garosaminide, along with unidentified disaccharide fragments. The parent monosaccharide is designated as garosamine. Periodate oxidation studies on methyl garosaminide and n.m.r. studies on its N-acetate led to structure VI for garosamine; the configuration at C-4 is still unknown (51).



VI

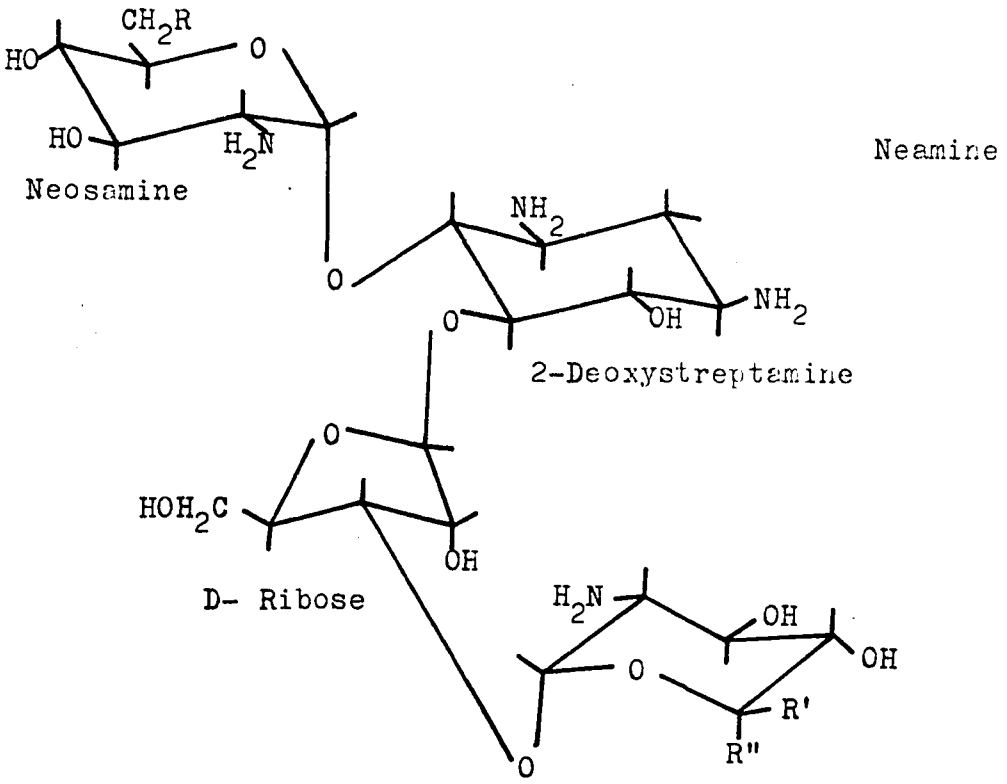
Garosamine is the first and only naturally occurring sugar which has been found to possess both a branched chain and a nitrogen function.

C. Diamino sugars

1. 2,6-Diamino Sugars in Neomycins and Paromomycins

a. In the Neomycins

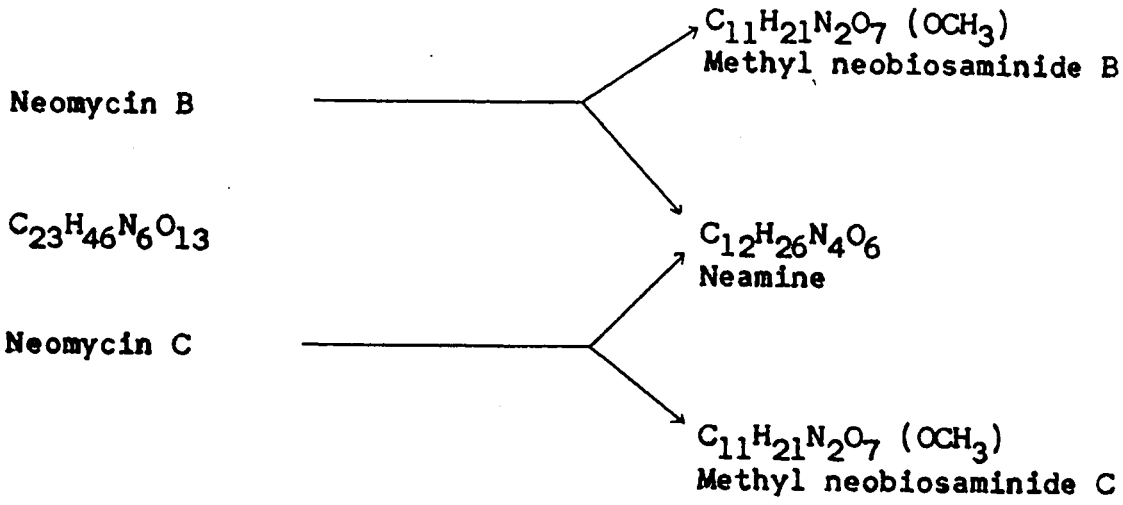
Neomycin, a basic antibiotic produced by Streptomyces fradiae, was isolated by Waksman and Lechevalier in 1949 (52). Further extensive investigations resulted in the separation, from the crude antibiotic, of three distinct entities, neomycin A (53), B (54) and C (55). Neomycin A (neamine) was subsequently identified as a common degradation product of neomycins B and C (56) (Fig. V). The structures of the neomycins were elucidated mainly by Rinehart (9,57,58).



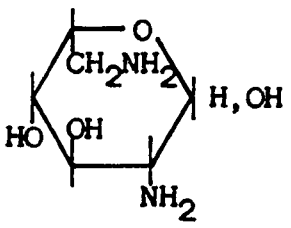
	R	R'	R"
Neomycin C	NH_2	CH_2NH_2	H
Neomycin B	NH_2	H	CH_2NH_2
Paromomycin II	OH	CH_2NH_2	H
Paromomycin I	OH	H	CH_2NH_2

Fig.V. Neomycins and Paromomycins

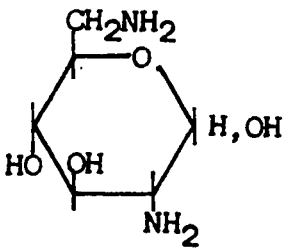
Neomycins B and C are cleaved to give two fragments, neamine and the methyl glycosides of neobiosamines (55).



Detailed degradation studies on both neosamines B and C permitted the assignment of the structure 2,6-diamino-2,6-dideoxy-L-idose (VII) (59,60,61) and 2,6-diamino-2,6-dideoxy-D-glucose (VIII) (62), respectively. Neomycin B and C are the first carbohydrate antibiotics to be known in complete stereochemical detail.



VII



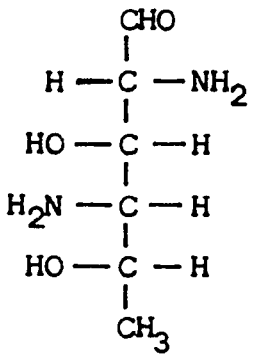
VIII

b. In the Paromomycins

Paromomycin, obtained by Frohardt et al. (63) in 1956 from culture filtrates of a strain of Streptomyces, contains two isomers, paromomycins I and II (57,64). The two antibiotics are a pair of epimers and both contain 2,6-diamino sugars as shown in Fig. V (58,63,65,66).

2. 2,4-Diamino Sugars (Bacillosamine) in Bacterial Polysaccharide

Jeanloz and Sharon, during their study of the acid hydrolysate of a polysaccharide from Bacillus subtilis (67), discovered a hexosamine fraction (68) which was different from either D-glucosamine or D-galactosamine, the two usual amino sugar components of complex polysaccharides. They were able to isolate this new amino sugar (bacillosamine) in pure form and identified it as a diamino-trideoxy-hexose (69). This is the first 2,4-diamino sugar ever isolated from a natural source. Further studies led to the establishment of the structure, 2,4-diamino-2,4,6-trideoxy-L-altrose (IX) (70).



IX

III. General Methods of Synthesis

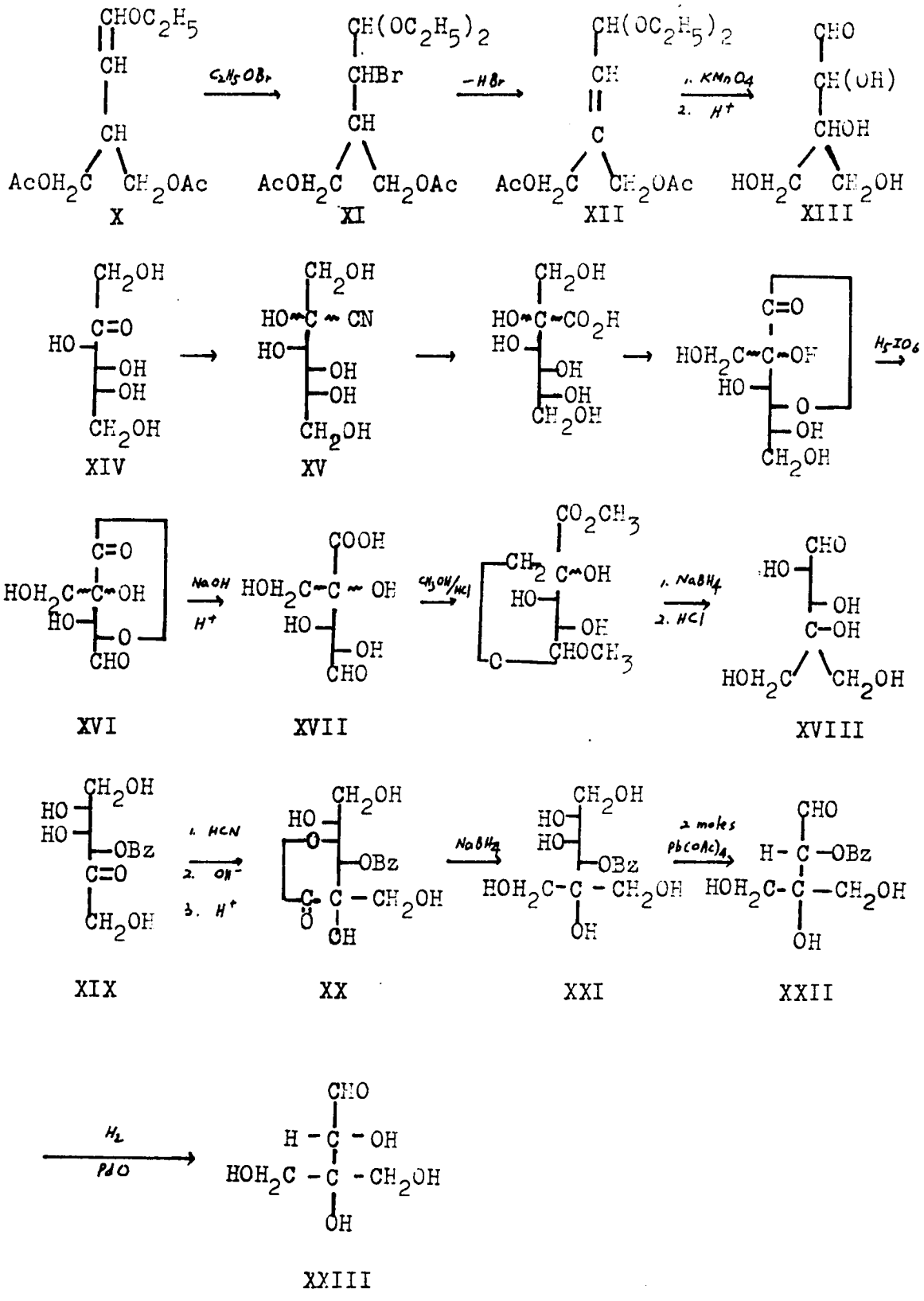
A. Methods for the Synthesis of Branched-chain Sugars and Branched-chain Amino Sugars

a. Synthesis of branched-chain sugars

Several possible routes to the synthesis of branched-chain sugars have been examined with success in the past two decades.

The first natural branched-chain monosaccharide to be synthesized was DL-apiose (71). By the action of ethyl hypobromite upon β,β-bis(acetoxymethyl)-propenyl ethyl ether (X), the corresponding saturated α-bromo-acetal (XI) was obtained. Dehydrobromination, hydroxylation and hydrolysis then gave DL-apiose (XIII).

DL-Cordycepose (72) has also been prepared from small units, namely, ethyl sodiomalonate and bromoacetaldehyde diethylacetal as starting materials. However, there are limitations in the utility of small building units for the synthesis of branched-chain sugars. Several groups of workers have therefore devoted considerable efforts to transforming derivatives of simple sugars of known configuration into branched-chain sugars and to date, this has remained the general approach.


X
XI
XII
XIII
XIV
XV
XVI
XVII
XVIII
XIX
XX
XXI
XXII
XXIII

(i) Cyanohydrin Reactions

A synthetic pathway to D-apiose was suggested by Woods and Neish (73). These workers prepared the cyanohydrin derivative (XV) of D-fructose (XIV) and, in a sequence of straightforward reactions (XIV to XVIII), transformed it to 4-C-(hydroxymethyl)-D-threo-pentose (XVIII). It was quite apparent that D-apiose should be obtainable from this new branched-chain sugar by a one-step descent of the chain. However, attempts to achieve this goal by Weerman degradation (74) or by partial lead tetraacetate oxidation (75) resulted in the production of only trace amounts of the desired product. An alternative synthetic approach, also involving cyanohydrin derivatives, was more successful (76). In it, 3-O-benzyl-D-fructose was transformed into 3-C-(hydroxymethyl)-D-glycero-tetrose (D-apiose) as shown in the sequence XIX $\longrightarrow$ XXIII.

(ii) Action of Organometallic Reagents upon Sugar Anhydrides and Oxo Sugars

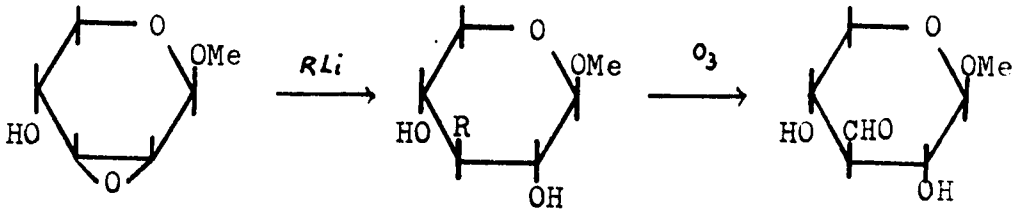
It is well known that anhydrides of the ethylene oxide-type can be prepared from carbohydrate derivatives, and the scission of such epoxides with a variety of organometallic reagents has been studied by several workers in the hope that a pathway to branched-chain sugars might be developed (77-80). C-Alkylation by the action of alkyl

magnesium halides on sulphonyl esters (81) did not succeed in the carbohydrate series (82).

Recently, Overend et al. (83) succeeded in preparing some branched-chain sugars by the scission of sugar epoxide with organolithium reagents. The major part of the work was carried out with methyl 2,3-anhydro-β-D-ribopyranoside (XXIV) and 2,2-dimethylvinyl-, phenylacetylene- and cis and trans-styryl lithium to give the corresponding C-alkylated products (XXV, XXVI, XXVII and XXVIII). The stereochemistry of the 3-C-substituted derivatives was correlated by converting them to the same methyl 3-deoxy-3-C-formyl-β-D-xylopyranoside (XXIX) by ozonolysis.

The introduction of branching into sugar by the action of organometallic reagents on another type of intermediates, namely, oxo sugars, is probably the most widely used and successful method.

Starting with methyl 3,4-O-isopropylidene-2-oxo-β-L-erythro-pentoside (XXX) (84), which was subjected to the action of various Grignard reagents, a number of 2-C-substituted sugar derivatives were isolated. The stereochemistry of two such compounds, namely, the 2-methyl- and 2-vinyl- derivatives (XXXVII and XXXI), was correlated by conversion to the same deacetonated product XXXVIII. Other Grignard reagents RMgX (R=Et, Ph, $-CH-CH=CH_2$, -CH=CH-Ph cis and trans, $-C\equiv C(CH_2)_3Me$ and $-C\equiv C$-Ph) also furnished the respective 2-C-alkylated products. Reduction of compound



XXIV

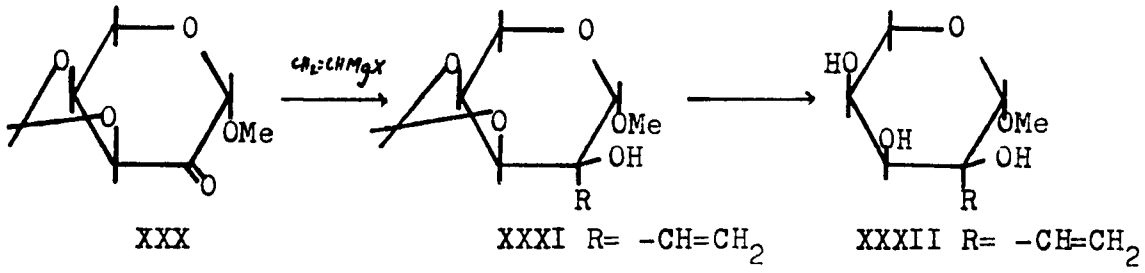
XXV R= $-CH=C(Me)_2$

XXVI R= $-C\equiv C-Ph$

XXVII R= cis $-CH=CHPh$

XXVIII R= trans $-CH=CHPh$

XXIX



XXX

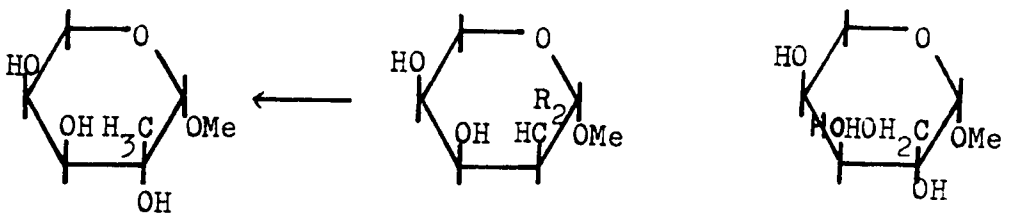
XXXI R= $-CH=CH_2$

XXXII R= $-CH=CH_2$

XXXVII

XXXIV

XXXIII



XXXVIII

XXXVI R= $-SCH_2C_6H_5$

XXXV

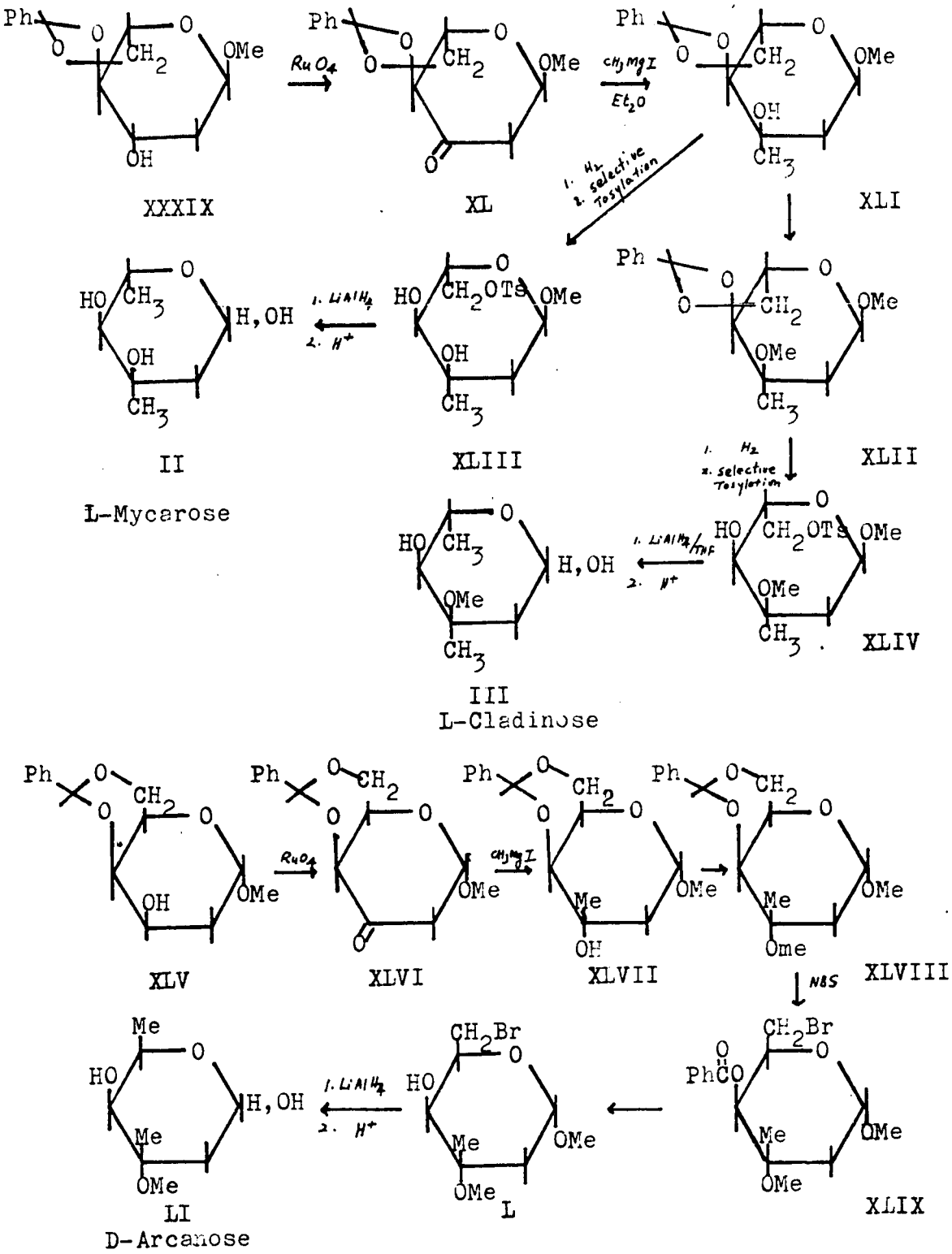
XXXIII gave a sugar with hydroxymethyl branching at C-2 (XXXV).

The deacetonated product XXXII has been used to synthesize L-hamamelose (85), the enantiomer of naturally occurring D-hamamelose from Hamameli tannin, by acid hydrolysis, sodium borohydride reduction and ozonolysis.

The application of the action of Grignard reagents upon appropriate oxo sugars enabled Jones and co-workers to accomplish the synthesis of L-mycarose and L-cladinose in 1967 (86) as well as D-arcanose in 1968 (87), the latter being the D-enantiomer of the branched-chain sugar in the antibiotic, lankamycin (32,33).

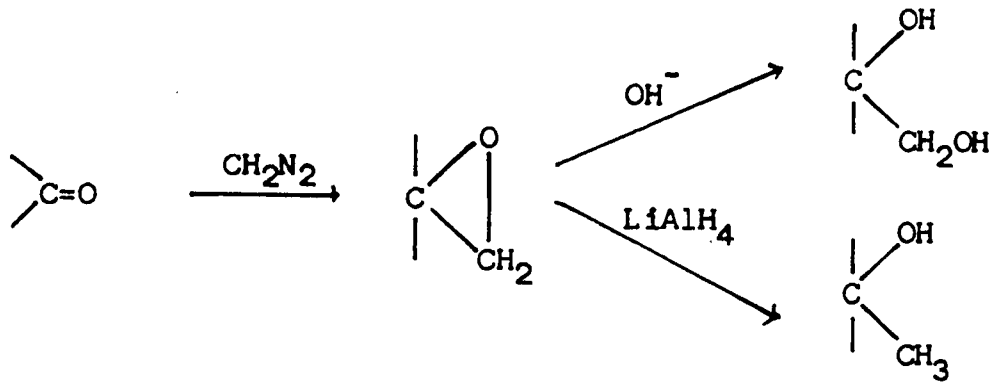
For the synthesis of L-mycarose and L-cladinose, methyl 4,6-O-benzylidene-2-deoxy-α-L-erythro-hexopyran-3-uloside (XL), obtained from oxidation of XXXIX with ruthenium tetroxide, was used as an intermediate. Reaction of the oxo sugar (XL) with methyl magnesium iodide introduced branching at C-3 to yield the 3-C-methyl-α-L-riboside (XLI). Identical sequential conversions on XLI and on its methyl ether XLII furnished L-mycarose (II) and L-cladinose (III), respectively.

Grignard reaction with the oxo sugar derivative XLVI followed by the reaction sequence XLVII $\longrightarrow$ LI afforded D-arcanose.


XXXIX
XL
XLI
II
L-Mycarose
XLIII
XLII
III
L-Cladinose
XLIV
XLV
XLVI
XLVII
XLVIII
XLIX
LI
D-Arcanose
L

(iii) Reaction of Diazomethane with Oxo Sugars

Another sequence of reactions performed on derivatives of oxo sugars provided branched-chain sugars as depicted below (88):



In this way a methyl or hydroxymethyl branching could be introduced readily. The reaction has been found to be less highly stereospecific than that between the oxo sugars and Grignard reagents. An illustrative example is the reaction between diazomethane and methyl 3,4-O-isopropylidene-β-D-<u>erythro</u>-pentopyranosidulose (LII) (89). The reaction gave a mixture of two isomeric methyl 2,2'-anhydro-2-C-hydroxymethyl-3,4-O-isopropylidene-β-D-pentosides (LIII and LIV). The major deacetonated product isolated was methyl 2-C-hydroxymethyl-β-D-ribopyranoside (LV), which was then hydrolyzed to D-hamamelose (LVI). Similar reactions with methyl 3,4-O-isopropylidene-β-L-erythro-pentopyranosidulose (XXX) afforded L-hamamelose (85).

