"Hypotheses non fingo."

I. Newton

P R E F A C E

Introductory remarks in this thesis give a brief account of the general features of the Henry addition. This account is followed by a discussion of methods used in the synthesis of α-nitroalkenes, and more specifically, carbohydrate nitroolefins. The introduction is concluded by a discussion of nucleophilic addition reactions in carbohydrate nitroolefins, with emphasis on the formation of vicinal nitroamines.

The thesis is divided into three parts. Part I deals with a reinvestigation of the synthesis of 3-nitro sugars by the Henry addition of nitromethane to sugar dialdehydes. Part II describes a study concerning the nitromethylene acidity and the mechanism of epimerization of partially blocked nitro hexoses. The synthesis of α-halonitro sugars is also discussed in this connection. Part III is concerned with the synthesis and some reactions of nitroolefins. Special emphasis is placed on a comparative study of four isomeric, 2,3-unsaturated nitro hexopyranosides in reductions, epoxidations, and addition reactions with N-bromoacetamide.

The results of Part II, Chapters A, B, C, and Part III, Chapter C have been published.*

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* H.H. Baer and W. Rank, Can.J.Chem., 49, 3197 (1971);
W. Rank and H.H. Baer, Can.J.Chem., 49, 3236 (1971);
H.H. Baer and W. Rank, Can.J.Chem., 49, 3192 (1971).

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The candidate also likes to thank Professor T. Durst whose discussions exceeded by far the framework of research presented here.

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Part I

Stereoisomeric methyl 4,6-O-benzylidene-3-deoxy-3-nitro-hexopyranosides proved to be distinguishable by the chemical shifts of their benzylidene methine proton signals, and ratios of such isomers in mixtures could be estimated by signal integration. The method was applied to a reinvestigation of the epimeric distributions in which methyl 3-deoxy-3-nitro-α-D-hexopyranosides arise, firstly, in the nitromethane cyclization of D-hydroxymethyl-D'-methoxy-diglycolaldehyde and, secondly, in their base-catalyzed configurational equilibration via nitronates. Previous results were essentially confirmed as far as the preferred configurations are concerned but required some revision as to the relative abundance of less favored configurations. Preparative chromatography of benzylidene acetals afforded some isomers which were not isolated before. Debenzylidenation of the acetals furnished some nitrohexopyranosides of the α-D-series which were isolated for the first time. Separation of isomers in the β-D-series was improved by use of chromatography and by a new method involving differential reactivities of compounds toward alkali. The circular dichroism of benzylidenated 3-deoxy-3-nitro sugars was studied in this connection.

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

Part II

Chapter A.—— The extent of nitronate formation in methyl 4,6-O-benzylidene-3-deoxy-3-nitrohexopyranosides, methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitrohexopyranosides, and methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitrohexopyranosides in dilute potassium hydroxide solution was compared by means of u.v. spectroscopy. Considerable differences were found to exist in the nitromethylene acidities, and these were correlated with stereochemical features of the molecules.

Chapter B.—— A facile manno ⟶ gluco epimerization in benzylidenated 3-deoxy-3-nitro sugars was investigated. It was shown that, in alkaline alcoholic solution, the epimerization proceeds by an elimination-addition via an intermediate nitroalkene if the hydroxyl group at C-2 is acetylated. However, if the hydroxyl is free, the nitroalkene is not an intermediate and, in accord with the low nitromethylene acidity in this particular case, the mechanism is suggested to involve a reverse Henry reaction.

Chapter C.—— Acetylation of methyl 4,6-O-benzylidene-3-deoxy-3-nitro-β-D-galactopyranoside and its α- and β-D-manno isomers with acetyl chloride and triethylamine in ether furnished the expected 2-O-acetylated nitro glycosides in good yields. However, the same method applied to the α-D-talo isomer afforded a nitronic acid-acetic acid anhydride, namely, methyl 2-O-acetyl-3-(O-acetyl-aci-nitro)-4,6-O-benzylidene-3-deoxy-α-D-lyxo-hexopyranoside.

Chapter D.—— Bromination and chlorination of methyl 4,6-O-benzylidene-3-deoxy-3-nitro-D-hexopyranosides and methyl 4,6-O-

benzylidene-2,3-dideoxy-3-nitro-D-hexopyranosides furnished in most cases the 3-halo-3-nitro glycosides, a new class of carbohydrates. In some instances, the halogenation was complicated by the fact that two 3-epimeric products were formed, in other instances halogenation was accompanied by epimerization for which a retrograde Henry-type mechanism is postulated. Upon treatment with base, some of the halonitro sugars afforded epoxy-nitro sugars, another new class of carbohydrates. The nuclear magnetic resonance and circular dichroism of halonitro sugars was studied also.

Part III

Chapter A.—— The preparation β-nitrostyrene, 3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-xylo-hex-5-eno-furanose, and stereoisomeric methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-hex-2-enopyranosides is described briefly. The procedure for the preparation of the latter nitroolefins with D-threo configuration was improved in this connection, while the isomer with β-L-threo configuration was synthesized for the first time.

Chapter B.—— Reduction of the four stereoisomeric methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-hex-2-enopyranosides with sodium borohydride gave in excellent yields the corresponding saturated nitro glycosides that possess an equatorial nitro group. Reduction with zinc and acetic acid gave in similar yields the corresponding 2,3-dideoxy-3-oximino glycosides. Two of the latter were deoximated to 2,3-dideoxy-3-oxo sugar derivatives.

Chapter C.—— Action of hydrogen peroxide in a weakly alkaline medium upon stereoisomeric methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-hex-2-enopyranosides led to α-nitroepoxides in excellent yields. This reaction proceeded with a marked stereospecificity, which seemed to be mainly dependent on the anomeric configuration of the starting nitroolefins. The configurational assignments were based on n.m.r. and c.d. data.

Chapter D —— A new reaction, namely, the sodium acetate catalyzed addition of N-bromoacetamide across the carbon-carbon double bond of nitroolefins was discovered. Application of this reaction to β-nitrostyrene resulted in the formation of 1,1-dibromo-1-nitro-2-acetamido-2-phenylethane. Addition of NBA to 3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-xylo-hex-5-enofuranose led to the formation of 5-acetamido-3-O-acetyl-6,6-dibromo-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose and the corresponding β-L-idofuranose. The same compounds were synthesized also by an independent route starting with the addition of ammonia to the above-mentioned 5,6-unsaturated nitro sugar. The circular dichroisms of various 6-nitro hexofuranoses were recorded and from their dichroic behavior two rules were deduced allowing the distinction of C-5 epimers. Addition of NBA to methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-D-hex-2-enopyranosides led in a highly stereospecific reaction to the formation of methyl 2-acetamido-4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-D-hexopyranosides. The stereospecificity of the reaction was found to be governed by the anomeric configuration of the starting nitroolefins.

Derivatives of 2,3-diaminomannose, 2,3-diaminotalose, 2,3-diaminoglucose, and 2,3-diaminogalactose were synthesized in this way and their n.m.r. spectroscopic and dichroic behavior was studied.

INTRODUCTION

The amino sugars most commonly found as constituents of polysaccharides and glycoproteins in the animal kingdom are 2-amino-2-deoxy-D-glucose, 2-amino-2-deoxy-D-galactose, and sialic acid (a nine-carbon amino sugar acid) (1). It is surprising that, in spite of the great structural and functional variety of chemical substances produced by animals, only these three amino sugars seem to play a role. In contrast, microorganisms have been found to produce a multitude of different amino sugars, with great variations in constitution and configuration (2). The structural elucidation and the synthesis of amino sugars from microorganisms, and especially the chemistry of antibiotics, has been a continual challenge to carbohydrate chemists during the past two decades. The development of the chemistry of nitro sugars has contributed a great deal to that of the amino sugars, for the obvious reason of their close relationship. However, the study of nitro sugars is an interesting subject in itself since the presence of a nitro group in a carbohydrate molecule gives rise to mechanistic, stereochemical, and preparative problems and possibilities not encountered in ordinary sugars. Furthermore, the recent discovery of evernitrose, the first nitro sugar found in nature (3), added to the interest which this class of carbohydrate derivatives deserves.

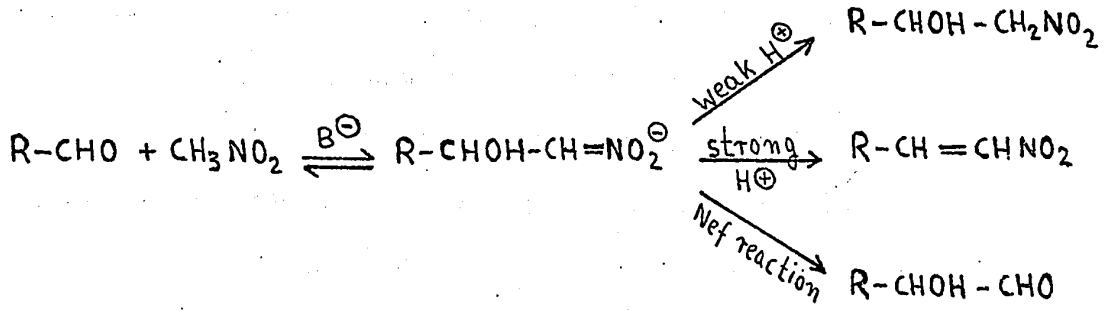
A. The Henry Addition

One of the more convenient methods for the synthesis of nitro sugars employs the Henry addition. Therefore, some of the general features of this reaction shall be briefly discussed.

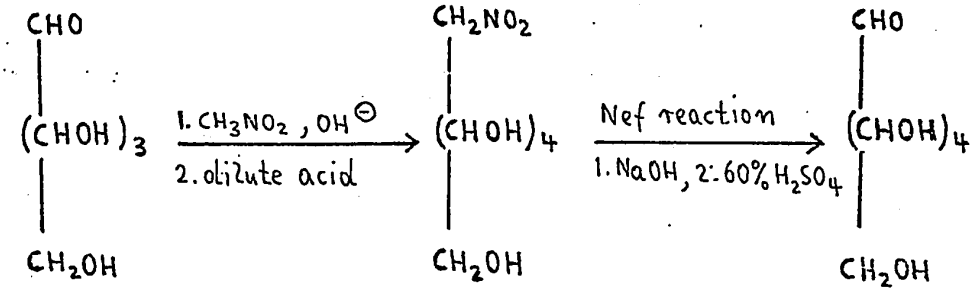
In 1895, L. Henry discovered the aldol-type, base-catalyzed addition of nitromethane (4) and homologous primary nitroalkanes (5) to aliphatic aldehydes. In subsequent work the reaction was extended to include secondary nitroalkanes and many substituted nitroalkane derivatives on the one hand, and ketones as well as aromatic aldehydes on the other. In this manner a large number of nitro alcohols including polyhydroxy nitro compounds were obtained, which, in turn, have served as intermediates for the synthesis of nitroolefins, amino alcohols, oximes and many other products. Review articles by Hass and Riley (6), Levy and Rose (7), Sowden (9), and a monograph by Perekalin (8) cover most of the early work, while more recent applications, particularly in the field of sugars and cyclitols have been reviewed by Lichtenthaler (10) and Baer (11).

The primary products in the Henry addition are alkali nitronates from which upon acidification with dilute, weak acids one obtains mixtures of two epimeric nitro alcohols. Acidification with strong acids may entail dehydration of the nitro alcohols leading to the formation of nitroalkenes, and this secondary process is especially facile in the case

of aromatic nitro alcohols (12). If the acidification of the salts is performed with an excess of strong mineral acid the Nef reaction (13, 14) frequently occurs, yielding a mixture of epimeric hydroxy aldehydes.

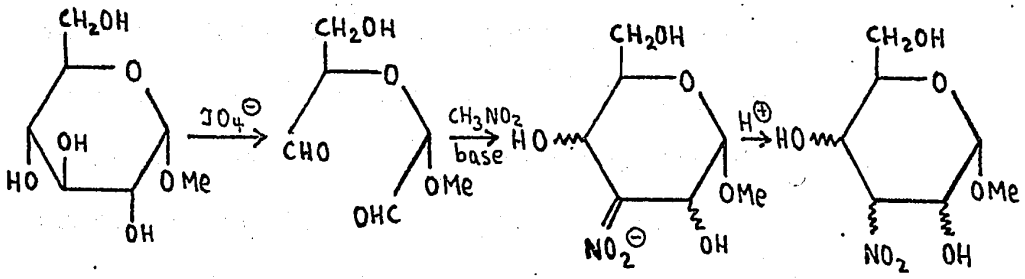


Sowden and Fischer (15) introduced both the Henry addition and the Nef reaction into carbohydrate chemistry where these reactions have found wide use as convenient means of lengthening the carbon chain. Thus, aldopentoses can be converted into aldohexoses via deoxynitro alditols:



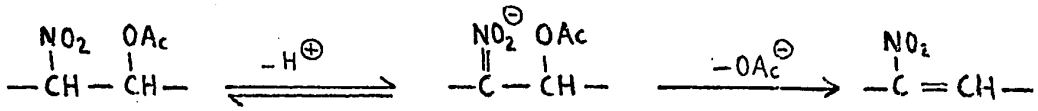
aldopentose — 1-deoxy-1-nitro alditol (2 epimers) — aldohexose

In 1958, Baer and Fischer (16) extended the Henry addition to sugar dialdehydes, which are readily available from methyl glycosides by periodate or lead tetraacetate fission (17). Cyclization of such dialdehydes with nitromethane provides a general and facile method of introducing a nitrogen function into position 3 of aldoses. By numerous applications of the method a large body of nitrogenous carbohydrate derivatives has been synthesized (10, 11). A reinvestigation of some stereochemical and preparative aspects of this cyclization, leading to the isolation of hitherto unknown 3-deoxy-3-nitro sugars, is reported in Part I of this thesis.



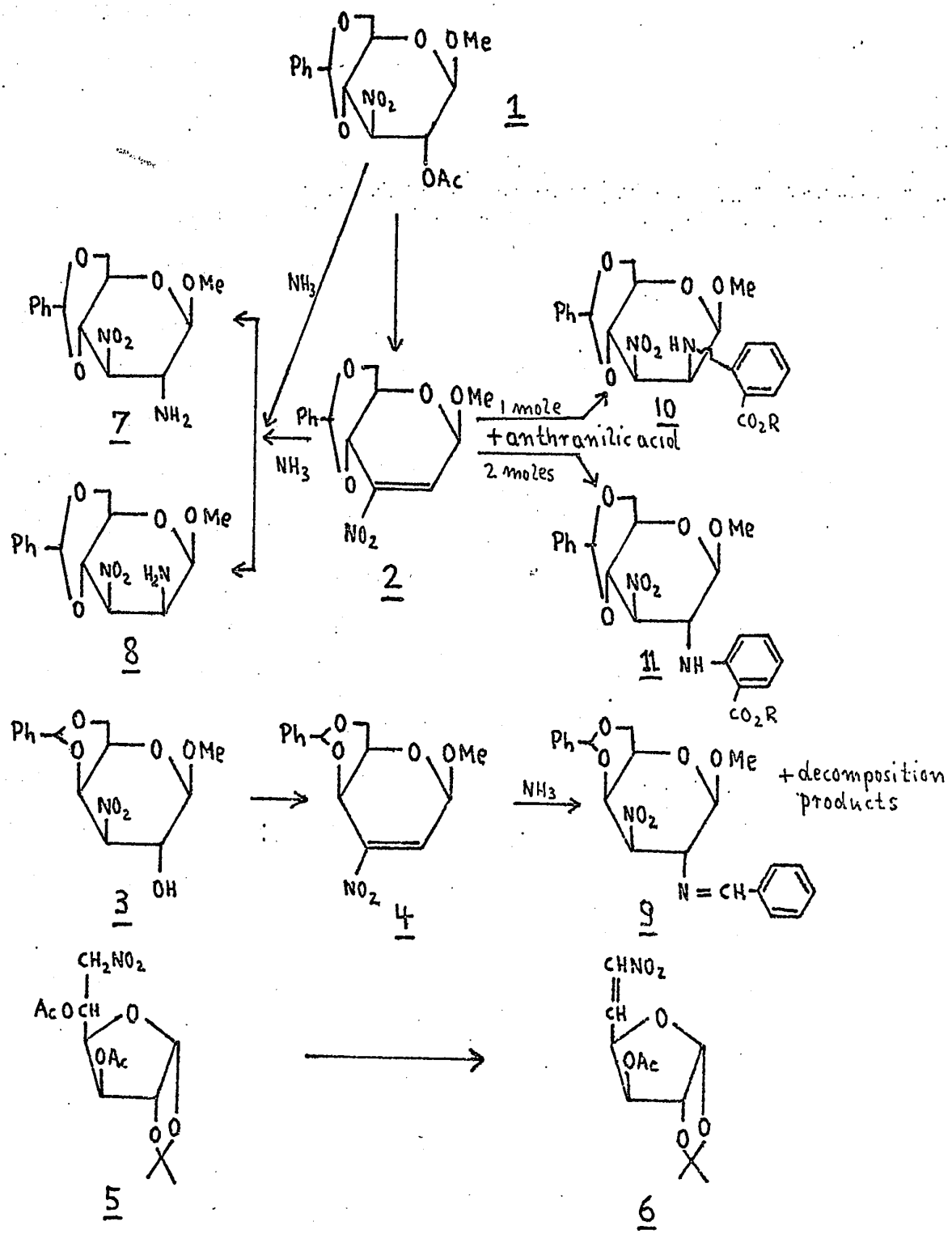
B. Synthesis and Reactions of Carbohydrate Nitroolefins.

Carbohydrate nitroolefins are versatile intermediates in the synthesis of a number of nitrogen-containing carbohydrate derivatives. In general, β-nitroalkenes are conveniently produced from β-nitroalkyl acetates by refluxing in a dry, inert solvent in the presence of sodium hydrogen carbonate.



Known as the Schmidt-Rutz reaction (18, 9), this dehydroacetylation has been widely employed for synthesis of carbohydrate nitroolefins. A sugar derivative containing a nitroolefin grouping as part of the glycoside ring was first synthesized in this manner by Baer and Neilson (19) who obtained from methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (1) the nitroolefin 2, methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-erythro-hex-2-enopyranoside. The corresponding α-anomer was synthesized in the same way (20). Isomers having the D-threo configuration are formed even more readily. Thus, heating of methyl 4,6-O-benzylidene-3-deoxy-3-nitro-β-D-galactopyranoside (3) in acetic anhydride in the presence of sodium acetate produced methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-threo-hex-2-enopyranoside (4) in a one-step procedure, i.e., it was not necessary to first prepare the 2-acetate of 3 (21).

The Schmidt-Rutz reaction was also applied successfully to 6-nitro sugars (22, 23). For example, the 5,6-unsaturated nitro sugar derivative 6 was obtained by refluxing of 3,5-di-O-acetyl-6-deoxy-1, 2-O-isopropylidene-6-nitro-α-D-glucofuranose (5) in the presence of sodium bicarbonate (22).


1
2
3
4
5
6
7
8
9
10
11
NH3
1 mole
+anthranilic acid
2 moles
+decomposition products

α-Nitroalkenes undergo a number of synthetically useful reactions such as catalytic reduction to saturated nitro compounds and oximes. Probably most important, however, is the versatility they display as acceptors of nucleophiles. For nucleophilic addition reactions it is often unnecessary to employ the nitroolefin as such; frequently, it may be generated in situ from an acetylated nitro alcohol or other suitable precursor in an elimination process brought about by the nucleophile.

The reactivity of the 2,3-unsaturated 3-nitro sugars has been exemplified by the facile addition of alcohols to form 2-O-alkyl derivatives (21). Thio ethers and amino derivatives were also prepared by refluxing partially blocked glycosides containing a vicinal nitro alcohol grouping, in toluene in the presence of basic aluminum oxide and such nucleophiles as thiobenzyl alcohol and diethylamine (24). Stereochemically, these and many similar nucleophilic addition reactions exhibited great specificity, in that single products were obtained in most cases, and these possessed the 2,3-diequatorial arrangement of substituents. Some exceptions to this stereoselectivity were encountered in the preparation of vicinal nitroamines. The action of concentrated, aqueous ammonia on both the nitroolefin 2 and the 2-O-acetyl compound 1 predominantly gave the 2,3-diequatorial product, methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (7) (25), but the latter was accompanied by the corresponding

β-D-mannopyranoside (8) which has an axial amino group (26). The most remarkable exception to the rule of 2,3-diequatorial addition occurred when anthranilic acid was added to the nitroolefin 2 (26). Under certain reaction conditions the preponderant adduct formed was that which has the C-2 substituent attached axially (10). Under different conditions, only the 2,3-diequatorial product (11) was formed. No such difference was observed in analogous reactions with the α-anomer of 2 or in additions of the isomeric m- and p-aminobenzoic acids, 2,3-diequatorial adducts being formed exclusively in all cases (28).

In the reactions mentioned above, good yields of products were obtained. However, complications have been encountered on occasion in this line of work. For example, in first attempts to add ammonia to the nitroolefin 4, of β-D-threo configuration, the desired 2-amino derivative could not be isolated since elimination of benzaldehyde and concomitant decomposition occurred. Under modified conditions it was possible to isolate part of the amine, as the Schiff base 9 which was formed with benzaldehyde that arose from degradation of part of the product (27).

The synthesis of nitroolefinic sugar derivatives and their conversion into various types of products by reductions and by addition reactions, with particular emphasis on stereochemical aspects will be elaborated further in Part III of this thesis.

C. Specification of the Aims of the present Thesis

It appeared desirable to extend our knowledge in the chemistry of nitro sugars in the following directions.

1. Although the main route to 3-deoxy-3-nitro glycosides, namely the nitromethane cyclization of sugar dialdehydes, has already been studied extensively, some nitro sugars which should be available by this method have never been isolated, and the isolation procedures employed for others could bear improvement. Furthermore, the distribution of stereoisomers formed in the methyl α-D-hexopyranoside series, and the distribution of stereoisomers in the base-catalyzed epimerization in that series, was not known accurately. A reinvestigation seemed to be warranted.

2. When a nitronate anion is formed from a nitro compound, the hybridization of the carbon atom to which the nitro group is attached changes from sp^3 to sp^2. It was of interest to study the stereochemical consequences of such a change in 3-deoxy-3-nitro sugar derivatives, with regard to reactions that involve nitronate formation.

3. It was desirable to extend the scope of the synthetic possibilities to which nitroolefinic sugars lend themselves. Special attention was to be paid to the development of stereoselective reactions.

PART I

PREPARATION OF 3-NITRO SUGARS AND DERIVATIVES THEREOF

D I S C U S S I O N

As was remarked in the Introduction, cyclization of sugar dialdehydes with nitromethane provides an easy access to nitro sugars. The first product formed in the cyclization of a given dialdehyde is a nitronate which possesses two newly-generated asymmetric centers. When the nitro sugar is liberated from its salt by acidification, a third asymmetric carbon is formed (see page 4). Hence there exists the possibility for formation of four stereoisomeric glycoside nitronates and of eight free nitro glycosides. However, the number of stereoisomers actually found is reduced by virtue of a marked stereoselectivity which prevails. Experience has shown that one or two of four possible nitronates preponderate strongly in the cyclization reaction which is kinetically controlled; the nitronates may subsequently epimerize by ways which will be the subject of further discussion later on in this thesis, and a thermodynamic equilibrium is established in which a different configuration may predominate (11). As far as the number of free nitro glycoside stereoisomers is concerned it has transpired that, as a rule, only one of the two 3-epimers derivable from a given nitronate is formed upon acidification. The nitro group has been observed to show a strong preference for being placed in an equatorial orientation (11). Recent investigations in this laboratory dealt with the stereochemistry of nitronates, their epimerization and acidification, in the

methyl 3-deoxy-3-nitropentopyranoside series, and resulted in a detailed discussion of steric factors governing these reactions (29). The conclusions arrived at would no doubt receive strong support if they proved to be applicable in other families of nitro glycosides as well.

It was known that nitromethane cyclization of D-hyroxymethyl-D'-methoxydiglycolaldehyde (2) leads to the methyl 3-deoxy-3-nitro-α-D-hexopyranosides having the gluco, manno, galacto, and talo configurations (30, 31). However, the nitro glycosides of this series had not been obtained in crystalline condition but only as amorphous mixtures, and only approximate estimates of the isomer ratios could be gleaned from the amounts of various amino sugars that were isolated upon catalytic hydrogenation. Configurational preferences in the cyclization of 2 and in the subsequent thermodynamic nitronate equilibration had thus been established in a qualitative way, but quantitative accuracy could not be claimed. It therefore appeared desirable to undertake a reinvestigation, with the aim of ascertaining isomer distributions and also for the purpose of characterizing the nitro hexosides in isolated and, if possible, crystalline form.

A few results that had been obtained subsequent to the original (30, 31) studies on the nitromethane cyclization of 2 must be mentioned. At least one of the products, namely methyl 3-deoxy-3-nitro-α-D-glucopyranoside, was isolated in low yield in crystalline form after chromatography of a mixture on a cellulose column. However, the amount isolated bore no relation to the proportion of the compound in the reaction mixture (21).

Furthermore, it had been shown that mixtures of isomers may be benzylidenated with benzaldehyde and zinc chloride, and small amounts of the crystalline 4,6-O-benzylidene acetals of the nitro glucoside just mentioned and of its talo epimer had been isolated (20, 21).