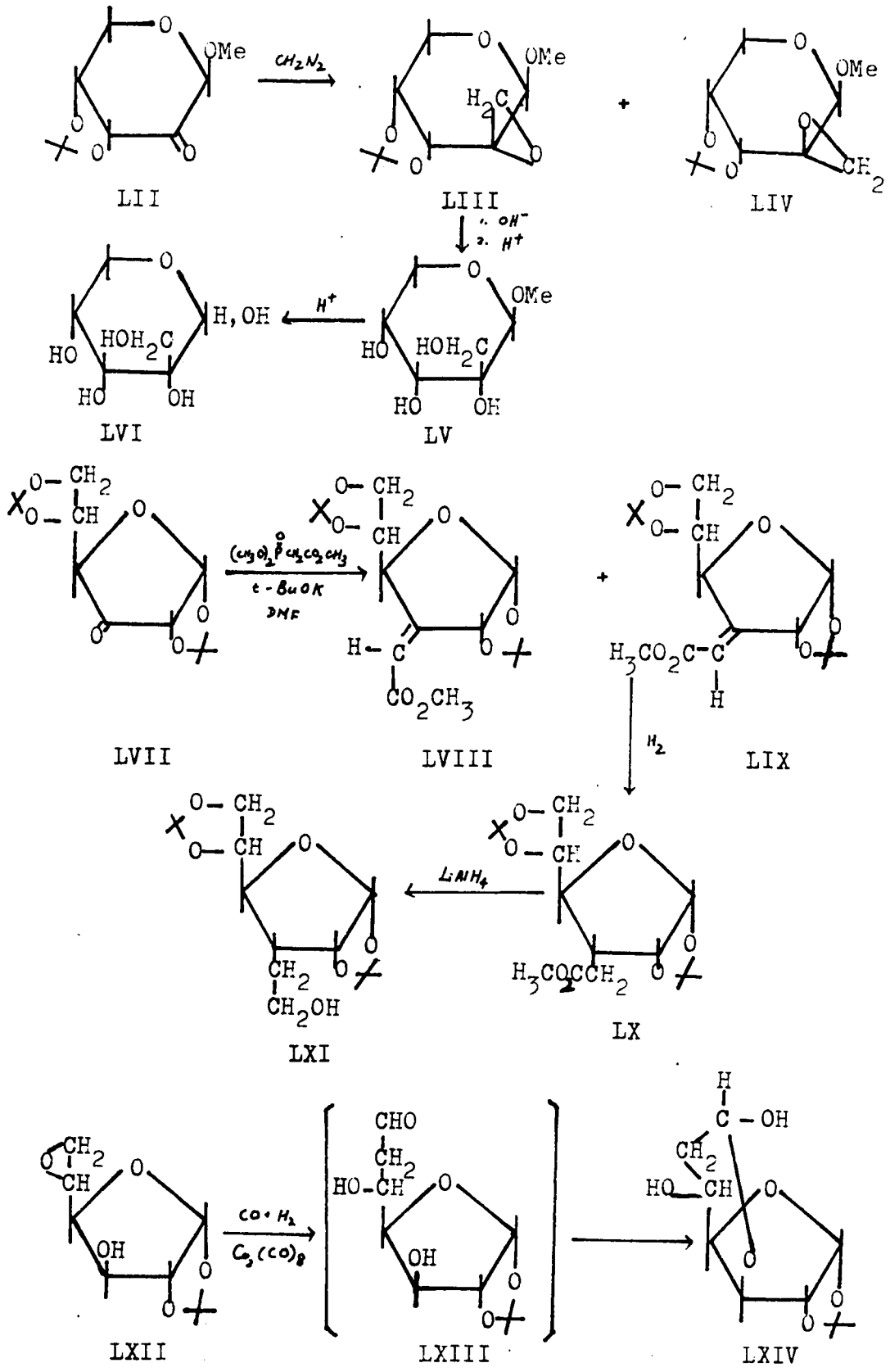
(iv) Miscellaneous Syntheses

1. Wittig reactions

The application of a modified Wittig reaction (90) to the oxo sugar LVII was investigated by Rosenthal (91). The reaction afforded novel branched-chain unsaturated sugars (LVIII and LIX), which were converted to the saturated branched-chain sugar (LXI) by catalytic hydrogenation followed by lithium aluminum hydride reduction.

2. Hydroformylation of carbohydrate epoxides

Rosenthal (92) hydroformylated 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose (LXII) in the presence of dicobalt octacarbonyl catalyst to introduce a terminal aldehydro group as in LXIII. Extension of this mode of reaction to sugars possessing an endocyclic rather than an exocyclic epoxy grouping would be expected to give branched-chain sugars. Indeed, hydroformylations of methyl 5-O-acetyl-2,3-anhydro-β-D-ribofuranoside and of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside gave branched-chain sugars, but the nature of the branching is still under investigation (92).

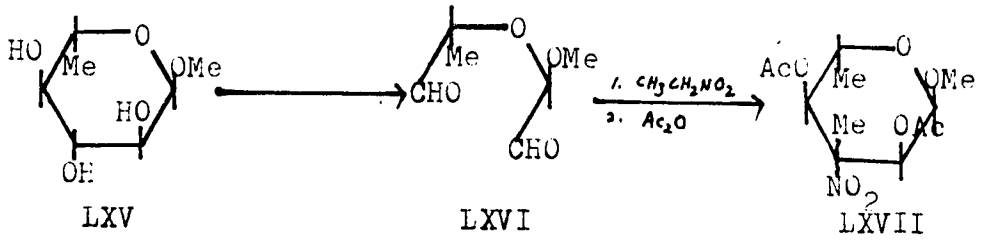

OMe
CH_2N_2
H_2C
LII
LIII
LIV
1. OH^-
2. H^+
H^+
H, OH
HOH_2C
HO
OH
LV
LVI
$(CH_3O)_2\overset{O}{P}CH_2CO_2CH_3$
t-BuOK
DMF
CO_2CH_3
LVII
LVIII
H_3CO_2C
LIX
H_2
$LiNH_4$
CH_2OH
H_3COCCH_2
LX
LXI
CO + H_2
$Co_2(CO)_8$
CHO
LXII
LXIII
LXIV

b. Synthesis of branched-chain amino sugars

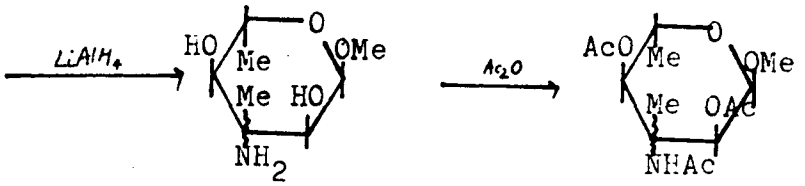
The alkali-catalyzed, twofold Henry condensation of nitromethane with sugar dialdehydes provides a facile method (93) for the incorporation of a nitrogen atom into sugar molecules (94-99) and nitroinositols (100). It was conceivable that the use of higher nitroalkanes in such cyclizations would lead to branched-chain nitro sugars and, upon subsequent reduction, to amino sugars.

In this manner, Overend et al. (101) cyclized the dialdehyde (LXVI) from periodate-oxidized methyl α-L-rhamnopyranoside (LXV) with nitroethane to the corresponding branched-chain nitro- and amino-sugars (LXVII and LXVIII).

Baer and Rao (102) studied the nitroethane cyclization of the sugar dialdehydes, D'-methoxy-D-hydroxymethyl-diglycolic aldehyde (LXX) and L'methoxy-D-hydroxymethyl-diglycolic aldehyde (LXXVII), obtained from methyl α-D-glucopyranoside and methyl β-D-glucopyranoside, respectively. The first dialdehyde (LXX) gave a crystalline product of the composition expected for a methyl 3-deoxy-3-C-methyl-3-nitro-hexopyranoside. The product was a molecular complex of the two diastereoisomers LXXI and LXXII. Reduction furnished the two corresponding amines LXXIII and LXXIV, which could be isolated. The reducing amino sugars (LXXV and LXXVI) that were obtained by acid hydrolysis of their respective glycosides turned out to be enantiomers of each other. The

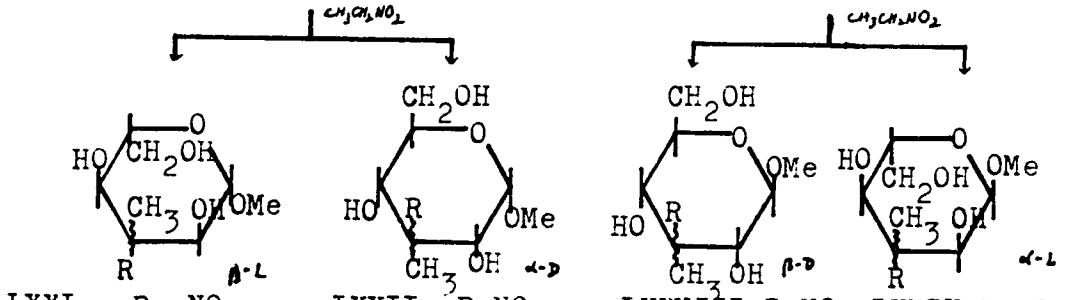


LXV LXVI LXVII



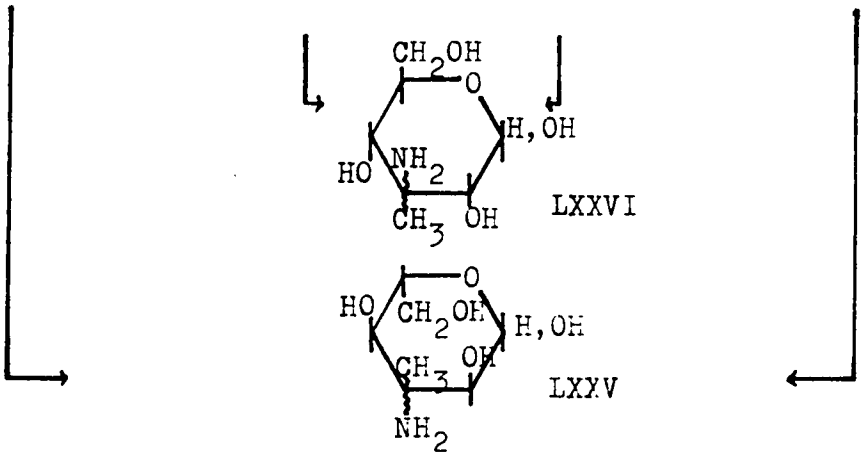
LXVIII LXIX

LXX LXXVII



LXXI R= NO_2 LXXII R=NO_2 LXXVIII R=NO_2 LXXIX R=NO_2

LXXIII R= NH_2 LXXIV R=NH_2 LXXX R=NH_2 LXXXI R=NH_2



LXXVI LXXV

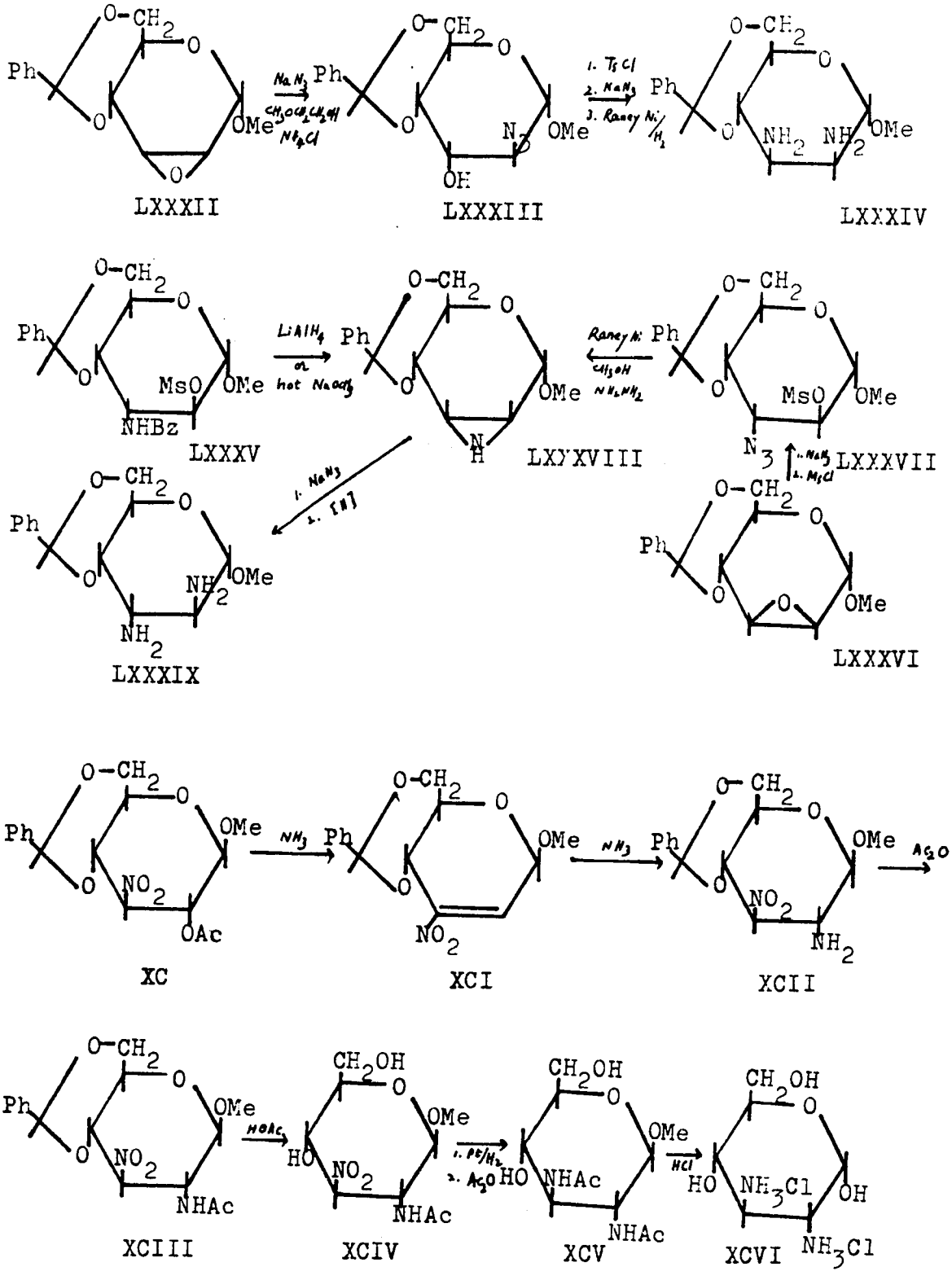
same sugars (LXXV and LXXVI) were obtained in an identical series of reactions starting from the second dialdehyde (LXXVII). Hence it had to be concluded that the dialdehydes had undergone, during the nitroethane reaction, partial epimerization at the carbon bearing the hydroxymethyl group (i.e., the carbon atom that becomes C-5 in the cyclized products). Such epimerizations had never been encountered in analogous syntheses with nitromethane.

B. Methods for the Synthesis of Diamino Sugars

Syntheses of a number of diamino sugars have been accomplished in recent years. 2,6-Diamino-2,6-dideoxy-D-glucose (103,104,105) and its stereoisomers with D-galacto (106,107), D-gulo (108), D-allo (109,110), D-manno (111,112, 113) and L-ido (113) configurations have been synthesized. As for 3,6- and 2,3-diamino hexoses, derivatives of the former class with D-ido (114,115,116a), D-gulo (115), D-allo (116b) and D-altro (117) configurations, and of the latter group, derivatives with D-allo (109,118), D-altro (119), D-manno (120,121) and D-gluco (109,119,122) configurations have been made. Since part of the experimental work of this thesis concerns the synthesis of 2,3-diamino sugar derivatives, this particular class of compounds will be briefly reviewed in the following sections.

The majority of the 2,3-diamino sugars described to date have all been obtained through displacement reactions on suitably substituted sugar sulfonates with or without neighboring group participation and with or without intermediary production of epimino derivatives (121,122, 123,124,125). The displacement reaction without neighboring group participation is best illustrated by the conversion of sugar anhydride LXXXII to 2,3-diamino sugar LXXXIV via double azide ion displacements (121). One of the displacement reactions with neighboring group participation and involving epimino intermediate is shown by the transformation of LXXXV and LXXXVII to LXXXIX (121).

Recently, an approach which involves nucleophilic addition of ammonia to suitable nitroolefinic sugar derivatives, proved very successful in the synthesis of 2,3-diamino sugars. Thus, Baer and Neilson (126) obtained methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (XCII) as the preponderant product when ammonia was added to the nitroolefin, methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-<u>erythro</u>-hex-2-enopyranoside (XCI). They found that the olefin need not be employed as such, but may be generated <u>in situ</u> from a more readily accessible precursor, methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (XC). The N-acetyl derivative (XCIII) of the addition product was converted in good yield into 2,3-diamino-2,3-dideoxy-D-glucose dihydrochloride (XCVI).


LXXXII
LXXXIII
LXXXIV
LXXXV
LXXXVIII
LXXXVII
LXXXIX
LXXXVI
XC
XCI
XCII
XCIII
XCIV
XCV
XCVI

SPECIFIC AIMS OF THIS THESIS

In view of the importance attached to branched-chain sugars and amino sugars in the field of the chemistry of antibiotics, it was decided to undertake synthetic studies aimed at augmenting our knowledge in these classes of carbohydrates. As has been outlined in the Introduction, many nitrogen-free branched-chain sugars on the one hand, and many straight-chain amino sugars including some diamino sugars on the other hand, have been found among antibiotics constituents, but so far, only one branched-chain monoamino sugar (Garosamine, p.15) has been encountered in nature, and few have been synthesized (p. 30). No branched-chain diamino sugars are known, and in the group of straight-chain diamino hexoses, that with the 2,3-diamino D-galacto structure (among others) is unknown. In consideration of these gaps in the literature the following plans were conceived:

1. To examine the possibility of synthesizing branched-chain dinitro sugars, as potential precursors for branched-chain diamino sugars, by applying to carbohydrates the Michael addition of nitroalkanes to nitroolefins;
2. To study the synthesis of new branched-chain mononitro and monoamino sugars by Michael and aldol-type reactions;
3. To perform a synthesis of 2,3-diamino-2,3-dideoxy-D-galactose.

RESULTS AND DISCUSSION*

PART I

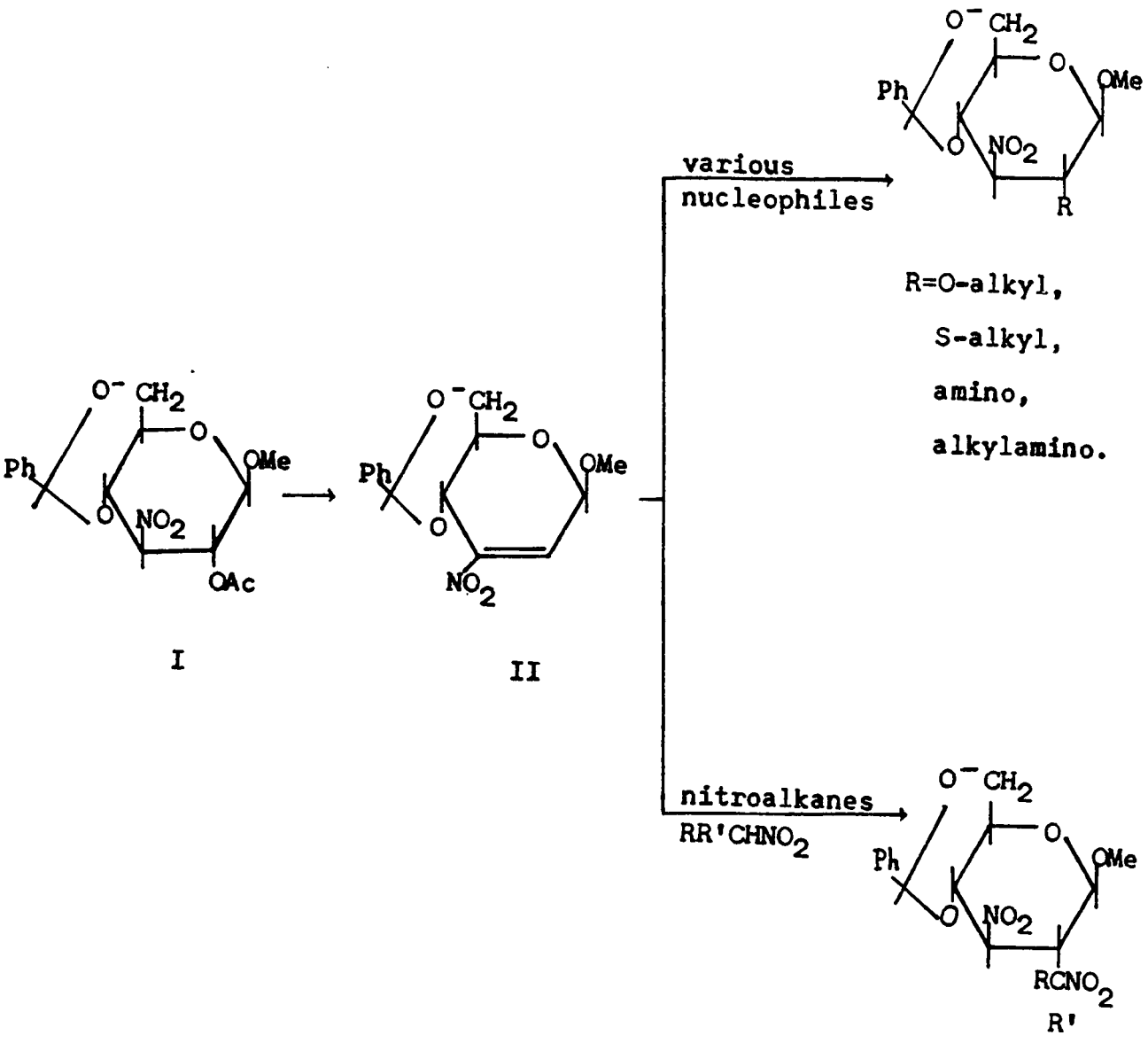
A. Branched-chain Dinitro Sugars by Michael Addition Reactions

1. Statement of the Problem

Previous work had shown that the unsaturated nitro sugar, methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-erythro-hex-2-enopyranoside (II), is capable of adding with great ease various nucleophiles such as alcohols, thio-alcohols, and amines. The products, 2-substituted 3-nitro sugar derivatives, are obtained also when II is not employed as such but generated in situ from methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (I) by base-catalyzed dehydroacetylation (126-128). It was well known, moreover, that simple α-nitroolefins undergo similar nucleophilic addition reactions with nitroalkanes to afford α,γ-dinitroalkanes (129), and it has been reported (130) that such Michael reactions, too, can be performed using β-nitroalkyl acetates instead of α-nitroolefins as starting materials. It was therefore

*For convenience, a new set of Roman numerals is adopted from hereon.

decided to attempt addition reactions of nitroalkanes with I or II (and with stereoisomers thereof), which would lead to 2-(α-nitroalkyl)-3-nitro sugars, i.e., branched-chain α,γ-dinitro sugars.



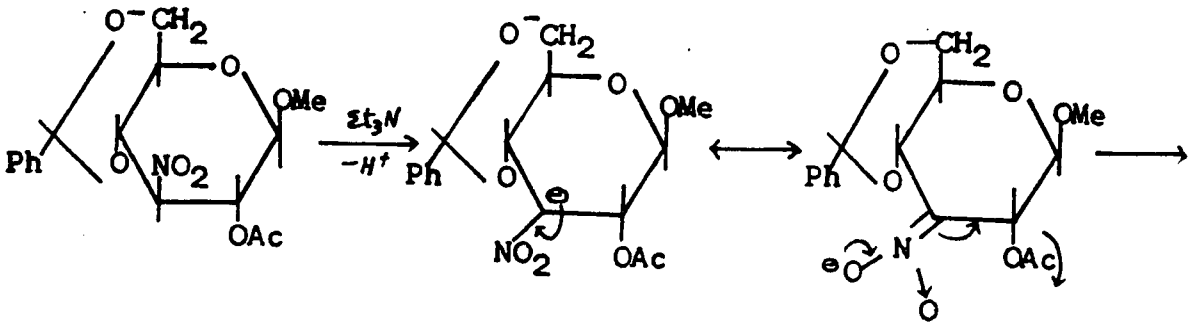
2. Synthesis of Methyl 4,6-O-benzylidene-2, 3-dideoxy-2-(1-nitroalkyl)-3-nitro-β-D-glucopyranosides

At the outset, the acetyl derivative I (131) was treated with sodium acetate and nitroalkanes in aqueous methanolic solutions, the conditions being those which had been elaborated for syntheses of dinitroalkanes (130). However, regardless of the nitroalkane employed the product was in all cases the methyl ether, methyl 4,6-O-benzylidene-3-deoxy-2-O-methyl-3-nitro-β-D-glucopyranoside, a known compound. Obviously, solvent methanol had added to intermediate II more rapidly than the nitroalkanes.

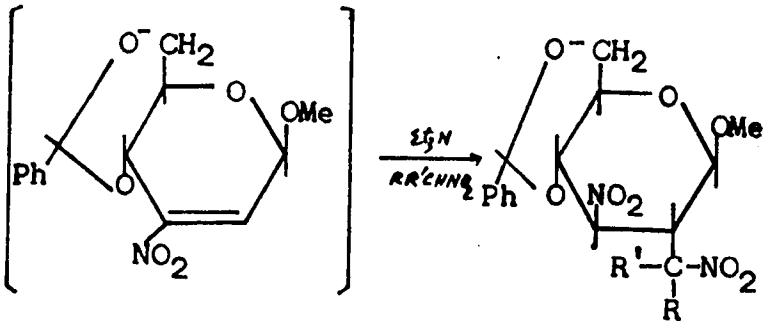
In order to prevent competition by a nucleophilic solvent, reactions of I with nitroalkanes were attempted in inert solvents. When I was refluxed in benzene in the presence of sodium acetate and sodium alkanenitronates, the starting material disappeared and a different product arose, as indicated by thin layer chromatography. However, the product upon isolation proved to be the known nitroolefin II, irrespective of the nitroalkane used. That is to say, dehydroacetylation of I had taken place as desired, but subsequent Michael addition to the olefin formed did not occur under these conditions. The dehydroacetylations were complete after 52, 20 and 3 hours in the presence of the aci-salts of nitroethane, 1-nitropropane, and 2-nitro-

propane, respectively. It is believed that these different reaction rates reflect differences in the alkalinity of the sodium nitronates, with the anion of 2-nitropropane being the strongest base. Performance of the reaction with sodium ethanenitronate at a higher temperature, namely, in refluxing toluene, shortened the time from 52 to 16 hours, but II was the only product in that case, too.

Success was finally achieved when the acetyl derivative I was dissolved in excess nitroalkane, which served as reactant and solvent, and when the elimination-addition process was catalyzed by triethylamine and allowed to proceed at room temperature. Nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane furnished the corresponding methyl 4,6-O-benzylidene-2,3-dideoxy-2-(α-nitroalkyl)-3-nitro-β-D-glucopyranosides (III, IV, V, VI) in yields of 60-85% (III-V) and 45% (VI) according to the following scheme.



I



II

III R=R'=H

IV R=H, R'=CH_3

V R=H, R'=C_2H_5

VI R=R'=CH_3

The formation of the branched-chain dinitro glycosides generally was complete within 16 hours and could be monitored by thin layer chromatography on silica gel, on which they travelled faster than the starting compound I. The products crystallized without difficulty and gave correct elemental analyses. The most significant infrared data are compiled in Table III. It can be seen that the dinitro sugars exhibited double bands in the region of the asymmetric nitroalkane vibration (1544-1575 cm^{-1}) while the ester carbonyl peak characteristic of I (1730 cm^{-1}) was no longer present.

3. Stereochemical Considerations

Since the formation of the products (III-VI) undoubtedly proceeded via the 2,3-unsaturated intermediate II, the process involved generation of asymmetric centers at C-2

TABLE III

Asymmetric nitro and other characteristic infrared frequencies (cm^{-1}) in Nujol

III	1575, 1550 (NO_2); 1095, 1085 (C-O-C); 795, 695 (phenyl)
IVa*	1565, 1552 (NO_2); 1080 (C-O-C); 770-750 (three bands, phenyl)
IVb**	1563, 1550 (NO_2); 1100 (C-O-C); 750 (phenyl)
V	1562, 1554 (NO_2); 1080 (C-O-C); 742, 690 (phenyl)
VI	1562, 1550 (NO_2); 1095, 1085 (C-O-C); 770, 710 (phenyl); 1385, 1375 (gem-dimethyl splitting of 1380)

---

* m.p. 169-170°

**m.p. 134-135°

and C-3. It was therefore necessary to prove the configurations at these carbons, although it could be anticipated with some degree of certainty that the nitro and nitroalkyl substituents had adopted the most favorable, equatorial orientation, thus placing the compounds into the D-gluco series as depicted in the formulas. That this would probably prove to be the case could be assumed considering the results of the previous additions, of other nucleophiles to the same nitroolefin II, which had led to gluco adducts (126-128). The assumption was borne out by n.m.r. spectroscopy as will be discussed on the following pages.

Another point of stereochemistry must be considered. Compound IV and V, obtained from nitroethane and 1-nitropropane, respectively, contain an asymmetric carbon atom in their side chains. On account of this, two epimeric forms are theoretically still possible for each of these two adducts even when there is no stereoisomerism as far as the sugar ring is concerned. Whether there would in fact arise, in these particular reactions, mixtures of such side-chain epimers, or whether one epimer would be strongly favored was difficult to predict. Evidence will in a subsequent paragraph be presented for side-chain epimers existing in IV, whereas no such evidence was uncovered for V.

4. Proof of the D-gluco Configuration in Compounds III-VI

The D-gluco configuration in the branched-chain dinitro sugar derivatives (III-VI) was ascertained by n.m.r. spectroscopy. First of all, the spectra confirmed certain structural features which were common to all of the compounds and which were expected to be present in view of the latters' origin and mode of synthesis. Thus, signals of integrated intensity corresponding to five protons, representing the phenyl group of the benzylidene acetal, are seen at lowest field, and the benzylic proton of that acetal structure appears as a sharp singlet near 4.40 τ. All spectra exhibit a three-proton singlet near 6.2-6.6 τ, caused by the glycosidic methoxyl group (Fig. VI-IX and Table IV). The assignments mentioned could readily be made on the basis of well-documented precedence (132,133). The various nitroalkyl side chains, the only structural feature in which compounds III-VI differed from one another, gave rise to signals that will be discussed individually later on, but it may be mentioned already at this point that they were in full agreement with the formulas depicted.

The signals associated with substituents having been accounted for, the remaining signals had to be attributed to the ring protons and the protons at C-6.

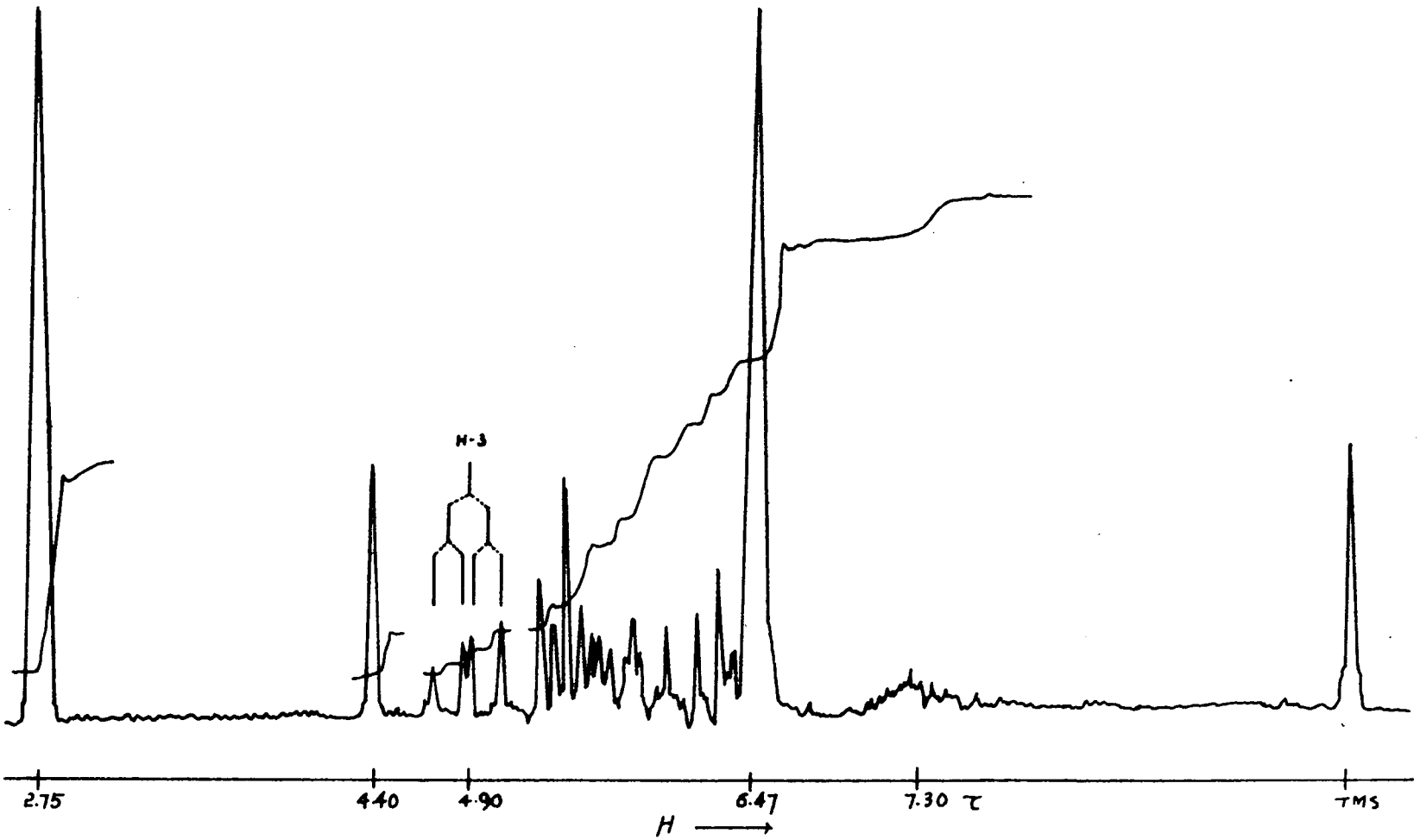


Fig. VI. N.M.R. spectrum of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-nitromethyl-β-D-glucopyranoside (III) in deuteriochloroform

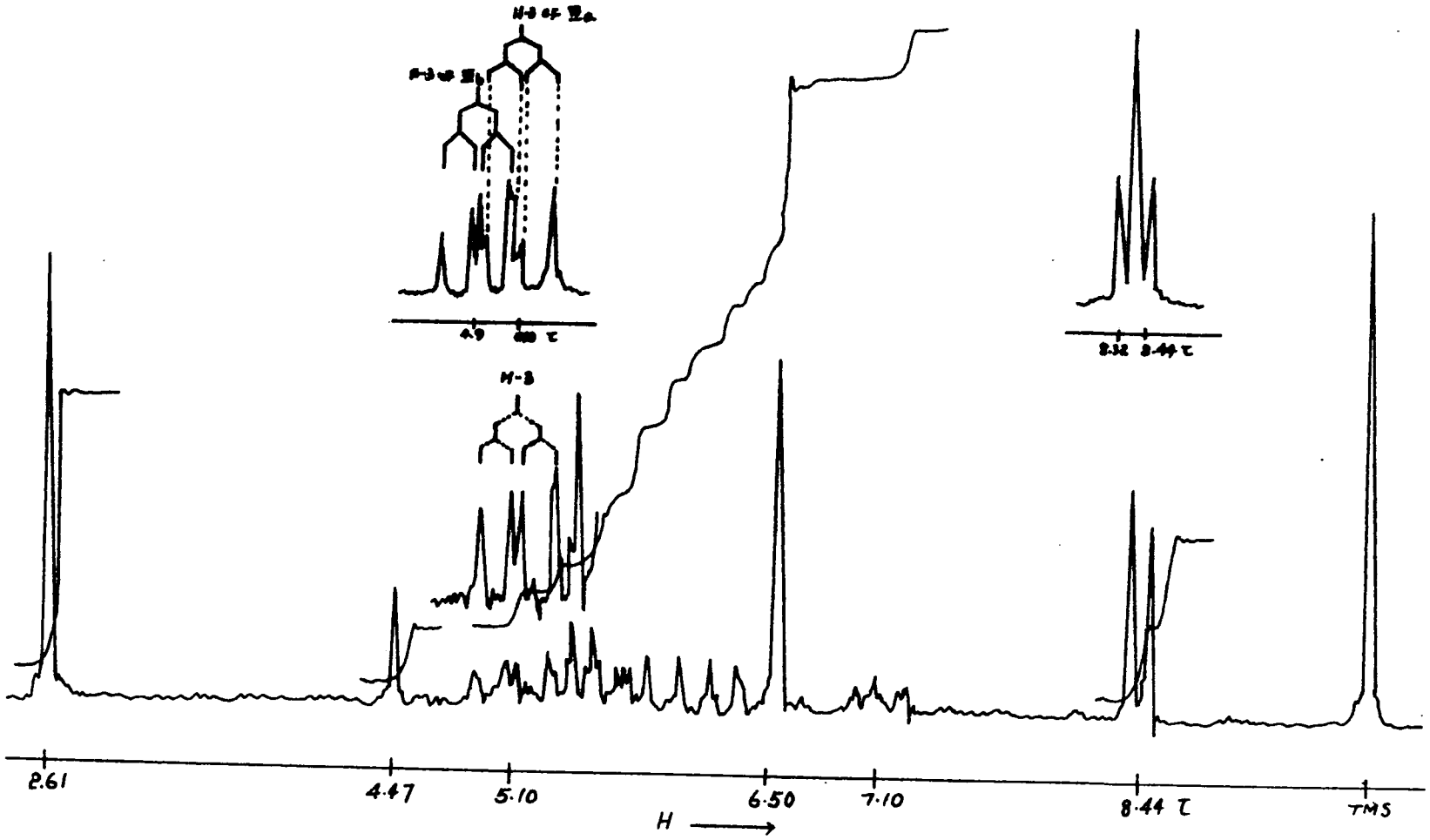


Fig. VII. N.M.R. spectrum of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-nitroethyl)-β-D-glucopyranoside (IVa) in deuteriochloroform.

Insert: Crude product (IVa and IVb)

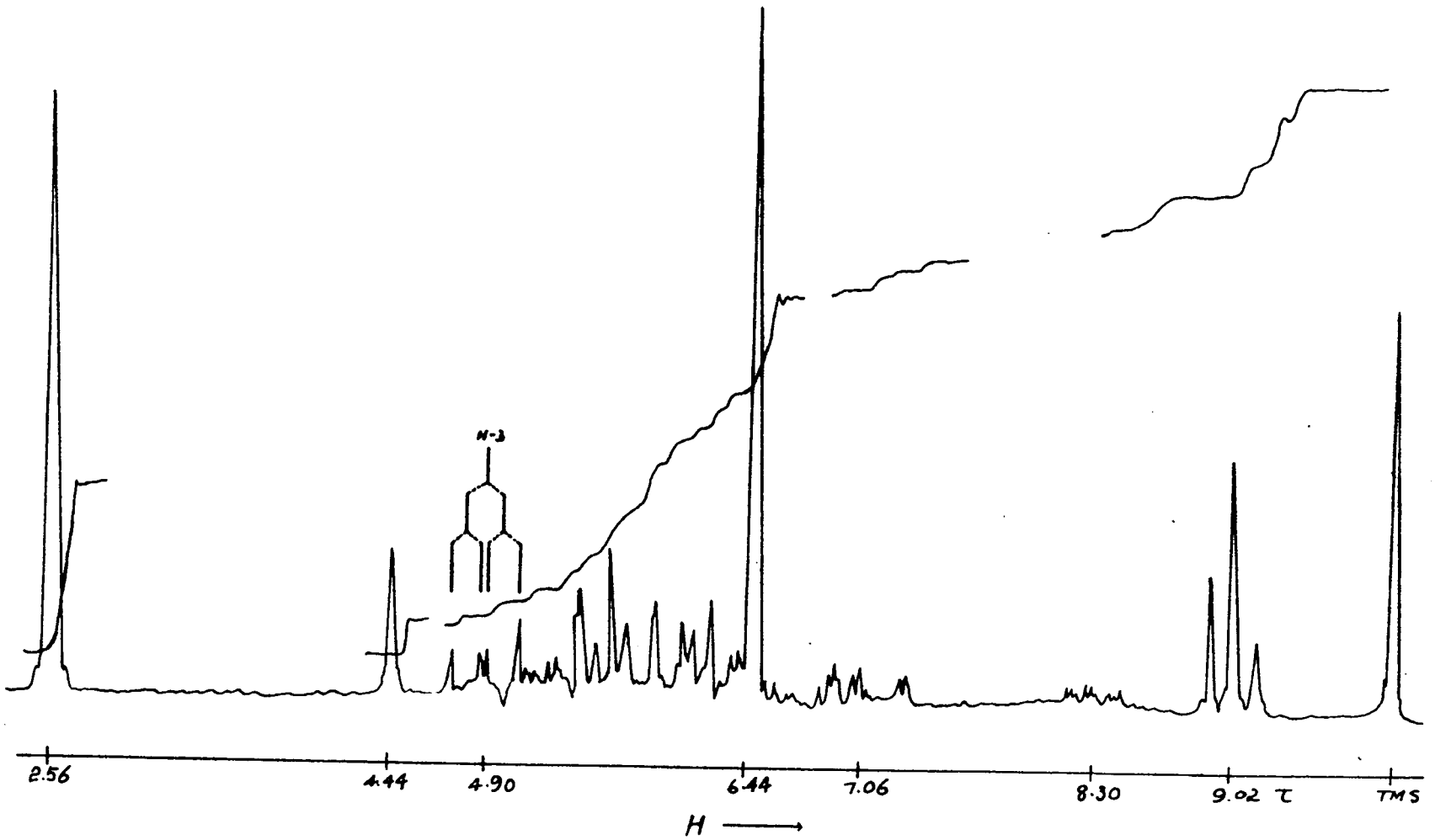


Fig. VIII. N.M.R. spectrum of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-nitropropyl)-β-D-glucopyranoside (V) in deuteriochloroform

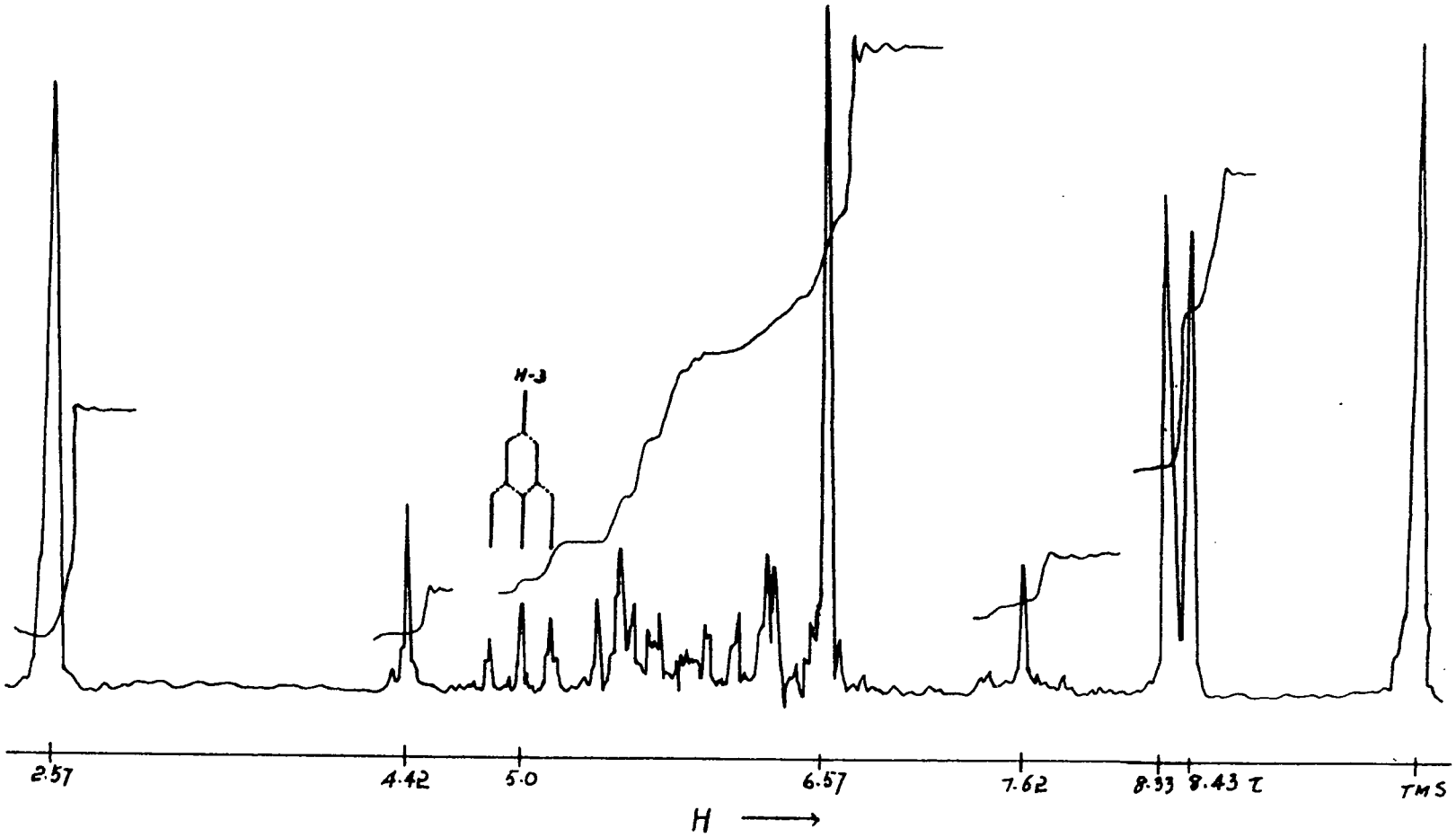


Fig. IX. N.M.R. spectrum of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-methyl-1-nitroethyl)-β-D-glucopyranoside (VI) in deuteriochloroform

TABLE IV

Chemical shifts (τ values) and relative intensities of substituents signals (number of protons in parentheses), in deuteriochloroform

	Phenyl	Ph-C<u>H</u>=O_2	O-CH_3	C-CH_3
III	2.75(5)	4.40(1)	6.47(3)	
IVa*	2.61(5)	4.47(1)	6.50(3)	8.44(3)**
V	2.56(5)	4.44(1)	6.44(3)	9.02(3)***
VI	2.57(5)	4.42(1)	6.57(3)	8.33(3), 8.43(3)

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* Major component m.p. 169-170°

** Doublet with spacing 7 c.p.s.

*** Triplet with spacing 7 c.p.s.

Most of these signals were bunched together in the 5-6.4 τ region so that individual assignments were difficult to make. Fortunately, however, there was one signal in each spectrum that was clearly set apart from the rest. It was a symmetrical one-proton triplet or quartet occurring near 4.9 τ, i.e., at lowest field excepting the benzylidene group signals. The signal was well separated from those adjoining upfield, or at least sufficiently so for its character to be readily discernible (Fig. VI-IX). By its chemical shift and multiplicity the signal was established to belong to H-3, the proton on the ring carbon bearing a nitro group. In another, similar series of 3-deoxy-3-nitro glycosides, H-3 has likewise been found to resonate at lower field than the remaining ring hydrogens (127). In the present case the following values were found for H-3:

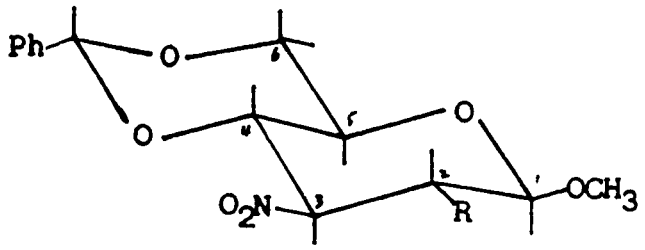
III: quartet centered at 4.9 τ; spacings, 10.0 and 11.8 cps.
IV*: quartet centered at 5.1 τ; spacings, 10.0 and 11.7 cps.
V: quartet centered at 4.9 τ; spacings, 9.7 and 11.3 cps.
VI: triplet centered at 5.0 τ; spacings, 10.0 and 10.0 cps.

According to the Karplus relation (132,133), it follows from the large spacings that H-3 is axially oriented and coupled with <u>axial</u> protons H-4 and H-2. The

---

* Predominant epimer; see p.51.

axial orientation of the hydrogen at C-4 had of course been known before since this center was not involved in the chemical reaction. The demonstration of axial protons, and hence equatorial substituents, at C-3 and C-2 in compounds III-VI unequivocally proves the gluco configuration.



III - VI, R = 1-nitroalkyl

5. The Individual Compounds (III-VI)

a. Methyl 4,6-O-benzylidene-2,3-dideoxy-2-(nitromethyl)-3-nitro-β-D-glucopyranoside (III) was obtained in a yield of 67%. It had m.p. 168-170° and $[\alpha]_D$ -74.6° (c, 1.0 in chloroform). The n.m.r. spectrum (Fig. VI and Table IV) exhibited, besides the features discussed in the preceding Section 4, a one-proton multiplet centered at 7.3 τ. This signal was attributed to H-2, the multiplicity being

caused by coupling with H-1, H-3 and the two protons of the nitromethyl group. Signals for the latter two protons apparently were bunched together with ring protons in the 5-6.4 τ region.

b. Methyl 4,6-O-benzylidene-2,3-dideoxy-2-(1-nitroethyl)-3-nitro-β-D-glucopyranoside (IV) represented a special case in this series. The crude product was obtained in a yield of 84.5%. It was free from starting material as judged by thin layer chromatography, gave correct elemental analyses, and exhibited an n.m.r. spectrum which, generally speaking, was in line with expectations. Yet, the product was not uniform: although it appeared to travel as a single spot on 7.5 -cm thin layer plates, two ill-separated spots developed on 20 -cm plates. Furthermore, a closer inspection of the n.m.r. spectrum suggested that the crude product contained two components, for the quartet centered at 5.1 τ and assigned to H-3 was partially overlapped by a similar but weaker quartet centered at 4.9 τ, the combined intensities of the two quartets corresponding to one proton.

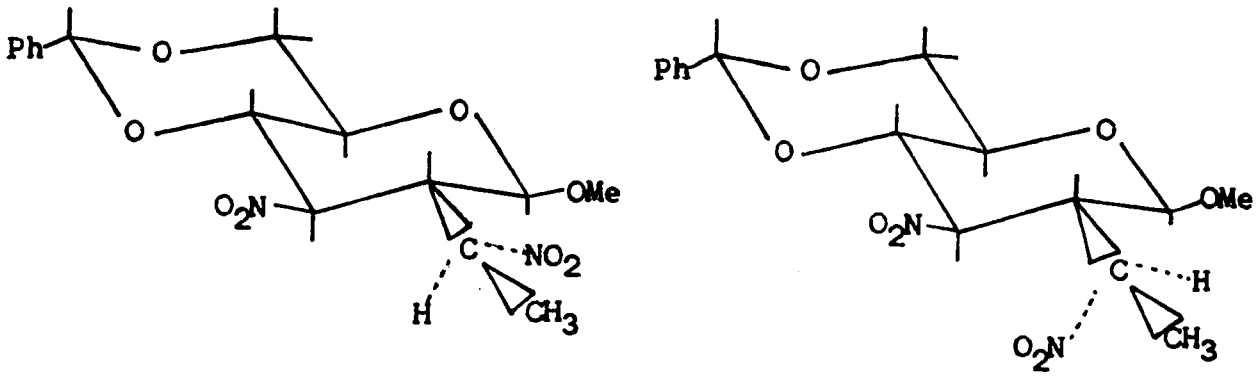
Fractional crystallization of crude IV led to the isolation of one chromatographically uniform compound. It represented the faster-moving component of the mixture, melted at 169-170° and had $[\alpha]_D$ -71.2° (c, 1.0 in chloroform). Designated now as IVa, this compound was found to be the one which gave the H-3 quartet at 5.1 τ. The methyl

portion of its nitroethyl group produced a sharp doublet (intensity, 3 protons) at 8.44 τ with a splitting of 7 cps caused by coupling with the neighboring α-hydrogen (Fig. VII).

The second component contained in crude IV could not be isolated in pure state. The fractional crystallization yielded, in addition to pure IVa, a fraction of crystals showing a reasonably sharp melting point (133-134°). However, thin layer chromatography revealed that these crystals, although enriched in the slow-moving component (now designated as IVb), still contained a considerable amount of IVa, and attempts at further separation failed. It can nevertheless be stated that IVb, like IVa, possesses the gluco configuration, since the quartet centered at 4.9 τ and assigned to its H-3 shows large splittings indicative of axial protons at C-2, C-3 and C-4. Consequently, IVa and IVb must be a pair of side-chain epimers. The small but significant difference in chemical shift observed for the H-3 protons no doubt is due to the configurational nonequivalence of the nearby side-chains. Conversely these structurally identical but enantiomorphic nitroethyl groups experience nonidentical chemical shifts in their asymmetric environments: the methyl doublet of IVa (at 8.44 τ) is superimposed, in the spectrum of the mixed crystals, by a doublet stemming from IVb (at 8.32 τ). Since, in a

fortuitous way, the chemical shift difference very nearly equals the coupling constant (6.5 cps), the two signals combine to give the appearance of a symmetrical triplet.

The infrared spectrum in Nujol of the mixed crystals (IVa and IVb) differs slightly from the spectrum of the pure epimer IVa (Fig. X). Noteworthy are differences in the intensity ratios of two asymmetric nitro vibrations at 1565 and 1552 cm^{-1}, and 1563 and 1550 cm^{-1}, and different patterns in the 750 cm^{-1} region.



IVa or vice versa IVb

It appeared of interest to study whether different conditions in the production of IV would lead to a similar mixture of epimers or whether one of the epimers might perhaps be formed to the exclusion of the other. When nitro-

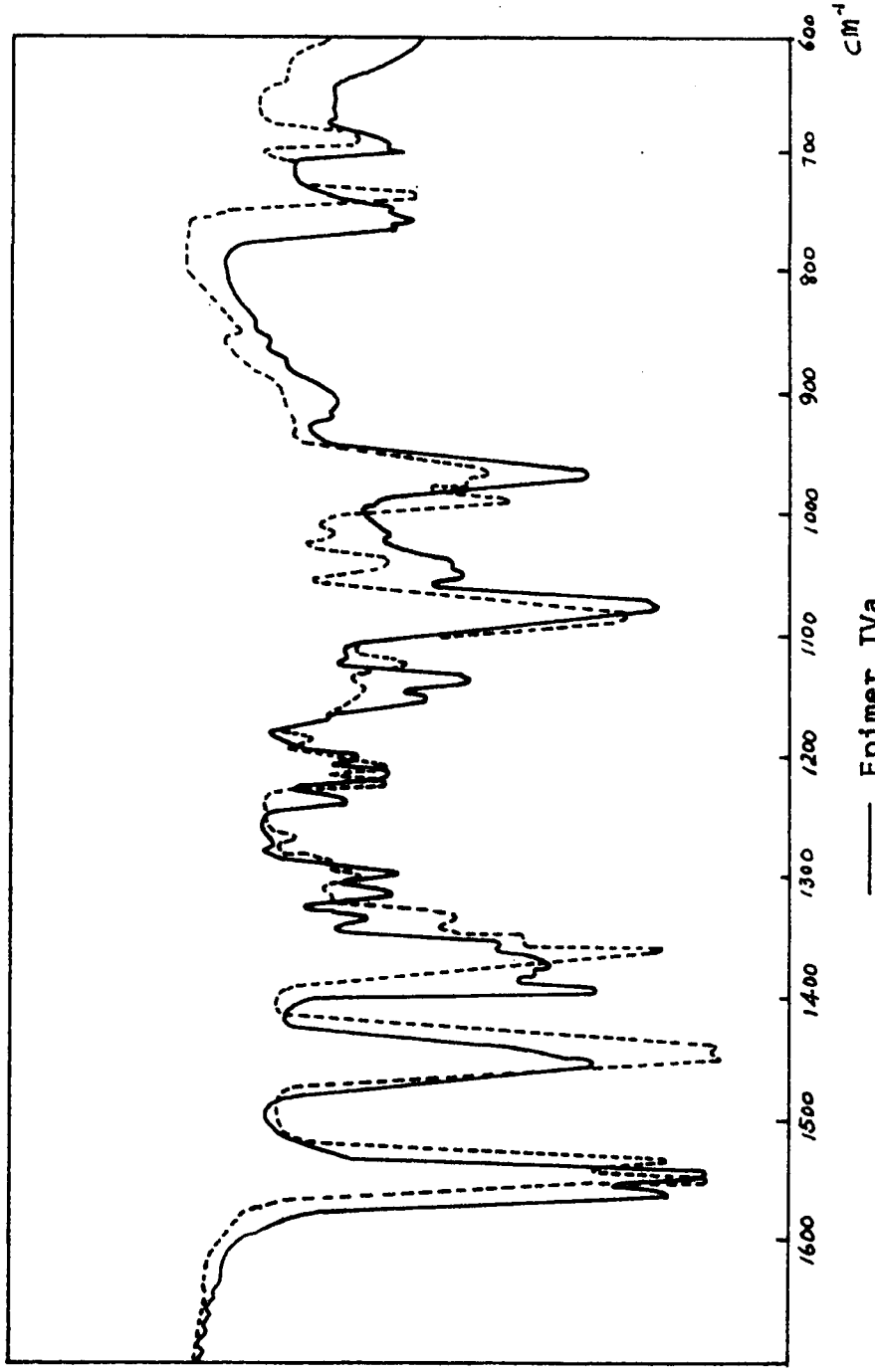


Fig. X. Infrared spectra of pure epimer IVa and mixed crystals (IVa and IVb) in Nujol mull

ethane was allowed to react, not with the acetate I but with the olefin II, thus circumventing the dehydroacetylation and starting immediately at the stage of the addition reaction, the time required was reduced to 30 minutes. It was thought that, if one epimer was favored kinetically and if thermodynamic equilibrium was not reached in this short reaction period, the product composition should be different. However, this was not the case: the chromatographic and spectroscopic pictures of crude IV obtained in this way were unchanged.

c. Methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-nitropropyl)-β-D-glucopyranoside (V) was obtained as a chromatographically homogeneous product in 60% yield. It melted at 184° and showed $[\alpha]_D$ -67.0° (c, 1.3 in chloroform). Although the possibility of side-chain epimerism existed in this case like in the nitroethyl analog, no evidence for the formation of a second isomer was found. The n.m.r. spectrum of V (Fig. VIII and Table IV) showed a triplet of three-proton intensity at 9.02 τ. It was split by 7 c.p.s. and signified the methyl portion of the nitropropyl chain. The methylene portion of that chain gave a multiplet centered at 8.3 τ, with splitting caused by the adjacent methyl group and α-hydrogen. Another multiplet occurred around 7.06 τ and was assigned to ring proton H-2.