At the outset of the present investigation it was found that the benzylidene derivatives can be distinguished by n.m.r. spectroscopy due to variations in the chemical shift of the sharp singlet given by the benzylidene methine proton. Well separated signals were seen in benzylidenated mixtures of nitrohexosides. It proved possible to analyze such mixtures qualitatively by the use of these signals, and moreover, it proved possible to determine isomer ratios quantitatively by signal integration. Later, an improved chromatographic method of separation using silica gel columns was developed, and the hitherto unknown benzylidene derivatives with α-D-manno and α-D-galacto configurations were isolated in crystalline form in addition to the previously known epimers with the α-D-gluco and α-D-talo configurations.

The chemical shifts of the methine proton signals of the four α-D-isomers and some β-D-anomers are given in Table I, p. 15. They proved indicative of sets of isomers, as follows. Although in chloroform-d solution the shifts differed little in compounds having the gluco and galacto configurations, they permitted differentiation between these and manno and talo isomers. In dimethylsulfoxide-d_6, on the other hand, the gluco and talo derivatives had similar shifts but could be distinguished from the manno and galacto derivatives. The chemical

shift of the methine proton was scarcely influenced by the anomeric configuration; anomers, however, may be distinguished by their methoxyl proton resonances (Table I) which tend to occur at higher field for axial groups than for equatorial ones (32). Examples for the quantitative determination of the isomer ratio in three-component test mixtures are given together with the determination of the isomer ratio in unknown component mixtures (mixture A and B) in the experimental section (Table XIII, p. 158).

TABLE I

Benzylidene methine and methoxyl proton n.m.r. signals (τ-scale)

Compound	Configuration	PhCH		OCH_3	
		in $CDCl_3$	in DMSO-d_6	in $CDCl_3$	in DMSO-d_6
3	α-D-manno	4.34	4.24	6.61	6.67
4	α-D-talo	4.42	4.32	6.60	6.66
5	α-D-gluco	4.48	4.34	6.55	6.63
6	α-D-galacto	4.50	4.40	6.56	
19	β-D-gluco	4.48	4.33	6.46	6.57
20	β-D-galacto	4.48	4.38	6.40	6.57
21	β-D-manno	4.32	4.26	6.44	6.58

Since the variations in the chemical shifts of the methine protons in different isomers were distinctly larger than those recorded (33) for a number of non-nitro analogs, a possible explanation for these differences should perhaps take into consideration the anisotropic character of the nitro group. The nitro group causes shielding in a conical zone normal to the plane formed by the nitrogen and oxygen atoms and deshielding in the plane (34), as depicted in Figure II, page 29. Thus the long range effects will depend on the torsional conformation of the nitro group. Inspection of molecular models suggests that certain torsional angles (35) of the nitro group may be favored over others due to non-bonded interactions of the nitro group with neighboring substituents. Thus the most favored conformation of the nitro group in the manno isomers is in all likelihood about 45°. Such an arrangement would place the methine proton in the deshielding plane and hence cause it to resonate at lower field, as was observed. Similarly one may assume that the nitro group in the talo isomer has a preferred conformation corresponding to a torsional angle of 0°, and the methine proton should therefore be located in a neutral region. On the other hand, the most favored conformations for the gluco and the galacto isomers presumably have a torsion angle of about 90° and -45°, respectively. Such conformations would direct the shielding cone of the nitro group towards the methine proton in these isomers and hence give rise to upfield shifts, which were in fact observed. Projections of molecular models along the carbon-nitrogen bond depicting the

nitro group in the most favored conformation are presented in Figure II, page 29.

Prompted by the feasability of spectral identification and quantitative assay of certain benzylidene acetals, the nitromethane cyclization of dialdehyde 2 was reinvestigated. The configurational distribution in which the stereoisomeric methyl 3-deoxy-3-nitro-α-D-hexopyranosides are formed (30, 31) in the cyclization and also those in which they exist after thermodynamically controlled epimerization (31) were determined after benzylidenation of the nitro glycoside mixtures.

A mixture of nitro glycosides was prepared, essentially as described (31), by the reaction of dialdehyde 2 with nitromethane followed by deionization[1]. Exhaustive benzylidenation with benzaldehyde and zinc chloride (Reaction Scheme A) gave a mixture of 4,6-acetals (Mixture A) that showed methine proton signals assignable to the manno (3), talo (4), gluco (5), and galacto (6) isomers. In $CDCl_3$, there occurred three signals having an intensity ratio of 37 : 12 : 51, corresponding to 3, 4, and 5+6 (Figure I-B, p. 21). In DMSO-d_6, there occurred three signals with an intensity ratio of 42 : 49 : 9, corresponding to 3, 4+5 and 6 (Figure I-A). From these data one can conclude that the manno and gluco compounds, 3 and 5, were present as main products in similar amounts (about 40% each), whereas the talo and galacto compounds, 4 and 6, were minor products present to the extent of about 10% each.

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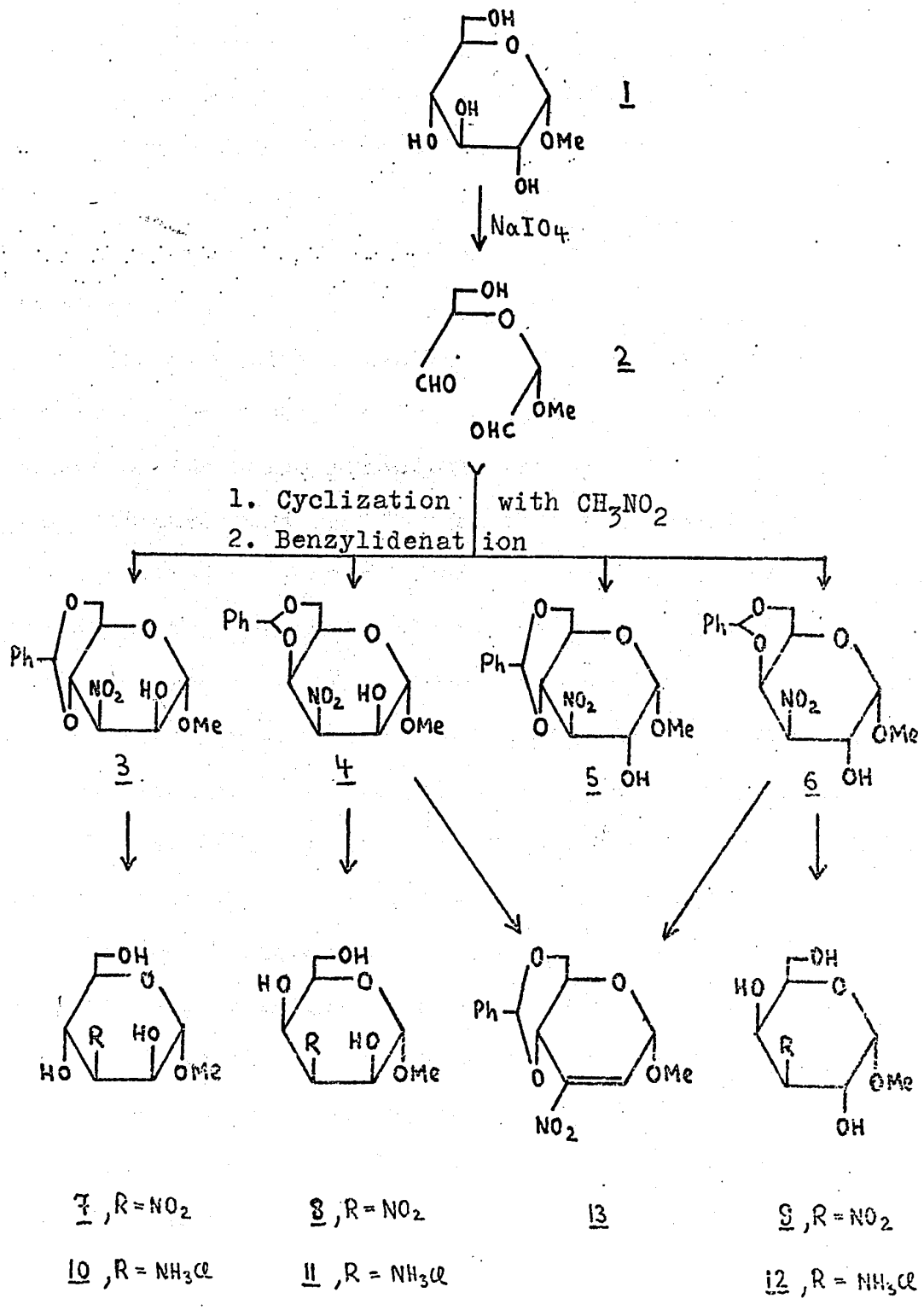
1. The reaction time allowed for the cyclization was 45 minutes whereas in the previous work (31) it was 25 minutes.

Reaction Scheme A



The acetal mixture was then chromatographed on silica gel, and substantial amounts of each isomer could be isolated in crystalline form. Complete separation was not achieved, but the proportions of isomers contained in mixed fractions were estimated spectroscopically, and summation of the yields indicated a ratio of 42 : 8 : 41 : 9 for 3, 4, 5, and 6, in good agreement with the ratio found spectroscopically in the mixture prior to chromatography.

These results established in a more reliable, quantitative way what had been deduced from preparative separations of products on the amine stage (31), namely, that the manno and gluco configurations are favored in the nitromethane cyclization of 2 when kinetic control prevails. The results revealed, moreover, that the talo and galacto configurations are formed to a significant extent. The former had previously been observed to arise in an unspecified, small proportion and the latter had not been detected at all under similar reaction conditions. Since initially-formed nitro glycosides may epimerize while being in an alkaline reaction medium, minor changes in such conditions as reaction time, temperature or alkalinity of the medium could produce measurable variations in product ratios. For example, in the nitromethane cyclization leading to the analogous 6-deoxy glycosides the gluco to manno ratio was about 1 : 1 after a reaction time of 25 minutes, but about 2 : 1 after 40 minutes; talo and galacto derivatives were minor products in either event (36).

It was also of interest to examine in the same way the isomer ratio that exists after the aforementioned nitro glycosides have been allowed to epimerize in aqueous, alkaline

solution to the thermodynamic equilibrium of their nitronates. Equilibration and subsequent deionization of the nitronate mixture was performed as previously described (31), and the product was then benzylidenated. The syrupy product (mixture B) so obtained was investigated by n.m.r. spectroscopy in $CDCl_3$ solution. The spectrum showed three peaks in the methine proton region (τ4.34, 4.42, and 4.49), and their intensity ratio was 15.5 : 52.5 : 32 in a 3-day epimerization experiment[2] (Figure I-C). The first two signals corresponded to the manno and talo isomers, 3 and 4 respectively, and the third signal was due to the gluco and galacto isomers (5+6). Column chromatography confirmed this pattern, indicating the presence of 3, 4, 5, and 6 in the ratio 15.5 : 51.5 : 20 : 13.

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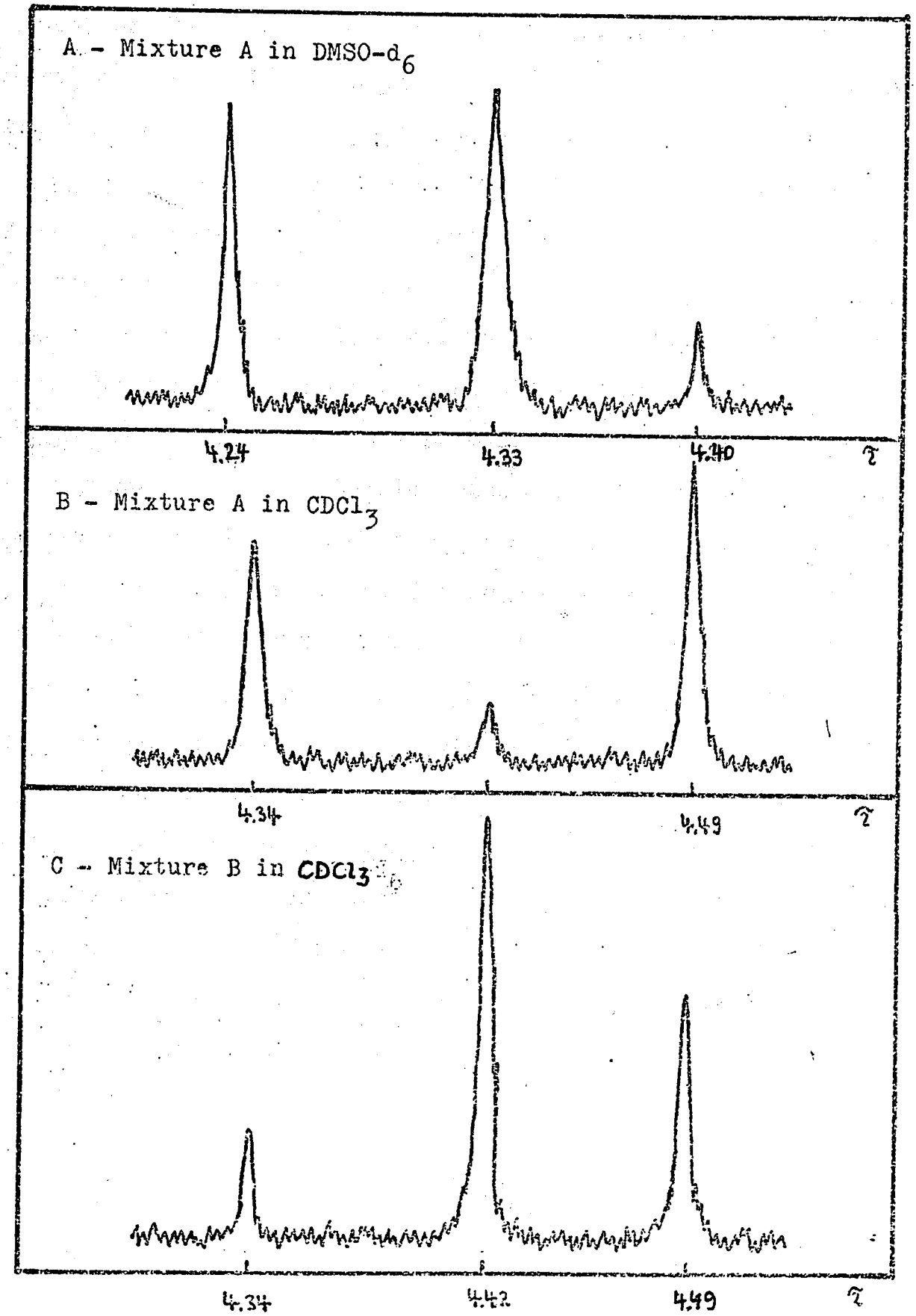
2. In an independent experiment, almost no difference was found in spectra from benzylidenations performed after nitronate epimerizations running for 3 and 5 days. This indicated that epimerization was essentially complete within 3 days.

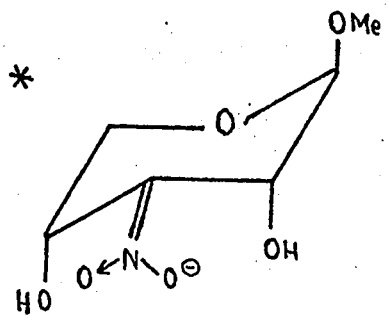
Figure I. - Benzylidene Methine Proton Signals

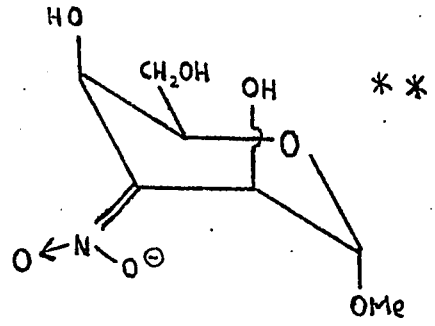


The direct evidence so obtained confirms the principal statement (31) which was based on conversion into amine derivatives, namely, that the nitro glycosides produced in the nitromethane cyclization of 2 epimerize, as nitronates, so as to generate chiefly the talo configuration at the expense of the manno and gluco configurations. Clearly, the nitronate of the talo compound is the thermodynamically most stable one. The experiment showed, furthermore, that the amount of galacto isomer increases, if only slightly, during the epimerization. However, the relative stabilities of the nitronates of the gluco and galacto isomers have now been revealed to be in fact rather similar whereas in the earlier work (31), the former had been underrated and the latter, overestimated. The present results are for the most part in good agreement with those from a recent study (37) on analogous 6-deoxy glycosides in which, after nitronate equilibration, the ratio of manno : talo : gluco : galacto was approximately 28 : 59 : 7 : 6.

The predominance, in thermodynamic equilibrium, of the nitronate of the α-D-talo glycoside is not surprising if one considers a conformational factor which has recently been shown to influence strongly the stability of glycoside nitronates (29, 37). This is the $A^{(1,3)}$ effect (38), the non-bonded interaction between the nitronate grouping and an adjacent hydroxyl group. When the latter is axial, the dihedral angle between the C=N bond and the C-O bond is about 120° and interaction can be assumed to be negligible. But when the hydroxyl group is equatorial, that angle is about 0° and considerable strain

arises from interaction between the hydroxyl group and an oxygen atom of the nitro group. The interaction energy has been estimated to be about 2 kcal/mole, thus exceeding in magnitude the cis-diaxial hydroxyl interaction. It has been demonstrated (29) that methyl 3-deoxy-3-aci-nitro-β-D-erythro-pentopyranoside sodium* exists in the conformation depicted and is more stable than any of its stereoisomers in spite of the unfavorable cis-diaxial hydroxyl interaction. The nitronate of the α-D-talo hexopyranoside, which can be assumed to prefer the conformation shown** and may therefore be regarded as the analog of the pentoside mentioned, owes its stability to the same condition, namely, freedom from $A^{(1,3)}$ strain.





In the course of the chromatographic separations just mentioned, methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-mannopyranoside (3) and its α-D-galacto isomer (6) were isolated for the first time. These acetals as well as the previously described (19) α-D-talo isomer (4) were debenzylidenated to furnish methyl 3-deoxy-3-nitro-α-D-mannopyranoside (7), -α-D-talopyranoside (8), and -α-D-galactopyranoside (9) as new, crystalline compounds. The structures of 7 and 9 were ascertained by catalytic hydrogenation giving the known (31), crystalline amino glycoside hydrochlorides 10 and 12, respectively.

Similarly, 8 afforded the corresponding amine hydrochloride 11 in crystalline form. In this case, however, further structural proof was needed since the amine had been obtained earlier (31) as a syrup of questionable purity only, and data of comparison were lacking. The α-D-galacto configuration was established by dehydration of the acetal 6 with hot acetic anhydride and sodium acetate, which produced the known methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-threo-hex-2-eno-pyranoside (13), i.e. the same nitroolefin that was formed (20) by such dehydration from the α-D-talo isomer 4. The procedure for preparing 13 was improved in this connection, but the formation of nitroolefinic carbohydrates is discussed in more detail in Part III, Chapter A.

Further preparative improvements to be recorded concern the separation of the three β-glycosides which are available (39, 40) by the nitromethane cyclization of D-hydroxymethyl-L'-methoxydiglycolaldehyde (15), namely, methyl 3-deoxy-3-nitro-β-D-glucopyranoside (16), -β-D-galactopyranoside (17), and -β-D-mannopyranoside (18). Although preparation of 16 and 17 by direct crystallization from isomer mixtures is easy enough (41), it was desirable to augment the yields by working up mother liquors that retain considerable quantities of material. Benzylidenation of such isomer mixtures from mother liquors had previously served (19) to separate components as their crystalline acetals (19 - 21). The separation methods were substantially improved in the course of the present work. They involved, depending on which isomer was desired, fractional

crystallization, separation by column chromatography, or extractive separation via nitronate formation. The first method is favored for isolation of the galacto isomer 20 only, since this isomer is less soluble than the others. Column chromatographic separation allows a complete separation of the galacto and manno isomers and is the method of choice if the manno isomer (21) is desired. The third method involves treatment with alkali to form nitronates. The manno isomer is thereby converted into the gluco isomer (19) which does not form a water-soluble nitronate whereas the galacto isomer readily does, and the two isomers can be separated on this basis. The facts underlying this procedure are discussed in more detail in Part II, Chapters A and B.

Circular Dichroism of 4,6-O-Benzylidene Acetals of 3-Nitro Sugars

The occurrence of a Cotton effect requires a chromophore in an asymmetric molecule (no symmetry element) or a dissymmetric molecule (no alternating axis of symmetry). The nitro group is such a chromophore which exhibits a Cotton effect if the rest of the molecule is optically active by itself or when it is attached asymmetrically to the chromophore. In both cases, however, the free rotation around the C-N bond must be more or less restricted. Snatzke undertook a detailed study of the dichroic behavior of nitro steroids (43) and the conformational symbols defined therein are also adopted in the discussions of circular dichroism in this thesis. He found that the Cotton effect of asymmetric axial nitrocyclohexanes is governed by the torsion angle (35) of the nitro group about the C-N bond, a positive angle leading to a positive Cotton effect, and a negative angle leading to a negative effect. For equatorial nitrocyclohexanes with a favored torsion angle of zero or 90^{o} the sign of the Cotton effect is the opposite of that given by the octant rule for the corresponding ketones, whereby in the analysis the whole molecule is divided into four spheres beginning with the chromophore and then progressing to the more remote atoms. It may be postulated that in such an analysis the sphere with pronounced dissymmetry which is nearest to the chromophore mainly determines the Cotton effect according to the octant rule. These generalizations hold well for the interpretation of the dichroic behavior of a number of nitro steroids.

In contrast to the situation in nitro steroids, in the nitro sugars studied in this present work the energetically most favored conformations of the equatorial nitro group may not necessarily be those with a torsion angle of zero or 90°. The problem is further complicated by the uncertainty of the location in space of the nodal planes and hence the sectors making either positive or negative contributions to the Cotton effect. This problem is less pronounced in nitro steroids where usually fewer substituents than in nitro sugars are present. Therefore, a more empirical analysis of the dichroic results was attempted for the nitro sugars discussed in this thesis, using the absolute configurations of neighboring asymmetric centers as criterium. A similar approach was successfully applied to acyclic nitro polyols by Satoh et al. (44).

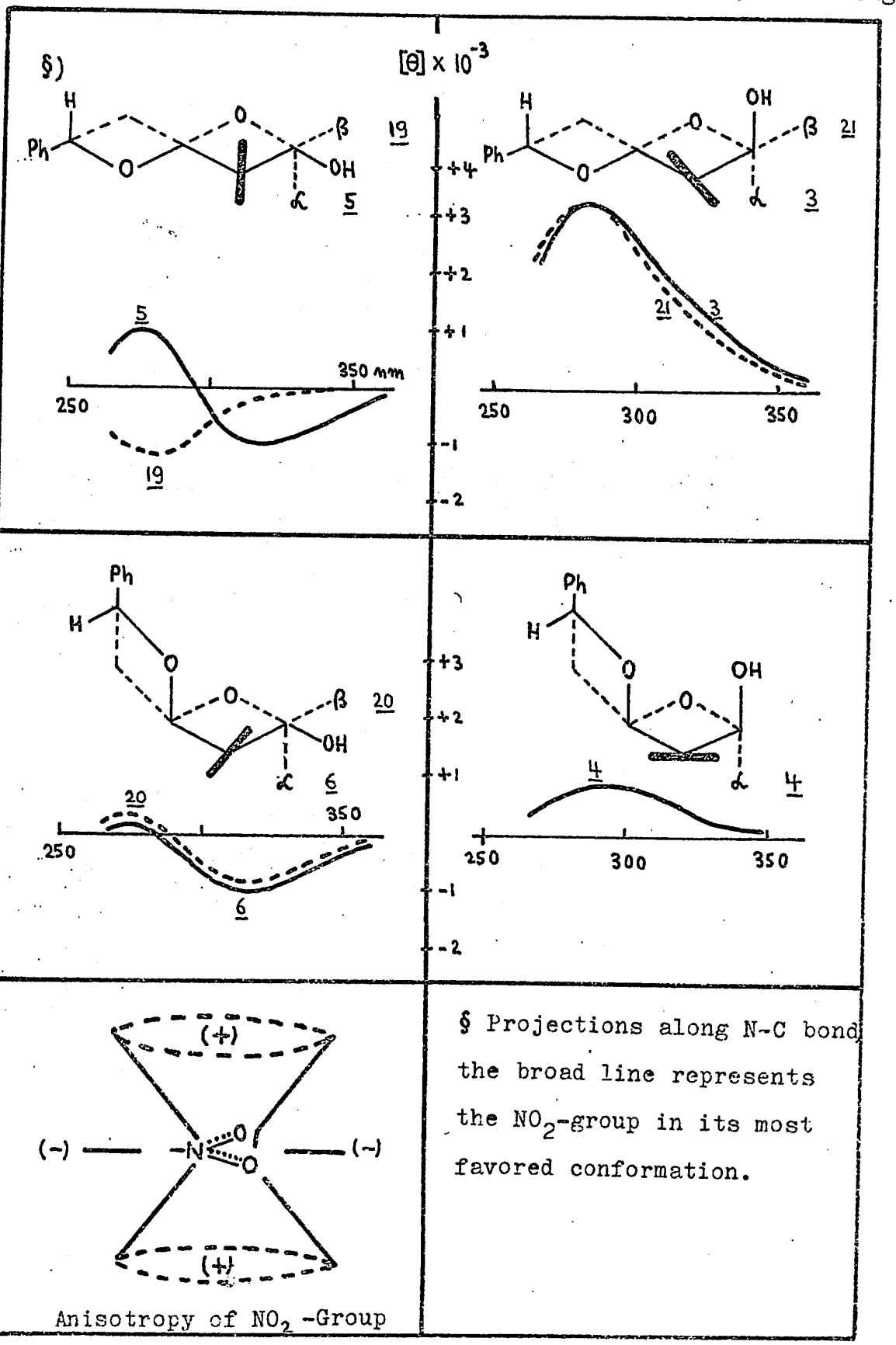
As mentioned before, the sphere with pronounced dissymmetry located nearest to the chromophore should make the main contribution to the Cotton effect, i.e., in our 3-nitro sugars the asymmetry at C-2 and C-4 is more important with respect to the Cotton effect than the asymmetry at C-1 and C-5. Since almost all nitro sugars discussed in this thesis belonged to the D-series (absolute configuration at C-5: R), the contributions originating from C-5 were neglected.