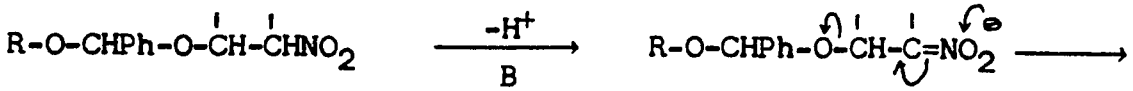
The configuration in the side-chain of V has not been determined, nor has it been investigated whether epimers might arise under other reaction conditions.

d. Methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-methyl-1-nitroethyl)-β-D-glucopyranoside (VI) was less readily obtained than the aforementioned analogs. Using essentially the same reaction conditions (which involved the presence of one molar equivalent of triethylamine), the reaction between I and 2-nitropropane did not give satisfactory results. Although thin layer chromatography suggested that VI was formed, there remained unreacted starting material and, apparently, some nitroolefin II, making VI difficult to isolate. Increase of the amount of triethylamine to 2.5 molar equivalents, however, led to isolation of VI in a yield of 45%. Probably the lesser ease of formation is connected with the greater bulk of the addend and with its smaller acidity.

Compound VI showed m.p. 187.5-189.5° and $[\alpha]_D$ -92.7° (c, 1.0 in chloroform). The n.m.r. spectrum showed two high field singlets, each of three-proton intensity, at 8.33 and 8.43 τ which were attributable to the geminal methyl groups of the side chain (Fig. IX). The hydrogen at C-2 appeared as a poorly resolved signal, presumably a triplet, at 7.62 τ.

6. Synthesis of Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-(1-nitroalkyl)-3-nitro-β-D-galactopyranosides

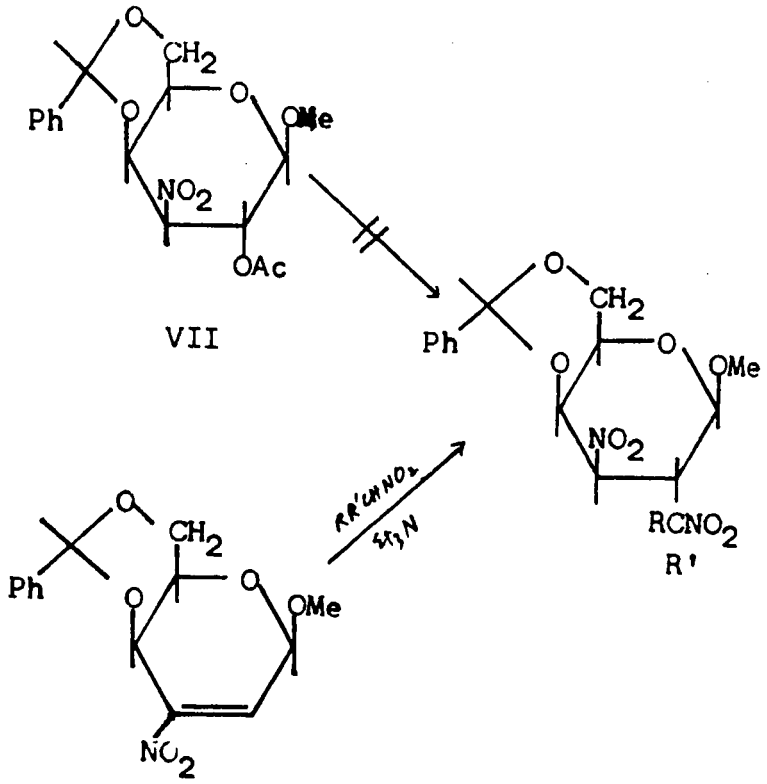
Next, it was deemed desirable to extend the work just described to another configurational series. The D-galacto isomer of I, methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-galactopyranoside (VII) was available (134) and seemed to offer itself for that purpose. However, its use was unsuccessful under the reaction conditions elaborated for the gluco isomer. The reactions were accompanied by decomposition, liberation of benzaldehyde was noticed, and no identifiable dinitro sugars could be isolated. The release of benzaldehyde gave a clue as to what happened in these instances. It is known that acetal linkages activated by a nitro group in β-position are liable to be cleaved by base. This cleavage, several examples of which have recently been encountered (135,136,137) is a β-elimination quite analogous to the β-elimination of acyloxy groups:



Now, one would normally expect an acetal to suffer such elimination less readily than an ester function. Indeed, the benzylidene acetate I can be converted into the benzylidene olefin II by the action of sodium bicarbonate in benzene, and in the elimination-addition reactions between I and nitroalkanes described in the preceding sections, the benzylidene blocking group proved stable, at least to the extent that was reflected in the good yields of products III-VI. Therefore, when the experiments with the galacto isomer VII resulted in debenzylidenation (which, in turn, doubtless caused further complications), we were surprised at the unexpected ease of this competitive event although its occurrence could be understood in principle. It is to be noted that the only stereochemical difference between I and VII is an equatorial acetal bond at C-4 in the former versus an axial one in the latter, and the observed differential resistance of these bonds toward base-catalyzed elimination is an interesting phenomenon, to be remembered in future synthetic projects of a similar nature.

The synthesis of branched-chain dinitro sugars in the D-galacto series eventually succeeded with the use of the nitro olefin VIII as starting material. This compound, methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-threo-hexopyranos-2-enide (138) readily added the three primary nitroalkanes (nitromethane, nitroethane and 1-nitropropane)

to give crystalline 4,6-O-benzylidene-2,3-dideoxy-2-(1-nitroalkyl)-3-nitro-β-D-galactopyranosides (IX-XI) in yields of 60-85%.



IX R=R'=H

X R=H, R'=CH_3

XI R=H, R'=C_2H_5

XII R=R'=CH_3 (?)

The additions took place in the presence of one mole of triethylamine and required a short reaction time (1 h) at room temperature. The progress of the reactions was monitored by thin layer chromatography. Since the nitro olefin (VIII) - as opposed to the nitro ester (VII) - cannot

form an *aci* nitro salt with triethylamine, it is not liable to suffer eliminative debenzylidenation. The formation of the desired Michael adducts can therefore proceed without competition by an unwanted side reaction, and owing to their rapid formation the products can be isolated before they might deteriorate by prolonged exposure to an alkaline medium.

Whereas primary nitroalkanes added to VIII without difficulties, this was not the case with secondary nitroalkane, 2-nitropropane. Under the conditions stated above the reaction was found to be incomplete. An increase in the amount of triethylamine (3 moles) or a prolongation of the reaction time (6-12 h) caused serious debenzylidenation, and the desired adduct could not be isolated. Similar negative results were obtained when triton B (benzyltrimethyl ammonium hydroxide) was employed as a catalyst. The latter catalyst had proved very useful in other Michael additions (139). Probably the bulkiness as well as the low acidity of 2-nitropropane are factors causing a sluggish reaction; it may be recalled that in the *gluco* series, too, the formation of the adduct VI was less facile than with the primary nitroalkanes. By allowing more time for the reaction, or by increasing the basicity of the medium, 2-nitropropane apparently does add to VIII, but the adduct subsequently seems largely to decompose as judged by the release of benzaldehyde.

7. Proof of the D-*galacto* Configuration in Compounds IX - XI

The products obtained from VIII and nitroalkanes gave analytical data in agreement with their expected structures. Infrared spectra (Table V) exhibited asymmetric nitro vibrations which, just as in the *gluco* analogs, had the appearance of double peaks. The gross structures were confirmed by the substituent resonances in n.m.r. spectra. These resonances are listed in Table VI, and their interpretation is entirely parallel to those of the *gluco* series discussed on p. 43.

Furthermore, the n.m.r. spectra revealed that the products IX - XI possessed the D-*galacto* configuration. It was predictable that this configuration should be the most likely one to arise, as it has a diequatorial substituent orientation at the newly generated asymmetric centers C-2 and C-3. Proof was afforded by the nature of the signal given by H-3, the proton at the ring carbon bearing a nitro group. The reasoning in the interpretation of this signal was fully analogous to the discussion of the corresponding signal in the *gluco* series, and reference is made to p.49. In the present series, quartets of one-proton intensity were found which displayed one small and one large coupling: (p.64).

TABLE V

Asymmetric nitro and other characteristic infrared frequencies (cm^{-1}) in Nujol

IX	1566, 1552 (NO_2); 1095, 1085 (C-O-C); 745, 700 (phenyl)
Xa*	1560, 1533 (NO_2); 1090, 1070 (C-O-C); 740, 700 (phenyl)
Xb**	1560, 1547 (NO_2); 1100, 1065 (C-O-C); 760, 700 (phenyl)
XI	1563, 1557 (NO_2); 1090, 1080, 1050 (C-O-C); 755, 723, 700 (phenyl)

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* Epimer m.p. 222-223°

** Epimer m.p. 196-197°

TABLE VI

Chemical shifts (τ values) and relative intensities of substituents signals (number of protons in parentheses), in deuteriochloroform unless otherwise indicated

	Phenyl	Ph-CH=O_2	O-CH_3	C-CH_3
IX*	2.58(5)	4.27(1)	6.58(3)	
Xa¶ *	2.58(5)	4.27(1)	6.63(3)	8.52(3)†
Xb#	2.60(5)	4.43(1)	6.56(3)	8.23(3)†
XI	2.62(5)	4.47(1)	6.56(3)	9.01(3)‡

* In dimethylsulfoxide-d_6

† Doublet with spacing 7 c.p.s.

‡ Triplet with spacing 7 c.p.s.

¶ Epimer m.p. 222-223°

Epimer m.p. 196-197°

IX : quartet centered at 4.7τ; spacings, 4.0 and 12.0 cps.

Xa*: quartet centered at 4.6τ; spacings, 4.0 and 11.0 cps.

Xb*: quartet centered at 4.8τ; spacings, 3.7 and 12.0 cps.

XI : quartet centered at 4.95τ; spacings, 4.0 and 12.0 cps.

Since in these compounds H-4 was known to be equatorial as a consequence of the C-4 configuration of the starting material, it followed that its dihedral angle with H-3 must be 60°, regardless of whether H-3 was oriented axially or equatorially, and that therefore the coupling $J_{3,4}$ must be small, according to the Karplus relation. Consequently, the large one of the two observed couplings was assignable with certainty to H-2, H-3, and these two protons were clearly shown, by the magnitude of $J_{2,3}$, to be in a diaxial position. Thus the D-galacto configuration was established.

The considerations of p. 42 pertaining to the possible occurrence of side-chain epimers equally apply to the present series of D-galacto derivatives. It will be shown in a subsequent paragraph that the addition of nitroethane to VIII led to two isomers (Xa and Xb). Since both of them exhibited the spectral feature just discussed, they must possess identical sugar ring configuration and therefore, must be side-chain epimers.

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*a and b refers to side-chain epimers of X to be discussed subsequently.

8. The Individual Compounds (IX - XI)

a. Methyl 4,6-O-benzylidene-2,3-dideoxy-2-(nitromethyl)-3-nitro-β-D-galactopyranoside (IX) was obtained in a yield of 68%. It had m.p. 227° and $[\alpha]_D$ +8.6° (c, 0.6 in butanone). The n.m.r. spectrum (Fig. XI and Table VI) exhibited, besides the features discussed in the preceding Section 7, a one-proton multiplet centered at 7.0τ. This signal was attributable to H-2. Signals for the two protons of the nitromethyl group apparently were bunched together with ring protons in the 4.6-6.4 τ region.

b. Methyl 4,6-O-benzylidene-2,3-dideoxy-2-(1-nitroethyl)-3-nitro-β-D-galactopyranosides (X) was obtained crystalline from nitroolefin VIII and nitroethane, in a yield of 62%. It had a specific rotation of $[\alpha]_D$ +8.3° (c, 1 in butanone). Thin layer chromatography revealed the presence of two components in this crude product. Careful fractional crystallization led to the isolation of both components in chromatographically uniform, crystalline condition. The slow-moving epimer (Xa) showed m.p. 222-223° and $[\alpha]_D$ +2.3° (c, 1.2 in butanone), the fast-moving epimer (Xb) melted at 196-197° and had $[\alpha]_D$ +23.2° (c, 0.8 in butanone). The epimers displayed slight differences in their infrared spectra (Table V and Fig. XII). They are also distinguished in their solubilities, Xa being only sparingly soluble in chloroform.

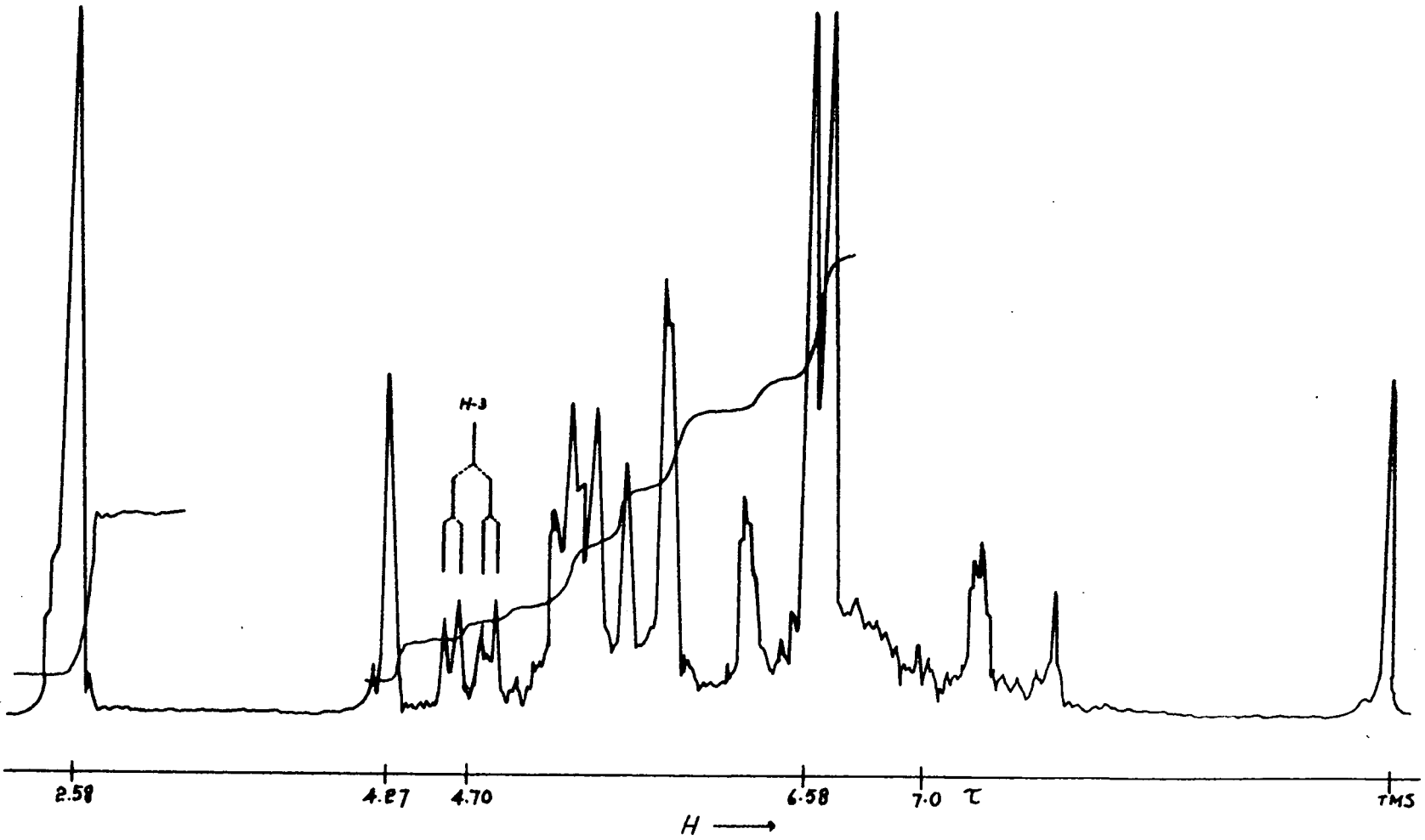


Fig. XI. N.M.R. spectrum of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-nitromethyl-β-D-galactopyranoside (IX) in deuterated dimethylsulfoxide

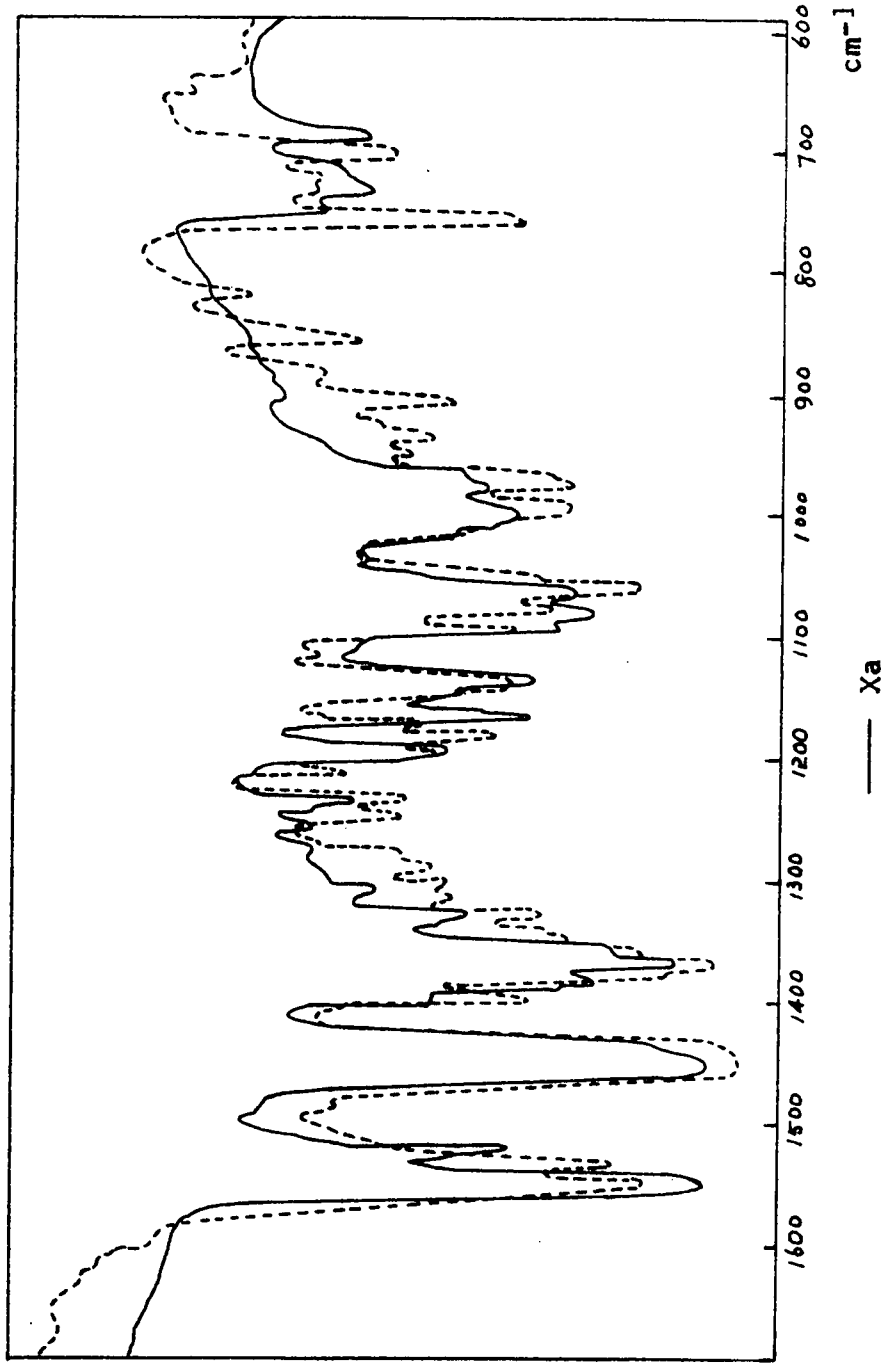
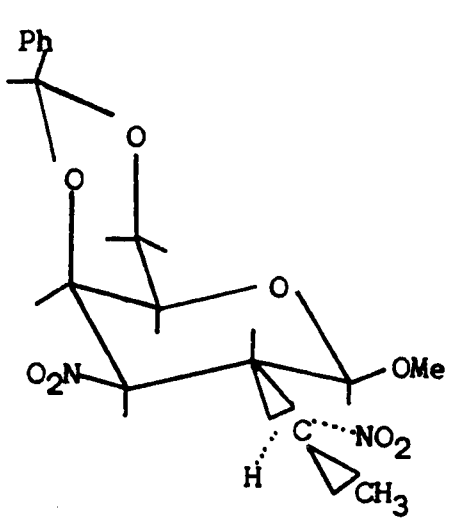


Fig. XII. Infrared spectra of Xa and Xb

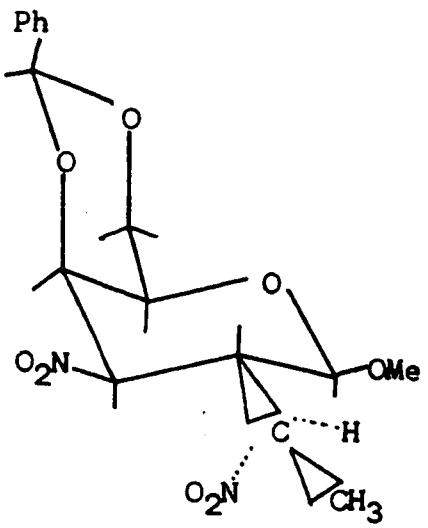
Special features in the n.m.r. spectra of Xa and Xb (Fig. XIII and XIV and Table VI) are the signals due to the side-chain nitroethyl groups. Epimer Xa exhibits a doublet centered at 8.52τ, and Xb shows a doublet centered at 8.23τ, each of three-proton intensity and attributable to the methyl portion of the side-chain. In the spectrum of Xb (which was taken in deuteriochloroform) one can see also a one-proton multiplet in the 7.1τ region which is assigned to the ring proton at C-2. In the spectrum of Xa (which was taken in dimethylsulfoxide - d_6) the analogous signals could not be distinguished because of the interference by bands from the solvent which contained some incompletely deuterated dimethylsulfoxide.

Formulas for Xa and Xb are given below, but it has not yet been studied which side-chain configuration belongs to which epimer.