The c.d. curves of the nitro sugars discussed in this part are depicted in Figure II, p. 29. The ellipticity values are compiled in Table XIII in the experimental part.

For the gluco isomers 5 and 19 the effect of the absolute configurations at C-2 (R) and at C-4 (S) might be

expected to cancel each other, hence the Cotton effect should be determined by the configuration at C-1. Indeed, the α-anomer 5 with S configuration at C-1 shows a small positive Cotton effect, while the β-anomer 19 with the R configuration at C-1 shows a small negative Cotton effect. The absolute configurations at C-2 and C-4 in the α-D-talo isomer 4 compensate each other also. The configuration at C-1 of this compound is S, and again a small positive Cotton effect is observed. For the α- and β-D-manno isomers 3 and 21 the absolute configuration of both C-2 and C-4 is S, and a strong positive Cotton effect is observed. For this pair of anomers there was no difference in the Cotton effect, although the configuration at C-1 in one anomer is S and in the other, R. The contribution from the assumed torsional angle of the nitro group cannot be estimated in this case. However, for the anomeric pair with the D-galacto configuration 6 and 20 a strong contribution caused by the torsional dissymmetry of the nitro group has to be assumed since both anomers give rise to a positive Cotton effect, while a consideration of the absolute configuration at C-2 and C-4 (both R) would demand a negative Cotton effect. This anomaly is not well understood as yet. The occurrence of an additional band around 320 nm, which in nitro steroids appeared around 350 nm, is also not well understood.

Figure II. - C.D. Curves of Benzylidene Acetals of 3-Nitro Sugars

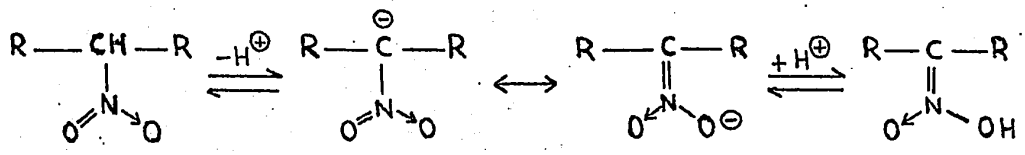


PART II

INVESTIGATIONS CONCERNING THE NITRONATE FORMATION IN PARTIALLY BLOCKED 3-NITROHEXOSES

D I S C U S S I O N

Primary and secondary nitroalkanes are weak acids which form water-soluble, stable salts (nitronates) with alkalis. This is due to the electron-withdrawing effect of the nitro group which renders the α-hydrogen reactive and easily abstracted by base. The anion is considered to be a resonance hybrid, as shown:

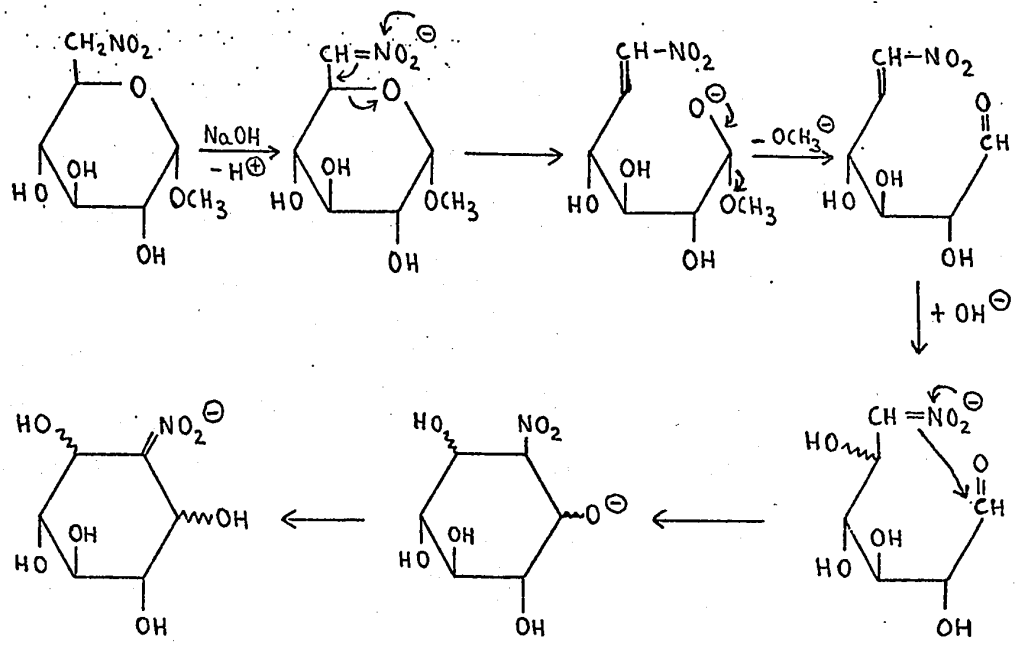


nitro compound nitronate nitronic acid

When the nitronate is acidified, protonation at oxygen is more rapid than at carbon and a tautomer of the original nitro compound is formed (nitronic acid). The nitronic acid is thermodynamically less stable, and unless it is stabilized by some structural feature (e.g., by phenyl substitution) it cannot normally be isolated but reverts to the original nitro compound very quickly.

Nitronate formation is centrally involved in many reactions of nitro carbohydrates (11). Synthesis of nitro sugars by nitroalkane addition to aldoses or sugar dialdehydes is one example; the alkanenitronate ion attacks the carbonyl group, and the salt of a nitro alcohol is formed (see Introduction and Part I). Another instance is the alkaline cleavage of

nitro-substituted acetal linkages by β-elimination as in the following reaction sequence which, incidentally, also exemplifies the nitroalkane-aldehyde addition (22):



Nitronate intermediates are also believed to play a role in nitro sugar epimerizations as well as in syntheses and certain transformations of nitroolefinic sugar derivatives. Therefore, studies were devoted to the interrelation of nitronate formation and stereochemical features in carbohydrate molecules, and these will be the subject of the following chapters.

A. Ultraviolet Spectra of Anions of 3-Nitrohexoses

Nitroalkanes and nitrocycloalkanes exhibit weak u.v. absorption bands at 270-280 nm and more intense bands near 200 nm. By contrast, the *aci* salts show intense absorption bands in the region 226-244 nm (45). In carbohydrate nitronates, the maximum tends to occur at slightly larger wavelengths, around 250 nm (46). This high intensity absorption was utilized for an examination of the extent of nitronate formation in correlation with configurations in various methyl 4,6-O-benzylidene-3-deoxy-3-nitro- and -2,3-dideoxy-3-nitro-D-hexopyranosides (see formulae p.34). The compounds were examined in 0.01-0.001 N ethanolic potassium hydroxide solutions. It is known that establishment of the nitro-nitronate equilibrium, though rapid, is not instantaneous, and in systems developing a reasonably strong absorption the growth of the nitronate peak can be readily monitored in an automatic spectrometer. This is illustrated in Figure III, p.35 . For example, the hexopyranoside with α-D-talo configuration 1* showed absorbances of 13600, 15400, 20400 and 21700 after 0.6, 1.5, 4, and 8 minutes (in 0.001 N KOH in ethanol). Then the peak decreased again (absorbance: 21000 and 19300 after 16 and 64 minutes), with concomitant appearance of a new peak near 300 nm. The latter phenomenon is believed to be due to a slow elimination reaction leading to a Δ 4,5-unsaturated nitronate (46).

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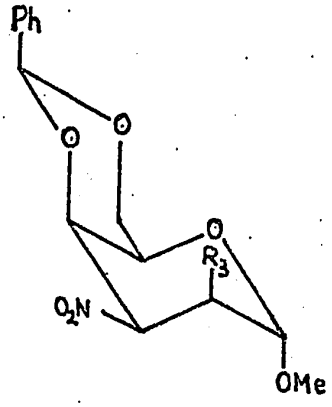
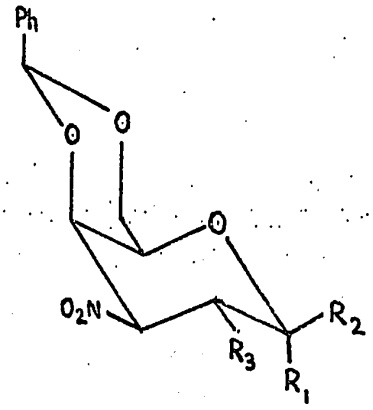
* see p. 34.

Formulae



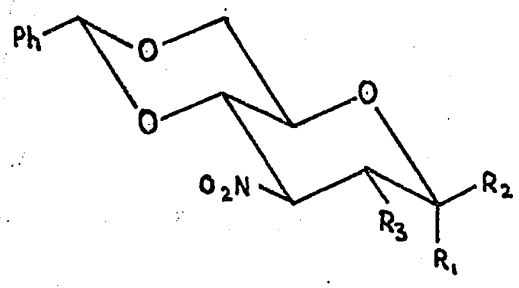
R_3 =OH : 1

R_3 =NHAc : 12



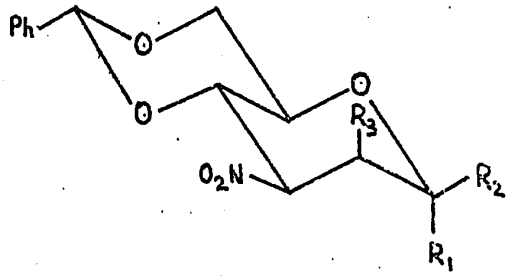
R_3 =OH : 2 R_1=OMe / 3 R_2=OMe

R_3 =NHAc: 13 R_2=OMe



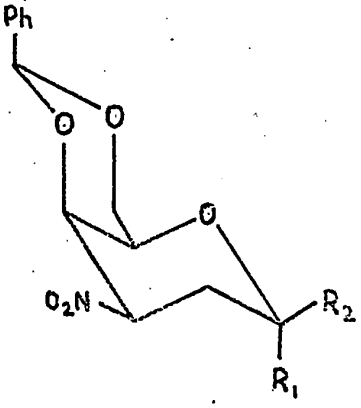
R_3=OH : 4, R_1=OMe / 5, R_2=OMe

R_3=NHAc: 14, R_1=OMe / 15, R_2=OMe

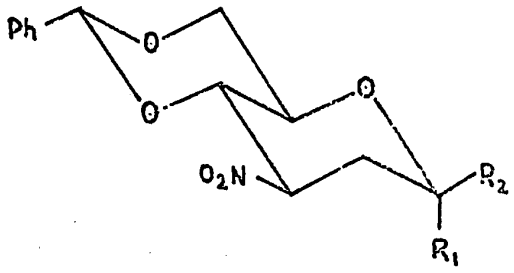


R_3=OH : 6, R_1=OMe / 7, R_2=OMe

R_3=NHAc: 16, R_1=OMe / 17, R_2=OMe



8, R_1=OMe / 9, R_2=OMe



10, R_1=OMe / 11, R_2=OMe

Figure III. - U.V. Spectra of nitro glycosides in alkaline solution

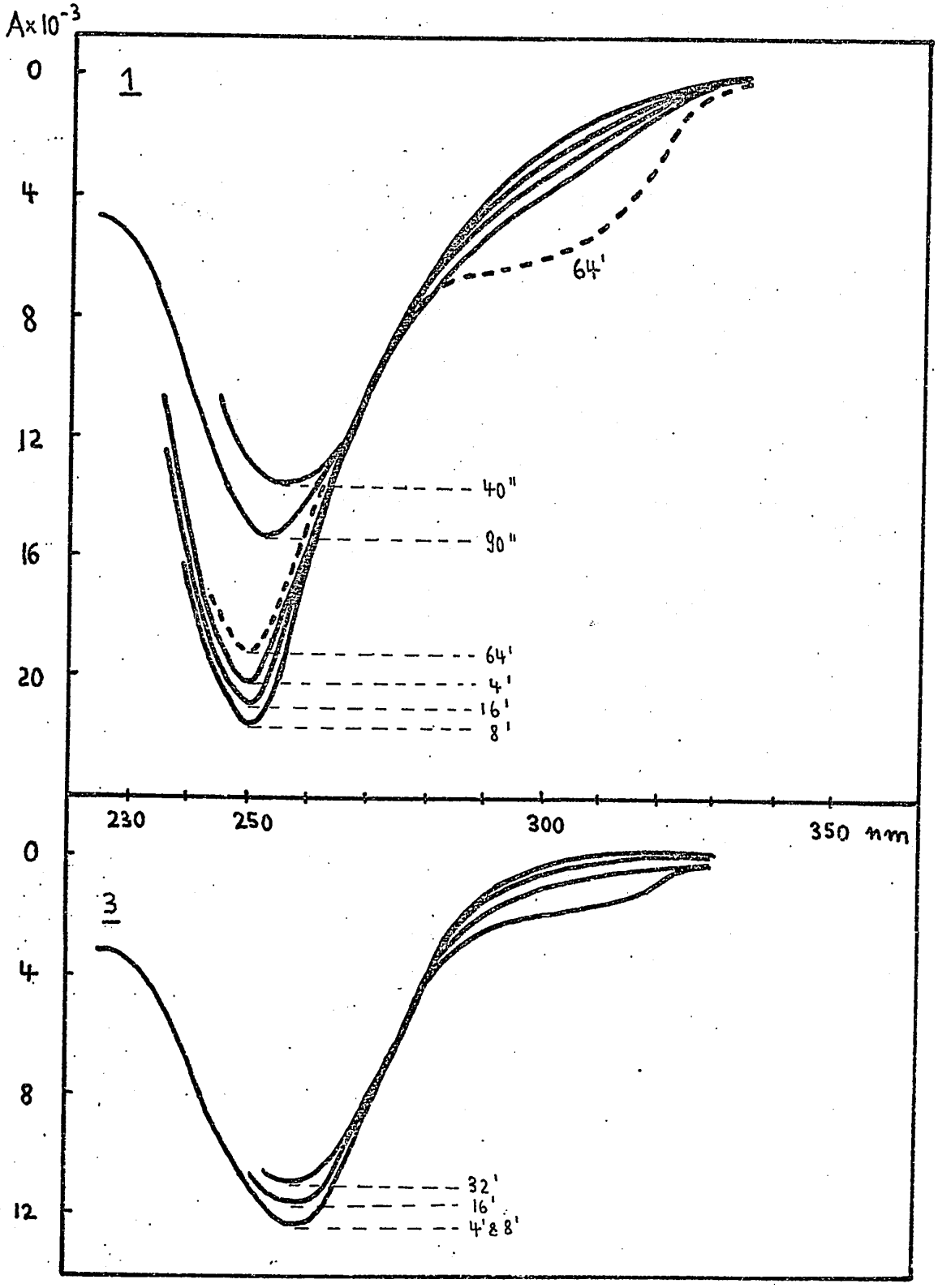
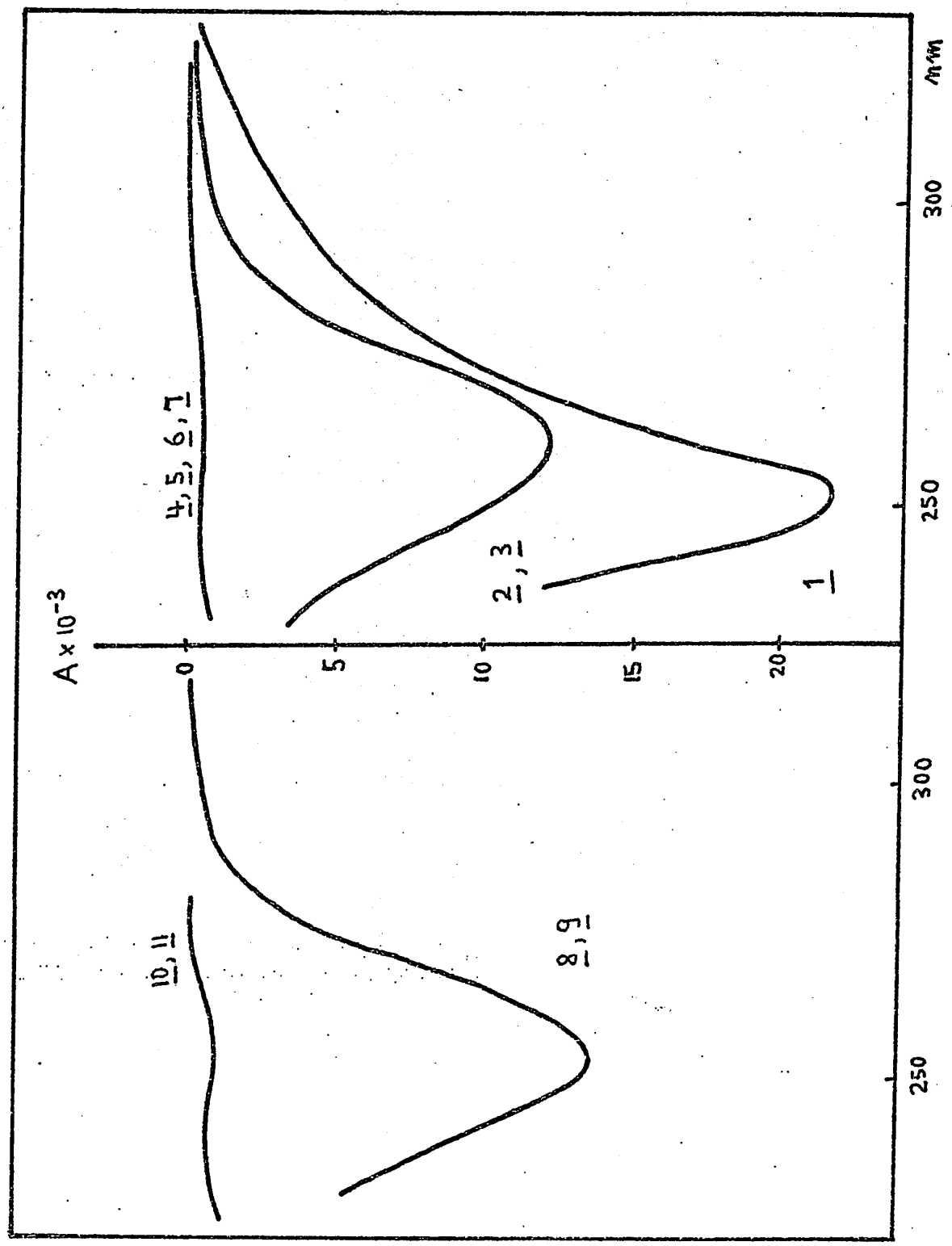


Figure IV.- U.V. Spectra of nitro glycosides in alkaline solution



All the compounds thus examined showed maximum absorbance during a time interval of 6-10 minutes after addition of the base. It was noted that changes within that interval were insignificant, and therefore, the maximum absorbance values recorded in Table II, p.44 , are those which were measured after 8 minutes in all cases. The absorbance, A, refers to 10^{-4} M solutions and may be taken as a measure for the amount of nitronate present under the given conditions of alkalinity. Comparative absorption curves are plotted in Figure IV, p.36.

It is seen that methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-talopyranoside (1) shows the highest absorption maximum (A 21700), followed by the α-D-and β-D-galacto isomers 2 and 3 (A 10900 and A 12100, respectively). The α-D- and β-D-gluco isomers, 4 and 5, produce hardly any nitronate absorption and the amount of salt formed must be very small.[3] The α-D- and β-D-manno isomers 6 and 7 give rise to the same insignificant absorptions and thus appear to behave like the gluco isomers. This seemed surprising at first sight but became understandable when their chemical fate was examined as will be disclosed in a subsequent paragraph. The methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-α- and β-D-lyxo-hexopyranosides (8 and 9) appear to form nitronate somewhat more readily than the D-galacto derivatives, and their α- and β-arabino

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3. At higher concentration of alkali (0.1 N aqueous NaOH), 5 does produce a peak at 253 nm (46).

isomers (10 and 11) behave similar to the D-gluco derivatives, but give rise to slightly greater absorptions (see also Fig.IV). In summary, high-intensity absorption is observed when the oxygen atom O-4 is linked axially, and low absorption, when it is linked equatorially. In both cases, replacement of an equatorial hydroxyl group at C-2 by hydrogen moderately enhances the absorption. An axial hydroxyl at C-2 causes a strong increase when O-4 is axial also, but is without visible effect when O-4 is equatorial. The following explanation is offered for these observations.

In the nitronates expected to arise from the compounds that bear a trans-fused acetal ring (4-7, 10, and 11), one of the nitronate oxygens faces nonbonded interaction from the equatorial O-4. This condition [$A^{(1,3)}$effect (38)], which is associated with an interaction energy of at least 2 kcal/mole (29) and which cannot, in these rigid bicyclic systems, be relieved by a conformational change, constitutes a severe impediment to nitronate formation. In the compounds having a cis-fused acetal ring (1-3, 8, and 9), the (axial) O-4 does not so interfere. An equatorial hydroxyl group at C-2 could likewise be expected to hinder nitronate formation, and the lower extinctions given by the D-galacto and D-gluco compounds in comparison with their respective 2-deoxy analogs might be taken to bear this out. However the differences are small, and they may in fact be due entirely to a change in the inductive effect of C-2. At any rate it is clear that an equatorial hydroxyl at this position does not seriously interfere with

nitronate formation, and one may therefore assume that its $A^{(1,3)}$ interaction is diminished substantially by a distortion of the pyranoside chair. A molecular model shows that flattening which the chair tends to incur by sp2 hybridization of C-3 will mainly affect the position of C-2 (in the more flexible part of the ring), allowing an equatorially attached hydroxyl to move downward and thus to recede from the nitronate oxygen atom. This movement should be opposed by an axial anomeric methoxyl group and indeed, the α-D-galactoside 2 seems to produce slightly less nitronate than its β-anomer 3 while the corresponding anomers 8 and 9 of the 2-deoxy series expectedly exhibit no significant difference. The ring distortion just mentioned also implies a lessening of steric interaction between an axially attached oxygen at C-4 and an opposing axial atom or group at C-2. Undoubtedly this is conducive to nitronate formation in the galacto and lyxo compounds, and it provides an especially pronounced driving force in the talo isomer 1.

We have also estimated the pK_a values of some of the compounds by half-titration with sodium hydroxide in aqueous dioxane (Table III). The nitromethylene acidities so found qualitatively parallel the spectroscopically determined tendencies of salt formation, bearing out the influence of configuration.

Table III

Nitromethylene acidities

Compound	Configuration	pK_a*
1	α-D-talo	8.1
2	α-D-galacto	9.6
4	α-D-gluco	10.8
5	β-D-gluco	10.8
6	α-D-manno	11.0
8	α-D-lyxo	8.8
9	β-D-lyxo	8.3
10	α-D-arabino	10.7
11	β-D-arabino	10.5

* The pH-values observed potentiometrically in approximately 0.01 M solutions in dioxane upon halftitration with 0.002 N sodium hydroxide in water. The candidate thanks Dr. Jan Kovář for kindly performing these measurements.

Although an equatorial disposition of O-4 obviously is the chief obstacle to facile nitronate formation in these benzylidenated glycosides, it nevertheless seemed remarkable that the mannosides 6 and 7, with their axial 2-hydroxyl, did not perceptibly differ spectroscopically from the glucosides. However, it is recalled that the mannoside 7 was epimerized to 5 by refluxing in toluene or benzene in the presence of basic alumina or solid potassium hydroxide catalyst (47, 48). Compound 7 has now been found to epimerize more rapidly yet in alcoholic, alkaline solution at room temperature, and the observed u.v. spectrum therefore may well represent largely 5 rather than 7. The facile occurrence of this epimerization was ascertained by isolation of 5 in preparative experiments using ethanolic potassium hydroxide or methanolic sodium methoxide solutions (and which was also performed with the α-anomer 6). A mechanism for the epimerization reaction is presented in the next chapter (Reaction Scheme B, p. 49).

To summarize the above observations, one can state that the different U.V. absorbances of the configurationally isomeric nitronates of 3-nitrohexoses allow a distinction between the isomers and provide a convenient means for configurational assignments.

In a study of the synthesis of vicinal aminonitro sugars (Part III, Chapter D), various stereoisomeric methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-D-hexopyranosides were obtained. It was therefore of interest to investigate whether the differential characteristics in nitronate

formation described above are paralleled in the 2-acetamido derivatives, which would allow the uv. absorption to be used for configurational assignments in this series also.

Time dependent measurements of the absorbances of 10^{-4} M solutions of the 2-acetamido derivatives in 0.01 N ethanolic potassium hydroxide solution showed again that the establishment of the nitro-nitronate equilibrium is not instantaneous (Figure V). Thus, the 2-acetamido derivative with α-D-talo (12) configuration exhibited maximum absorbances of 16 000, 18 600, 21 200 and 22 400 after 1.5, 3, 5, and 10 minutes. The intensity of the nitronate peak then decreased slowly (absorbance: 21000 after 60 minutes) and the appearance of an absorption band around 300 nm was noticed. The absorption at this wavelength was substantial already after 10-20 minutes for the isomers with β-D-galacto (13) and β-D-gluco (15) configuration (Figure V). Therefore, in the comparative study of absorbances of the various acetamido isomers a time interval of 5 minutes only was allowed before the measurements were taken. The results obtained in this way are listed in Table II and comparative absorption curves are depicted in Figure VI. Again it is seen that the isomer with axial substituents at C-2 and C-4, methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-talopyranoside (12), shows the highest absorbance (A 21200). The maximum absorbance for the β-D-galacto isomer (13) assumes about half the value of that of the D-talo isomer (A 10100) while the isomers with the α- and β-D-gluco (14 and 15), and α- and β-D-manno (16 and 17) configuration show low absorbances

(A 900-2750). Thus the differences in absorbance of the nitronates having an acetamido substituent at C-2 qualitatively parallel those of the 2-hydroxy analogs and hence can be used for configurational assignments.

TABLE II

U.V. absorptions produced by nitro glycosides in ethanolic potassium hydroxide solution

Compound	Configuration	Normality of KOH	λ_{max} (nm)	A *
1	α-D-talo	0.001	251	21700
2	α-D-galacto	0.01	254	10900
3	β-D-galacto	0.001	258	12100
		0.01	258	13500
4	α-D-gluco	0.001	250-260	500
5	β-D-gluco	0.001	250-260	500
6	α-D-manno	0.001	250-260	500
7	β-D-manno	0.001	250-260	500
8	α-D-lyxo	0.01	251	14100
9	β-D-lyxo	0.001	253	13800
		0.01	253	14500
10	α-D-arabino	0.001	252	1050
11	β-D-arabino	0.001	252	1050
12	α-D-talo	0.01	250	21200
13	β-D-galacto	0.01	256	10100
14	α-D-gluco	0.01	250-260	900
15	β-D-gluco	0.01	250-260	2750
16	α-D-manno	0.01	250-260	950
17	β-D-manno	0.01	250-260	1600

A* - Molar absorbance. The value would represent the molar extinction coefficient of the nitronate anion only in case of complete ionization.

Figure V. - U.V. Spectra of nitro glycosides in alkaline solution

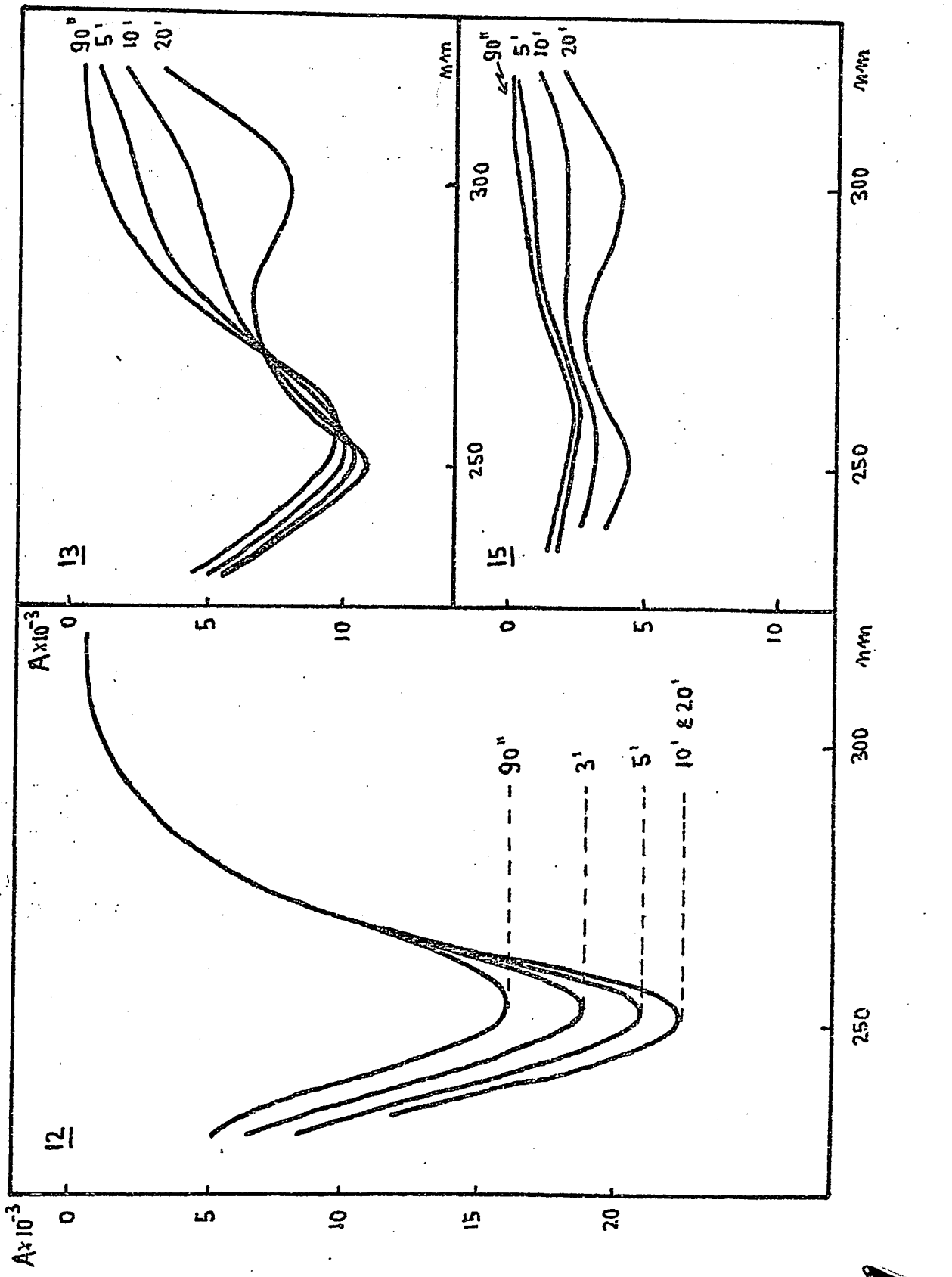
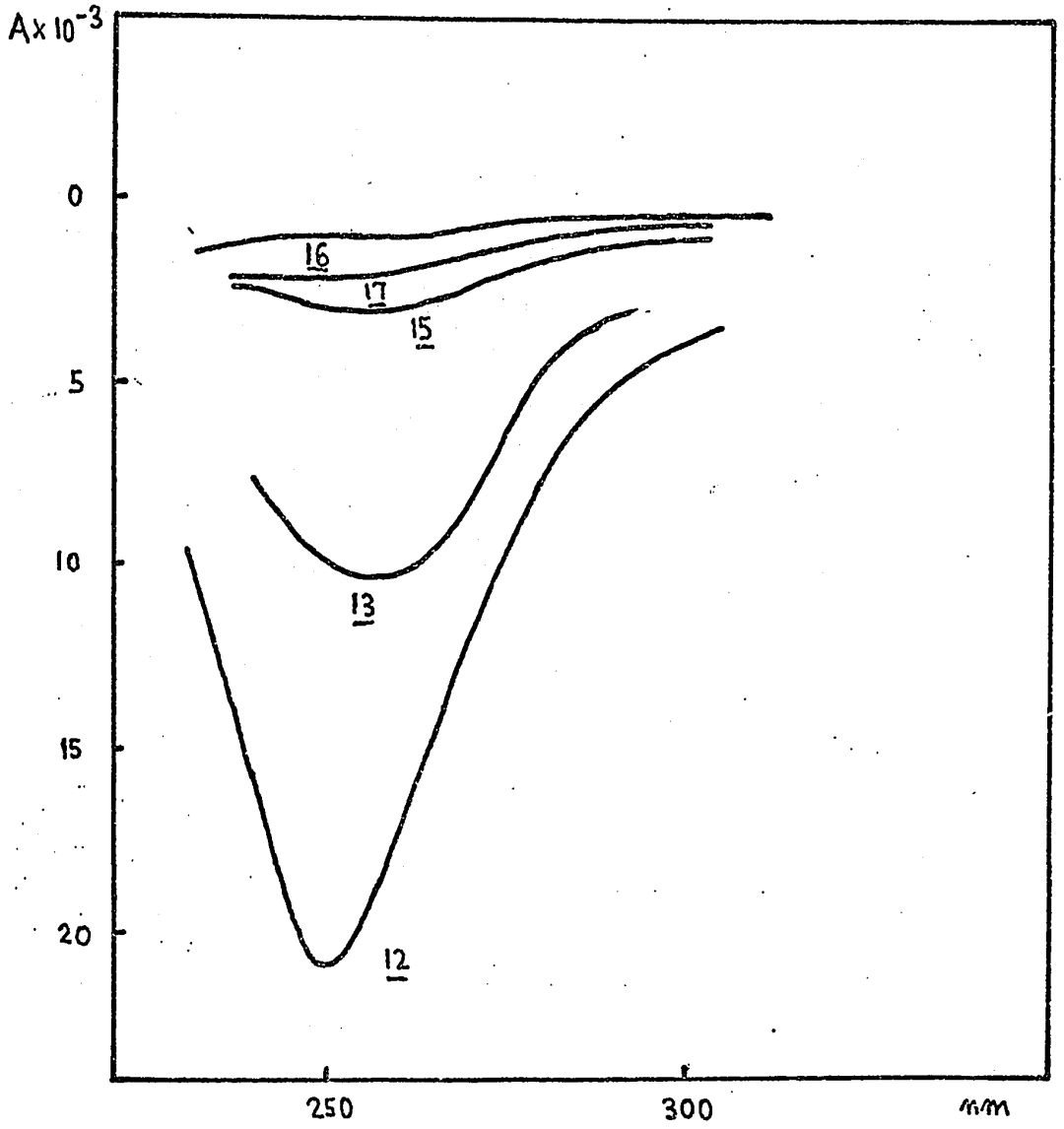


Figure VI. - U.V. Spectra of nitro glycosides in alkaline solution



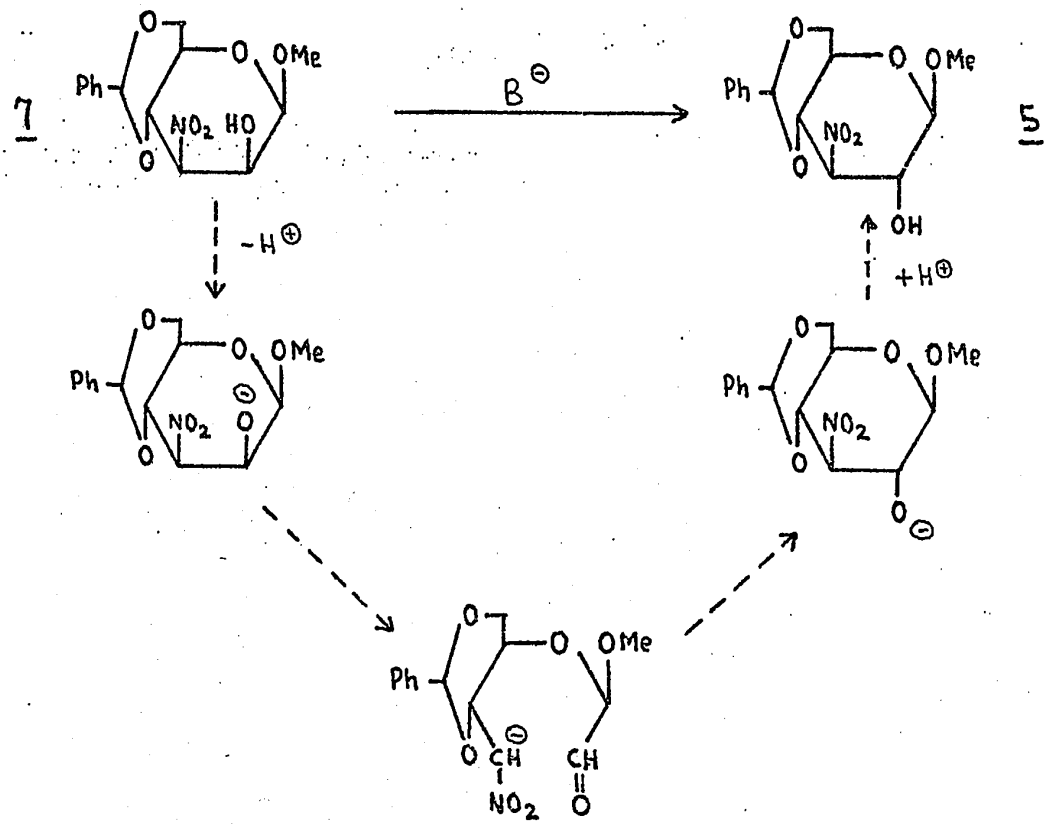
B. Mechanism of the Epimerization Reaction converting the D-Manno into the D-Gluco Isomer

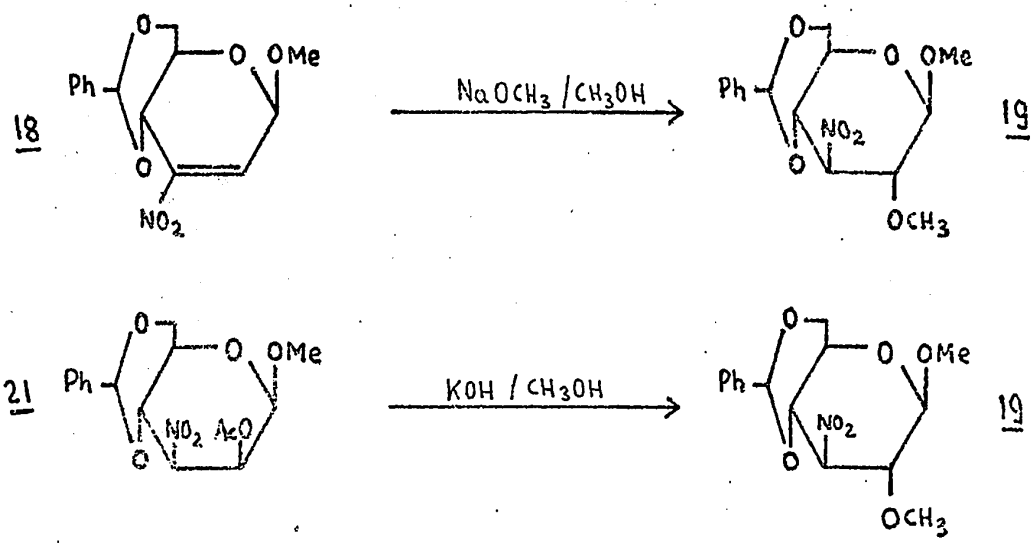
Deoxynitroinositols (49) and deoxynitro glycosides (30, 31) have long been known to epimerize in alkaline solution at asymmetric centers adjacent to the carbon bearing the nitro group. These epimerizations are of preparative utility, and some aspects of them have been dealt with in Part I of this thesis. Grosheintz and Fischer (49) have explained the epimerization in terms of a retrograde Henry-type reaction, but experimental proof was not given. It appeared also possible, however, that epimerization in these nitro alcohols takes place via a reversible dehydration and readdition of water, that is, via nitroolefin intermediates. Since much evidence accumulated for the part of such nitroolefins in various base-catalyzed transformations of nitro sugar derivatives (11), the latter mechanism was favored in later discussions. As will now be shown, the facile epimerization of methyl 4,6-O-benzylidene-3-deoxy-3-nitro-D-mannopyranosides 6 and 7 to the corresponding D-gluco isomers 4 and 5 represents the first example for which the olefin mechanism must definitely be ruled out, leaving the retrograde Henry mechanism as the only plausible alternative.

It had been shown (47, 48) that the glucoside 5 is dehydrated by heating in toluene (or benzene) in the presence of a solid base to give the nitroolefin 18, and that 18 in turn can be easily hydrated back to 5. Under the same, anhydrous conditions at high temperature the mannoside 7 had been

found (47) to epimerize to the gluco epimer 5, and it was therefore reasonable to assume that the reaction proceeded by way of the olefin 18. There is still no evidence to discount that pathway for the reaction under the conditions then employed. However, a mechanism that does not involve 18 has now been established to operate under the conditions of the u.v. spectroscopic assay described in Chapter A. (Reaction Scheme B, p. 49). If 18 were produced from 7, then, in a methanolic medium containing sodium methoxide, 18 should add methanol to produce the 2-O-methyl ether (19) of 5, rather than 5 itself. It had been shown previously (24) that 18 does indeed give 19 with great ease. This finding was now supported by the same result which was obtained in a control experiment in which 1 mole of water was provided per mole of 18 in excess methanol so as to simulate the conditions that would obtain upon dehydration of 7. Furthermore, when 7 was treated with the strong nucleophile, sodium benzylmercaptide in methanol, the product was 5 and not the known benzylthio derivative (24). An intermediacy of 18 can therefore be ruled out for these reactions. On the other hand, the 2-O-acetyl derivative (21) of 7 furnished the methyl ether 19 in 88% yield upon reaction with methanolic potassium hydroxide, the reaction being complete within a few minutes at room temperature. This can only be explained by β-elimination of the acetoxy group to give intermediate 18 followed by subsequent nucleophilic addition of methanol. For if the O-acetyl derivative 21 had suffered methanolysis rather than β-elimination of its acetoxy group, then 7 and hence 5 would have resulted.

Reaction Scheme B





Numerous elimination-addition reactions of this kind had previously been performed with the 2-O-acetyl derivatives of 4 and 5. The conclusion can be drawn that abstraction of H-3 by base, however small its extent, is sufficient in the 2-O-acetyl derivatives to permit elimination of the good leaving group, acetate ion, whereas in 7 it is not effective enough to induce departure of the poor leaving group, hydroxyl ion. Because of its difficulty in forming nitronate, 7 is considered to incur competitive deprotonation of the 2-hydroxyl group, and this leads to ring opening by reversal of a nitroalkane cyclization. Subsequent recyclization produces the thermodynamically more stable β-D-gluco isomer 5. When the nitromethylene acidity is strongly reduced for steric reasons, as seems to hold in the present case, the secondary nitro group might be termed "pseudo-tertiary", and it is suggested that a retrograde Henry reaction, known to be facile only in β-hydroxy-tert-nitro compounds, must then account for epimerization.

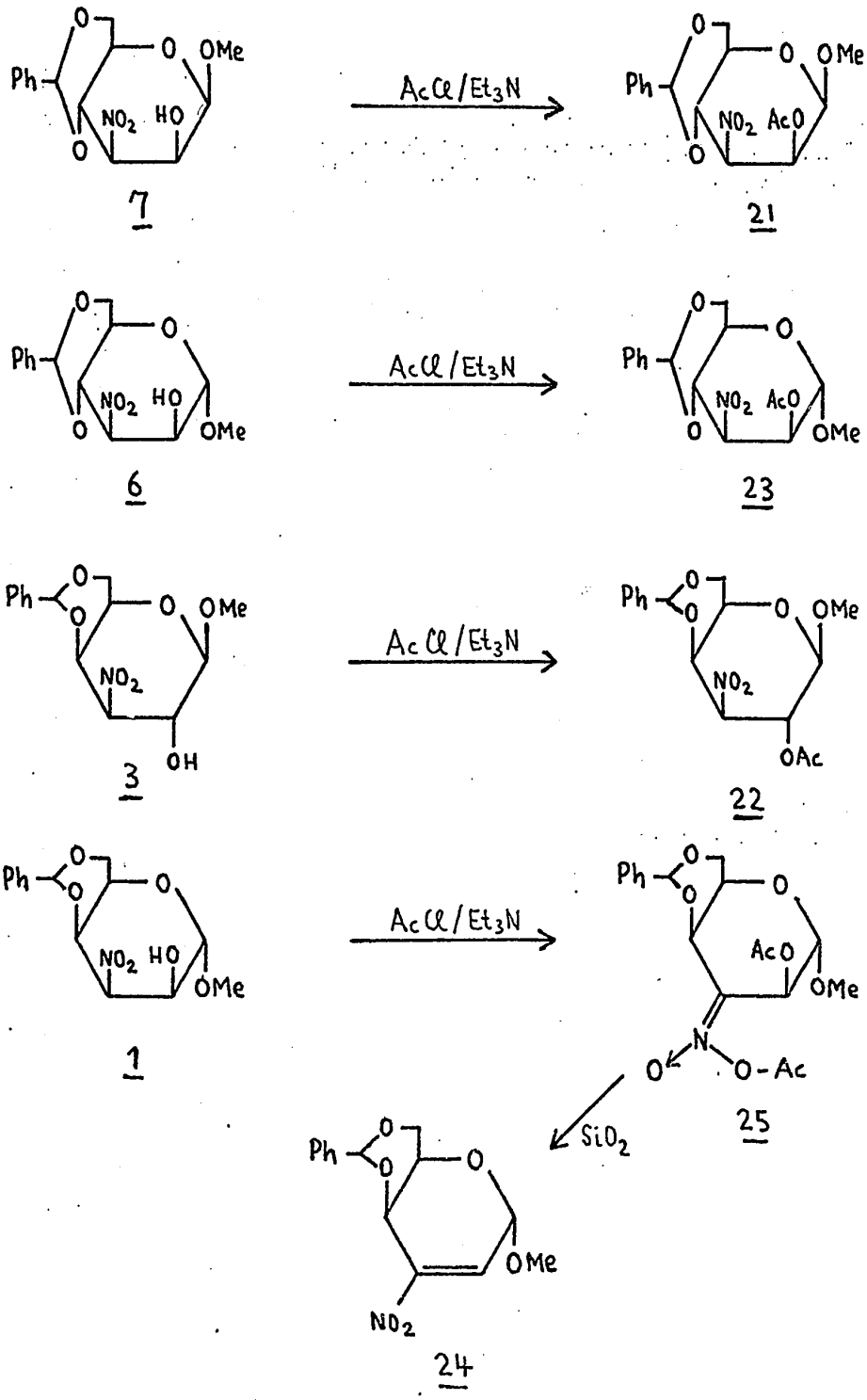
The findings reported in this and the previous chapter were exploited preparatively in connection with the synthesis and separation of methyl 4,6-O-benzylidene-3-deoxy-3-nitro-β-D-hexopyranosides. As discussed in Part I of this thesis, nitromethane cyclization of D-hydroxymethyl-L'-methoxy-diglycolaldehyde followed by benzylidenation furnished a mixture of acetals consisting of the β-D-gluco (5), β-D-manno (7), and β-D-galacto (3) isomers. When a solution of such a mixture in chloroform was treated with alcoholic potassium

hydroxide the manno isomer was readily converted into the gluco isomer while the galacto isomer remained configurationally unaltered. The galacto isomer easily forms a water-soluble nitronate salt and because of this, it could be separated from the gluco isomer which does not give a nitronate under the conditions employed but remains soluble in chloroform. Liberation of the nitro sugar from the nitronate solution by deionization with ion exchange resin afforded methyl 4,6-O-benzylidene-3-deoxy-3-nitro-β-D-galactopyranoside (3), and evaporation of the chloroform solution furnished methyl 4,6-O-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (5) in an improved yield.

C. Acetylation with Acetyl Chloride and Triethylamine

Preparation of nitro sugar acetates by standard acetylation techniques is sometimes attended with difficulties due to occurrence of dehydration or dehydroacetylation and other complications that may ensue (11). Some of the difficulties had been circumvented when acetylations were catalyzed with boron trifluoride (48, 50), but in one recent instance this has caused acetolysis of a trityl ether function (51). This was overcome by using an acylation mixture consisting of equivalent amounts of acetyl chloride and triethylamine in ether solution at 0^{o}. The method, which involves an *in situ* generation of ketene, has now been applied to methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-mannopyranoside (6), -β-D-mannopyranoside (7), -β-D-galactopyranoside (3), and -α-D-talopyranoside (1) (Reaction Scheme C).

Reaction Scheme C



Compounds 3, 6 and 7 gave high yields of the expected and known 2-O-acetyl derivatives 22, 23 and 21. Since there was a discrepancy between the melting point of 21 (162-163°) and the reported melting point (136-137°) (21), preparation of the compound was repeated by the previously reported method which now gave a material melting at 159-160°. A mixture melting point of the two acetates prepared by different methods proved their identity, as did comparison of infrared spectra.

In contrast to the normal behavior of compounds 3, 6 and 7, the taloside 1 furnished upon acetylation an abnormal product in a yield of 92%. Elemental analysis of the crystalline material corresponded to the composition $C_{18}H_{21}NO_9$, and the n.m.r. spectrum revealed that two acetyl groups had entered although the benzylidene acetal as well as the anomeric methoxyl group were retained. The i.r. spectrum was free from hydroxyl absorption and lacked the band expected for the nitro group in the 1550 cm^{-1} region. Instead, there was a sharp peak at 1800 cm^{-1} attributable to an acid anhydride structure, and an intensive band occurred at 1620 cm^{-1}, in the region where nitronic acids and their esters show strong C=N absorption (52). Another strong band was located at 1750 cm^{-1} and is attributed to an ester carbonyl. The product exhibited high-intensity absorption in the ultraviolet region (λ_{max} 242 nm, ϵ 8000, in methanol), in the range in which nitronic acids and their salts are known to absorb strongly (52) in contrast to nitroalkanes that have very low absorption in this range. Although

the compound was remarkably stable in the crystalline state and could be recrystallized from ethyl acetate, it suffered loss of both acetyl groups when chromatographed on silica gel, yielding (85%) the known methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-threo-hex-2-enopyranoside 24. This fact demonstrated that the acetylation of 1 had masked but not irreversibly altered or removed the nitro group at C-3.On the basis of all the spectroscopic and chemical evidence the structure 25, a mixed nitronic acid-acetic acid anhydride was assigned to the new compound. Since only a few nitronic carboxylic anhydrides have been described in the literature and since spectral data do not seem to be available (52, 53), no comparison of the findings presented here with reported ones was possible. The structural formula depicted for 25 is arbitrary with respect to the C=N bond geometry; geometrical isomerism, as observed in nitronic esters, may be predicted to be possible in anhydrides of this type.