Xa

or vice versa



Xb

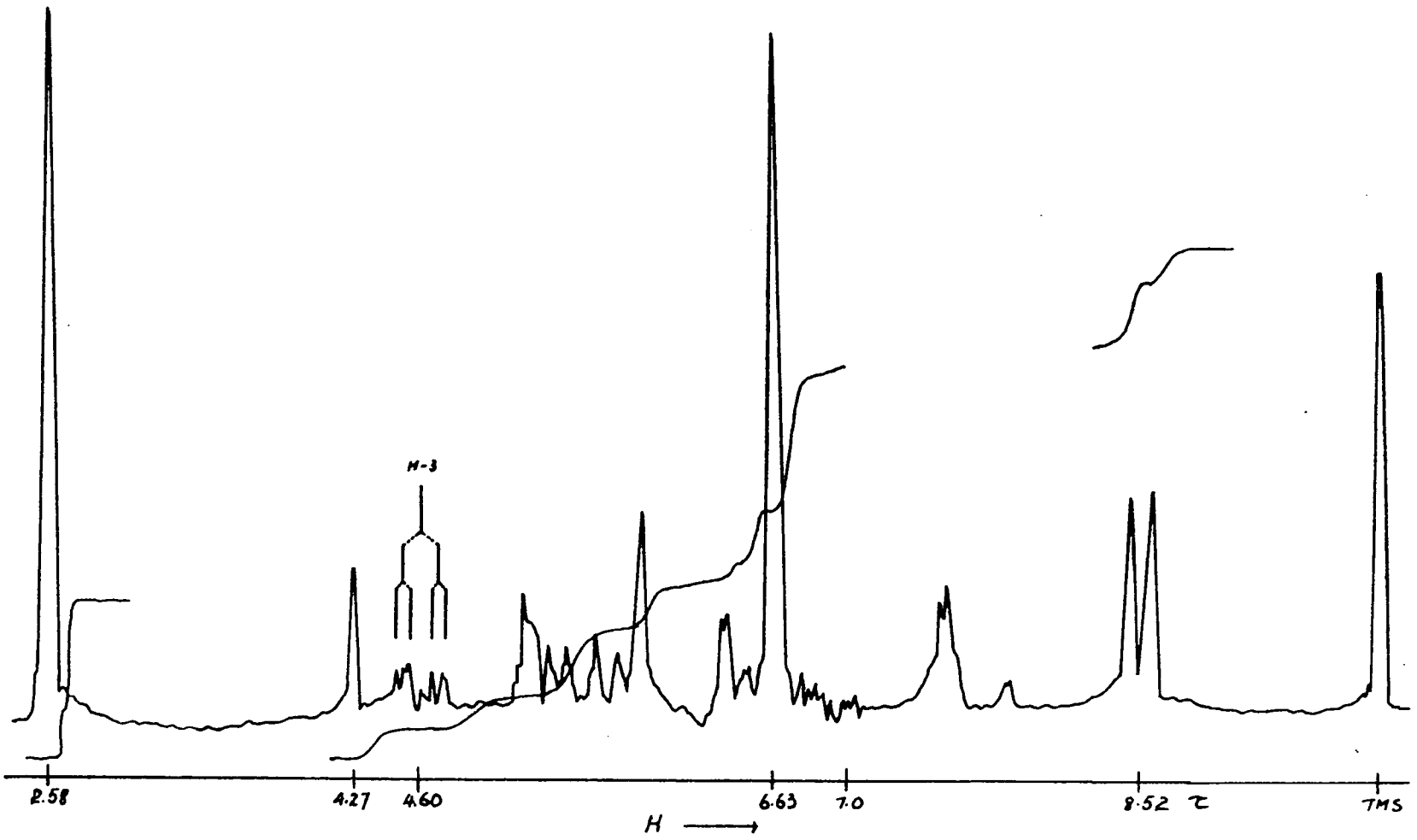


Fig. XIII. N.M.R. spectrum of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-nitroethyl)-β-D-galactopyranoside (Xa) in deuterated dimethylsulfoxide

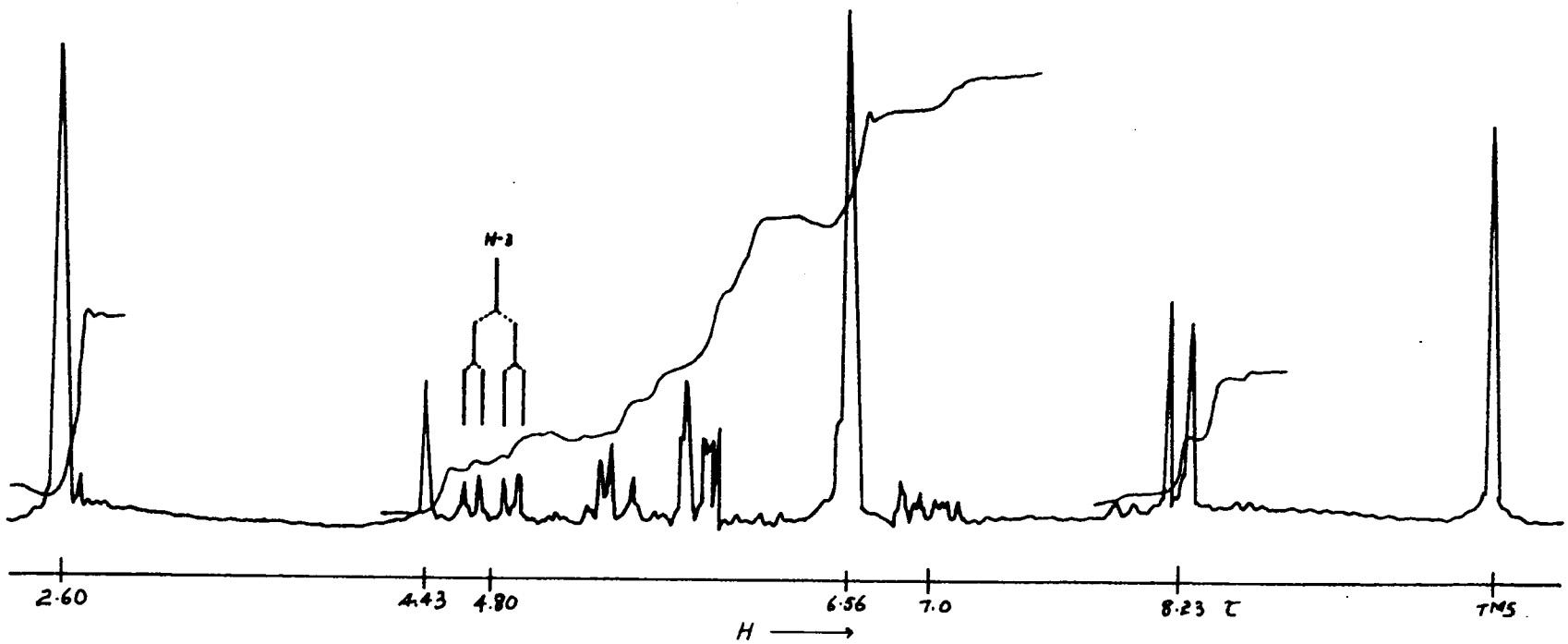


Fig. XIV. N.M.R. spectrum of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-nitroethyl)-β-D-galactopyranoside (Xb) in deuteriochloroform

c. Methyl 4,6-O-benzylidene-2,3-dideoxy-2-(1-nitropropyl)-β-D-galactopyranoside (XI) was obtained in 89% yield from 1-nitropropane and olefin VIII. The crude product melted at 170-174° and had a specific rotation $[\alpha]_D$ +20°. Chromatographic examination of this crude product revealed two spots, with the slower-moving one of relatively weak intensity. The latter component persisted to accompany the major component even when the product was recrystallized to constancy of the physical data (m.p. 181°, $[\alpha]_D$ +23°). The infrared spectra of the crude and the recrystallized substances were virtually identical, and the same was true for their n.m.r. spectra.

The n.m.r. spectrum of the recrystallized product (XI) showed a triplet in 9.0τ region, assignable to the methyl protons of the side-chain nitropropyl group. This triplet was accompanied by a weak, but recognizable, satellite triplet 0.03 ppm upfield, which presumably was caused by the presence of some epimer (Fig. XV). Regardless of this contamination, there was only one quartet discernible (see p. 64). It is believed that the minor component present in XI represents the side-chain epimer of the main product, but this cannot be assumed with certainty until it will be substantiated by further investigations.

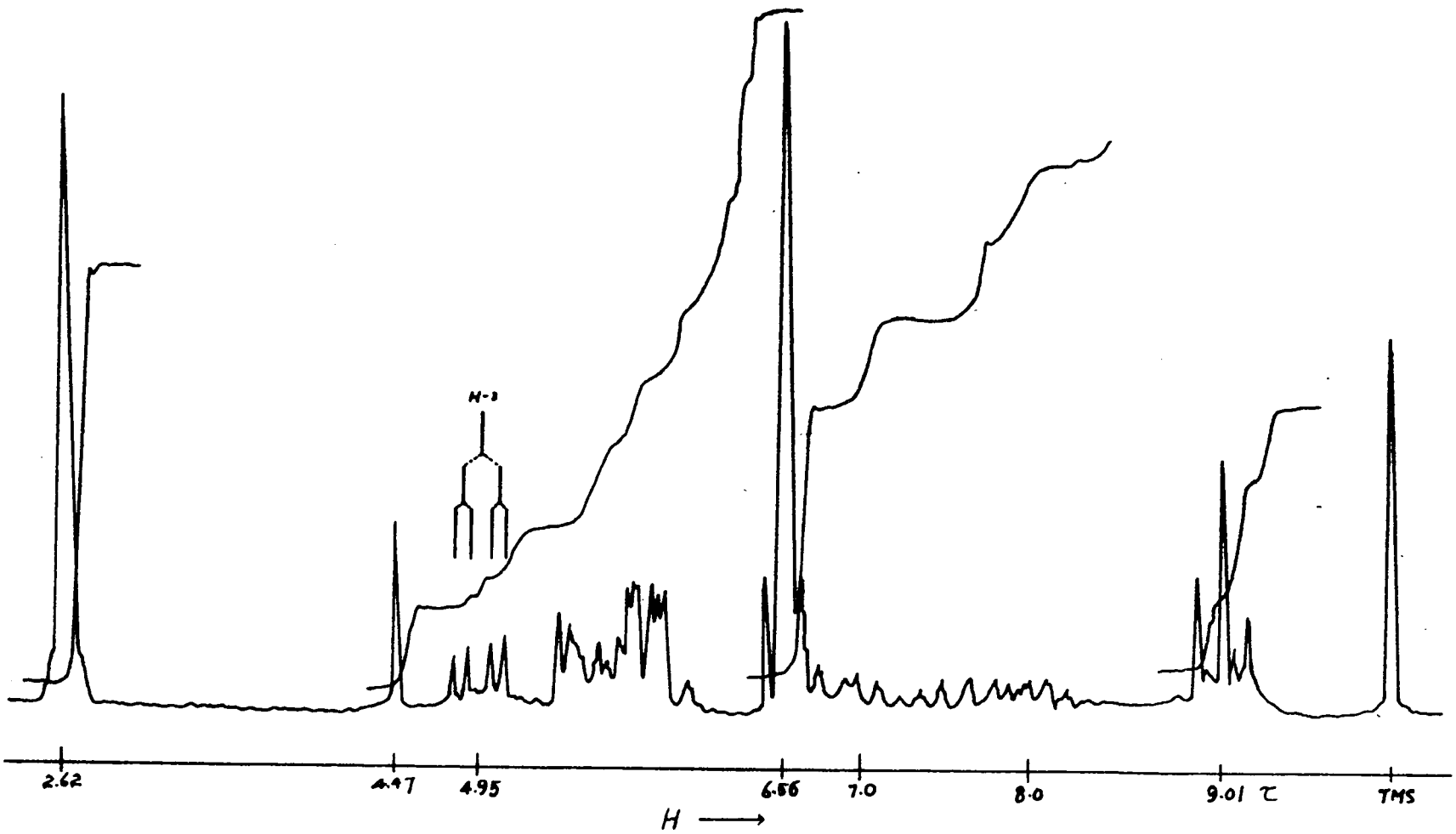
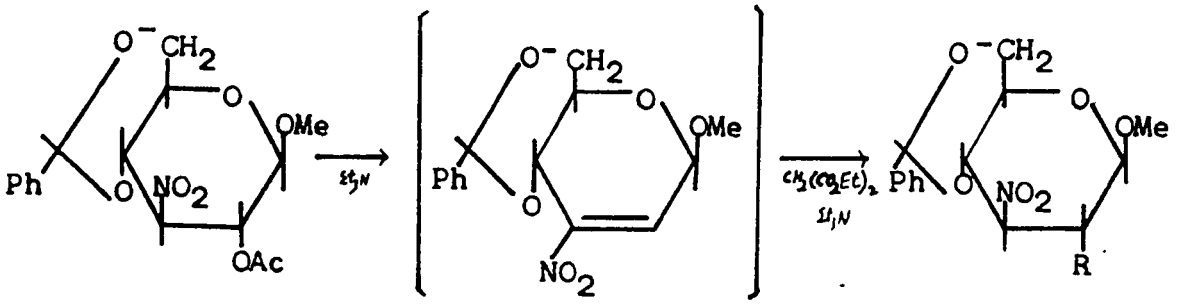


Fig. XV. N.M.R. spectrum of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-nitropropyl)-β-D-galactopyranoside (XI) in deuteriochloroform

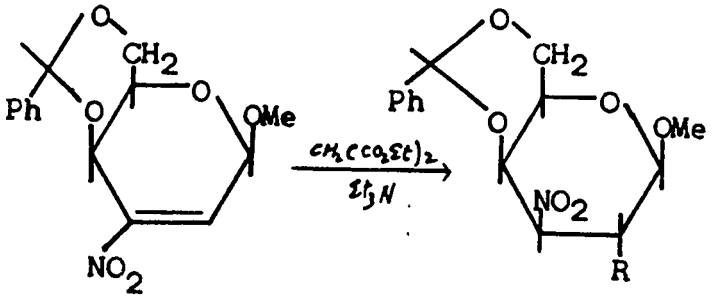
B. Branched-chain Mononitro Sugars

9. Michael Addition of Diethyl Malonate to Nitro Sugar Derivatives

It was expected that the Michael reactions described in the preceding Section 1 could be extended to the use of non-nitrogenous addends, so that mononitro sugars having a nitrogen-free branch would arise. This was verified with diethyl malonate which was allowed to react with the nitro glycoside acetate I and the nitroolefinic glycoside VIII. The reactions were promoted with excess triethylamine, and crystalline adducts (XIII and XIV) were obtained in yields of 83 and 62%, respectively.



I II XIII R=-CH(CO$_2$Et)$_2$



VIII XIV R=-CH(CO$_2$Et)$_2$

Compound XIII, methyl 4,6-O-benzylidene-2,3-dideoxy-2-[bis (ethoxycarbonyl)]methyl-3-nitro-β-D-gluco-pyranoside, exhibited an asymmetric nitro frequency at 1555 cm^{-1} and two carbonyl bands at 1753 and 1730 cm^{-1}. There was a strong C-O-C band at 1228 cm^{-1}, and bands due to the benzylidene group appeared at 755 and 698 cm^{-1}.

The n.m.r. spectrum of compound XIII in deuteriochloroform (Fig. XVI), showed at 8.71 τ a triplet of intensity six assignable to the two methyl groups of bis-ethoxycarbonyl function. At low field were seen the signals caused by the benzylidene group. The remaining fifteen protons including those of the glycosidic methoxyl group gave signals scattered over the region 4.7 to 7.4 τ. Among these signals was a quartet centered at 4.9 τ, which corresponded to H-3. The spacings were of the order of 9 to 10 c.p.s., requiring the three hydrogen atoms at C-2, C-3 and C-4 to be in axial dispositions. Hence it was possible to assign the D-gluco configuration to compound XIII.

Compound XIV, methyl 4,6-O-benzylidene-2,3-dideoxy-2-[bis(ethoxycarbonyl)]methyl-3-nitro-β-D-galactopyranoside, exhibited infrared absorptions at 1755 and 1735 cm^{-1} due to the bis-ethoxycarbonyl function and at 1555 cm^{-1} due to the nitro group. Also, there were bands at 1245 cm^{-1} (C-O-C) and at 755 and 705 cm^{-1} (benzylidene group). The n.m.r. spectrum of XIV is depicted in Fig. XVII. The substituent

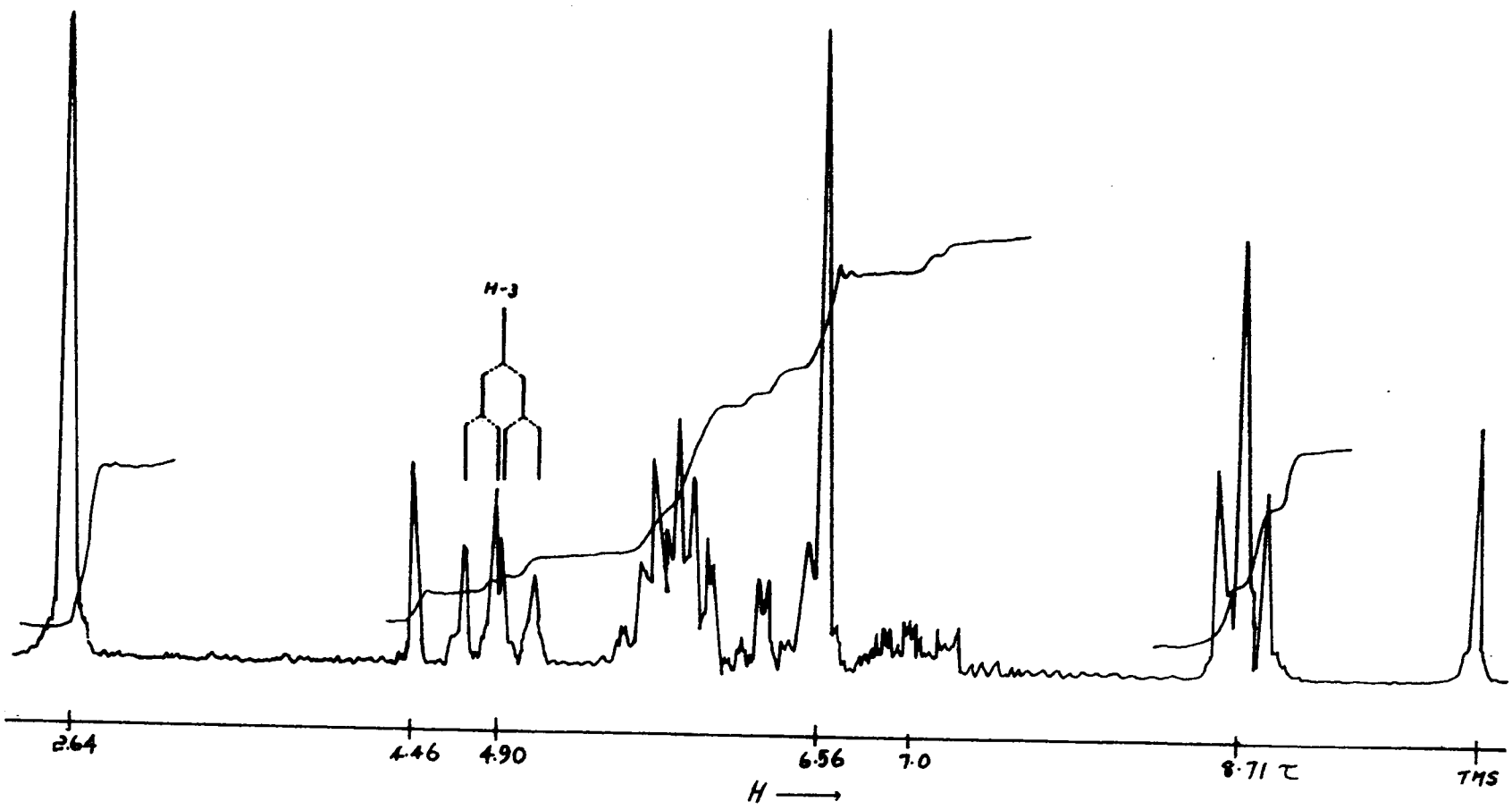


Fig. XVI. N.M.R. spectrum of methyl 4,6-O-benzylidene-2,3-dideoxy-2-[bis(ethoxycarbonyl)] methyl-3-nitro-β-D-glucopyranoside (XIII) in deuteriochloroform

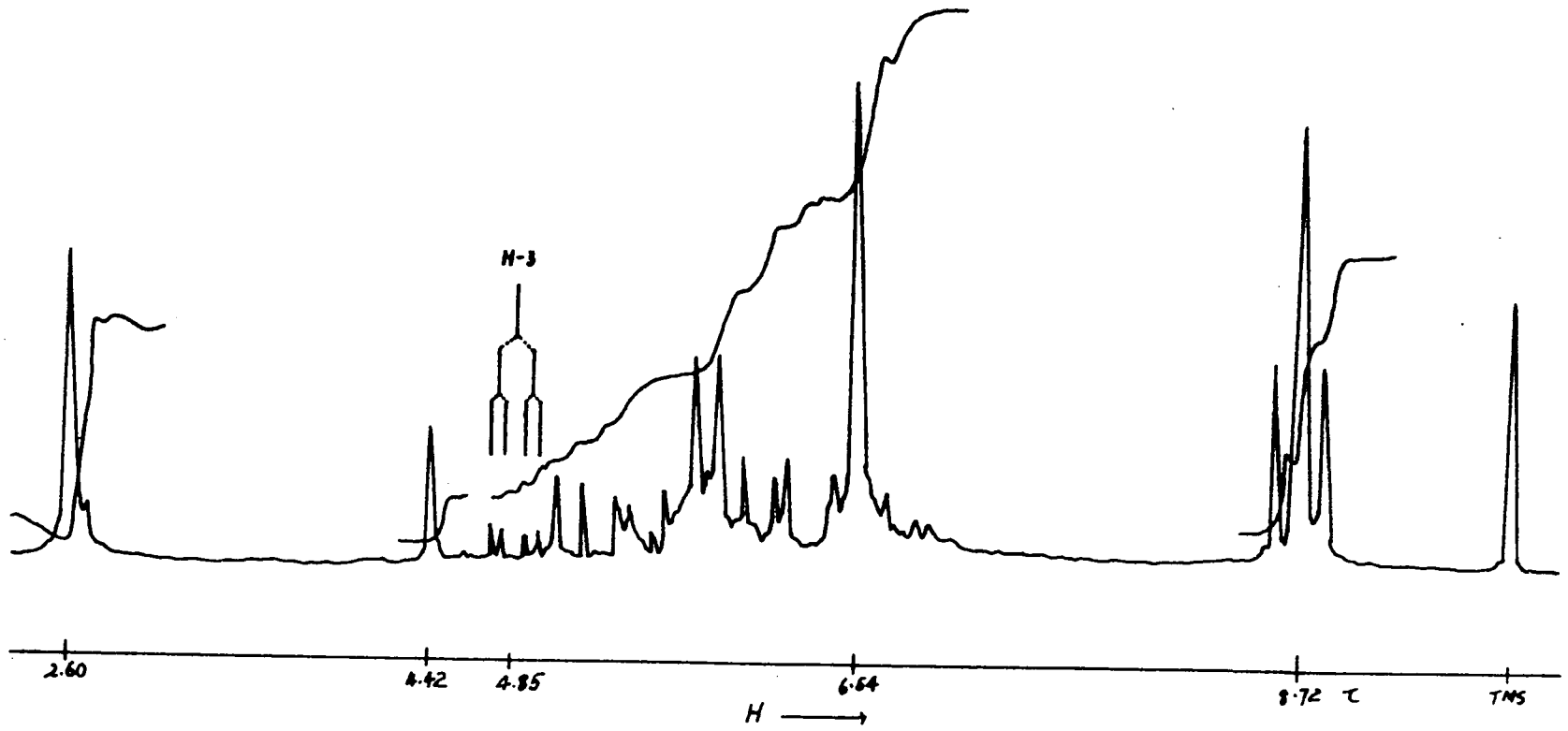
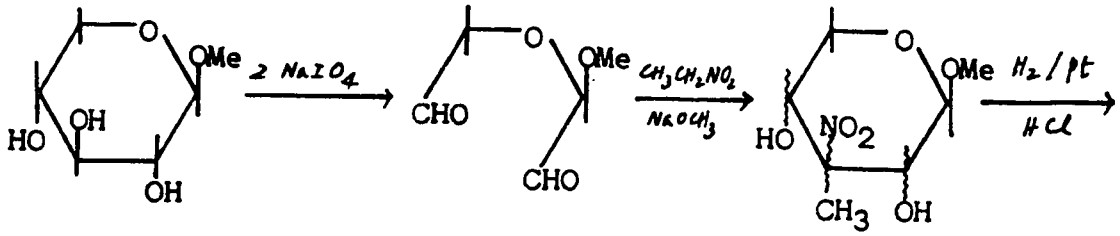


Fig. XVII. N.M.R. spectrum of methyl 4,6-O-benzylidene-2,3-dideoxy-2-[bis(ethoxycarbonyl)] methyl-3-nitro-β-D-galactopyranoside (XIV) in deuteriochloroform

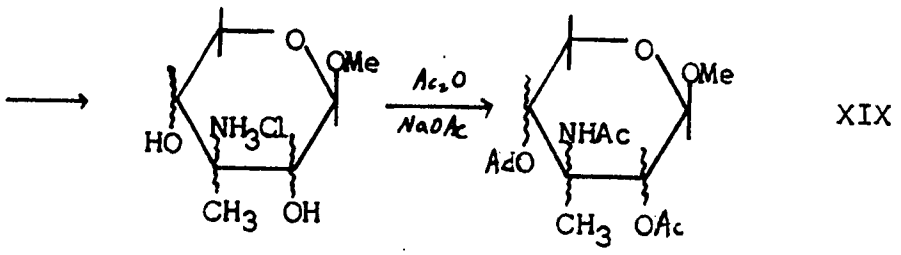
resonances are seen to be similar to those in the isomer XIII and are interpreted analogously. The only major difference was the character of the signal belonging to H-3, the proton at the carbon bearing the nitro group. This signal was a quartet centered at 4.85 τ and had spacings of 4 and 12 cps. According to the arguments outlined on p.64 these spacings permitted assignment to XIV of the D-galacto configuration.

10. Branched-chain Sugars by Cyclization of Sugar Dialdehydes with Nitroethane

Glycosides that carry a nitrogen function as well as a C-methyl group at carbon atom 3 can be made by the cyclization of "sugar dialdehydes" (see Introduction, p.30). Some 3-C-methyl-3-nitro hexopyranosides and the corresponding amines had been obtained in this way (101,102), and it was decided to extend the method to the pentose series. The dialdehyde XVI, obtained from the periodate oxidation of methyl β-D-xylopyranoside (XV) (140,94) was chosen for this study, and the following reaction sequence was planned:



XV XVI XVII



XVIII XIX

The cyclization of dialdehyde XVI with nitroethane in the presence of one mole-equivalent of sodium methoxide yielded a crystalline product which was revealed by thin layer chromatography to consist of one major component accompanied by three minor components, two of the latter moving more slowly and one faster than the major product. The various by-products presumably were stereoisomers of the main product, for it follows from the generation of three new asymmetric centers that 8 stereoisomers can theoretically arise. Recrystallization largely removed the three minor components, and the yield of nitro sugar XVII was 11-14%. Although compound XVII appeared uniform on silica gel plates, its n.m.r. spectrum in deuterium oxide still showed two weak satellite peaks to the main C-CH_3 signal, which suggested that a small contamination by isomers had persisted through the recrystallizations. However, after reduction, to be described in a subsequent paragraph, one major component could be isolated in practically pure form.

Compound XVII showed correct analyses for the composition $C_7H_{13}NO_6$ of a methyl 3-deoxy-3-C-methyl-3-nitro-pentopyranoside. In its infrared spectrum, the asymmetric nitro stretching vibration was at 1550 cm^{-1} and the hydroxyl band was at 3560 cm^{-1}.

Catalytic hydrogenation of the nitro glycoside XVII in the presence of hydrochloric acid furnished a pure amine hydrochloride (XVIII), after recrystallizations. On paper chromatography the amine hydrochloride XVIII appeared uniform with R_{Gm} = 1.47* while the mother liquor showed an additional spot at R_{Gm} = 1.15. The n.m.r. spectrum of XVIII in deuterium oxide showed single sharp signals for the C-CH_3 protons and the methoxyl group. Infrared absorptions due to the ammonium group appeared as a broad peak at 3100 cm^{-1}, and as bands at 1600 and 1530 cm^{-1}.

The amino glycoside hydrochloride (XVIII) was then acetylated with acetic anhydride and sodium acetate, to give the methyl 3-acetamido-2,4-di-O-acetyl-3-deoxy-3-C-methyl-pentopyranoside (XIX). This triacetyl derivative in its infrared spectrum showed an NH band at 3300 cm^{-1}, acetate carbonyl absorptions at 1740 cm^{-1}, an amide-I band at 1650 cm^{-1}, and an amide-II band at 1550 cm^{-1}.

---

* Speed relative to glucosamine hydrochloride.

The n.m.r. spectrum of XIX in deuteriochloroform (Fig. XVIII) gave a single peak at 8.55 τ, of intensity three, which was attributable to the C-methyl protons. The three sharp signals at 8.10, 7.90 and 7.87 τ, each corresponding to three protons, were readily assignable to the methyl protons of the one acetamido and two acetoxyl groups. The anomeric methoxyl group gave a three-proton singlet at 6.55 τ, and the amide NH signal occurred at 3.7 τ.

The remaining signals were due to the ring hydrogens and could be used to make partial configurational assignments as follows.