The divergent behavior of 1 in acetylation is probably a result of its relatively high nitromethylene acidity which was already illustrated in Chapter A. Apparently the unusual acetylation at the nitro oxygen is another manifestation of the special ease with which this isomer is converted into the aci-nitro form.

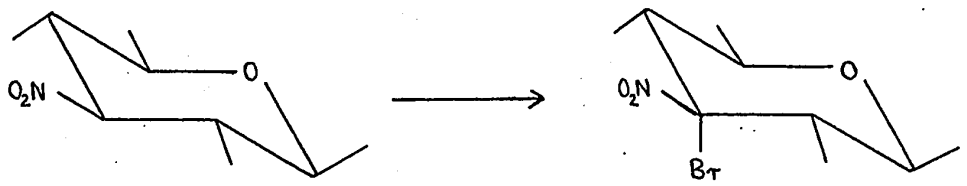
D. Synthesis and Reactions of α-Halonitro Sugars

Halogenation of nitro paraffins in α-position is achieved by addition of halogen to the aci-nitro form or the nitronate salt (7). The reaction is so rapid that it can serve as a method to determine the amount of aci-nitro form present in a tautomeric mixture (54).

It was considered that halogenation of nitro sugars, which had never been attempted, would be an interesting subject of study. Several partially blocked 3-nitrohexose derivatives were therefore chlorinated and brominated by methods now to be described, to give products having geminal halonitro substitution at C-3. Usually halogenation led to single products in high yields and these, which are believed to bear the nitro group in equatorial and the halogen in axial orientation are referred to as "normal" products. Occasionally, formation of two isomers was observed in which case the minor component was believed to have the reverse configuration at C-3 ("abnormal product"). These configurational assumptions suggested themselves by analogy with the nitronate protonation in 3-nitro pyranosides which invariably results in an equatorial nitro group (29), and they were consistent with circular dichroism and nuclear magnetic resonance data as outlined in separate chapters later on. However, it must be admitted that definite proof for the assignment of absolute configurations at C-3 was not obtained.

The terminology of the halonitro sugar configurations presented another problem as there does not yet exist a generally adopted rule of nomenclature. Following a proposal by Horton (55),

a combination of generic carbohydrate names and the sequence rules of Cahn, Ingold and Prelog (56) was employed. For example, the configuration of a 3-halonitro derivative is described as D-gluco if the C-3 substituent of highest priority (according to the sequence rules) takes the place of 3-OH in D-glucose. Assuming that the configuration at all carbon atoms other than C-3 remains unaltered, bromination of the 3-nitro sugar with D-gluco configuration would give as normal product with axial bromine, the 3-bromo-3-nitro derivative with the D-allo configuration.



D-gluco D-allo

For bromination, two different methods were applied, usually with equal success. The method referred to as direct bromination method consisted of prior formation of the nitronate by treatment of the nitro sugar with base in alcoholic solution and at low temperatures. Dropwise addition of bromine then afforded the bromonitro derivative, mostly in good yield. The second method consisted of bromination of the nitro compound with N-bromoacetamide (NBA) in the presence of sodium acetate, the acetate ion apparently being basic enough to ionize the nitro form. This method proved advantageous for nitro compounds containing O-acetyl groups, as it avoided hydrolysis of the latter.

The chlorination reactions were performed by treatment of ethanolic solutions of the nitro sugar with 5% aqueous hypochlorite solutions (reagent grade), and the chloronitro sugars were usually obtained smoothly and in good yields. Commercial Javex solution could be substituted for the reagent with equal success.

i) Halonitro Glycosides having a cis-fused Benzylidene Acetal Group

In accord with the observed ease of nitronate formation, the nitro sugars with a cis-fused benzylidene group, namely the α-D-talo (1), α-D-galacto (2), β-D-galacto (3), α-D-lyxo (8) and β-D-lyxo (9) compounds readily furnished halonitro derivatives in good yields (Reaction Scheme D, p. 60).

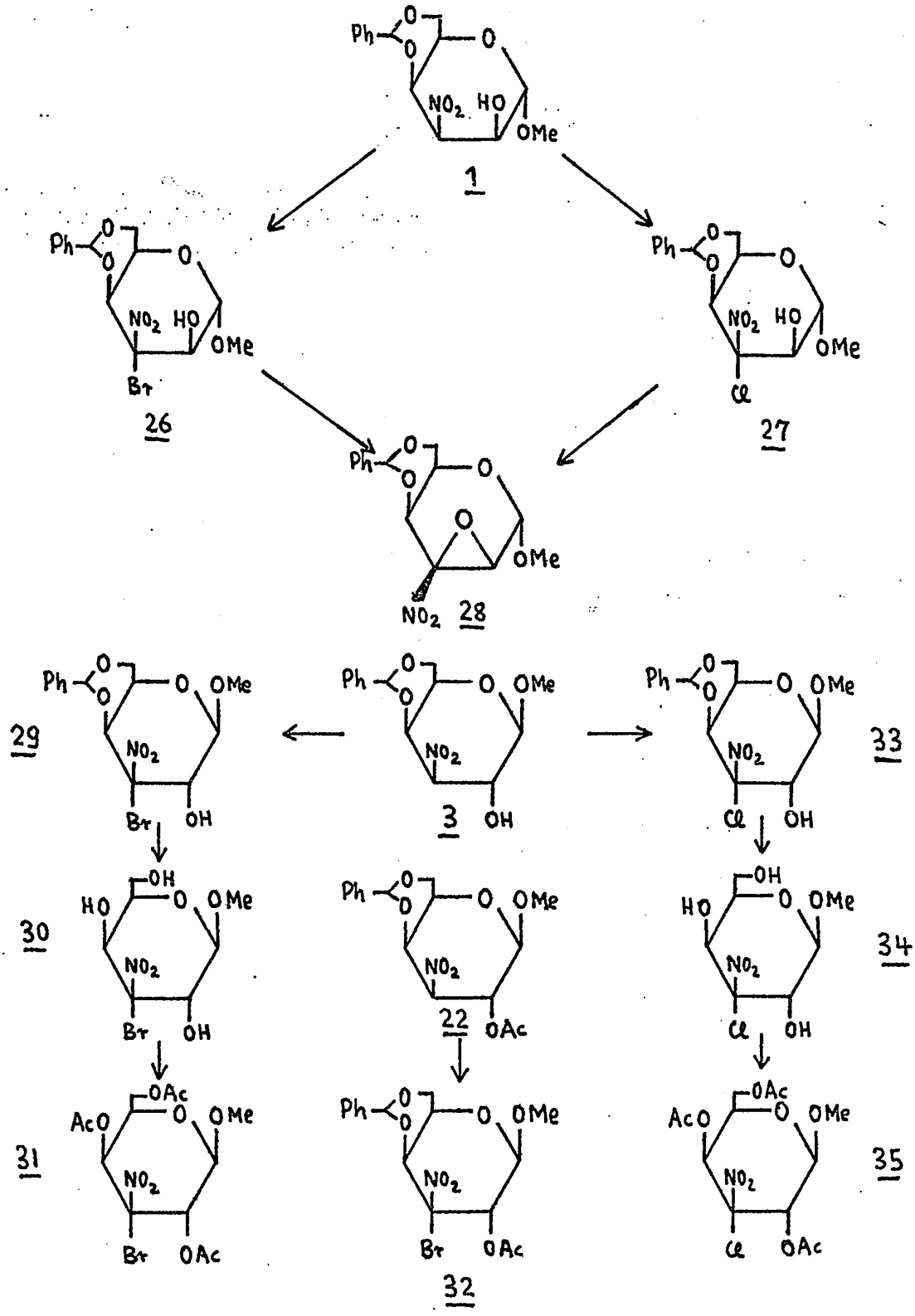
Bromination of the nitro taloside 1 by the direct method or with NBA led to methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-idopyranoside (26) in yields of 75-90%. Reductive removal of the bromine with sodium borohydride by the Iffland method (57) regenerated 1. On the other hand, treatment of 26 with aqueous N sodium hydroxide at room temperature for 15 minutes furnished methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-α-D-talopyranoside (28) in a yield of 90%. The facile formation of 28 supports the configurational assignment of 26, since it is a well-established fact that trans-diaxial halohydrins form epoxides rather readily (58). The same epoxynitro sugar 28 was formed directly in an attempt to chlorinate 1. When a methanolic solution of 1 was stirred at room temperature for 35 minutes with Javex, 28 was isolated in a yield of over 80%. Inspection by t.l.c. after a reaction time of 15 minutes showed

the presence of an intermediate which later disappeared. When the chlorination was carried out at 0° and monitored by t.l.c., the reaction could be quenched before epoxide formation became evident, and methyl 4,6-O-benzylidene-3-chloro-3-deoxy-3-nitro-α-D-idopyranoside (27) was isolated in 85% yield. Compound 27 proved to have the same t.l.c. mobility as the previously observed intermediate; hence the facile formation of 28 in the room temperature chlorination of 1 is assumed to proceed via the chloronitro sugar 27.

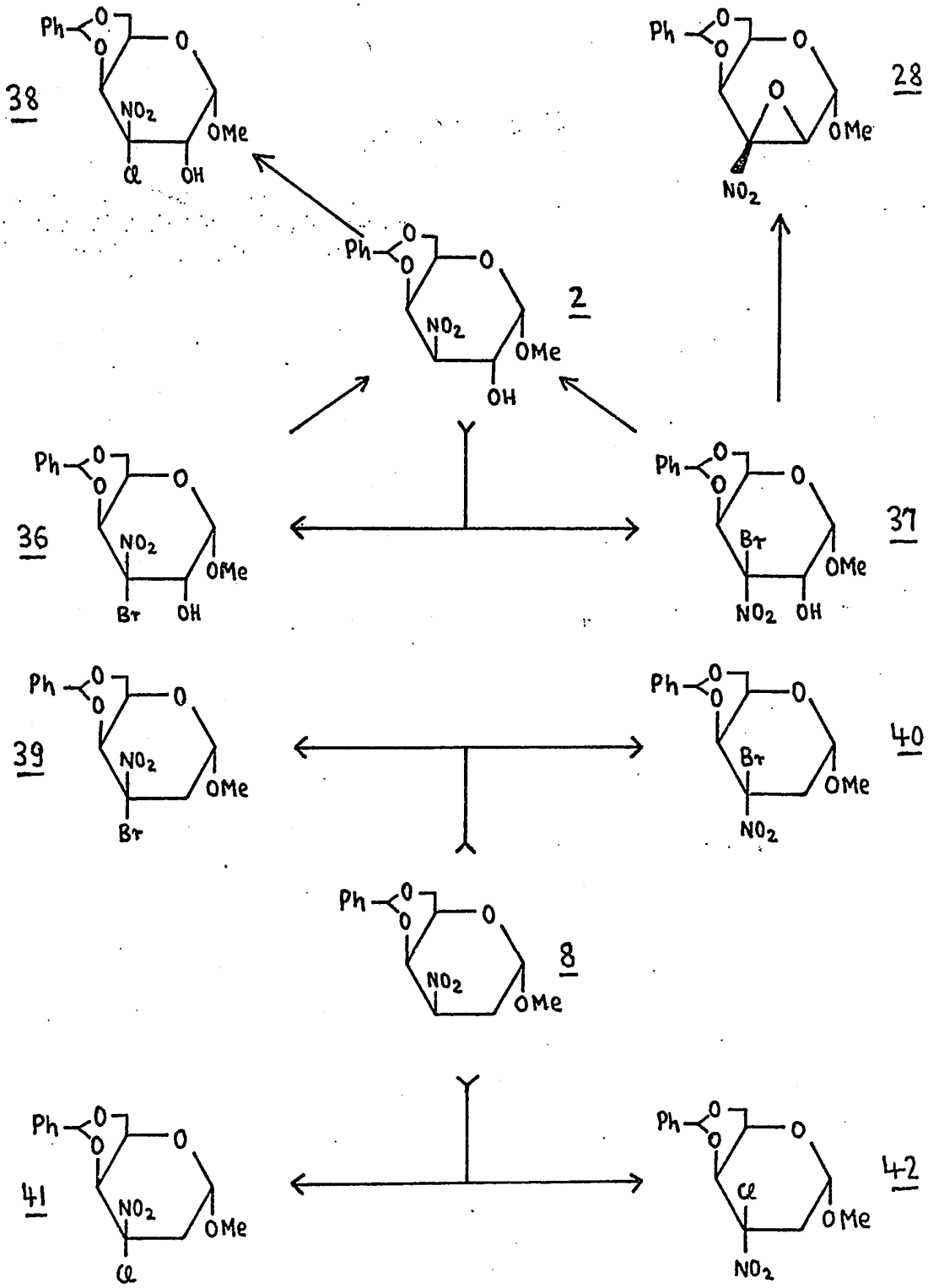
Bromination of the β-anomeric nitro galactoside 3, effected either by the direct method or by NBA, led to a uniform product, methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-gulopyranoside (29), in good yields.

Debromination of 29 with sodium borohydride regenerated the nitro sugar 3 in a yield of 90%. Treatment of 29 with aqueous N potassium hydroxide also gave 3, which was in contrast to epoxide formation as observed with 26. A positive starch/iodide test of the reaction mixture indicated that the bromine was abstracted as bromonium ion. When the bromonitro 29 was refluxed in methanolic, 0.1 N sodium methoxide for 20 minutes, mainly an unidentified product with very low mobility was seen on t.l.c. It is assumed that debenzylidenation had occurred, which was also indicated by the smell of benzaldehyde that was noticed. The only product isolated in this experiment was some unreacted starting material (20%). The fact that no epoxynitro sugar was formed in any of the base treatments suggests a cis halohydrin configuration for 29.

Reaction Scheme D



Reaction Scheme E



Debenzylidenation of 29 with trifluoroacetic acid led to the formation of a syrupy product which failed to crystallize. After acetylation, however, crystalline methyl 2,4,6-tri-O-acetyl-3-bromo-3-deoxy-3-nitro-β-D-gulopyranoside (31) was isolated in a yield of 72%.

Bromination of 22, the 2-O-acetyl derivative of 3, with NBA furnished in excellent yield methyl 2-O-acetyl-4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-gulopyranoside (32). Evidently an acetyl substituent in 2-position does not cause any impediment to bromination.

Chlorination of the nitro galactoside 3, either with a reagent grade hypochlorite solution or with Javex, readily afforded methyl 4,6-O-benzylidene-3-chloro-3-deoxy-3-nitro-β-D-gulopyranoside (33). The structure of 33 was confirmed by chemical means when debenzylidenation with trifluoroacetic acid, followed by acetylation, led to the formation of methyl 2,4,6-tri-O-acetyl-3-chloro-3-deoxy-3-nitro-β-D-gulopyranoside (35).

In contrast to the uniform products obtained in halogenations of the β-anomeric nitro galactoside 3, bromination of its α-anomer 2 furnished a solid material (91%) which according to t.l.c. consisted of two products in an estimated ratio of 1 : 1. An n.m.r. spectrum of this mixture exhibited two methine proton signals at 4.48τ and at 4.30τ with an intensity ratio of 55 : 45. Column chromatography allowed the separation of the two isomers and afforded the slow-moving product in pure form in a yield of 49%. It proved to be the normal product, methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-gulopyranoside

(36). The fast-moving material isolated in 33% yield proved to be the 3-epimer, methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-galactopyranoside (37). A smilar mixture of 36 and 37, but in a ratio of 85 : 15, was obtained when 2 was brominated with NBA. The epimerism of 36 and 37 was confirmed, by chemical means, when reductive removal of the bromine with sodium borohydride led to the same nitro galactoside 2 from both isomers 36 and 37. However the two bromonitro sugars behaved differently when treated with N sodium hydroxide at room temperature. Isomer 37 gave slowly (10 hours) but in high yield (78%) the epoxide 28 that had been encountered previously. Isomer 36 remained unaffected under these conditions even for a prolonged period of time (20 hours). However, it reacted when refluxed for 20 minutes in 0.1 N sodium methoxide solution to give, chiefly, an unidentified material of very low t.l.c. mobility (which may have been due to degradation) and, as minor product, the same epoxide 28 (isolated in 28% yield). (Reaction Scheme E, p. 61).

The formation of 28 from 37 and 36 appeared puzzling at first glance, for it implied epimerization at C-2. It is recalled from Chapter B that epimerization, although observed in compounds having a trans-fused 4,6-benzylidene acetal ring, had not occurred in analogous, cis-fused acetals: the manno, but not the talo and galacto derivatives, underwent epimerization and this was explained by invoking a retro Henry reaction to which the former appear prone owing to a relatively low nitromethylene acidity. However, the present observations on 3-bromo-3-nitro derivatives are not in contradiction with the

concept derived in Chapter B. In fact, they are explicable by it. The halonitro compounds, being tertiary nitro compounds, should be capable of undergoing retro Henry reaction (and thereby, epimerization) quite easily regardless of the configurations at C-2 and C-4. Since the abnormal epimer 37, with an axial nitro group, is expected to be the less stable one of the pair, it appears reasonable that it should suffer bond cleavage between C-2 and C-3 more readily than 36, thus being epimerized more easily and subsequently, producing epoxide in higher yield and under milder conditions, than 36. In the case of the β-glycoside 29 (the anomer of 36) no epoxide formation was observed, as mentioned earlier, and one might conclude that it did not incur C-2 epimerization. Presumably, because of the equatorial anomeric methoxyl group (implying absence of strain due to 1,3-diaxial interaction), there was no strong driving force for retro Henry-type ring cleavage. In the case of the glycoside 26, even though 1,3-diaxial interaction strain must exist, there was no incentive for ring cleavage and C-2 epimerization since the molecule is ideally set up for epoxide formation.

In contrast to the observed epimer formation in the bromination of 2, chlorination led to a single product, namely, methyl 4,6-O-benzylidene-3-chloro-3-deoxy-3-nitro-α-D-gulopyranoside (38), in a yield of over 90%.

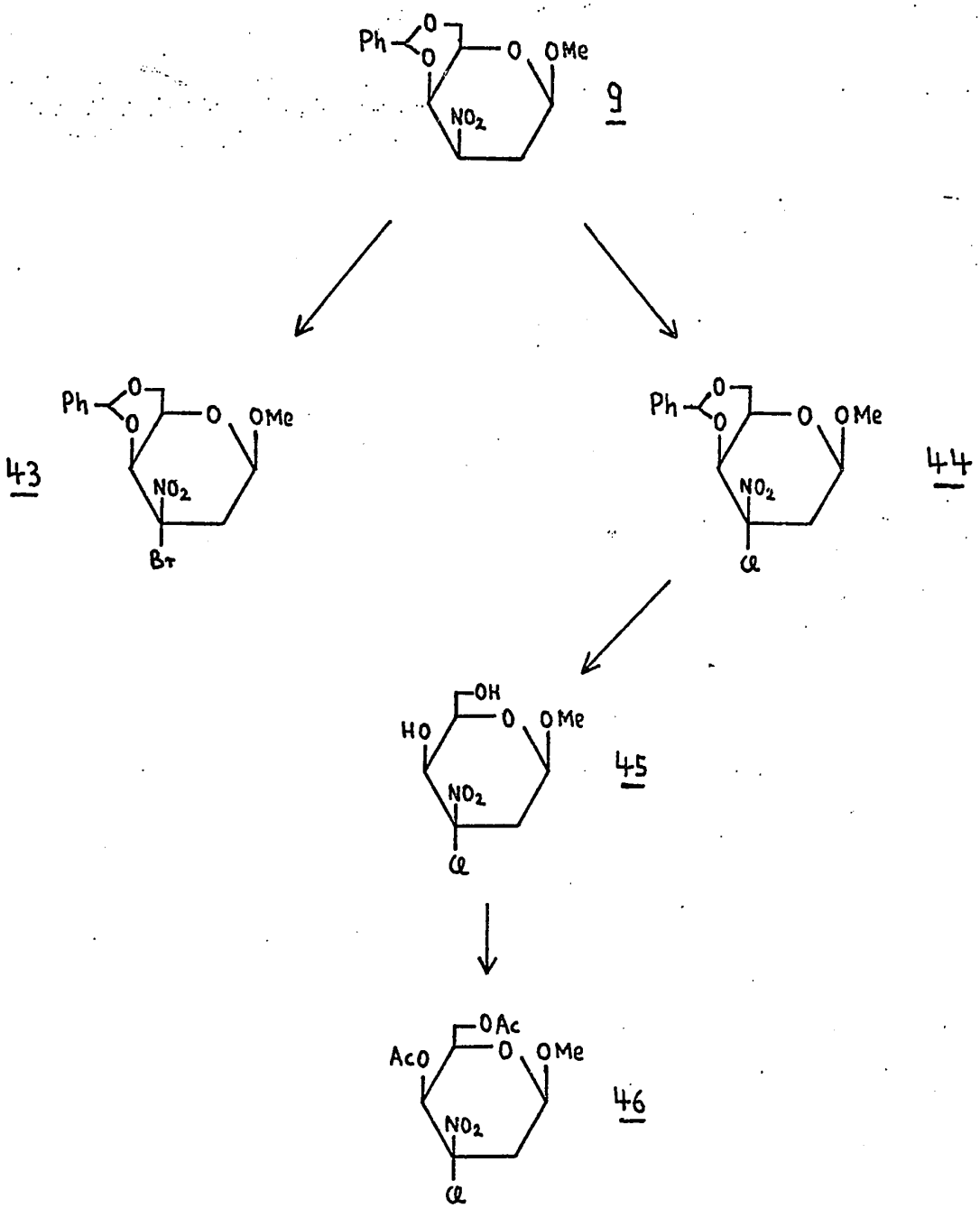
Similar halogenation studies were undertaken with the 2,3-dideoxy-3-nitro sugar 8. Bromination by the direct method or with NBA led again to the formation of isomeric mixtures in

ratios of approximately 25 : 75 in either case. Thus, the direct bromination method afforded a crude mixture (98%) which showed two spots on t.l.c. An n.m.r. spectrum of the mixture exhibited two methine proton signals at 4.41τ and at 4.28τ in an intensity ratio of 75 : 25. Separation by column chromatography afforded a pure compound in 69% yield which proved to be the normal product, methyl 4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-α-D-xylo-hexopyranoside (39). The minor, abnormal product, methyl 4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-α-D-lyxo-hexopyranoside (40), was obtained in a yield of 21%. (Reaction Scheme E).

Chlorination of the 2,3-dideoxy-3-nitro sugar 8 also led to formation of an isomeric mixture in a yield of 86%. The n.m.r. spectrum of the mixture showed two methine proton signals at 4.42τ and 4.28τ in an intensity ratio of 86 : 14. Column chromatographic separation of the mixture led to the isolation of the normal methyl 4,6-O-benzylidene-3-chloro-2,3-dideoxy-3-nitro-α-D-xylo-hexopyranoside (41) in a yield of 67%. The abnormal methyl 4,6-O-benzylidene-3-chloro-2,3-dideoxy-3-nitro-α-D-lyxo-hexopyranoside (42) was isolated in a yield of 13%. The abnormal products 40 and 42, which were isolated in small amounts only, were characterized by spectral and other physical data but not by elemental analysis. However, they were compared with the normal epimers by mass spectrometry (see special section on page 82), and the results thereof supported the assumed structures.

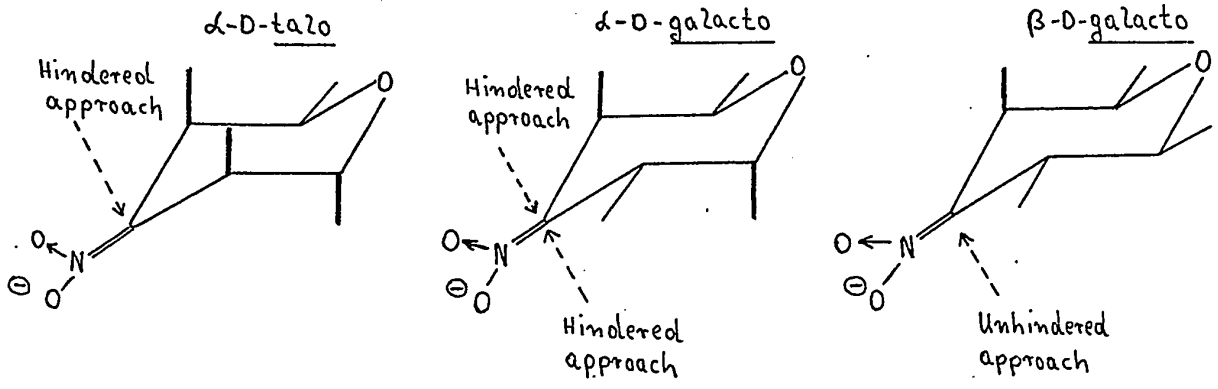
Next, it was also of interest to study if the halogenations of the β-anomeric 2,3-dideoxy-3-nitro glycoside 9 again furnished single products rather than epimeric mixtures.

Reaction Scheme F



Bromination of 9 with NBA led to the formation of methyl 4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-β-D-xylo-hexopyranoside (43) in a yield of 96%. Similarly, chlorination of 9 with Javex exclusively gave methyl 4,6-O-benzylidene-3-chloro-2,3-dideoxy-3-nitro-β-D-xylo-hexopyranoside (44), in a yield of 92%. Support for the structural assignment was also provided by the conversion of 44 into methyl 4,6-di-O-acetyl-3-chloro-2,3-dideoxy-3-nitro-β-D-xylo-hexopyranoside (46) via debenzylidenation followed by a subsequent acetylation.

In summary, the following comments can be made. It was found that 3-nitro sugars with a cis-fused 4,6-O-benzylidene group afford readily and in good yields 3-halo-3-nitro derivatives. For β-anomeric compounds, halogenation led to the exclusive formation of single products, referred to as normal products since they are believed to carry their nitro group in an equatorial position. The preferred formation of normal products can be explained by the lack of hindrance to the approach of halogen from below the plane of the ring. α-Anomeric nitro sugars, by contrast, often gave rise to a pair of epimers, the isomerism residing at C-3. The epimer ratio depended on the steric situation in the nitro sugar molecule, but also on the steric requirements of the entering halogen.



In the α-D-talo glycoside 1, bromination as well as chlorination produced single products only, which appears understandable since approach of the halogen from above the plane of the ring should be strongly hindered by the two axial substituents at C-2 and C-4. If the axial substituent at C-2 is replaced by the smaller hydrogen atom as is the case in 8, steric hindrance to an approach from above is diminished, and both normal and abnormal products were formed. Different product ratios were found for bromination and chlorination; in each case, however, the normal product was isolated as the main product. With the larger bromine atom, the abnormal product was formed to about 25%, while with the smaller chlorine atom, the abnormal product was formed to the extent of 14% only. Although the two results are not truly comparable since different reaction conditions prevailed, they suggest that the smaller chlorine atom experiences less hindrance from the axial anomeric methoxyl group. That the reaction conditions have an influence on the product ratio was clearly shown by the bromination of the nitro galactoside 2. The direct bromination method led to the formation of the abnormal product to the extent of 45%, while in the NBA bromination this was reduced to 15%. In brominations of 2,3-dideoxy-3-nitro sugar 8 no such difference was observed.

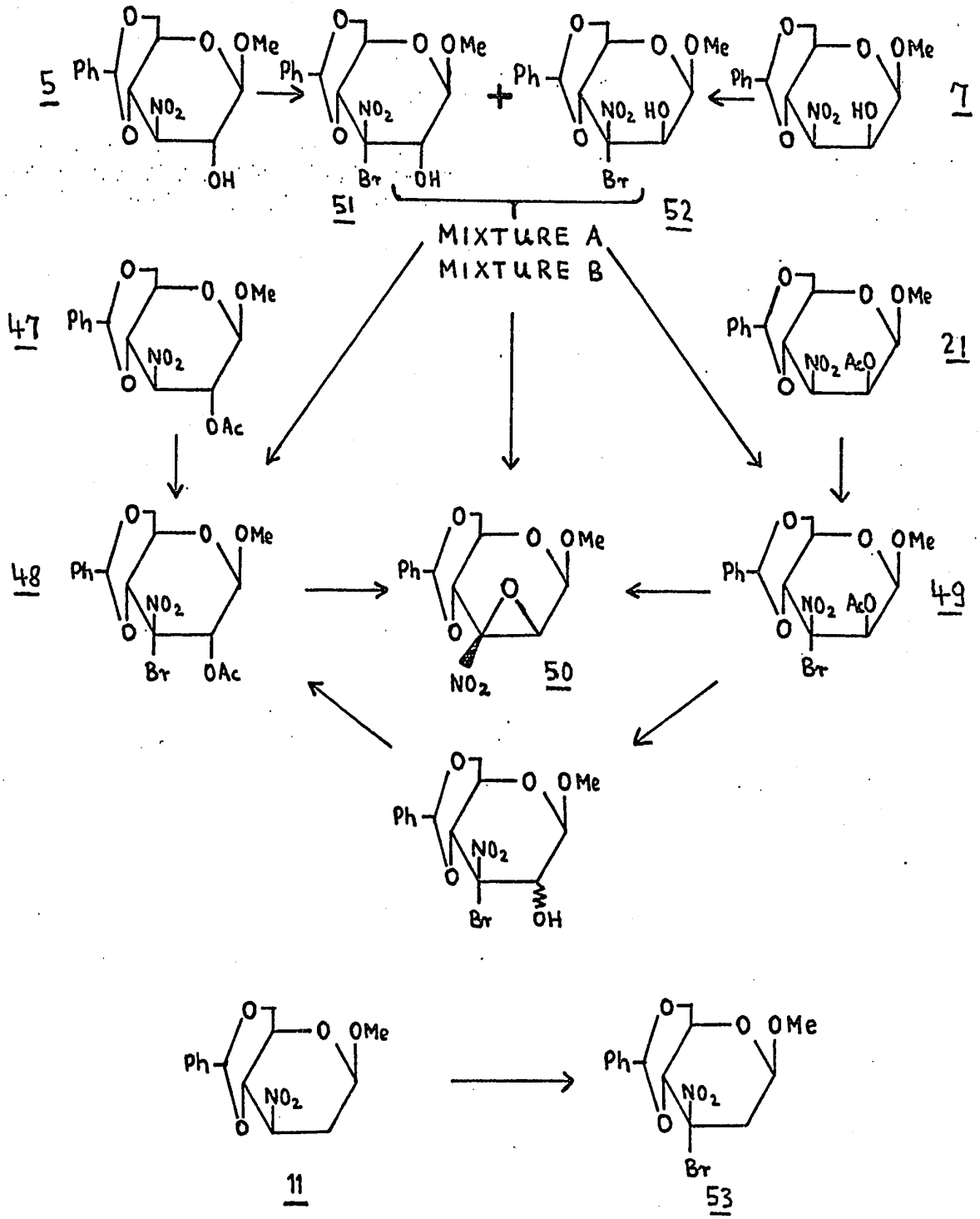
ii) Halonitro Glycosides having a trans-fused Benzylidene Acetal Group

As discussed previously, the nitro glycosides having a trans-fused benzylidene group (gluco and manno configurations) form nitronate much less readily. Moreover, in manno compounds

the action of alkali led to C-2 epimerization. These complications were also reflected in the halogenation of this type of compounds (Reaction Scheme G, p. 70).

When the β-D-mannoside 7 was brominated with NBA in refluxing methanol in the presence of sodium acetate, a new product was formed after 1 hour. It appeared uniform according to t.l.c. but was revealed to be a mixture by n.m.r. spectroscopy. In $CDCl_3$ solution this mixture A ($[\alpha]_D$-35.5°) exhibited two methine proton signals at 4.23 τ and 4.42 τ in an intensity ratio of 20 : 80, indicative of the presence of two benzylidene acetals. A closer inspection of the spectrum showed, besides a 5-proton multiplet at 2.64 τ for the aromatic protons and a 3-proton signal at 6.44 τ for the anomeric methoxyl group, the presence of a total of 6 other protons. Even though these could not be assigned individually, one can assume that bromination had occurred, since the nonbrominated glycoside would possess one additional proton. The introduction of the bromine atom at C-3 was also suggested by the observation that the i.r. band for the nitro group was shifted from 1550 to 1565 cm^{-1}, which is a fact generally observed for α-halo substitution in nitro compounds (59). When the bromination of 7 with NBA was carried out at room temperature, completion of the reaction required a prolonged reaction time of 5 hours. The solid material so obtained gave an n.m.r. spectrum which was superimposable on that of mixture A; t.l.c. mobility of the material was the same also. A similar mixture with superimposable n.m.r. spectrum was obtained when the brominating reagent NBA was replaced by N-bromosuccinimide. Cleavage of the benzylidene ring by this reagent (Hanessian reaction) was not observed.

Reaction Scheme G



As discussed in Chapter B, the β-D-mannoside 7 epimerized to the β-D-glucoside 5 when nitronate formation was attempted. It was therefore of interest to compare the NBA bromination with the direct bromination, since the latter is performed under conditions of prior formation of the nitronate so that epimerization at C-2 can be expected.

When the manno nitro sugar 7 was brominated with bromine at 0° a white solid was isolated after work-up. Inspection of the material by t.l.c. showed one major spot with the same mobility as that of nitro sugar 5, one slightly faster moving spot, and traces of a slow-moving compound. The n.m.r. spectrum of the reaction product in $CDCl_3$ exhibited a complex pattern, but four distinct methine proton signals at 4.23τ, 4.32τ, 4.42τ and at 4.48τ were recognizable, indicating the presence of four products in an intensity ratio of 5 : 10 : 35 : 50. Column chromatography of the mixture gave, after appropriate pooling of fractions, a fast-moving product with a rotation of $[\alpha]_D$-39.8°, which appeared homogeneous on t.l.c. An n.m.r. spectrum of this material in $CDCl_3$ still exhibited two methine proton signals at 4.23τ and 4.42τ, with an intensity ratio of 15 : 85. Furthermore the spectrum was superimposable on that of mixture A obtained in the previous brominations. The product of intermediate mobility which according to t.l.c. was formed in a major proportion, was isolated in pure form and indeed proved to be nitro glucoside 5. It was responsible for the methine proton signal at 4.48τ. The slow-moving product, present in traces only, proved to be unreacted starting material 7, with

a methine proton signal at 4.32 τ. Thus for the direct bromination experiment it has to be concluded that bromination had occurred only to the extent of about 40%. Moreover, the mannoside 7 was largely epimerized to the glucoside 5, even under such extremely mild conditions. Therefore it was suspected that the mixture A, encountered in all the bromination attempts of 7, consisted mainly of methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-allopyranoside (51) to which the stronger methine proton signal at 4.42 τ was attributed, and of methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-altropyranoside (52) to which the weaker signal at 4.23 τ was attributed. Although the two isomeric bromonitro sugars were never obtained in a pure state, but always in a 4 : 1 mixture, these assignments were supported by the result of an acetylation experiment.

When mixture A was acetylated by the acetylchloride/triethylamine method, a solid material was obtained which showed a major, fast-moving spot and a minor, slow-moving spot on t.l.c. An n.m.r. spectrum of the solid in $CDCl_3$ revealed the presence of two acetylated compounds in a ratio of 80 : 20. Separation of the mixture by column chromatography furnished a pure, fast-moving material (70%) which proved to be methyl 2-O-acetyl-4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-allopyranoside (48), also obtained and identified in connection with the action of NBA on methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-erythro-hex-2-enopyranoside as shown in Part III, Chapter D. The slow-moving material (15%) proved to be methyl 2-O-acetyl-4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-altropyranoside (49), which was also obtained by an independent route and identified there. Since it can be assumed that no

epimerization had occurred during the acetylation with acetylchloride/triethylamine (see also Chapter C), one can conclude that mixture A consisted of about 80% of bromonitro sugar 51 and about 20% of bromonitro sugar 52. Thus the methine proton signal of mixture A appearing at 4.23τ can be attributed to 52, and that at 4.42τ to 51, which is in good agreement with the methine proton signals found for the corresponding 2-acetates 48 and 49 at 4.39τ and 4.21τ, respectively. From these observations one can furthermore conclude that the basicity of acetate ion suffices to cause epimerization at C-2 leading to the formation of the gluco isomer from the manno isomer. However, complete epimerization as observed in the base treatment of 7 and discussed in Chapter B was not detected in any of the halogenation experiments. Instead, equilibrium mixtures were formed in which the epimerized bromonitro sugar 51 preponderated. It is believed that these mixtures were the result of a thermodynamic equilibrium established between the bromonitro sugars 51 and 52 via a retrograde Henry reaction.[5] This belief is supported by results obtained in the bromination starting from the pure nitro sugar isomer 5, as well as by results obtained upon base treatment of mixture A.

Bromination of the nitro sugar 5 with NBA in the presence of sodium acetate gave a crude solid material (mixture B, $[\alpha]_D$ -41,2°) which on t.l.c. exhibited a major spot together with a trace spot, the latter corresponding to starting material 5. The n.m.r. spectrum of mixture B in $CDCl_3$ was, except for some minor signals, identical with that of mixture A and showed methine proton signals at 4.22τ, 4.41τ, and 4.48τ in an intensity

ratio of 15 : 75 : 10, attributable to 52, 51, and 5 respectively. The i.r. spectrum of mixtures B and A were also almost identical. The close relationship between mixture A and mixture B was further exemplified by the formation of the same epoxynitro sugar 50 upon base treatment. When mixture A was treated with a boiling, 0.1 N solution of sodium methoxide in methanol for 30 minutes, this epoxide, methyl 2,3-anhydro-4,6-0-benzylidene-3-nitro-β-D-mannopyranoside (50), was isolated in a yield of 84%. Mixture B, subjected to the same reaction conditions, furnished the epoxynitro sugar 50 in a yield of 78%. The structure of 50 was ascertained by comparing its physical and spectral properties with those of an authentic sample (see compound 27, Part III, Chapter C). The epoxynitro sugar 50 can only be formed from the trans-diaxial halohydrin 52, which is the minor component in mixtures A and B. Therefore one has to postulate that an equilibrium between 51 and 52 in mixtures A and B is shifted towards 52 as the concentration of 52 is depleted by formation of 50. This represents therefore another example of an epimerization reaction proceeding via a retrograde Henry reaction. The experiments thus have demonstrated the amazing fact that, when the nitro mannoside 7 is brominated and then treated with base to produce the expected epoxide 50, the latter is formed for the most part not directly but by a detour involving two successive epimerizations at C-2.

The bromonitro acetates 48 and 49 were also synthesized from the acetylated nitro sugars 47 and 21, respectively. In this case C-2 is no longer available for epimerizations involving a retrograde Henry mechanism, and, provided that the

2-O-acetyl group remains intact, uniform products should be obtained, which is exactly what was observed. Thus, bromination of the 2-acetate 47 with NBA in the presence of sodium acetate gave in high yield the bromonitro sugar acetate 48 as the only product. Comparison of its physical and spectral properties with those of a sample obtained previously ascertained the identity of 48. As expected, no epimerization had occurred during the bromination. However, when 48 was treated for 30 minutes with a boiling 0.1 N solution of sodium methoxide in methanol, it afforded the epoxynitro sugar 50 in a yield of 41%. The formation of 50 from 48 is explained by deacetylation leading to the hydroxyl derivative 51, which in turn is convertible into, and in equilibrium with, its 2-epimer 52. The bromonitro sugar 52, being a trans-diaxial halohydrin, is then perfectly set up for the formation of the epoxynitro sugar 50.

Bromination of the β-D-manno 2-acetate 21 with NBA in the presence of sodium acetate afforded, after a reaction time of 1 hour at room temperature, the bromonitro sugar acetate 49 in a yield of 95%. The structure of 49 was ascertained in this connection by elemental analysis and spectroscopy.

Treatment of the bromonitro acetate 49 with refluxing 0.1 N sodium methoxide for 30 minutes furnished the epoxynitro sugar 50 in a yield of 37%. A reaction sequence similar to that proposed for the conversion of 48 into 50 is also postulated here. This postulate was supported by the result obtained when 49 was treated with sodium methoxide as above, but at room temperature. The crystalline product isolated in 82% yield ($[\alpha]_D$ -38.2°) appeared uniform on t.l.c. but the n.m.r. spectrum

revealed it to be a mixture, the spectrum being superimposable on that of mixture A and exhibiting again the two methine proton signals at 4.22τ and 4.41τ in an intensity ratio of 20 : 80. Acetylation of the mixture gave a solid material, from which after recrystallization the previously obtained bromonitro acetate 48 was isolated in pure form in a yield of 65%. This represents further evidence supporting the idea that an equilibrium between the bromonitro sugars 51 and 52 is rapidly established, with 51 being the main product. Even at 0°, treatment of 49 with sodium methoxide led to the formation of a mixture of 52 and 51 in a ratio of 15 : 85.

For comparative spectroscopic and dichroic studies it was also of interest to prepare methyl 4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-β-D-*ribo*-hexopyranoside (53). This compound was readily obtained in excellent yield when the 2,3-dideoxy-3-nitro sugar 11 was brominated with NBA. The structure of 53 was ascertained by elemental analysis and its spectroscopic properties.

When the bromination of α-anomeric nitro glycosides having a *trans*-fused benzylidene group was investigated it was found that in addition to the complications encountered in the β-series, the reactions were more sluggish. An attempt to brominate the nitro glucoside 4 with NBA in the presence of sodium acetate failed and, on work-up after a reaction time of 10 hours at 64°, starting material 4 was recovered to 78%. According to t.l.c., 4 was the only material present in the reaction mixture. A similar inertness towards bromination was observed for 54, the 2-O-acetyl derivative of 4. Therefore

it seems that the axial, α-anomeric methoxyl group exerts a strong hindrance to the introduction of bromine at C-3, which is probably due to a combination of steric and polar effects. When the substituent at C-2 is in an axial position, as for derivatives with the α-D-manno configuration, hindrance seemed to be diminished somewhat and bromination was observed to occur, although not as readily as with the β-anomeric compounds.

Bromination of the nitro mannoside 6 with NBA led to the formation of a partially brominated product mixture. On the basis of the chemical shifts of methine protons in the analogous β-series, it was speculated that signals occurring at 4.24 τ and 4.42 τ can be attributed to methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-altropyranoside (57) and the isomeric α-D-allopyranoside (58), respectively. The least intense signal of the product mixture appeared at 4.34 τ and was attributed to unreacted starting material, while a signal at 4.48 τ was associated with nitro glucoside 4, i.e., epimerized starting material. From the intensity of the methine proton signals it was estimated that bromination had occurred to at least 60% and that the isomeric bromonitro sugars were formed in a ratio of approximately 1 : 1. The presence of bromination products was further confirmed when base treatment of the mixture afforded methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-α-D-mannopyranoside (55) in a yield of 51%. Since the brominated mixture contained only about 30% of the trans-diaxial halohydrin 57 from which the nitro epoxide 55 is thought to arise, one has to assume that the isomeric bromonitro sugar 58 contributes to epoxide formation by being epimerized at C-2, as had been found for

β-anomeric analogs. Furthermore one has to conclude that the bromonitro sugar 58 arose by such epimerization and not by bromination of 4 since the latter had been shown to resist bromination under similar conditions. (Reaction Scheme H, p. 81).

Epimerization during bromination was prevented when 23, the 2-O-acetyl derivative of 6, was brominated with NBA to afford methyl 2-O-acetyl-4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-altropyranoside (56). The structure of 56 was ascertained in this connection by elemental analysis and its spectral properties. The structure of 56 was also supported by chemical means when its treatment with a boiling solution of sodium methoxide led to formation of the previously obtained nitro epoxide 55 in a yield of over 80%. Deacetylation of 56 obviously was the first step in this reaction.

On the other hand, treatment of 56 with sodium methoxide at room temperature gave a different material (mixture C). According to its i.r. spectrum it did not contain an acetyl group but possessed a hydroxyl group instead. The n.m.r. spectrum of mixture C exhibited two methine proton signals at 4.24τ and 4.43τ in an intensity ratio of 40 : 60, the signals being assigned to 57 and 58, respectively. All attempts to separate the two isomers as such or after acetylation were unsuccessful. However, the experiment did show that base treatment of a pure compound (56) led to a mixture of isomers. A retrograde Henry reaction is again postulated to be involved.

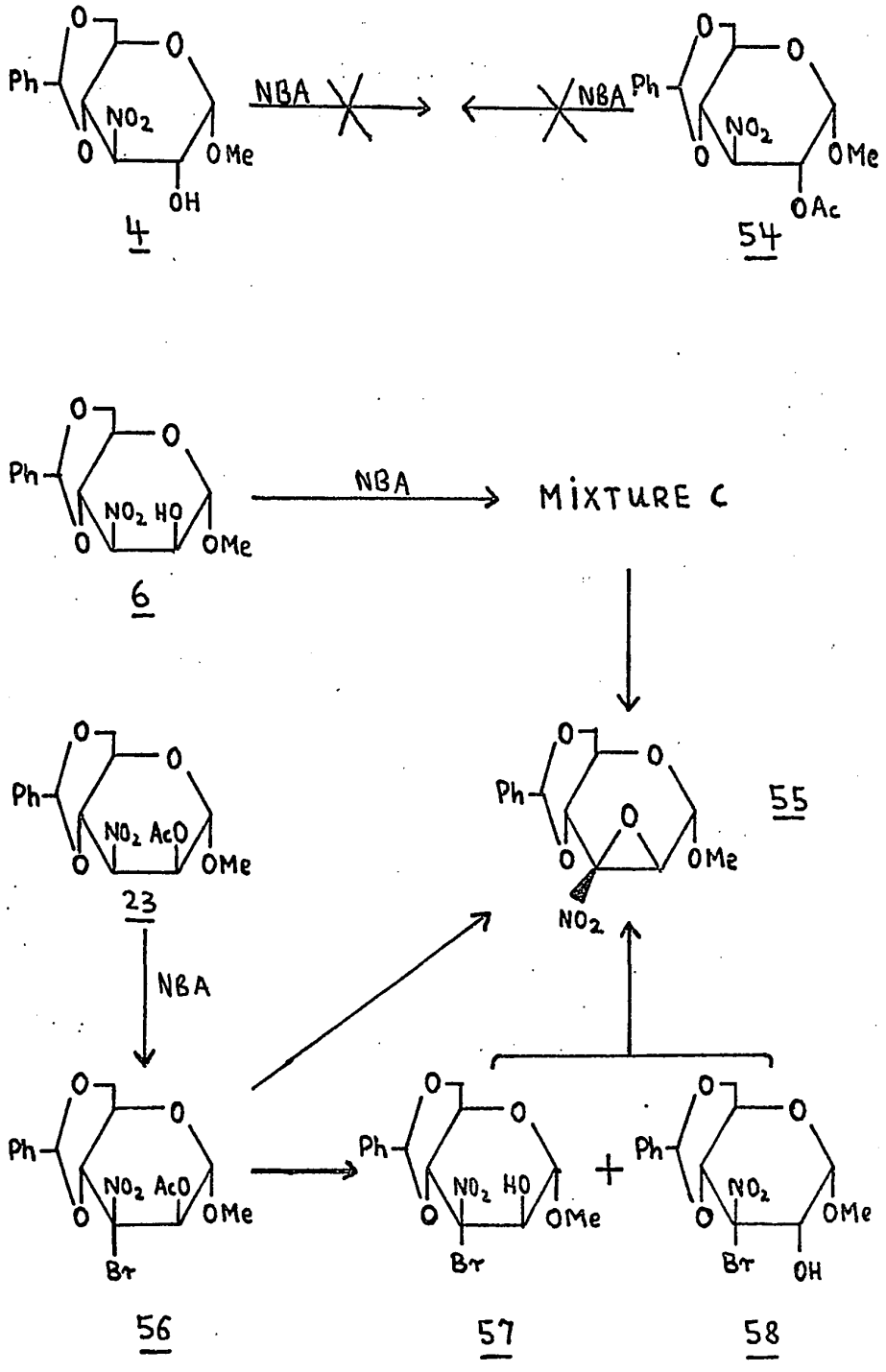
Treatment of mixture C with methanolic sodium methoxide at reflux temperature afforded the nitro epoxide 55 in a yield of 76% and hence presented chemical proof that mixture C consisted

of bromonitro sugars.

In summary, it has been found that the bromination of the β-anomeric nitro sugars having a trans-fused benzylidene group proceeds well but is complicated by accompanying epimerization reactions at C-2, for which a retrograde Henry mechanism is postulated. In the bromination of α-anomeric nitro sugars having a trans-fused benzylidene group the same complications were encountered, but in addition it was found that the ease of bromination is strongly dimished due to the axial anomeric methoxyl group. Thus, the α-D-glucoside could not be brominated under the usual conditions, while bromination of the corresponding α-D-mannoside was more sluggish than that of the β-anomer. Steric and polar effects are most likely the cause of this diminution of reactivity. Such effects were also reflected in the composition of the mixtures of bromonitro sugars obtained. In the β-series, the isomer with an equatorial hydroxyl group at C-2 arose to an approximate extent of 80%, while the epimer with the axial hydroxyl group was encountered only to about 20%. In the α-series, the isomer with the equatorial hydroxyl group at C-2 outweighed the epimer with an axial hydroxyl group only slightly, the former occurring to approximately 60% and the latter, to about 40%. Presumably the polar interaction of an axial hydroxyl group in a β-anomeric system (Δ2-effect) is responsible for this difference. Both equilibria seem to be quite mobile under conditions leading to the formation of epoxy nitro sugars since these are formed smoothly and in good yields and invariably have the configuration expected to arise from trans-diaxial halohydrins although the latter are minor components in the mixtures. Both in the

α- and β-series epimerization is prevented as long as the hydroxyl group at C-2 is blocked by an acetylation.