A quartet centered at 4.53 τ and having splittings of 3.2 and 2.5 c.p.s. can be assigned to H-4. The splittings are caused by vicinal coupling with the two protons at C-5 and should therefore recur in the signals of these protons. Indeed, there are two further quartets, one centered at 5.85 τ and the other at 6.40 τ (partially overlapping with the OCH_3-singlet), and these quartets show spacings of 2.5 and 13.0 c.p.s., and 3.2 and 13.0 c.p.s., with the splittings of 13.0 c.p.s. being due to geminal coupling. The H-5 proton resonating at higher field probably is the axial one. The small values of both vicinal H-4 to H-5 couplings ($J_{4,5a}$=3.2 and $J_{4,5e}$=2.5 c.p.s.) require H-4 to be equatorial, for otherwise one of these couplings ($J_{4,5a}$) would have to be large (see p.49). Consequently, compound XIX must bear an

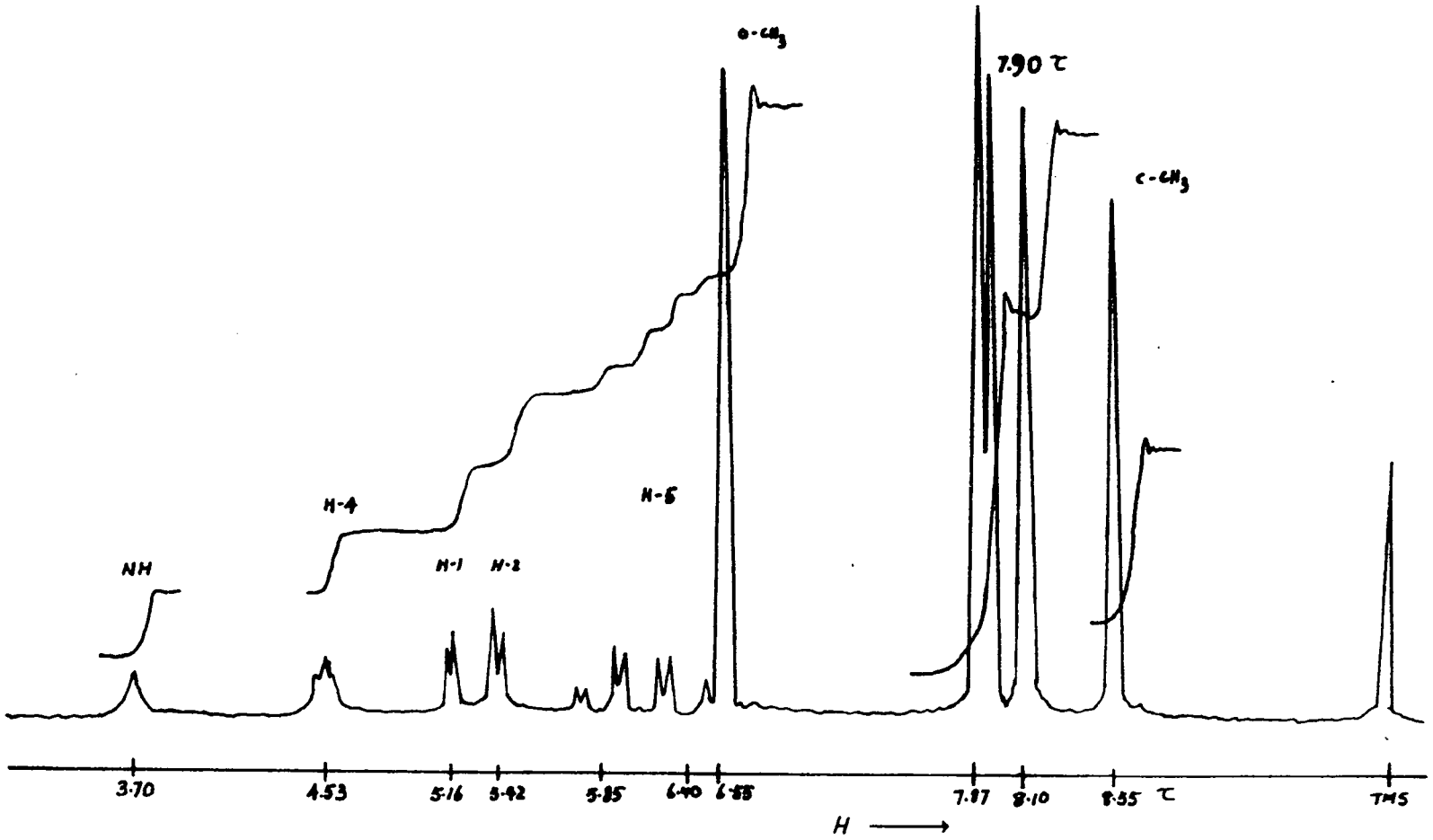
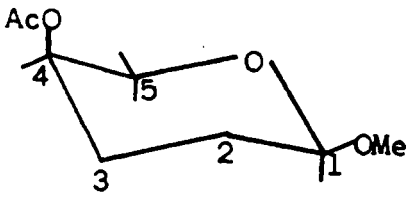
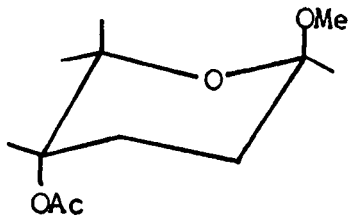


Fig. XVIII. N.M.R. spectrum of methyl 3-acetamido-3-deoxy-3-C-methyl-2,4-di-O-acetyl-pentopyranoside (XIX) in deuteriochloroform

axial acetoxy group at C-4, and one can draw the partial formulas A and B (which take into account also the configuration at C-1 that is known from the starting dialdehyde):

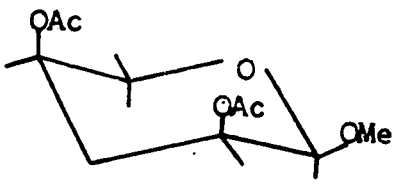


A

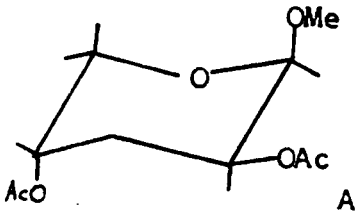


B

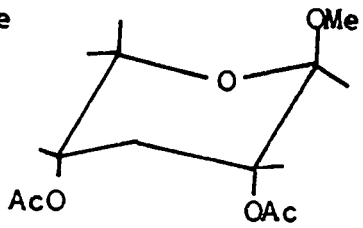
Furthermore, the spectrum shows two doublets, at 5.16 and 5.42 τ, which belong to H-1 and H-2 (or vice versa). The vicinal coupling is $J_{1,2}$=2.5 c.p.s., and this again rules out diaxial arrangement of these protons but allows either axial-equatorial or diequatorial arrangement. One can therefore expand formula A to C, and B to D and E.



C



D



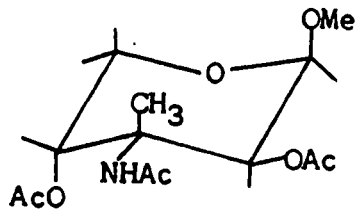
E

While the spectrum shows with certainty that XIX must be represented by any one of these partial formulas C, D and E, a firm decision between them is not possible at present, nor can they be expanded without ambiguity so as to include the configuration at C-3, the carbon bearing the acetamido and C-methyl groups.

Certain conformational arguments and some pieces of circumstantial evidence which speak for or against one or the other formula may be discussed without intending a final assignment. Thus, if XIX possessed the configurations at C-1, C-2, and C-4 shown in C, it would hardly exist in the depicted conformation but prefer to adopt the inverted chair form which would relieve the diaxial acetoxy interaction and especially the unfavorable "Δ-2 interaction"*. Moreover, the anomeric effect (141), tending to make an axial glycosidic group more stable conformationally than an equatorial one, would operate in the direction of chair inversion, although this would create, of necessity, a 1,3-diaxial interaction with one of the C-3 substituents. Upon chair inversion, however, the configuration C would no longer accord with the spectrum. Formulas D and E, because of the absence of a Δ-2 interaction, appear more stable, and D in particular would be a preferred form as it has no

* The "Δ-2 effect" is an important factor which confers conformational instability. It is present when an oxygen substituent at C-2 bisects the angle between the anomeric and the ring oxygen (141).

diaxial acetoxy interaction, so that no conformational arguments would speak against the formation, in the cyclization reaction, of a product derived from this formula D. As far as the configuration at C-3 is concerned, it seems likely that the acetamido group is in the equatorial, and the C-methyl group in the axial position. The τ-value of 8.10 for the acetamido methyl protons lies within the range (8.03-8.12τ) established for equatorial position, rather than in the range (7.92-7.96τ) found for axial position (142-146), although these ranges refer to acetamido groups on unbranched sugar rings. Acetamido signals in C-methyl substituted sugars have been found at slightly higher field (8.15-8.17τ) (101,102,146), but insufficient data are available for comparison to reach a definite conclusion from our value. On the other hand, the τ-value of the C-methyl group in XIX (8.55τ) might well signify an axial C-CH_3 on the same side of the ring as an axial methoxyl and thus accord with formual D'. This reasoning comes from comparing data given (102) for two pairs of analogous branched-chain acetamido glycosides whose methyl groups at C-3, believed to be axial, had chemical shifts of 8.53 and 8.54 τ when the glycosidic methoxyl was axial also, but 8.45 and 8.46 τ when the latter was equatorial.



D'

Formula D', then, could be a likely representation of compound XIX. It would be methyl 3-acetamido-2,4-di-O-acetyl-3-deoxy-3-C-methyl-β-D-arabinoside.

PART II

Synthesis of Derivatives of 2,3-Diamino-2,3-dideoxy-D-galactose

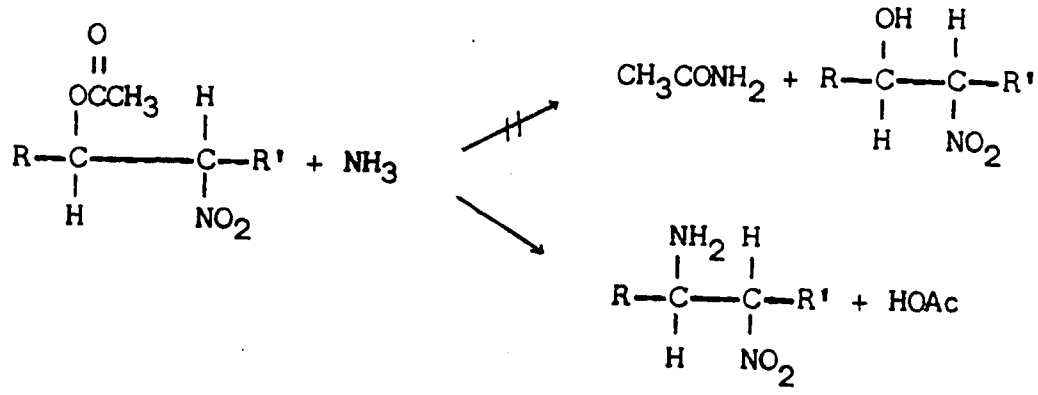
1. Statement of the Problem

Introduction of an amino function into a position vicinal to the nitro group of a nitro sugar would give a nitroamine representing a potential precursor of a vic-diamino sugar.

Owing to activation by the nitro group, α-nitroalkenes readily add ammonia, amines and other nitrogenous bases across the olefinic bond, where the incoming nitrogen atom is introduced in β-position to the nitro group.

$$-C(NO_2) = CH- + NH_3 \longrightarrow -CH(NO_2)-CH(NH_2)-$$

In this manner, some aliphatic and aromatic amines as well as ammonia had been added to a variety of simple nitroalkenes (147-152). Chattaway (153) discovered that the action of ammonia upon the acetates of certain β-nitro alcohols also furnished vic-nitroamines, instead of effecting ammonolysis to acetamide as had been expected at the time:



This phenomenon was later verified by Irving and Fuller (154) who proposed that nitroacetates underwent base-catalyzed elimination of acetic acid to give intermediary nitroalkenes which then added ammonia to give the vic-nitroamines. The behavior of β-acetoxy-nitroalkanes as potential α-nitroalkenes has since become quite familiar, and use has been made of it in Part I of this thesis.

The application of the ammonia addition to the α-nitroalkene system in carbohydrates has been rather limited, insofar as most examples that were studied concerned derivatives, such as alditols and blocked sugars, which carried a nitro group at a terminal carbon of the chain (155-161). Recently, however, the principle has also been applied successfully to cyclic nitro compounds, namely to deoxynitroinositol (162) as well as to the 3-deoxy-3-nitro-D-glucose derivatives I and II (126). The

last-mentioned work has led to a novel synthesis of 2,3-diamino-2,3-dideoxy-D-glucose, and in the light of these results it was to be investigated for the present thesis whether hitherto unknown 2,3-diamino-2,3-dideoxy-D-galactose may be obtained analogously from suitable nitro sugar derivatives. In other words, the action of ammonia upon the galactose derivative VII and the related olefin VIII was to be studied.

2. Action of Ammonia upon Methyl 2-O-Acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-galactopyranoside (VII)

When the acetate VII was allowed to react with ammonia in aqueous tetrahydrofuran at room temperature for one hour, the resulting syrup strongly smelled of benzaldehyde, an indication of serious debenzylidenation, and no crystalline water-insoluble substance could be isolated. This negative result contrasted with the facile production of the desired nitroamine from the isomeric gluco acetate I (126), but it constituted an experience parallel to the failure of VII to serve as a suitable starting material in the Michael reactions of Part I (p.58). As will be recalled, debenzylidenation occurred there, too, and a remarkable difference in stability between an axial and an equatorial

acetal linkage vicinal to the nitro group was noted. Consequently, the use of VII was abandoned and attention was focused on the nitroolefin VIII which has served well in the Michael additions in Part I.

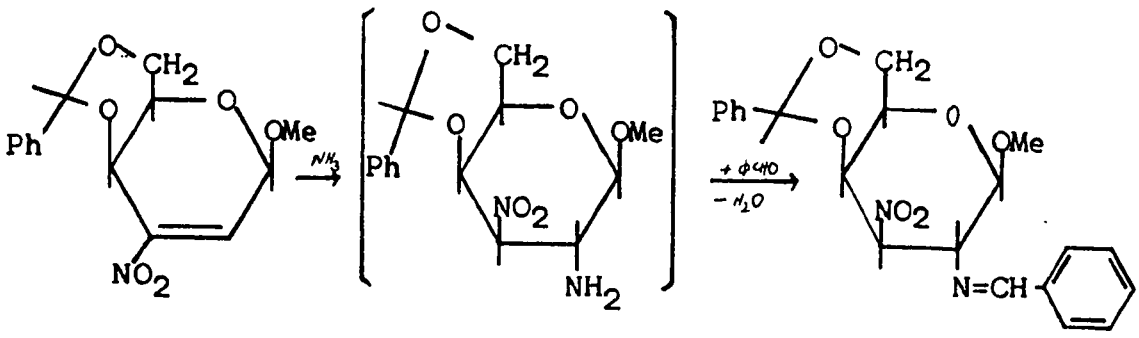
3. Action of Ammonia upon Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-β-D-threo-hex-2-enopyranoside (VIII)

When methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-threo-hex-2-enopyranoside (VIII) was refluxed with concentrated ammonia in aqueous tetrahydrofuran for three minutes, there was isolated a crystalline product. This product showed no distinct asymmetric and symmetric stretching vibrations of a primary amine expected to be found in the 3300-3500 cm^{-1} region, but instead, there was a strong and sharp peak at 1645 cm^{-1} which at first sight was unexplained. Absorption bands at 690 and 750 cm^{-1} indicated retention of the benzylidene blocking group in this product. Elemental analysis and mass spectrometry confirmed that the product was not the expected free nitroamine (XX). Had the product possessed the desired composition of XX with the molecular formula $C_{14}H_{18}N_2O_6$ (mol. wt. 310.3), the analytical values for carbon, hydrogen and nitrogen should have been 54.19, 5.85 and 9.03% respectively.

The values found were 63.74, 5.83 and 7.63% respectively, that is, extremely high for carbon and low for nitrogen. The possibility of the product being a hydrate was ruled out on account of the high carbon value. The mass spectrum of the product gave a parent peak at 399 m/e, strikingly higher than expected.

The compound proved too insoluble for n.m.r. spectroscopy in chloroform, acetone, or methanol. A spectrum in deuterated dimethylsulfoxide was obtained but was not resolved well enough for complete interpretation. Nevertheless, a sharp singlet at 4.2τ could be assigned to the benzylic proton of the benzylidene acetal group, and when its intensity was compared with the integrated intensity of the aromatic protons in the 2.58τ region, which was about 10-11 times as high, it could be concluded that not one but two phenyl rings were present. It was therefore assumed that the product had the structure XXI, thought to have arisen by reaction of primarily-formed nitroamine XX with benzaldehyde originating from a partial decomposition of XX. Such a Schiff base structure would explain the observed infrared band at 1645 cm^{-1} as a C=N stretching vibration. The molecular formula of XXI ($C_{21}H_{22}N_2O_6$, mol. wt. 398.4) would be in agreement with the mass spectral parent peak if one assumes formation of a protonated molecular ion, and the values calculated for carbon (63.30), hydrogen (5.56) and

nitrogen (7.03) would fit the analytical data fairly well though not perfectly. Chemical behavior to be described later was in accord with structure XXI. The yield of the compound was 22% in terms of the production of usable derivative or 44% considering that 2 moles of VIII are required to form 1 mole of XXI.



VIII XX XXI

In view of the partial debenzylidenation which obviously occurred during the reaction of aqueous ammonia with olefin VIII, another approach was tried in the hope that this complication might be minimized. It was reasoned that molten ammonium acetate, used as a nonaqueous reaction medium, might act as a source of ammonia without rendering the medium too basic:

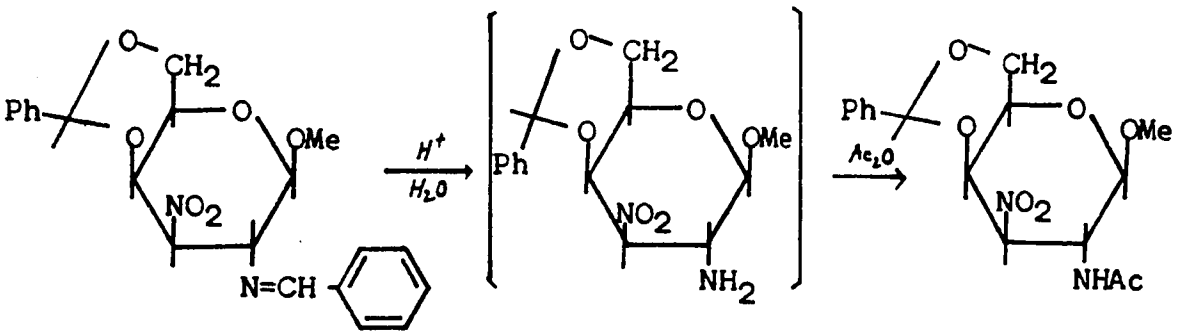
$$NH_4OAc \rightleftharpoons NH_3 + HOAc$$

However, when VIII and ammonium acetate were melted together for 1-2 min., the product was again the benzylideneamino compound XXI and not the desired amine XX. Moreover, the yield was low (8.8%), so that this trial did not mean any improvement. Perhaps the low yield was due to extensive decomposition at the rather high temperature of molten ammonium acetate (114°), and possibly the liberated acetic acid had an adverse effect, promoting loss of the 4,6-O-benzylidene grouping. The use of ammonium carbonate as a potential aminating agent was therefore tried, but no improvement was achieved. Commercial "ammonium carbonate" is a mixture of variable proportions of ammonium carbamate, bicarbonate and carbonate. It decomposes at about 60° without melting, and this fact no doubt made it unsuitable for the purpose of reacting with VIII.

Eventually, the following modification was worked out. The olefin VIII was melted for 2-3 min. in a mixture of ammonium acetate (one part) and acetamide (two parts). Work-up gave a water-insoluble product whose infrared spectrum was very similar to that of XXI. Without further purification the product was treated with acetic anhydride in aqueous methanol solution, and the N-acetylated glycoside XXII was obtained in an overall yield of 35-38% based on VIII. The overall yield of the same N-acetylated glycoside was only 18% when the olefin VIII had been aminated with

ammonia in aqueous tetrahydrofuran and XXI so produced was subsequently N-acetylated. Hence, employment of the ammonium acetate-acetamide procedure was an obvious improvement.

Apparently, when the Schiff base XXI is treated with acetic anhydride in aqueous methanol, the N-benzylidene group is slowly replaced by an N-acetyl group. The reaction required 24 h at room temperature, while N-acetylations of free primary amines normally proceed much more rapidly. [For example, the gluco analog of XX was completely N-acetylated within 1 h (126)]. When in an early experiment the reaction was interrupted after 6 h, the C=N stretching band at 1645 cm^{-1} was still visible in the infrared spectrum of the product.



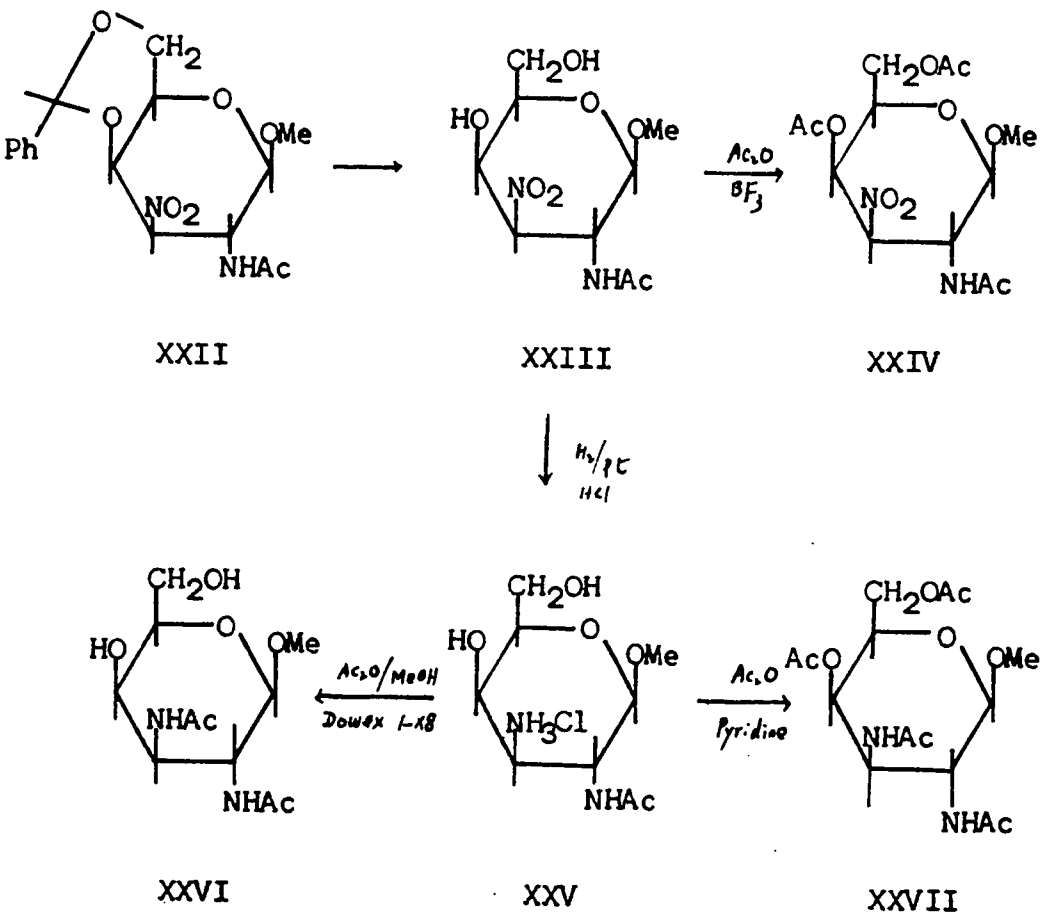
XXI XX XXII

The elemental analysis of the N-acetylated product agreed with the structure XXII of methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-galactopyranoside. The compound exhibited infrared bands at 3310 cm^{-1} (NH), 1660 cm^{-1} (amide-I band) and 1555 cm^{-1} (overlapping amide-II and nitro bands). Bands due to the O-benzylidene blocking group were found at 750 and 700 cm^{-1}. Owing to poor solubility in both chloroform and methanol no useful n.m.r. spectrum could be obtained, but proof of the galacto configuration was afforded by studies of derivatives to be described in subsequent paragraphs. Like in the Michael additions of Part I and in similar aminations in the gluco series (126,127), the substituents at the newly generated asymmetric centers C-2 and C-3 have adopted the most favorable, diequatorial orientation.

4. Further Conversions of XXII, and Proof of Configuration

Next, the 4,6-O-benzylidene blocking group in XXII was removed by refluxing the compound in aqueous methanol in the presence of a cation exchange resin, Rexyn 101 (H^+). The crystalline, debenzylidenated product, methyl 2-acetamido-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXIII), showed infrared bands attributable to OH and NH stretching vibrations at 3660, 3780 and 3100 cm^{-1} and it still showed

amide-I and amide-II bands (the latter overlapping with the NO_2 band) at 1660 cm^{-1} and 1640 cm^{-1}, respectively, but the bands due to the benzylidene group in the 700 cm^{-1} region were no longer present.



XXII XXIII XXIV

XXVI XXV XXVII

The glycoside XXIII was next acetylated with acetic anhydride and boron trifluoride (134), to furnish methyl 2-acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXIV). The compound exhibited ester CO and C-O-C bands at 1745 and 1720 cm^{-1}, in addition to bands at 3320 (NH), 1660 (amide-I), and 1555 cm^{-1} (amide-II and NO_2).

The n.m.r. spectrum of the acetamidodi-O-acetyl-nitro compound XXIV (Fig. XIX) in deuteriochloroform gave three sharp resonances of equal intensities, each corresponding to three protons, at 8.10 τ, 7.94 τ and 7.90 τ. These can readily be attributed to the methyl protons in $NHCOCH_3$, CH_2OCOCH_3 and $OCOCH_3$ at C-2, C-5 and C-4 respectively (146). The glycosidic methyl protons resonated at 6.50 τ. Two of the five ring proton signals were bunched together with the signal for C-6 methylene group, giving a total intensity of four and the two others were at 4.0-4.5 τ region. There was, however, a clearly resolved doublet corresponding to one proton, with a spacing of 9 c.p.s. centered at 5.10 τ, which must be due to the anomeric proton. The magnitude of the spacing indicated that this proton, known to be axial, must be coupled with an axial hydrogen atom at C-2. Consequently, the acetamido group at C-2 must be in equatorial disposition which is consistent with its chemical shift at 8.10 τ.