Reaction Scheme H



Mass Spectrometric Data of Halonitro Sugars

The mass spectrum of the abnormal bromonitro derivative 40 showed an intense peak for the molecular ion at m/e= 373, with an isotopic distribution pattern typical for a monobromo derivative. A less intense peak was observed at m/e=342, which is probably the result of a loss of OCH_3 from the molecular ion. Another, but single, peak of medium intensity was observed at m/e=262 which could have arisen by a loss of HBr from the m/e=342 fragment. For comparison, the mass spectrum of the analyzed, normal product 39 was recorded also. The molecular ion peak at 373 was again relatively intense and showed the presence of one bromine by its isotopic distribution pattern. The fragmentation pattern was similar to that of the abnormal isomer with fragment ions at 342 and 262. However, the normal isomer with the equatorial nitro group showed an intense peak at m/e=221, which was lacking in the spectrum of the abnormal isomer. This fragment could have arisen by a loss of C_6H_5CHO (106) and NO_2 (46) from the molecular ion. Thus it seems that the two isomers can be distinguished by their mass spectrum. This finding was also supported when the corresponding chloro derivatives were analyzed similarly.

The mass spectrum of the abnormal product 42 showed an intense molecular ion peak at m/e=329, the isotopic distribution pattern being typical of a monochlorinated product. The prominent peak at m/e=298 is likely a result of a loss of OCH_3 from the molecular ion. Another prominent peak

was found at m/e=180. Less intense peaks were observed at 223 (loss of C_6H_5CHO) and at 193 (loss of C_6H_5CHO and OCH_3). For comparison, the mass spectrum of the analyzed, normal product 41 was taken also. Again an intense molecular ion peak was observed at m/e=329. The fragmentation pattern was quite similar to that of the abnormal product except for the medium intense peak at m/e=177, which was practically absent in the abnormal isomer. A similar difference between normal and abnormal isomers was observed for the bromo derivatives discussed above. A detailed analysis of the mass spectra would probably show more differences still, however no such attempt was made.

Discussion of N.m.r. Data of Halonitro Sugars

In Table IV the nitro glycosides having a cis-fused 4,6-O-benzylidene group are listed together with their corresponding halogenated derivatives. It can be seen that the chemical shifts of the methine proton signals in the region of 4τ and of the methoxyl signals in the region of 6.5τ are not significantly different in the nonhalogenated and halogenated compounds in all those cases where single halo derivatives were formed. The observation holds for the compounds with β-anomeric configuration and in the α-series for 1 and its halo derivatives 26 and 27. Insignificant differences are still observed in the normal halo derivatives in those cases where two epimers were formed (compare 2 with 36 or 38, and 8 with 39 or 41). In the abnormal products, however, the methine proton signal experiences in all cases a small but distinct downfield shift, while the signal for the methoxyl group experiences an upfield shift. The consistency that is evident herein appears to permit the use of these chemical shifts for assignment of the C-3 configuration. Similarly, in the cases where an assignment of the H-1 signal was possible a comparison between nonhalogenated compounds and halogenated products revealed that this signal occurs slightly downfield in the normal products, while it is clearly upfield in the abnormal products. The H-4 signal of normal products is found upfield of that of abnormal products, but the latter differences are relatively small.

In Table V are compiled the n.m.r. data for the nitro

glycosides having a trans-fused 4,6-O-benzylidene group, together with those of their corresponding brominated derivatives. It can be seen that there is no significant difference between the brominated products and the corresponding nonbrominated precursors as far as the chemical shift of the anomeric methoxyl group is concerned. The chemical shift of the equatorial acetoxyl group is also the same in compounds 47 and 48. However, if the acetoxyl group is attached axially, its signal is shifted upfield in the brominated derivatives. Since the methine proton signals were to be used as an analytical indicator it is more important to notice the general downfield shift (8-12 Hz) for these signals in all the brominated products. Although this trend can only be stated in a definite manner for the O-acetyl derivatives that were isolated and identified, it is perhaps allowed to assume that the same trend pertains in the nonacetylated products present in the mixtures A and C. The correctness of this assumption is supported by another observation. It can be seen from Table V that there is no significant difference in the chemical shift of the methine protons between acetylated and nonacetylated nitro sugars of the same configuration. Thus it seems justified to assume a similar relationship for the acetylated and nonacetylated bromonitro derivatives. This would then allow to attribute, in mixture A, the methine proton signal at 4.23τ to compound 52 and that at 4.42τ to compound 51. By a similar argument one can attribute, in mixture C, the signal at 4.24τ to 57 and that at 4.42τ to 58. The latter assignment finds further support from the chemical shift

of the methoxyl group which is different for 57 and 58, the signals being qualitatively in the same ratio as the methine proton signals in mixture C. Table V further shows a strong downfield shift of the H-1 signal occurring on bromination of the β-glycosides 47 and 22. No such effect on the H-1 signal was found in the α-anomeric series (compare 23 and 56). The signals for H-2 are also shifted downfield in the bromo-nitro compounds 48 and 56 whereas in 49 this effect is negligible.

Comparison of the methine proton shifts of halogenated compounds with cis-fused and trans-fused benzylidene groups reveals yet another regularity. It was seen in Table IV that the methine proton signal experienced a downfield shift only in the abnormal halogenated products, while all compounds in Table V showed this effect. Inspection of molecular models showed that this effect was only operating in compounds where the halogen substituent at C-3 and one of the nonbonding electron orbitals of the oxygen attached to C-4 are parallel. A consideration of covalent and van der Waals radii suggests an interaction when the relationship between the halogen substituent and one of the electron orbitals of the oxygen is 1,3-diaxial or 1,3-diequatorial. As a hypothesis one can perhaps assume that this interaction causes some change in the trans-diaxial geometry between the methine proton and one of the electron orbitals of the nearby oxygen, and thus influences the shielding of the methine proton. An analogous observation was made in connection with brominated 2-acetamido sugars as discussed in Part III, Chapter D.

TABLE IV

N.m.r. data of halonitro sugars with cis-fused benzylidene group

Compound	$PhCHO_2$	OCH_3	H-1	H-2	H-3
1	4.41**	6.59	5.02(0)	5.02(0)***	
27	4.39	6.57	4.95(0)	5.21(0)	
26	4.39	6.57	4.95(0)	5.12(0)	
3	4.48	6.40	****		
33	4.50	6.43	5.48(8)	5.26(8)	5.45(0)
29	4.51	6.44			5.50(0)
32	4.51	6.51	5.42(8)	4.20(8)	5.32(0)
2	4.51	6.56	5.03(2)		5.27(0)
38	4.48	6.56	5.01(0)		5.38(0)
36	4.48	6.55	4.99(4)		5.22(0)
37*	4.30	6.64	5.08(4)		5.16(0)
8	4.43	6.66	4.99(1)		5.27(0)
41	4.42	6.64	4.92(4)		5.47(0)
42*	4.28	6.76	5.14(3)		5.32(0)
39	4.41	6.63	4.89(4)		5.33(0)
40*	4.28	6.78	5.21(3)		5.30(0)
9	4.46	6.51			
43	4.44	6.48	5.52(2,8)		5.56(0)
44	4.45	6.49	5.28(3,8)		5.43(0)

* Abnormal products.

** The chemical shifts are expressed in τ-values.

*** The numbers in brackets refer to coupling constants expressed in Hz.

**** Protons not accounted for in the table were present in the spectrum as could be seen from the integration, however, no definite chemical shifts could be assigned in these cases due to the complexity of the spectrum.

TABLE V

N.m.r. data of halonitro sugars with trans-fused benzylidene group*

Compound	$PhCHO_2$	OCH_3	$OOCCH_3$	H-1	H-2
47	4.47	6.52	7.95	5.52(8)	4.61(8,10)
48	4.39	6.51	7.93	5.37(8)	4.47(8)
22	4.33	6.50	7.89	5.48(0)	4.13(0,3.5)
49	4.21	6.49	7.95	4.96(0)	4.12(0)
23	4.33	6.61	7.94	5.26(1)	4.47(1,4)
56	4.21	6.61	8.00	5.28(0)	4.35(0)
11	4.43	6.53			
53	4.33	6.50		5.21(3,8)	
5	4.50	6.46			
7	4.32	6.44			
mixture A	4.23	6.44			
	4.42	6.44			
4	4.50	6.55			
6	4.35	6.61			
mixture C	4.24	6.61			
	4.43	6.65			

* Legend as for Table IV, see previous page.

Figure VII. - C.D. Curves of halonitro sugars with cis-fused benzylidene group

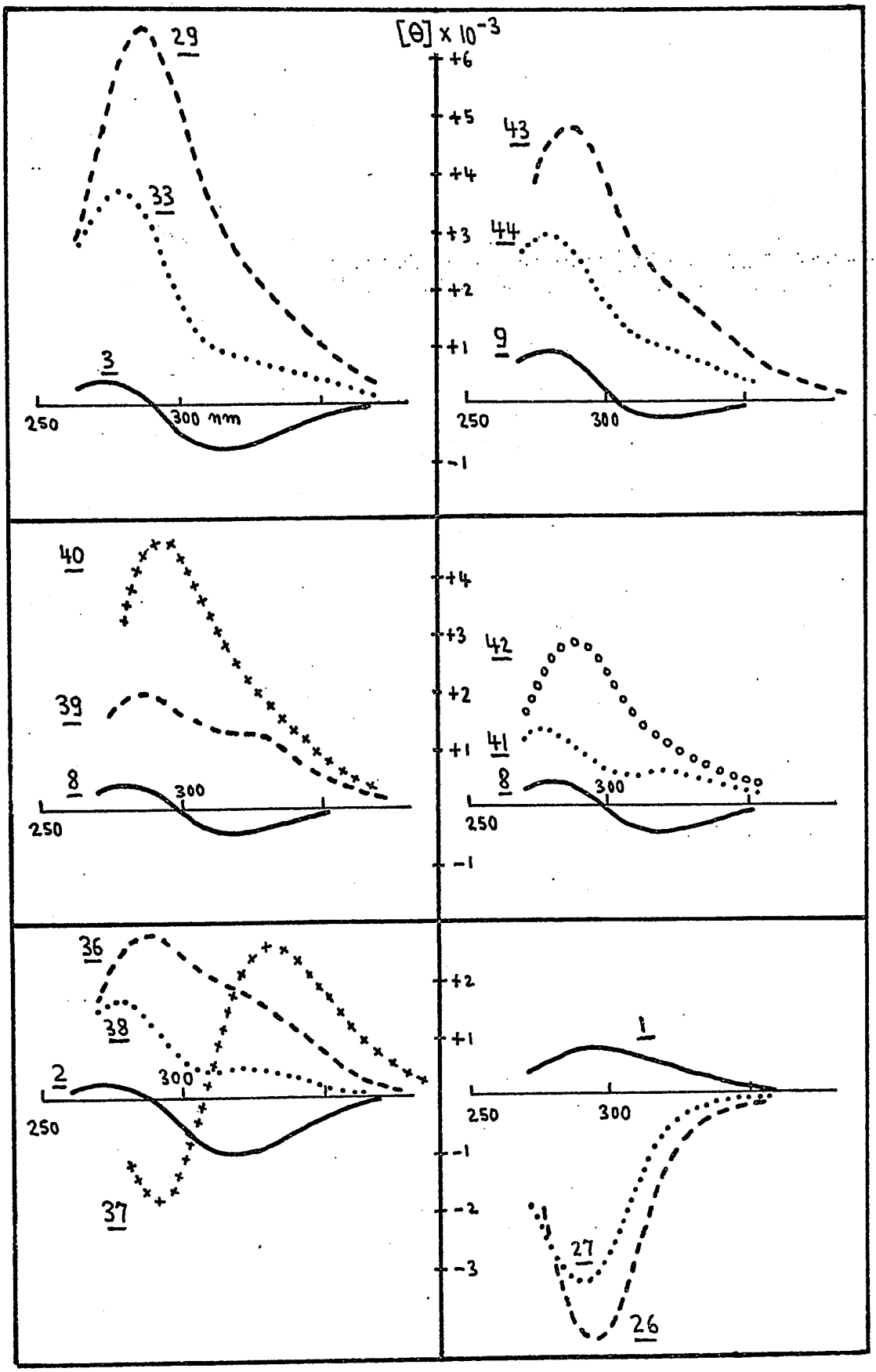
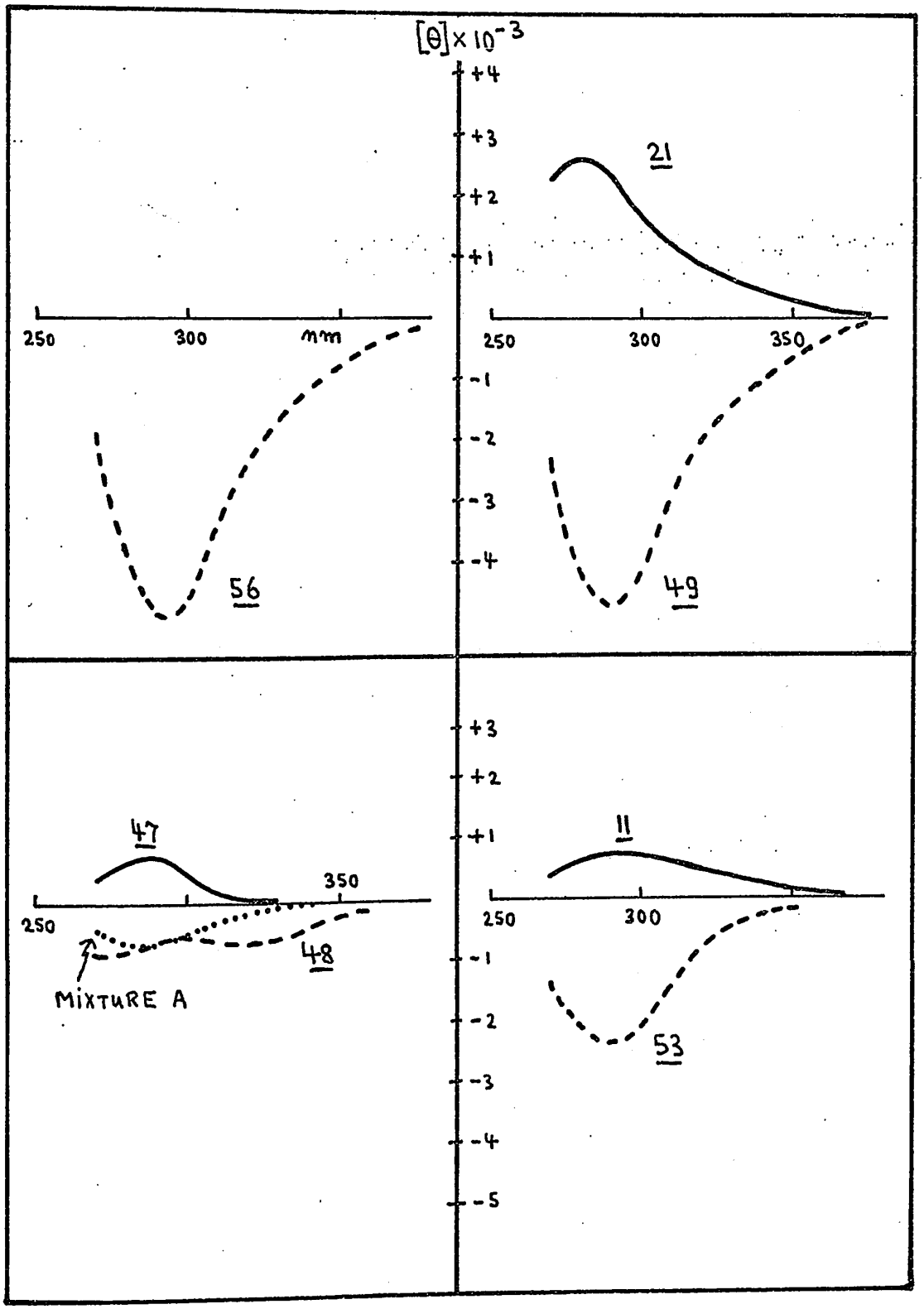


Figure VIII. - C.D. Curves of halonitro sugars with trans-fused benzylidene group



Circular Dichroism of Halonitro Sugars

As discussed in Part I, the interpretation of the dichroic behavior of nitro sugars is complicated by the rotameric mobility of the nitro group and furthermore, in some cases by possible conformational changes in the whole molecule. Because of all these variables no general rule has been derived as yet although certain trends have been noticed. Such trends were also observed in the dichroic behavior of halonitro sugars. In general, introduction of an α-halogen into the nonhalogenated precursors caused a drastic change in the dichroic behavior. To supplement these comparative studies it became necessary to include methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-D-hexopyranosides into the dichroic investigations.

It was found that the 2,3-dideoxy-3-nitro sugars with D-arabino configuration exhibit similar Cotton effects as the 3-deoxy-3-nitro-D-mannosides (see Part I), i.e. the dichroism is determined by the S configuration at C-4, giving rise to a positive Cotton effect. On the other hand, the isomers with D-lyxo configuration exhibited similar Cotton effects as 3-deoxy-3-nitro-D-galactosides (see Part I). In this latter case the dichroic behavior was not explicable by the absolute configurations of neighboring asymmetric centers.

According to the priority rules, introduction of an atom with higher atomic number than oxygen at C-3 causes a change in the absolute configurations of adjacent asymmetric centers.

In accord with this fact the Cotton effect of nitro sugars was reversed upon halogenation in all those cases where it was explicable by the absolute configurations at C-2 and C-4. However, the halogen substituent must have a more direct influence on the Cotton effect, since in general the magnitude of the maximal ellipticities were much larger for the halogenated compounds. Furthermore, as a general rule, the bromonitro derivatives showed more intense Cotton effects than the chloronitro derivatives, the sign being the same for the same configurations of either type of compound. Similar observations were made for α-halogenated ketones and resulted in the formulation of the axial haloketone rule (85). In this connection it was noted by Djerassi et al. (86) that the rotativity contribution of various atoms parallels their atomic refractivities. Thus it is believed that the halogen atoms in the examples investigated in this work have a direct influence on the Cotton effect rather than an indirect influence by altering the torsional angle of the nitro group, as suggested by Snatzke (43).

The c.d. curves of halonitro sugars with a cis-fused 4,6-O-benzilidene group are depicted in Figure VII, the ellipticities are compiled in Table X V, p.211.

In the halonitro derivatives with β-D-gulo configuration 29 and 33, and in the normal products with the α-D-gulo configuration 36 and 38 the absolute configuration at C-2 and C-4 is S and a positive Cotton effect is expected, which indeed was observed. The abnormal product with α-D-galacto configuration 37 has the same absolute configurations at C-2 and C-4 as 36

and 38 but exhibited (abnormally) a negative Cotton effect. In contrast, the abnormal products with α-D-lyxo configuration 40 and 42 showed positive Cotton effects like their normal epimers 39 and 41. This difference in the dichroism of the abnormal products cannot be explained readily as yet. The halonitro sugars with β-D-xylo configuration 43 and 44 possess the S configuration at C-4 and gave, as expected, positive Cotton effects. The halonitro D-idosides 26 and 27 exhibited a negative Cotton effect, which does not follow from a consideration of the absolute configurations at C-1, C-2 and C-4.

The c.d. curves of halonitro sugars with a trans-fused 4,6-O-benzylidene group are depicted in Figure VIII, and the ellipticities are compiled in Table X V.

The anomeric pair with D-altro configuration 49 and 56 possesses the R configuration at C-2 and C-4 and as expected, a negative Cotton effect was observed. The bromonitro sugar 53 showed also a negative Cotton effect as demanded by its R configuration at C-4. In compound 48 the contributions from the asymmetric centers at C-2 (S) and at C-4 (R) cancel each other and the C-1 configuration (R) should determine the Cotton effect. As expected, a small negative Cotton effect was observed.

Although no definite rule governing the Cotton effect of halonitro sugars could be deduced, similarities of c.d. curves for similar compounds were noticed.

PART III

SYNTHESIS AND REACTIONS OF NITROOLEFINS

D I S C U S S I O N

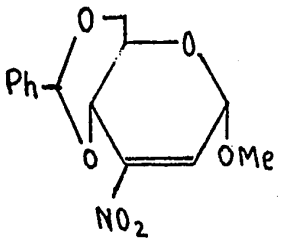
A. Synthesis of Nitroolefins

Nitroolefins are versatile intermediates in synthetic organic chemistry. Some of the more interesting aspects of their utility are due to the activating effect which the nitro group exerts on the carbon-carbon double bond. Many reactions which they undergo, such as aminations, alkoxylations, and additions of sulfur-containing nucleophiles, dienes, and 1,3-dipolar addends (12) are based on this effect. Part of the synthetic importance of a class of compounds rests, of course, on convenient availability. As already outlined in the Introduction, nitroolefinic sugars can be prepared conveniently by dehydroacetylation (Schmidt-Rutz reaction (18)) or, in certain cases, dehydration of partially blocked precursors (12).

Methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (1) and its β-anomer 2, which were required as starting materials for the present investigations, were prepared in excellent yields by the Schmidt-Rutz reaction as described in the literature (20, 19). Occasional difficulties were encountered in the preparation of the corresponding α- and β-D-*threo* isomers 3 and 4. When the published procedure for dehydration (19, 21) of the hydroxy precursor was applied, failure due to decomposition was sometimes experienced, especially in larger-scale runs. This was remedied by a minor change in the procedure which consisted of lowering the reaction temperature from 140° to steam bath temperature and in extending the

reaction time to 30 minutes. In this way the nitroolefins 3 and 4 were obtained in reproducible yields of over 80%. In the course of these investigations it was found, not unexpectedly, that the nitroolefin 3 which had previously been prepared by dehydration of methyl 4,6-O-benzylidene-3-deoxy-3 nitro-α-D-talopyranoside, can be made by the improved procedure from the α-D-galacto isomer also. The enantiomer of 4, namely, the β-L-threo nitroolefin 5, was synthesized for the first time.

3-O-Acetyl-5,6-dideoxy-1,2-isopropylidene-6-nitro-α-D-xylo-hex-5-enofuranose 6 (22) and β-nitrostyrene 7 (60) were required for the study of certain reactions, and they were prepared as directed in the literature.



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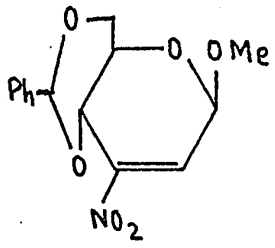

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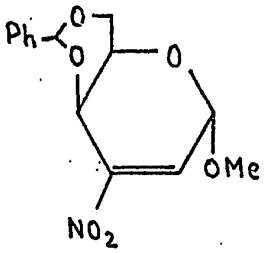

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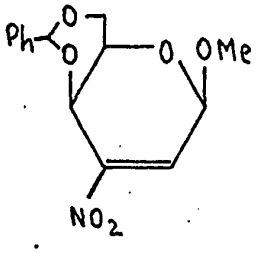

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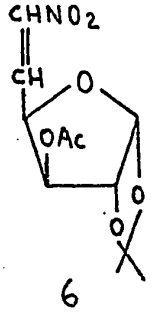

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B. Reduction of Nitroolefins

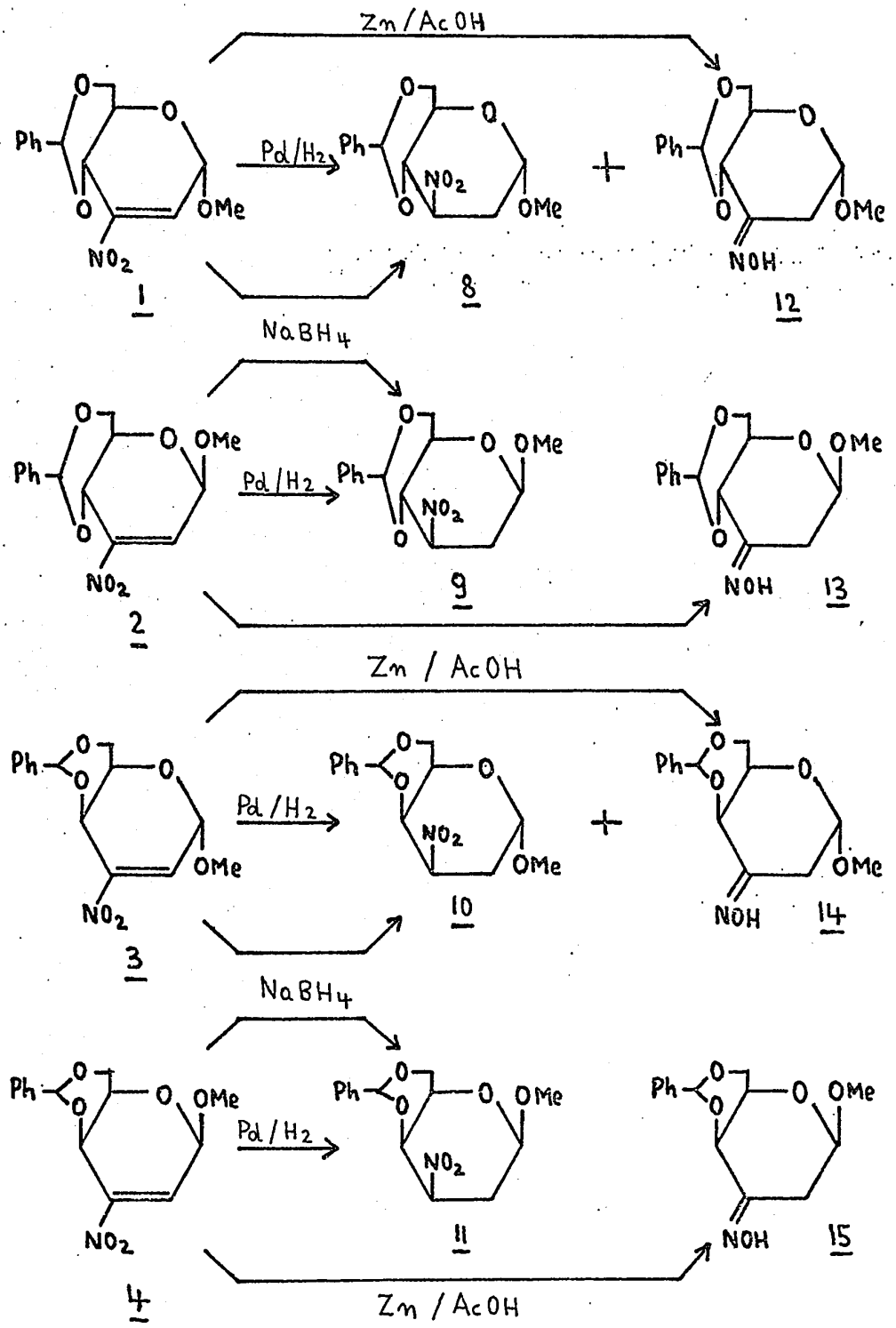
Catalytic reduction of the 2,3-unsaturated nitro sugars 1 - 4 with palladium on charcoal has led (19, 20) to two types of products, depending on the anomeric configuration. Thus, the β-glycosidic nitroolefins 2 and 4 gave smoothly and in yields of 60-90% the expected saturated nitro sugars 9 and 11. By contrast, the α-glycosidic nitroolefins 1 and 3 gave saturated derivatives (8 and 10) in lesser yields, with simultaneous formation of the oximino derivatives 12 and 14, respectively (20). Formation of the oximes was explained as a result of a retardation of the hydrogenation of the carbon-carbon double bond due to the steric requirement of the nearby axial methoxyl group. When such steric hindrance is operative, hydrogenation of the nitro group to the hydroxylamino stage becomes competitive. The hydroxylamino compound, being an enamine-type molecule, tautomerizes to the oxime before further reduction can occur. Because of these complications encountered in the conversion of 2,3-unsaturated α-glycosides into saturated nitro compounds, it was desirable to find more general, yet selective, reduction methods.