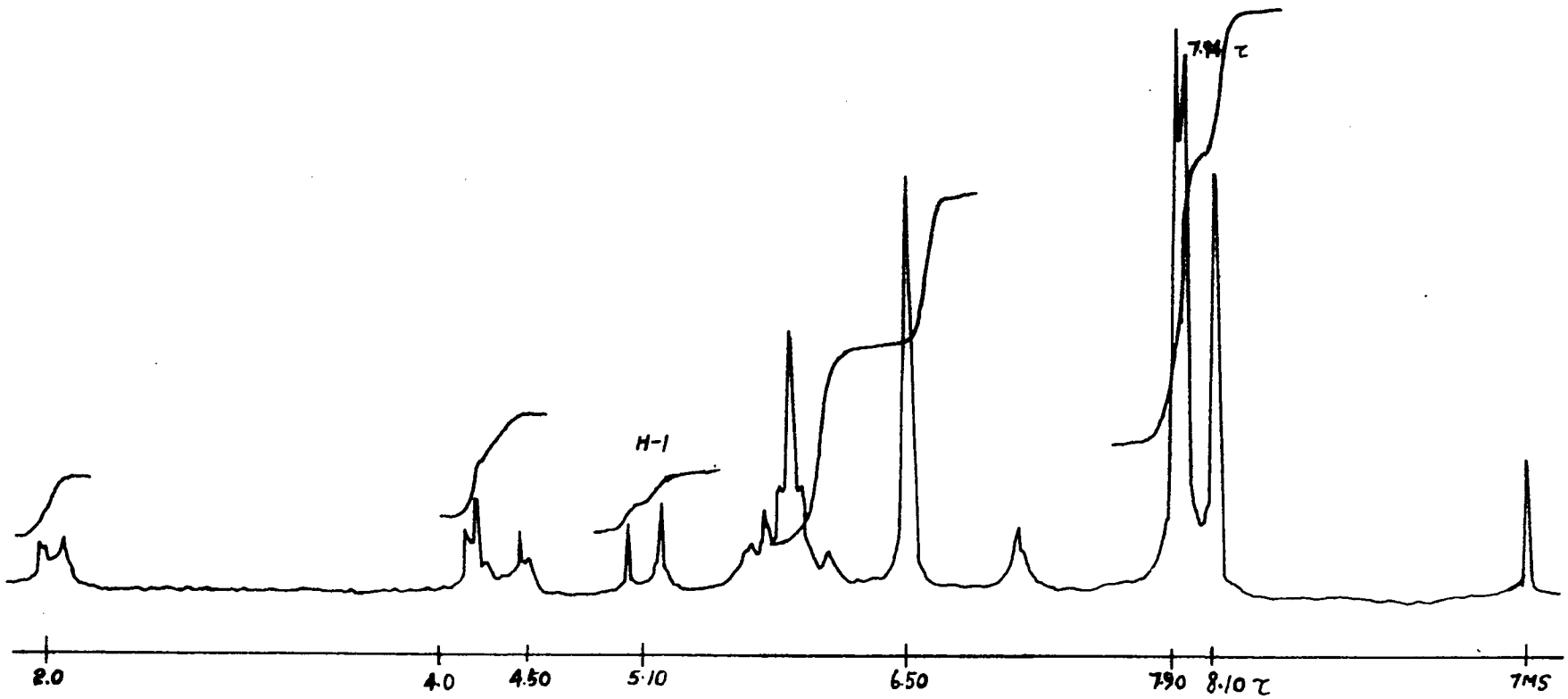
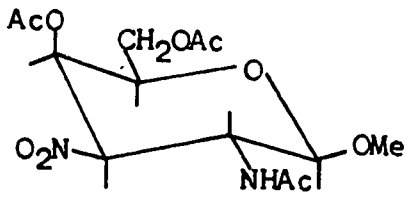


Fig. XIX. N.M.R. spectrum of methyl 2-acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXIV) in deuteriochloroform (with addition of two drops of deuterated dimethylsulfoxide)

Evidence for the equatorial disposition of the C-3 substituent in this series of compounds came from the n.m.r. study of the diacetamido-di-O-acetyl derivative XXVII to be described later.



XXIV

Reduction of methyl 2-acetamido-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXIII) with Adams' catalyst in 0.1 N hydrochloric acid furnished chromatographically uniform, crystalline methyl 2-acetamido-3-amino-2,3-dideoxy-β-D-galactopyranoside hydrochloride (XXV).

Compound XXV exhibited the characteristic, broad ammonium band of primary amine salts in the 3000 cm^{-1} region with overtones at 2600 and 2670 cm^{-1}. The hydroxyl band was found at 3350 cm^{-1} overlapping with NH absorption, and asymmetric and symmetric bending vibrations of NH_3^+ were found at 1555, 1590 and 1620 cm^{-1}.

Since the catalytic hydrogenation of the acetamido nitro compound XXIII was carried out in acidic medium, which is known to proceed with retention of configuration at the carbon atom bearing the nitro function (163), there is no doubt that XXV possessed the same configuration as its precursor.

The acetamido amino hydrochloride XXV was then N-acetylated to give methyl 2,3-diacetamido-2,3-dideoxy-β-D-galactopyranoside (XXVI). The reaction was carried out with acetic anhydride in water, in the presence of an anion exchange resin, Dowex 1-X8 (carbonate form). The infrared spectrum of the product no longer showed the broad absorption at 3000 cm^{-1} (amine salt), but bands attributable to OH and NH stretching vibrations were at 3580, 3420, 3340, 3290 and 3100 cm^{-1}, and strong amide-I and amide-II bands occurred at 1645 and 1560 cm^{-1}. Elemental analysis suggested that XXVI crystallized with water of crystallization (0.5 mole) which was not removed on drying the sample in vacuo. The substance was poorly soluble in chloroform and tended to form gels in methanol, so that no n.m.r. spectrum was taken. For the latter purpose, the fully acetylated derivative XXVII proved more suitable.

When the amine hydrochloride (XXV) was acetylated with acetic anhydride in pyridine at room temperature for

fifteen hours, there was isolated a crystalline product whose infrared spectrum showed a medium strong carbonyl absorption for an O-acetate at 1730 cm^{-1}, a weak C-O-C acetate stretching band at 1240 cm^{-1} and a hydroxyl band at 3480 cm^{-1}. Thin layer chromatography of the crystalline product as well as of its mother liquor, revealed that the mother liquor contained two well-separated main products, a fast-moving and a slow-moving one, with the crystalline product corresponding to the latter. On account of the observed hydroxyl absorption in the infrared and the relative slow migrating aptitude, it was presumed that the crystalline product was a partially acetylated glycoside, most likely methyl 2,3-diacetamido-6-O-acetyl-2,3-dideoxy-β-D-galactopyranoside. However, further characterization of this product was not undertaken. Instead, it was re-acetylated for an additional period of fifteen hours at room temperature, and after that time there was isolated a crystalline product chromatographically corresponding to the above-mentioned fast-moving component. Its infrared spectrum showed a strong carbonyl absorption for O-acetyl at 1740 cm^{-1} and a C-O-C stretching band at 1240 cm^{-1}, besides the amide-I and II bands at 1660, 1650 and 1540 and 1550 cm^{-1}. The NH stretching vibrations were at 3300 and 3320 cm^{-1}. There was no longer a hydroxyl band. This product was the desired, fully acetylated compound, methyl

2,3-diacetamido-4,6-di-O-acetyl-2,3-dideoxy-β-D-galacto-pyranoside (XXVII).

The n.m.r. spectrum of XXVII in deuteriochloroform (Fig. XX) permitted the elucidation of the configuration at C-3. The resonance of the glycosidic methyl group occurred at 6.55τ and the signal for the C-6 methylene group was bunched together with four of the five ring protons in the 5.5-6.0τ region, giving a total intensity of six. The remaining one ring proton resonated at 4.80τ. There were four sharp signals of equal intensities, each corresponding to three protons, at 7.87, 7.98 and 8.09 and 8.16τ. The first two signals could be assigned to the methyl protons of an axial acetoxyl at C-4 and an equatorial acetoxyl at C-6, respectively. The signals at 8.09 and 8.16τ could readily be attributed to two equatorial acetamido groups at C-2 and C-3 (or vice versa), on the grounds that the signals clearly fell into the chemical shift region established (142-146) for equatorial orientation (see also p.89). The assignment of an equatorial disposition to the acetamido group at C-2 in XXVII is consistent with the deduction made for the acetamidodi-O-acetylnitro compound XXIV. Thus the D-galacto configuration was established for XXVII and consequently for its precursors XX-XXVI.

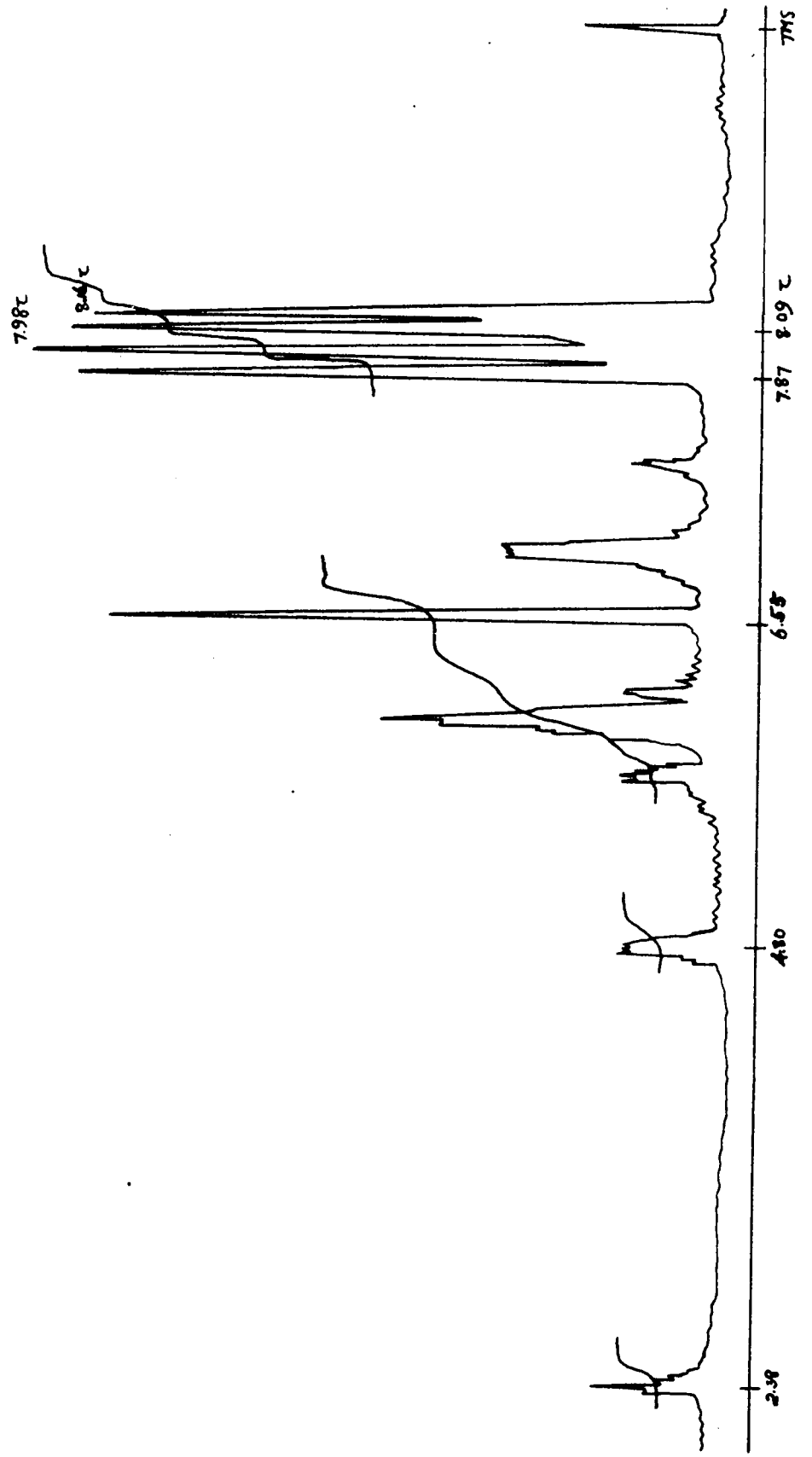
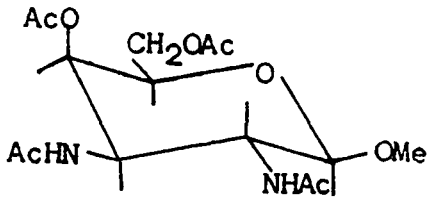


Fig. XX. N.M.R. spectrum of methyl 2,3-diacetamido-4,6-di-O-acetyl-2,3-dideoxy-β-D-galactopyranoside (XXVII) in deuteriochloroform (with addition of two drops of deuterated dimethylsulfoxide)



XXVII

EXPERIMENTAL

The melting points were determined in capillaries in an electrically heated aluminum block equipped with a calibrated thermometer. Thin layer chromatography (t.l.c.) was performed on silica gel G; 7.5-cm plates (microscope slides) were adequate unless otherwise mentioned. The solvent systems employed for irrigation were butanone-n-heptane, 1:2.5 (solvent A); butanone-n-heptane, 1:1 (solvent B), ethyl acetate-petroleum ether (b.p. 30-60°), 1:1 (solvent C), or chloroform-methanol, 9:1 (solvent D). The spots were made visible by spraying with 1% ceric sulfate in 10% sulfuric acid. Paper chromatography for amino sugars was performed by the descending technique on Whatman No. 1 paper, irrigated with pyridine-ethyl acetate-acetic acid-water 5:5:1:3, v/v (164). The spots were indicated with ninhydrin solution (0.6 g of triketohydrindene hydrate, 175 ml of butanol, 15 ml of 2N acetic acid and 300 ml of methanol). Optical rotations were measured at about 23° in a Perkin-Elmer automatic polarimeter, model 141. Infrared spectra were recorded from Nujol mulls on a Beckman IR-8 instrument, unless mentioned otherwise. The n.m.r. spectra were obtained from a Varian HA-60 spectrometer.

PART I

A. Branched-chain Dinitro Sugars by Michael Addition Reactions

Reactions of Nitroalkanes with Methyl 2-O-Acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (I)

Compound I was prepared according to Baer and Neilson (131). For the reactions with nitroalkanes, compound I was dissolved in an excess of the particular nitroalkane, triethylamine was then added, and the reaction mixtures were allowed to stand at room temperature. The amounts of reactants used are specified below. The progress of the reactions was monitored by t.l.c. with solvent A. The formation of products (III-VI) migrating faster than compound I was noticeable at an early stage, and complete or almost complete disappearance of I was observed within 16 h. Toluene (10 ml) was then added, and the mixtures were evaporated to dryness at 35° *in vacuo*. This operation was repeated twice and, if the residue was markedly yellowish, a treatment with decolorizing charcoal was included. Finally the solid residues were evaporated with ethanol and recrystallized from ethyl acetate-petroleum ether (b.p. 30-60°) unless indicated otherwise. The materials obtained

in the first recrystallization are referred to as the "crude products" in the following sections.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-2-nitromethyl-β-D-glucopyranoside (III)

Compound I (450 mg), nitromethane (15 ml) and triethylamine (0.18 ml) gave 372 mg of crude product, m.p. 160-169°. Two further recrystallizations from the same solvents gave 302 mg (67%) of III as fine colorless needles, m.p. 168-170°, $[\alpha]_D$ -74.6° (c, 1.0 in chloroform). The n.m.r. spectrum is shown in Fig. VI.

Anal. Calcd. for $C_{15}H_{18}N_2O_8$ (354.3): C,50.85; H,5.12; N,7.91. Found: C,50.79; H,5.21; N,8.11.

Infrared bands (in cm^{-1}): Asymmetric nitro, 1575, 1550 (strong); ether, 1085, 1095 (broad); phenyl, 695, 795 (medium); others, 975, 990, 1140, 1200, 1238, 1310, 1340.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-2-(1-nitroethyl)-β-D-glucopyranosides (IV)

Compound I (300 mg), nitroethane (5 ml) and triethylamine (0.12 ml) produced a reaction residue that exhibited two ill-separated spots on a 20-cm t.l.c. plate. The first recrystallization gave two fractions of crude products (154 and 110 mg, a total of 84.5%), the second

fraction being obtained by concentration of the mother liquor and addition of more petroleum ether (b.p. 30-60°). The first fraction, in which the faster moving component was enriched, melted over the range 155-164° and showed $[\alpha]_D$ -67.2° (c, 1.0 in chloroform). Two recrystallizations from chloroform-pentane removed the slow-moving component from this material and gave one epimer (IVa) in nearly pure state, m.p. 169-170°, $[\alpha]_D$ -71.2°. In a repeated experiment, several recrystallizations from ethyl acetate-petroleum ether led to a product of m.p. 170-170.5° and $[\alpha]_D$ -73.7° (c, 1.0 in chloroform).

Anal. Calcd. for $C_{16}H_{20}N_2O_8$ (368.4): C,52.17; H,5.47; N,7.61. Found: C,52.24; H,5.66; N,7.56.

The above-mentioned, second fraction (110 mg) chromatographically showed a preponderance of the slow-moving component, and it melted in the range of 130-140° and had $[\alpha]_D$ -59.2° (in chloroform). After a recrystallization from chloroform-pentane the melting point was reasonably sharp (133-134°) but t.l.c. still revealed two components.

A number of attempts were made to achieve a complete separation of the epimers present in crystal fractions from similar experiments. One batch, for instance, was dissolved in chloroform, and pentane was added in an amount insufficient to cause immediate crystallization.

In the course of 2 days the solution, which was stored at room temperature, deposited stout prisms and small aggregated crystals. By careful decantation and flotation with carbon tetrachloride it was possible to separate mechanically parts of the two kinds of crystals. The small crystals (m.p. 168-169°) gave a single, fast-moving spot and represented IVa; the stout prisms (m.p. 135-136°, $[\alpha]_D$ -57.4° in chloroform) showed both spots, with the slower one preponderating. A further recrystallization of these prisms from the same solvents did not change the chromatographic picture and resulted in m.p. 133-134°, $[\alpha]_D$ -59.0 (c, 0.7 in chloroform). The substance, designated here as IVb, apparently consisted of mixed crystals of IVa and its side-chain epimer.

The infrared spectra (in Nujol) of the high-melting (IVa) and low-melting (IVb) products were very similar in their gross patterns but differed as follows (in cm^{-1}). IVa: 1565 weaker than 1552 (asymmetric nitro stretchings); 1395, sharp, medium strong (symmetric nitro bands); 1080, strong (ether stretching); 770-750, three bands, medium strong (phenyl bands).

IVb: 1563 stronger than 1550 (asymmetric nitro stretchings); 1377, with shoulder at 1387, strong, superimposed on Nujol peak (symmetric nitro stretching); 1100, strong (ether band); 1003, medium strong (absent in IVa);

750, one sharp band (phenyl). Both IVa and IVb had prominent peaks near 970 and 700 (phenyl) and very similar groups of peaks in the 1350-1130 cm^{-1} region.

Nitroolefin II (131) (100 mg), nitroethane (2 ml) and triethylamine (0.04 ml) were allowed to interact at room temperature for 30 min. Work-up with toluene and ethanol gave a white, crystalline material (123 mg, 98%) whose infrared spectrum appeared as a superposition of the spectra of IVa and IVb. The rotation in chloroform was $[\alpha]_D$ -60.3° (-62.0° in a repeat experiment that had given a 95% yield), and the n.m.r. spectrum indicated a mixture of about equal amounts of epimers. Recrystallization from chloroform-pentane gave crystals of IVa melting at 169°, $[\alpha]_D$ -74.4° (c, 1.4 in chloroform) and from the mother liquor were obtained mixed crystals that melted at 131-133°.

The n.m.r. spectrum of IVa is shown in Fig. VII.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-2-(1-nitropropyl)-β-D-glucopyranoside (V)

Compound I (100 mg), 1-nitropropane (5 ml), and triethylamine (0.04 ml) gave 75 mg of crude product, m.p. 165-178°. Only one spot appeared on t.l.c. plates. One additional recrystallization furnished felt-like needles (65 mg, 60%) of m.p. 184° and $[\alpha]_D$ - 67.0° (c, 1.3 in chloroform).

Anal. Calcd. for $C_{17}H_{22}N_2O_8$ (382.4): C,53.40; H,5.80; N,7.33. Found: C,53.34; H,5.83; N,7.46.

Infrared bands (in cm^{-1}): Asymmetric nitro, 1562, 1544 (strong); ether, 1080 (strong); phenyl, 690, 742 (medium); others, 970, 1005, 1125, 1140, 1205, 1230, 1290.

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

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-2-(1-methyl-1-nitroethyl)-β-D-glucopyranoside (VI)

Compound I (200 mg), 2-nitropropane (10 ml) and triethylamine (0.2 ml, 2.5 molar equiv.) gave 118 mg of crude product, m.p. 170-188°. Two recrystallizations furnished 92 mg (45%) of pure VI, m.p. 187.5-189.5°, $[\alpha]_D$ -92.7° (c, 1.0 in chloroform).

Anal. Calcd. for $C_{17}H_{22}N_2O_8$ (382.4): C,53.40; H,5.80; N,7.33. Found: C,53.55; H,5.76; N,7.44.

The n.m.r. spectrum of compound VI is shown in Fig. IX.

Infrared bands (in cm^{-1}): Asymmetric nitro, 1562, 1550 (strong); ether, 1085, 1095 (strong); phenyl, 710, 770 (medium); others, 930, 980, 1145, 1165, 1220, 1235, 1300, 1320, 1330, 1350, and 1375, 1385 (gem-dimethyl splitting of 1380).

Attempted Reactions of Nitroalkanes with Methyl 2-O-Acetyl-4,6-O-Benzylidene-2,3-dideoxy-3-nitro-β-D-galactopyranoside (VII)

Compound VII (134) (50 mg) was dissolved in 6 ml of nitromethane with slight warming on a steam bath. The solution was cooled to room temperature and triethylamine (0.02 ml, one molar equiv.) was added. The reaction mixture was allowed to stand at room temperature for 3 h. The solution, which had turned dark brown, was evaporated *in vacuo* twice with toluene and several times with ethanol. A strong smell of benzaldehyde was detected in the resulting syrup, and no crystalline product could be isolated.

When compound VII was allowed to react with nitroethane in the same fashion, a dark brown solution resulted, indicating that decomposition had occurred. The reaction pattern was more or less the same when the reaction time was prolonged.

Reactions of Nitroalkanes with Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-β-D-threo-hex-2-enopyranoside (VIII)

Solutions of compound VIII (138) and triethylamine in an excess of the nitroalkane were allowed to stand at room temperature. The amounts of reactants used are specified below. The products (IX-XI) began to form within

a few minutes, and the reactions were complete after 1 h as indicated by t.l.c. with solvent B. (Since IX and X are sparingly soluble, trailing occurred on the plates unless smaller than usual amounts were applied.) The mixtures were then evaporated with additions of toluene (3 x 10 ml) and ethanol, to give nearly colorless to lightly yellow residues.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-2-nitromethyl-β-D-galactopyranoside (IX)

The crude product obtained from VIII (300 mg), nitromethane (10 ml) and triethylamine (0.12 ml) was dissolved in about 50 ml of ethyl acetate. The solution was decolorized with activated charcoal, filtered, and evaporated to a small volume. A colorless, crystalline product (256 mg, m.p. 210-220° with decomposition) separated and was collected after cooling to 4° for a few hours. Recrystallization from butanone-petroleum ether (b.p. 30-60°) gave 243 mg (68%) of compound IX as needles showing m.p. 227° (darkening from 210°) and $[\alpha]_D$ +8.6° (c, 0.6 in butanone).

Anal. Calcd. for $C_{15}H_{18}N_2O_8$ (354.3):: C,50.85; H,5.12; N,7.91. Found: C,50.74; H,5.06; N,8.06.

Infrared bands (in cm^{-1}): Asymmetric nitro stretchings, 1566, 1552 (strong); ether, 1095, 1085 (strong), 1000 (medium); phenyl, 745, 700; others, 1145, 1180, 1200, 1210, 1260, 1280, 1335, 1345.

The n.m.r. spectrum of compound IX taken in deuterated dimethylsulfoxide is shown in Fig. XI.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-2-(1-nitroethyl)-β-D-galactopyranosides (X)

The reaction mixture obtained from VIII (200 mg), nitroethane (2.5 ml) and triethylamine (0.08 ml) was evaporated with toluene (3 x 10 ml) and then with butanone to give a colorless crystalline residue decomposing at 175-185°, $[\alpha]_D$ +8.3° (c, 1 in butanone). T.l.c. showed two well-separated spots of comparable strength representing the two epimers of structure X; traces of unidentified products were seen in addition. The material was triturated thoroughly with ethyl acetate, chilled, filtered, and washed with cold ethyl acetate containing a small amount of pentane. The filtered residue (73 mg) as well as a crop of crystals (83 mg) deposited in the filtrate upon addition of pentane to incipient cloudiness consisted largely of a slow-moving epimer; m.p. 221° and 220-221°, with decomposition. A pure product giving the slow spot only was obtained by recrystallization from a rather large amount of boiling ethyl acetate. The fine needles (Xa) melted at 222-223° (decomp.) and had $[\alpha]_D$ +2.3° (c, 1.2 in butanone).

Anal. Calcd. for $C_{16}H_{20}N_2O_8$ (368.4): C,52.17; H,5.47; N,7.61. Found: C,52.29; H,5.65; N,7.43.

Infrared bands (in cm^{-1}): Asymmetric nitro stretchings, 1560 (strong), 1533 (medium); ether, 1010, 1070, 1090 (medium); phenyl, 700 (sharp), 740 (broad); others, 1140, 1175, 1205, 1245.

The mother liquors obtained above were allowed to evaporate in the air and gave crystalline residues enriched in the fast-moving epimer. The residues were dissolved in cold butanone or chloroform, whereby small quantities of sparingly soluble material (slow-moving epimer Xa) could be removed by filtration. Crystallization was then induced by careful addition of pentane or petroleum ether, and the fast-moving epimer Xb separated as beautiful prisms, m.p. 196-197° (decomp.), $[\alpha]_D$ +23.2° (c, 0.8 in butanone). Occasionally another recrystallization was necessary to attain these constants.

Anal. Calcd. for $C_{16}H_{20}N_2O_8$ (368.4): C,52.17; H,5.47; N,7.61. Found: C,52.30; H,5.60; N,7.51.

Infrared bands (in cm^{-1}): Asymmetric nitro stretchings, 1560, 1547 (both strong); ether, 1000, 1065, 1100 (strong); phenyl, 700, 760 (both sharp, strong); others, 825, 860, 915, 940, 985, 1145, 1185, 1200, 1210, 1245, 1255, 1405.

The n.m.r. spectra of Xa and Xb are shown in Figs. XIII and XIV.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-2-(1-nitropropyl)-β-D-galactopyranoside (XI)

Compound VIII (200 mg), 1-nitropropane (4 ml), and triethylamine (0.08 ml) gave a slightly yellowish crude product which was decolorized in toluene solution with activated charcoal. The material recovered (323 mg, 89%) showed m.p. 170-174° and $[\alpha]_D$ +20.1° (in butanone) and t.l.c. revealed the presence of a main product accompanied by a slightly slower by-product. Recrystallization from ethyl acetate-petroleum ether gave 200 mg (77%) of product, m.p. 175-177°. After two further recrystallizations from chloroform-pentane, the fine needles (XI) had m.p. 181° and $[\alpha]_D$ +23.0° (c, 1.0 in butanone), and these data remained unchanged although t.l.c. indicated that the by-product was still present.

Anal. Calcd. for $C_{17}H_{22}N_2O_8$ (382.4): C,53.40; H,5.80; N,7.33. Found: C,53.65; H,5.90; N,7.45.

Infrared bands (in cm^{-1}): Asymmetric nitro stretchings, 1563, 1557 (strong); ether, 1000, 1050, 1080, 1090 (medium strong); phenyl, 700, 725, 755 (sharp); others, 800, 1150, 1175, 1200, 1220, 1240, 1260, 1290, 1320, 1340, 1405.

The n.m.r. spectrum of XI is given in Fig. XV.

Attempted Synthesis of Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-2-(1-methyl-1-nitroethyl)-β-D-galactopyranoside (XII)

a) In the presence of triethylamine

To a solution of nitroolefin VIII (50 mg) and 2-nitropropane (5 ml), triethylamine (0.02 ml, one molar equiv.) was added. The reaction mixture was allowed to stand at room temperature for one hour. Work-up with toluene and ethanol gave a yellowish residue (20 mg) which was recrystallized from ethyl acetate-petroleum ether but retained an unsharp melting point, 145-160°. The infrared spectrum showed three asymmetric nitro stretchings at 1530, 1555 and 1565 cm^{-1}. The band at 1530 cm^{-1} was attributable to a nitroalkene grouping. Phenyl bands were at 700 and 750 cm^{-1}. There was no apparent splitting of the band at 1380 cm^{-1} characteristic of gem-dimethyl absorption, but instead, the 1300-1410 cm^{-1} region was very similar to that in the starting material (VIII). Incomplete reaction was also evidenced by t.l.c. where the spot corresponding to olefinic VIII still persisted.

In another two similar experiments, in which prolonged reaction times of 5 and 24 h were allowed, only very small amounts of crystalline material were isolated. Although in both cases the 1300-1410 cm^{-1} region of the infrared spectrum was quite different from that of the

starting material VIII, there was still no evidence of a gem-dimethyl splitting of the 1380 cm^{-1} band, and a shoulder to 1555 cm^{-1} at 1530 cm^{-1} was seen in both cases.

When three molar equivalents of triethylamine were used in one similar experiment of 30 min. duration, the yellow solid isolated melted over the 145-165° range and its infrared spectrum was similar to the above-mentioned.

b) In the presence of Triton B (Benzyltrimethylammonium hydroxide) (139)

A solution of Triton B (40% in methanol) (75 mg) was evaporated <u>in vacuo</u> to dryness. To the resulting residue, a solution of nitroolefin VIII (50 mg) and 2-nitropropane (5 ml) was added. The reaction mixture was stirred at room temperature for 12 h and was then poured into 400 ml of water. The solid which precipitated after 30 min of stirring was collected and dried. It weighed 10 mg and had m.p. 125-151°. Its infrared spectrum showed a shoulder to 1555 cm^{-1} at 1530 cm^{-1} and two others at 1550 and 1563 cm^{-1}. The shoulder to 1550 cm^{-1} at 1530 cm^{-1} suggested the presence of remnant starting material (VIII) and the expected product XII was not obtained in pure form.

B. Branched-chain Mononitro Sugars

1. Michael Addition of Diethyl Malonate to Nitro Sugar Derivatives

Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-[bis (ethoxycarbonyl)]methyl-3-nitro-β-D-gluco-pyranoside (XIII)

A solution of I (200 mg) in diethyl malonate (3 ml) and triethylamine (4 ml) was stirred for 16 h at room temperature. The mixture was poured into ice-water (400 ml). After stirring for 30 min. a white solid was isolated and washed very thoroughly, first with water and then with petroleum ether. The product, needles of m.p. 109-111°, was dried in a vacuum desiccator. The yield was 213 mg (83%), $[\alpha]_D$ -71.5° (c, 0.9 in chloroform).

Anal. Calcd. for $C_{21}H_{27}NO_{10}$ (453.5): C,55.62; H,6.00; N,3.09. Found: C,55.79; H,6.17; N,3.25.

Infrared bands (in cm^{-1}): Asymmetric nitro stretching, 1555 (single, strong); ester carbonyl bands, 1753 (medium), 1730 (strong); ether, 1090, 1115, 1170; ester C-O-C, 1228 (medium strong); phenyl, 755, 698; others, 910, 965, 975, 1015, 1260, 1305, 1390.

The n.m.r. spectrum of XIII is shown in Fig. XVI.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-[bis (ethoxycarbonyl)]methyl-3-nitro-β-D-galacto-pyranoside (XIV)

A solution of compound VIII (250 mg) in diethyl malonate (2 ml) and triethylamine (4 ml) was stirred at room temperature for 12 h, during which time partial crystallization occurred. The mixture was worked up as described for XIII and yielded 240 mg (62%) of needles exhibiting m.p. 164-166° and $[\alpha]_D$ +7.8° (c, 0.9 in chloroform). Its n.m.r. spectrum is shown in Fig. XVII.

Anal. Calcd. for $C_{22}H_{17}NO_{10}$ (453.5): C,55.62; H,6.00; N,3.09. Found: C,55.67; H,6.13; N,3.22.

Infrared bands (in cm^{-1}): Asymmetric nitro stretching 1555 (strong); ester carbonyl bands, 1755 (strong), 1735 (strong); phenyl, 705, 755; ester C-O-C, 1245 (medium strong); ether, 990, 1090, 1140, 1175 (medium strong); others, 1285, 1320, 1340, 1370, 1405.

2. Cyclization of Sugar Dialdehydes with Nitroethane:

Methyl 3-Deoxy-3-C-methyl-3-nitro-pentopyranoside (XVII)

Sodium metaperiodate (4.28 g) was dissolved in 50 ml of water, with gentle warming if necessary. After cooling to 5° there was added, with swirling, solid methyl

β-D-xylopyranoside (XV) (1.64 g) (m.p. 155-156°, $[\alpha]_D$ -65.4°) (94,140) in small portions in the course of 15 minutes. The reaction was then allowed to proceed in the dark at room temperature. About 30 minutes after the beginning of the operation, neutralization of the formic acid being generated was begun by careful, portionwise addition of 1M sodium bicarbonate solution. However, the reaction mixture was never allowed to become alkaline at any instant during the oxidation. After 2.5-3 h, the oxidation was complete as indicated by a potassium iodide-starch test performed with a withdrawn sample that had been mixed with excess sodium bicarbonate. The reaction mixture was neutralized with a total of 8.8 ml of 1M sodium bicarbonate solution (90%) until the pH was between 5 and 6. The dialdehyde XVI was then obtained as a syrup upon removal of sodium iodate and formate by precipitation with ethanol, concentration of the filtrate, and several repetitions of this procedure as described previously (94).

To a solution of dialdehyde XVI (from 1.64 g of methyl β-D-xyloside) in 20 ml of methanol, was added 4.2 ml (6 molar equivalents) of nitroethane. The flask was chilled in ice-water, and with continual swirling and cooling (5°) a chilled solution of sodium methoxide was added slowly in the course of 10 minutes. The amount of sodium methoxide added (11 ml of a solution of 3 g sodium in 100 ml of methanol) corresponded to 1.5 molar equivalents. The

reaction mixture was then allowed to stand at room temperature for 3 h, after which time the solution was deionized with 15 ml of Rexyn 101 (H^+) and stirred for 10 minutes. The resin was filtered off and washed with 10 ml of water, and the filtrate and the washing liquid were concentrated to a yellow syrup by several evaporations with absolute ethanol. The syrup was finally dissolved in 10 ml of chloroform and kept overnight at 4° with addition of seed crystals*. A crop of crystals (0.27 g, 13.8%) isolated from this reaction mixture showed on t.l.c. a major spot accompanied by three minor components, two moving more slowly and one faster than the main product (solvent D). The crude crystals had m.p. 145-160° and $[\alpha]_D$ -37.1° (c, 1 in water). Two recrystallizations from ethyl acetate-petroleum ether or from chloroform removed the minor components. The recrystallized product (XVII) had m.p. 159-161° and $[\alpha]_D$ -42° (c, 1 in water). Although the recrystallized product appeared uniform on silica gel plates, its n.m.r. spectrum in D_2O still revealed two weak satellite peaks accompanying the main C-CH_3 signal near 8.25 τ. Further recrystallizations did not change the physical constants.

Anal. Calcd. for $C_7H_{13}NO_6$ (207.2): C,40.57; H,6.32; N,6.76. Found: C,40.80; H,6.33; N,6.73.

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* Seed crystals were obtained from a preliminary experiment when a similar syrup was allowed to stand at room temperature in the air for several days.

Infrared bands (by Infracord, in cm^{-1}): Asymmetric nitro stretching, 1550 (strong); hydroxyl band, 3550 (strong); ether, 1025, 1060; others, 740, 820, 875, 965, 1105, 1150, 1210.

Methyl 3-Amino-3-deoxy-3-C-methyl-pentopyranoside Hydrochloride (XVIII)

A sample of XVII (200 mg) in water (5 ml) was hydrogenated with platinum catalyst (100 mg of platinum dioxide, prehydrogenated) in 9.7 ml of N/10 HCl. The hydrogen uptake was 71 ml after 6 h. (Calcd. for 3 moles, 67 ml at STP). After the filtration of the catalyst the solution was evaporated with several additions of absolute ethanol to give a colorless residue. The amine hydrochloride was crystallized from ethanol-ethyl acetate and the yield was 163 mg, m.p. 187-191° (decomp.). Two recrystallizations from the same solvents raised the melting point to 204-206° (decomp.), $[\alpha]_D$ -50.2 (c, 1 in water). Paper chromatographic investigation of the mother liquor and the recrystallized product revealed that the recrystallized product was uniform (one spot, R_{Gm} = 1.47) while the mother liquor contained, in addition to this, another product with R_{Gm} = 1.15.

The n.m.r. spectrum of recrystallized XVIII in D_2O showed only a single sharp signal for the C-CH_3 protons near 8.60τ and a single peak for methoxyl signal near 6.42τ.

Anal. Calcd. for $C_7H_{16}NO_4Cl$ (213.7): C,39.35; H,7.54; N,6.55. Found: C,39.52; H,7.63; N,6.80.

Infrared bands (by Infracord, in cm^{-1}): Ammonium band of primary amine, 3100 (broad); hydroxyl band, 3335 (sharp, strong); asymmetric and symmetric NH_3^+ bending, 1610 and 1520; ether, 1005, 1035, 1060 and 1095; others, 980, 990, 1150, 1215, 1270, 1370.

Methyl 3-Acetamido-3-deoxy-3-C-methyl-2,4-di-O-acetyl-pentopyranoside (XIX)

Amine hydrochloride XVIII (300 mg) was dissolved in 6 ml of acetic anhydride and anhydrous sodium acetate (0.5 g) was then added. The reaction mixture was boiled under reflux for 30 minutes. After cooling the mixture was poured onto 150 g of crushed ice, and when the decomposition of the excess acetic anhydride had taken place the mixture was extracted with chloroform (100 ml). The extract was washed with ice-cold 5% sodium bicarbonate solution and then with ice-water. The chloroform layer was then dried over magnesium sulfate. After filtration and three evaporations with addition of ethanol, the product was crystallized from ethyl acetate-petroleum ether. A crop of 0.34 g was obtained and melted at 149-154°. After two re-crystallizations from the same solvents it showed m.p. 150-152° and $[\alpha]_D$ = -71.4 (c, 1 in chloroform).

Anal. Calcd. for $C_{13}H_{21}NO_7$ (303.3): C,51.48; H,6.98; N,4.62. Found: C,51.67; H,6.99; N,4.81.

Infrared bands (by Infracord, in cm^{-1}): NH stretching, 3300; acetate carbonyl absorption, 1745; amide-I band, 1650; amide-II band, 1550; acetate C-O-C, 1220; ether, 1030, 1070, 1095; others, 990, 1115, 1155, 1300.

The n.m.r. spectrum of XIX in deuteriochloroform is given in Fig. XVIII.

PART II

Synthesis of Diamino Sugar Derivatives

Attempted Amination of Methyl 2-O-Acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-galactopyranoside (VII)

Compound VII (100 mg) (134) was dissolved in tetrahydrofuran (15 ml) with slight warming on a steam bath. After cooling under running water, concentrated aqueous ammonia hydroxide (4 ml) was added. The reaction mixture was stirred for one hour at room temperature and was then evaporated several times with additions of ethanol. There was obtained a syrup that strongly smelled of benzaldehyde. When water was added (2 ml), no crystalline, water-insoluble substance separated. Thin layer chromatography of the syrup with solvent D revealed the absence of starting 2-O-acetate VII, but there were at least four slower-moving components of more or less equal intensity.

Amination of Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-β-D-threo-hex-2-enopyranoside (VIII):

Methyl 4,6-O-Benzylidene-2-benzylideneamino-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXI)

a. Olefin VIII (500 mg) was dissolved in tetrahydrofuran (7 ml), and concentrated aqueous ammonium hydroxide

(1 ml) was added. The reaction mixture was refluxed with vigorous stirring for three minutes. After cooling, the reaction mixture was evaporated several times with added ethanol to give a yellowish residue which was finally taken up in 5 ml of methanol. On storage at 4° for a few hours, 132 mg of crude product (XXI) crystallized. Another crop of 18 mg was isolated when a few drops of water were added to the mother liquor. The product melted in the range of 180-208°. Two recrystallizations from methanol gave fine needles of m.p. 219°(dec.) $[\alpha]_D$ =+43.1° (c, 1 in dimethylformamide). The yield was 22%.

Anal. Calcd. for $C_{21}H_{22}N_2O_6$ (398.42): C,63.31; H,5.57; N,7.03. Found: C,63.74; H,5.83; N,7.63.

Infrared bands (in cm^{-1}): Asymmetric nitro stretching, 1550 (strong); ether, 1010, 1040, 1070; phenyl, 690, 745; C=N, 1645; others, 1145, 1180, 1200, 1250, 1280, 1300, 1330, 1340.

b. Ammonium acetate (300 mg) was melted in a 10-ml beaker on a steam bath, and olefin VIII (100 mg) was added with stirring. The olefin first dissolved but the mixture solidified after a short time (1-2 min.). The yellowish to light brown reaction mixture was then cooled immediately under running water, transferred with water (50 ml) into a larger vessel, and triturated thoroughly. The water-insoluble substance was collected and dried. One

crystallization from methanol gave a product (12 mg, 8.8%) which melted at 217-219° (dec.) and had an infrared spectrum identical to that of XXI.

c. A mixture of ammonium acetate (0.5 g) and acetamide (1.0 g) contained in a 10-ml beaker was melted on a steam bath. Olefin VIII (400 mg) was added with stirring. The olefin initially dissolved, and the molten mixture partially resolidified after 2-3 min. of stirring. The light brown or deep yellow reaction mixture was then cooled immediately under running water. Water was added for transfer into a larger vessel, and the material was triturated with another 100 ml of distilled water. The water-insoluble substance was filtered with suction and dried in a desiccator.

The water-insoluble substance showed a C=N band at 1645 cm^{-1} in the infrared comparable to that of XXI but the fingerprint pattern did not show considerable detail. The material gave a faintly positive ninhydrin test. The substance was dissolved in 70 ml of hot methanol and any remaining, insoluble matter was filtered off and discarded. The clear methanolic solution containing XXI was cooled to room temperature and used directly for acetylation as described in a subsequent paragraph.

Methyl 2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXII)

a. Crystalline compound XXI (120 mg) was dissolved with warming in 30 ml of methanol. Upon cooling, the solution turned turbid due to partial recrystallization of XXI. Regardless of this, acetic anhydride (2 ml) was added. The reaction mixture was stirred at room temperature for 24 h. during which time precipitation of XXII occurred. The reaction mixture was then evaporated with three additions of ethanol and the residue obtained was finally suspended in methanol. The crude product XXII was filtered off, washed, and recrystallized from hot nitromethane to afford 76 mg (71.6%) of XXII which gradually decomposed above 285° without melting but with slight sublimation at the neck of the capillary tube. The rotation was $[\alpha]_D$ +26.9° (c, 1 in DMF). The overall yield of XXII based on olefin VIII was 16%.

Anal. Calcd. for $C_{16}H_{20}N_2O_7$ (352.3): C,54.54; H,5.72; N,7.95. Found: C,54.68; H,5.84, N,8.03.

Infrared bands (in cm^{-1}): NH stretching, 3310, asymmetric nitro stretching, 1550 (strong); amide-I, 1660 (strong); amide-II, 1555 (overlapping asymmetric nitro stretching); phenyl, 700, 750; ether, 1000, 1020, 1070, 1095; others, 1155, 1185, 1240, 1255, 1290, 1320, 1335, 1340, 1405.

b. To the methanolic solution of XXI obtained under c) in the preceding section was added acetic anhydride (3 ml). The reaction mixture was stirred at room temperature for 24 h. Work-up as described above afforded 188 mg of crude XXII. Recrystallization from nitromethane furnished 178 mg of a product which according to its infrared spectrum was identical with XXII obtained under a). The overall yields based on olefin VIII ranged from 35-38% in several similar experiments.

Methyl 2-Acetamido-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXIII)

Benzylidene derivative XXII (640 mg) and 3.2 g of Rexyn 101 (H^+) in 65 ml of methanol-water (4:1 v/v) were refluxed and magnetically stirred for 6 h. The resin was removed and the filtrate on evaporation gave a crystalline residue which was taken up in water and, by filtration, freed from a small amount (ca. 5 mg) of insoluble matter. The solution was then brought to dryness by evaporation and several coevaporations with ethanol. The residue was recrystallized from methanol-ethyl acetate to yield 375 mg of XXIII, m.p. 200° (dec, with prior darkening at 180°). Another recrystallization afforded 340 mg of pure XXIII, m.p. 208° (dec, darkening around 195°), $[\alpha]_D = +16.6°$ (c, 1 in water).

Anal. Calcd. for $C_9H_{16}N_2O_7$ (264.2): C,40.90; H,6.10; N,10.60. Found: C,40.76; H,6.24; N,10.77.

Infrared bands (in cm^{-1}): Asymmetric nitro stretching, 1560 (strong); hydroxyl bands, 3630, 3500; NH stretching, 3340 (broad); amide-I, 1655; amide-II, 1540; ether, 1020, 1050, 1080, 1100; others, 980, 1125, 1155, 1190, 1220, 1245, 1310.

Methyl 2-Acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXIV)

To a suspension of compound XXIII (150 mg) in acetic anhydride (2 ml) was added boron trifluoride etherate (2 drops). Upon swirling, complete dissolution of XXIII occurred. The mixture was allowed to stand at room temperature for 20 min. and then taken up in 20 ml of methanol and evaporated three times with excess methanol and twice with ethanol. Some ice-water (ca. 1/2 ml) was added to the resulting syrup, whereby crystallization took place on scratching. The crystals were filtered and dried; they weighed 128 mg. The mother liquor was evaporated twice with ethanol giving a syrup with which the above operation was repeated. This gave another crop (12 mg), the total yield being 140 mg (71%). The melting point of 162-165° was raised by recrystallization from ethyl acetate-petroleum ether (30-60°) to 164-165°. Gel formation during

the recrystallization was overcome by careful addition of the petroleum ether in an amount insufficient to cause immediate turbidity. The rotation was $[\alpha]_D$ +8.8° (c, 1 in chloroform).

Anal. Calcd. for $C_{13}H_{20}N_2O_9$ (348.3): C,44.83; H,5.79; N,8.05. Found: C,44.66; H,5.95; N,8.14.

Infrared bands (in cm^{-1}): Asymmetric nitro stretching, 1552 (strong); NH stretching, 3360; acetate carbonyl, 1745 (strong); amide-I, 1660 (strong); amide-II, 1540; ether, 1020, 1040, 1070, 1090; others, 620, 700, 725, 870, 908, 935, 945, 996, 1110, 1130, 1155, 1172, 1198, 1220, 1235, 1280, 1360.

The n.m.r. spectrum of compound XXIV is shown in Fig. XIX.

Methyl 2-Acetamido-3-amino-2,3-dideoxy-β-D-galactopyranoside Hydrochloride (XXV)

Platinum dioxide (120 mg) was prehydrogenated in 12.4 ml of 0.1N hydrochloric acid. A solution of XXIII (320 mg) in water (50 ml) was added to the acidic suspension of the catalyst and hydrogenated with efficient shaking at 23° and atmospheric pressure. After 3 h there had been consumed 86.5 ml of hydrogen (calcd for 3 moles, 81.5 ml at STP), and uptake had ceased. The catalyst was then filtered off, and evaporation of the solution followed

by several evaporations with ethanol furnished a residue which was recrystallized from methanol-ethyl acetate. The yield was 304 mg of XXV, m.p. 210-215° dec. One further recrystallization gave 269 mg (82%) of material and raised the m.p. to 222-223° (dec); $[\alpha]_D$ = +0.6° (c, 1 in water). Compound XXV showed only one spot on paper chromatography with the Fischer-Dörfel solvent; R_{Gm} = 1.39.

Anal. Calcd. for $C_9H_{19}ClN_2O_5$ (270.7): C,39.96; H,7.07; N,10.35. Found: C,39.92; H,7.20; N,10.36.

Infrared bands (in cm^{-1}): Ammonium band of primary amine salt, 3000 (broad), overtones at 2670, 2600); hydroxyl band, 3350; NH stretching, 3330 (overlapping with hydroxyl band); asymmetric and symmetric bending of NH_3^+, 1555, 1590, 1620; ether, 1050 (broad), amide-I, 1660 (strong), amide-II, 1535; others, 720, 750, 965, 1150 (broad), 1215, 1270, 1310.

Methyl 2,3-Diacetamido-2,3-dideoxy-β-D-galactopyranoside (XXVI)

Amine hydrochloride XXV (320 mg) was N-acetylated with acetic anhydride (0.2 ml) in water (10 ml) containing methanol (1 ml) and 6 ml of Dowex 1-X8 ($CO_3^=$ form); the reaction mixture was magnetically stirred for 90 min. in an ice-water bath. The resin was then filtered off and a brief treatment of the filtrate with a small amount of

Rexyn 101 (H^+) was performed. After filtration, the solution was evaporated to give a colorless residue that was further evaporated with 20 ml of ethanol. For crystallization, the material was triturated with boiling acetone (10 ml) containing several drops of water. Gel formation was overcome by allowing the solution to cool slowly in a bath of warm water. Compound XXVI was isolated as microscopic needles, in a yield of 200 mg. The mother liquor was concentrated to a smaller volume and redissolved in acetone-water. This afforded another crop of 54 mg. The total yield was 254 mg of compound XXVI, m.p. 265-267° (dec). Another recrystallization from the same solvent mixture gave 232 mg of XXVI (71% yield) which decomposed at 269-270° when the temperature was raised very slowly. Decomposition occurred above 300° at a more rapid rate of heating. The rotation was $[\alpha]_D = -34.3°$ (c, 1 in water). The analytical sample was dried in vacuo at 56°, but in spite of this, water of crystallization corresponding to a hemihydrate appeared to be retained.

Anal. Calcd. for $C_{11}H_{20}N_2O_6$ (276.3): C,47.82; H,7.30; N,10.14. Calcd. for $C_{11}H_{20}N_2O_6.1/2H_2O$ (285.3): C,46.20; H,7.42; N,9.82. Found: C,46.04; H,7.37; N,9.66.

Infrared bands (in cm^{-1}): Hydroxyl bands, 3420, 3580; NH stretchings, 3300, 3340; amide-I, 1645 (strong); amide-II, 1555, 1565 (medium strong); ether, 1020, 1040, 1080; others, 730, 980, 1130, 1165, 1205, 1230, 1290, 1310.

Methyl 2,3-Diacetamido-4,6-di-O-acetyl-2,3-dideoxy-β-D-galactopyranoside (XXVII)

Amine hydrochloride (XXV) (100 mg) was acetylated with acetic anhydride (0.75 ml) and pyridine (4 ml), the gel-like reaction mixture being magnetically stirred at room temperature for 15 h. Exhaustive evaporations with ethanol, toluene and again ethanol furnished a gel which was dried under vacuum. For crystallization, the dried material (115 mg) was dissolved in methanol (4 ml) and ethyl acetate was carefully added. Gel formation was avoided by allowing the solution to cool slowly in a bath of warm water. A batch of crystalline material was isolated on the next day (80 mg, m.p. 265-267° (dec)). This compound showed a medium strong acetate carbonyl absorption at 1730cm^{-1} as well as a hydroxyl band at 3480 cm^{-1}. Thin layer chromatography with solvent D of this compound and its mother liquor revealed that the isolated crystals corresponded to the slower and less intense spot of two spots exhibited by the mother liquor. The crystals presumably represented a partially acetylated product, most likely methyl 2,3-diacetamido-6-O-acetyl-2,3-dideoxy-β-D-galactopyranoside. In order to obtain full acetylation, the product was subjected to another treatment with acetic anhydride (0.5 ml) in pyridine (4 ml) for 15 h at room temperature. Work-up as described above afforded 65 mg of compound XXVII as

colorless needles of m.p. 258-260° and $[\alpha]_D$ = -27.8° (c, 0.5 in chloroform). The product was now chromatographically homogeneous, corresponding to the above-mentioned faster moving spot.

Anal. Calcd. for $C_{15}H_{24}N_2O_8$ (360.4): C,50.00; H,6.71; N,7.78. Found: C,49.91; H,6.60; N,7.87.

Infrared bands (in cm^{-1}): NO hydroxyl; acetate carbonyl, 1740 (strong); NH stretchings, 3300, 3330; amide-I, 1650, 1665 (both strong); amide-II, 1540, 1550; ether, 1020, 1040, 1055, 1080; others, 690, 730, 870, 890, 930, 950, 995, 1115, 1130, 1145, 1175, 1230, 1265, 1280, 1295, 1315.

The n.m.r. spectrum of compound XXVII is shown in Fig. XX.

CLAIMS TO ORIGINAL RESEARCH

PART I

1. The Michael synthesis of α,γ-dinitroalkanes was applied to the carbohydrate field for the first time. It furnished several branched-chain dinitro sugar glycosides as representatives of a novel class of carbohydrate derivatives.
2. The Michael synthesis of two branched-chain mononitro sugars was accomplished.
3. Branched-chain nitrogenous pentose derivatives were synthesized by use of nitroethane cyclization of a dialdehyde.
4. The following new compounds were obtained:
   a) methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-nitromethyl-β-D-glucopyranoside (III)
   b) methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-nitroethyl)-β-D-glucopyranosides (IVa and IVb)
   c) methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-nitropropyl)-β-D-glucopyranoside (V)
   d) methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-methyl-1-nitroethyl)-β-D-glucopyranoside (VI)
   e) methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-nitromethyl-β-D-galactopyranoside (IX)
   f) methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-nitroethyl)-β-D-galactopyranosides (Xa and Xb)

g) methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(1-nitropropyl)-β-D-galactopyranoside (XI)

h) methyl 4,6-O-benzylidene-2,3-dideoxy-2-[bis(ethoxycarbonyl)]methyl-3-nitro-β-D-glucopyranoside (XIII)

i) methyl 4,6-O-benzylidene-2,3-dideoxy-2-[bis(ethoxycarbonyl)]methyl-3-nitro-β-D-galactopyranoside (XIV)

j) methyl 3-deoxy-3-nitro-3-C-methyl-pentopyranoside (XVII)

k) methyl 3-amino-3-deoxy-3-C-methyl-pentopyranoside hydrochloride (XVIII)

l) methyl 3-acetamido-3-deoxy-3-C-methyl-2,4-di-O-acetyl-pentopyranoside (XIX)

PART II

A synthesis of derivatives of hitherto unknown 2,3-diamino-2,3-dideoxy-D-galactose was elaborated. Introduction of an amino function into methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-threo-hex-2-enopyranoside (VIII) and further chemical transformations led to the following new compounds:

a) methyl 4,6-O-benzylidene-2-benzylideneamino-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXI)

b) methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-

3-nitro-β-D-galactopyranoside (XXII)

c) methyl 2-acetamido-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXIII)

d) methyl 2-acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-nitro-β-D-galactopyranoside (XXIII)

e) methyl 2-acetamido-3-amino-2,3-dideoxy-β-D-galactopyranoside hydrochloride (XXV)

f) methyl 2,3-diacetamido-2,3-dideoxy-β-D-galactopyranoside (XXVI)

f) methyl 2,3-diacetamido-4,6-di-O-acetyl-2,3-dideoxy-β-D-galactopyranoside (XXVII).

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