Reduction of nitroalkenes to nitroalkanes with sodium borohydride in ethanol is a well known method (61). When it was applied to the 2,3-dideoxy-3-nitro-hex-2-enopyranosides 1 - 4, the known saturated nitro sugars 8 - 11 were formed smoothly in excellent yields, quite independent of their anomeric configuration.

On the other hand, it was known that reduction of nitroalkenes with zinc and acetic acid gives rise to oximes (62).

When this method was applied to the 2,3-unsaturated nitro sugars 1 - 4, oximes were obtained in all cases in yields of 80-90% (Reaction Scheme J).

Reaction Scheme J



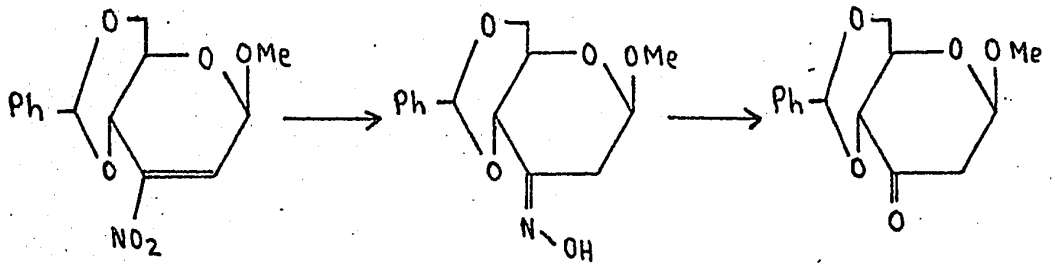
Two of the oximes, namely methyl 4,6-O-benzylidene-2,3-dideoxy-3-oximino-β-D-*erythro*-hexopyranoside (13) and methyl 4,6-O-benzylidene-2,3-dideoxy-3-oximino-β-D-*threo*-hexopyranoside (15) were hitherto unknown. They were characterized by elemental analysis and their spectral properties.

The i.r. spectrum of 13 showed broad absorption at 3360 cm^{-1} (hydroxyl) and a very weak band at 1660 cm^{-1} (C=N). Oxime 15 showed broad absorption at 3370 (hydroxyl) and a very weak band at 1650 (C=N). Neither spectrum showed peaks attributable to aliphatic nitro or amino groups.

The n.m.r. spectrum of oxime 13 in deuterochloroform (one drop of DMSO-d_6 was added because of poor solubility) showed a one-proton singlet for the oximino hydrogen at -0.49τ, which disappeared upon exchange with D_2O. Similarly, the oxime 15 showed a one-proton singlet at -0.70τ which was assigned to the oximino hydrogen and which disappeared upon exchange with D_2O. More detailed n.m.r. spectral data are recorded in Table VI. To further characterize the oximes 13 and 15, they were acetylated with acetic anhydride in pyridine. The corresponding acetoximino compounds 16 and 17 were obtained readily and in excellent yields. Both monoacetates gave correct elemental analyses and showed carbonyl absorptions at 1770 cm^{-1} but no hydroxyl absorption. The n.m.r. data are listed in Table VI.

It was considered to utilize the facile synthesis of oximino sugars from nitro sugars for the synthesis of oxo derivatives, as an alternative to oxo sugar synthesis by oxidative procedures (63). Oximino compounds have been deoximated with

levulinic acid in aqueous hydrochloric acid (64), and when this method was now applied to 12, the known (11) oxo sugar 18 was obtained in a yield of 77%. In a similar transoximation, the oxime 13 was converted quantitatively into the hitherto unknown methyl 4,6-O-benzylidene-2-deoxy-β-D-erythro-hexopyranosid-3-ulose 19. The compound exhibited i.r. absorption at 1725^{-1} corresponding to a keto carbonyl function, and the n.m.r. data (Table VI) were in accord with structure 19.



2 13 19

TABLE VI

N.m.r. data of oximes and derivatives thereof (τ-values)

Compound	Aromatic H	PhCH	OCH_3	Acetoximino	H-1	H-2	H-4
13 *	2.57	4.28	6.51		5.33(3,8)**	7.89(8,16)	5.61(9)
15 *	2.64	4.32	6.61				
16	2.55***	4.36	6.48	7.81	5.32(3,8)	7.6o(8,16)	5.52(9)
17	2.58***	4.38	6.46	7.85	5.71(0,10)	7.47(10,14)	5.39(0)
19	2.56***	4.41	6.46		5.22(4,8)		5.65(10)

* In DMSO-d_6.

** Coupling constants in Hz are given in parentheses.

*** Center of multiplet.

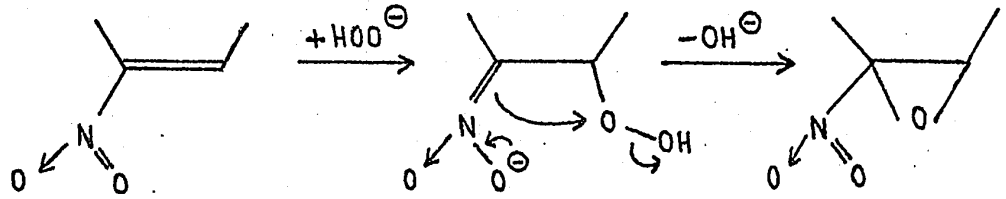
C. Alkaline Epoxidation of Nitroolefinic Sugar Derivatives

Recently Newman and Angier (66) reported the preparation of nitroepoxides by the action of alkaline hydrogen peroxide upon phenyl and cyclohexyl derivatives of nitroethylene. It was the first time that compounds containing this structural moiety were described. In our studies of the chemistry of carbohydrate nitroolefins we were prompted to synthesize α-nitroepoxy derivatives which, it was thought, hold much promise for a considerable range of synthetic purposes.

The methyl 4,6-O-benzylidene-2,3-didexy-3-nitro-hex-2-enopyranosides 1 - 4 all reacted smoothly, in ethanolic solution at room temperature, with aqueous, 30% hydrogen peroxide at pH 8-9. Crystalline methyl 2,3-anhydro-3-C-nitro-hexopyranosides were produced in yields at 75-90%. Epoxidation of the α- and β-D-erythro glycosides (1 and 2) and of the α-D-threo isomer (3) furnished single epoxides having the α-D-manno (20), β-D-allo (21) and α-D-talo (22) configurations, respectively. As no evidence for formation of the alternative diastereoisomers was uncovered, these reactions appeared to be highly stereoselective. A lesser degree of stereoselectivity was observed with the β-D-threo isomer (4) which gave a mixture from which the β-D-gulo (23) and the β-D-talo (24) products were isolated in a ratio of 5:1. In order to verify the differential behavior of 4, the same reaction was performed with its enatiomer (5), and the β-L-gulo (25) and β-L-talo (26) glycosides were obtained in a similar ratio of 6:1. Hence in all cases epoxidation occurred preferentially from the side of the ring opposite to

the glycosidic methoxyl group (Reaction Scheme K).

The mechanism of the epoxidation is believed to proceed by nucleophilic addition of the hydroperoxide anion at the β-carbon of the nitroolefin followed by intramolecular displacement of the hydroxide ion. A similar mechanism has been suggested for the epoxidation of β-unsaturated ketones (67).



Reaction Scheme K

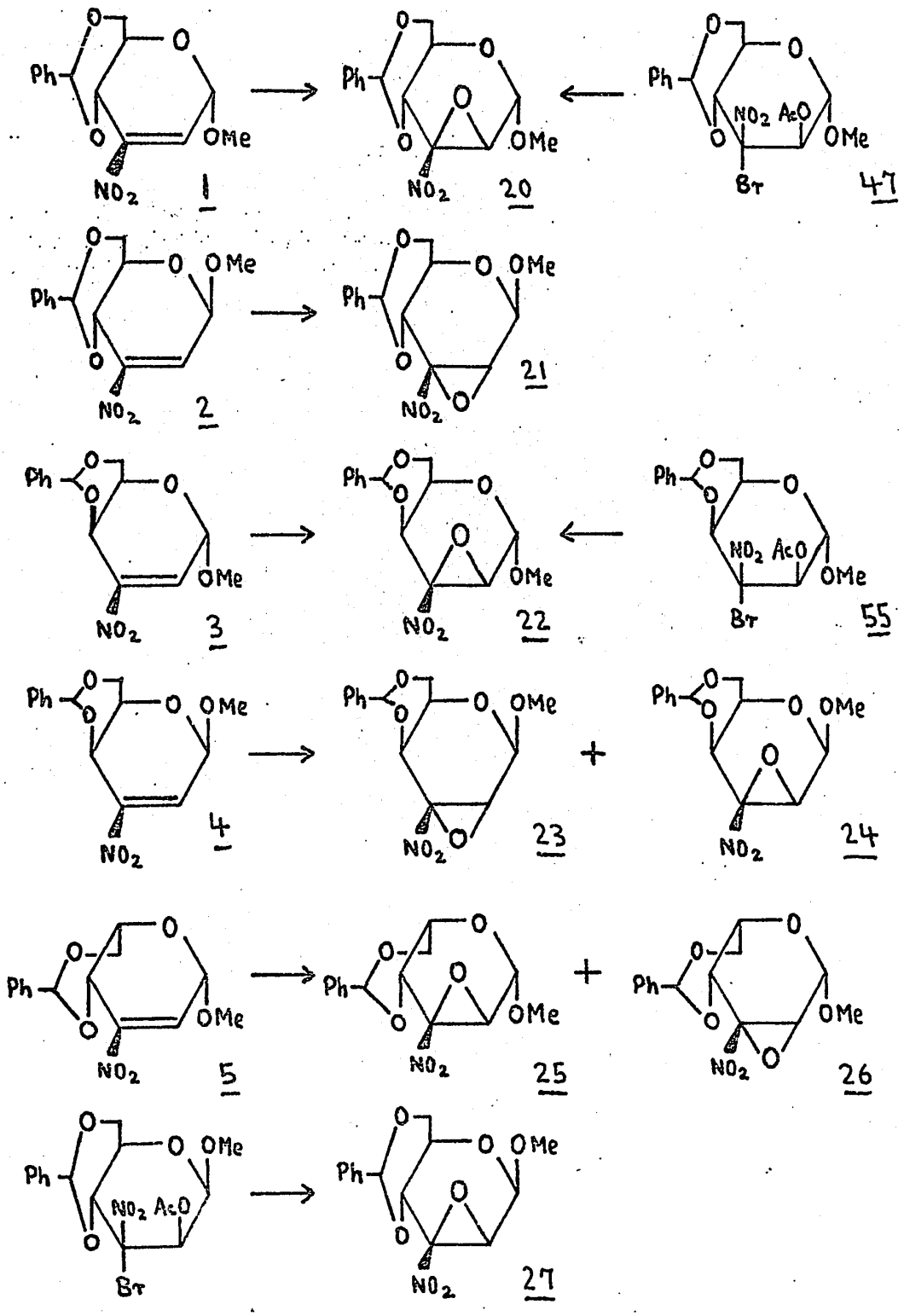
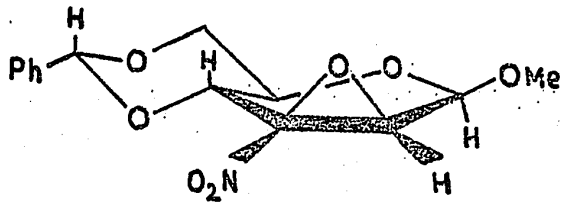


Figure IX. - Conformations of epoxynitro sugars



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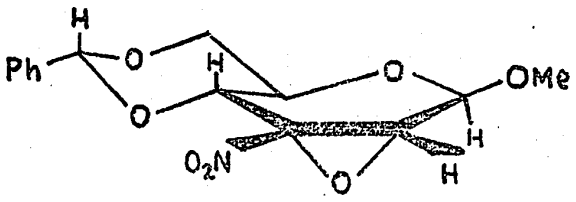

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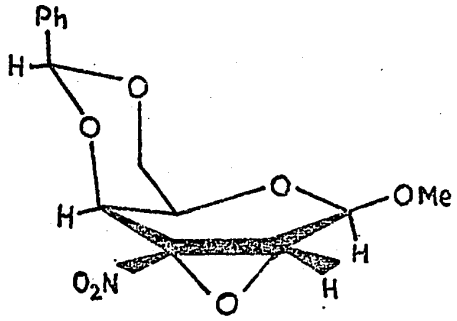

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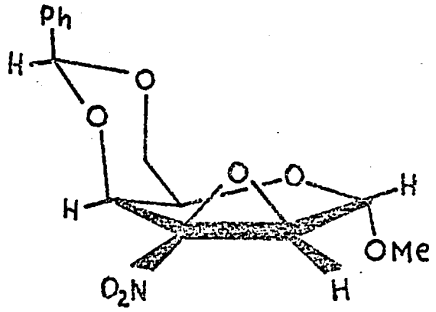


22

The structure of the stereoisomeric epoxides 20 - 26 was confirmed by elemental analysis and spectroscopy. Strong infrared bands at about 1560 cm^{-1} indicated the presence of the nitro group. N.m.r. spectra were obtained from all nitroepoxides except 24 and 26, which were insufficiently soluble. The chemical shifts of the various protons are given in Table VII. All spectra showed the presence of the benzylidene acetal group (aromatic 5-proton multiplet near 2.6τ and methine singlet near 4.3 - 4.4τ) and of the glycosidic methoxyl group (3-proton singlet at 6.42 - 6.46τ in β-anomers and at 6.55 - 6.56 in α-anomers). Integration of the remaining signals revealed the presence of six skeletal protons in each case, as required by the structure.

The configurations were assigned by means of n.m.r. data and circular dichroism curves (Figure IX). Since the configurations at C-1, C-4 and C-5 of each compound were defined by the configurations of the starting materials, it was necessary only to determine the steric dispositions of the epoxide oxygen atoms. Included in the following discussion is also the β-D-manno epoxide (27) which was mentioned in Part II, Chapter D (see compound 50, p. 74). It is recalled that bromonitro glycosides of the type from which 27 was formed are liable to incur epimerization at C-2. Consequently, the configuration of the epoxide could not be deduced with certainty from that of its bromonitro precursor; it was given as β-D-manno on the basis of the discussions that follow.

The nitroepoxides 21 and 27 which have identical

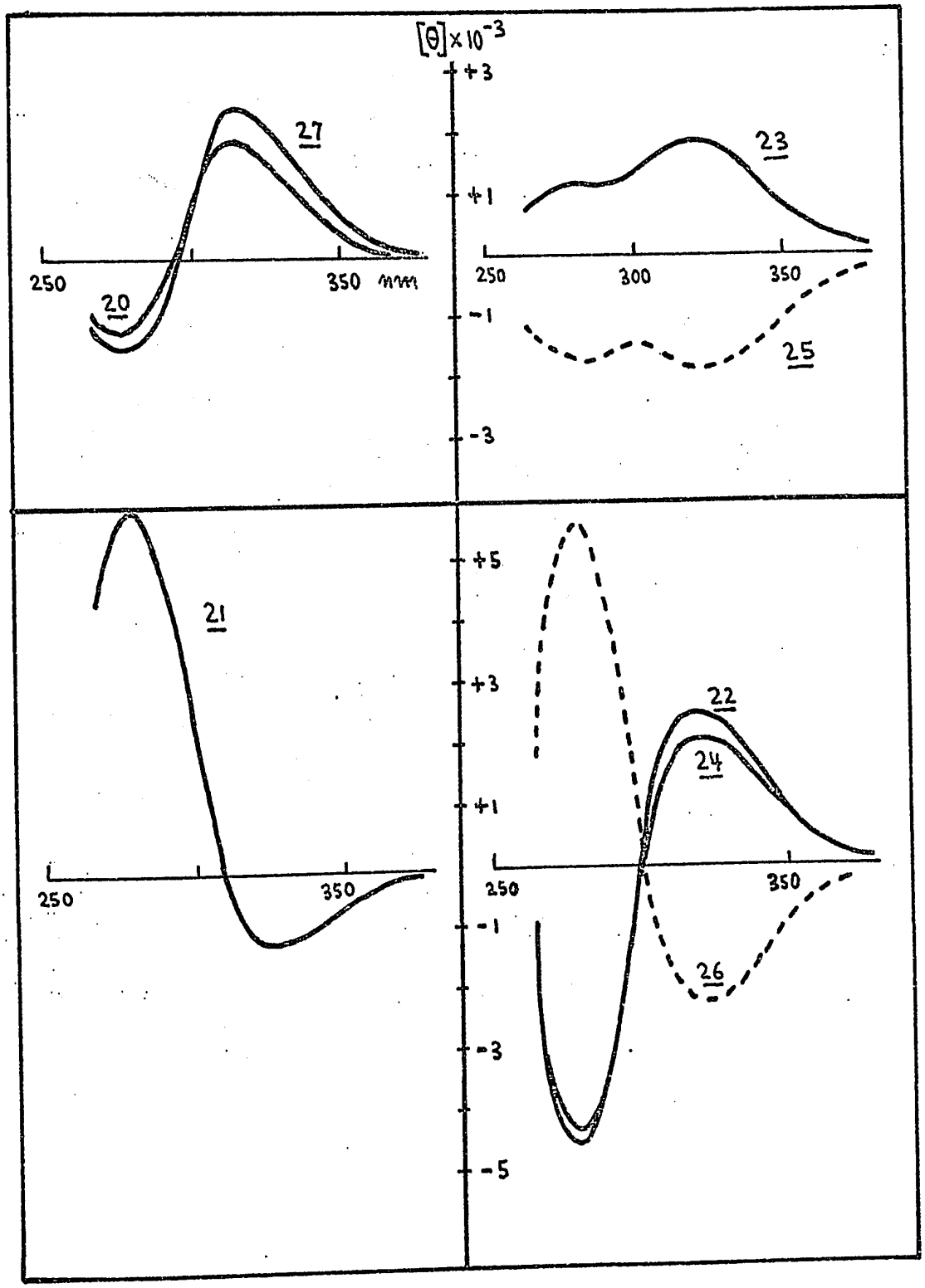
stereochemistry with respect to C-1, C-4 and C-5, evidently differ only in that they carry their epoxide rings on opposite sides. The stereochemical environment of the nitro chromophore is thereby made different, and as a result the compounds exhibit Cotton effects with opposite signs, even though they have the same anomeric configuration. Compound 20 (which on the basis of its origin could be the α-anomer of either 21 or 27) shows the same Cotton effect as 27 and consequently is assigned the same epoxide configuration. Further evidence was provided by the n.m.r. spectra. It has been pointed out (68, 69) that in 2,3-anhydro hexopyranosides (including 4,6-O-benzylidene derivatives) the anomeric proton shows no coupling with H-2 when these protons are trans-related, and that a small coupling is observed when they are cis-related. In 20 and 21 the H-1 signals were sharp singlets (100 MHz spectra at 250 Hz sweep width), whereas 27 gave an anomeric doublet with a splitting of 0.8 Hz. This is in agreement with the α-D-manno and β-D-allo configurations for 20 and 21, respectively, and with the β-D-manno configuration for 27. The reported coupling constants for trans relationships are $J_{1,2}$=0 Hz [methyl 2,3-anhydro-4,6-benzylidene-α-D-mannopyranoside (68) and methyl 4,6-di-O-acetyl-2,3-anhydro-α-D-mannopyranoside and its β-D-allo isomer (69)] while for cis relationships the values are $J_{1,2}$=2.5 Hz [methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (68)] and $J_{1,2}$=1.5 Hz [methyl 4,6-di-O-acetyl-2,3-anhydro-α-D-allopyranoside (69)] . The value found for 27 is somewhat smaller than had been anticipated from these references, but it is

to be noted that, in the half-chairs (Figure IX) which these compounds are assumed to occupy, the dihedral angle between 1,2-cis protons varies slightly, depending on whether the protons are situated on the upper side of the ring (as in the α-D-allo case) or on the lower side (as in the β-D-manno case). Moreover, the nitro group may well exert some influence on the magnitude of this coupling.

Among the epoxides with cis-fused benzylidene rings, 22 and 24 give virtually identical c.d.curves. For this reason 24, rather than 23, is thought to be the anomer of 22. The sign of the Cotton effect of 27 and 24 is the same as that of the anomeric pair 20 and 27 and the two pairs are therefore allocated identical configuration with respect to the epoxide ring. From the assignment of the α- and β-D-talo configurations to 22 and 24, respectively, follows that 23 must possess the β-D-gulo configuration. Although 23 shows an abnormal c.d. curve which is as yet unexplained, both 23 and 22 exhibit zero coupling of H-1 and H-2, conforming with trans arrangements of these protons. The enantiomerism of 23 and 25, and of 24 and 26, was borne out by physical constants (Table XVIII), identical i.r. spectra, mirror image c.d. curves, and (for 23 and 25) identical n.m.r. spectra.

Examination of the dichroic behavior of these nitro-epoxides suggests the general rule that the Cotton effect of the absorption band around 280 nm is positive when the oxirane ring is below, and negative when it is above, the plane of the molecule if the latter is depicted in the standard Haworth projection as shown in the Reaction Scheme K.

Figure X. - C.D. Curves of epoxynitro sugars



Inspection of TableVII reveals a number of noteworthy regularities in chemical shifts. Thus, in the compounds having a trans-fused benzylidene ring, the methine proton resonates at higher field when the epoxide ring is cis to it than when it is trans (4.44τ and 4.40τ vs. 4.28τ), and the same holds to a much stronger degree for H-4 (6.0τ and 5.88τ vs. 4.95τ). In the compounds having a cis-fused benzylidene ring the chemical shifts of the H-4 protons (5.10τ vs. 4.37τ) and of the methine protons (4.37τ vs. 4.33τ) follow the same trend. Ferrier and Prassad (69) have observed dependencies of H-4 shifts on the orientation of the 2,3-oxirane ring, but the effects they noted were much smaller than those in the nitroepoxides 20 - 27, and one has therefore to conclude that here the nitro group makes an important contribution. On the other hand, the chemical shifts of the H-2 protons differ little and the same applies to the H-5 protons. An exception is provided by 23 which gives an H-2 signal appreciably downfield, and an H-5 signal noticeably upfield, from the corresponding signals of the isomers. It is tempting to speculate that this is caused by the same stereochemical feature that gives rise to the anomalous c.d. curve. No doubt the preferred torsional angle of the nitro group, which presumably is governed by steric and/or dipolar effects originating chiefly from O-4 and O-2,3, is a determinant factor in both circular dichroism and proton magnetic resonance.

TABLE VII

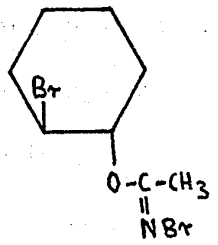
Chemical shifts (τ) of methyl 2,3-anhydro-4,6-O-benzylidene-3-nitrohexopyranosides

Compound	Configuration	$PhCHO_2$	H-1	H-2	H-4	H-5	H-6	H-6'	OCH_3
20	α-D-manno	4.44	5.15	6.29	6.0	6.23	5.71	6.0	6.55
21	β-D-allo	4.28	5.18	6.23	4.95	6.39	5.65	6.12	6.45
22	α-D-talo	4.33	4.91	6.29	4.37	6.24	5.63	5.76	6.56
23	β-D-gulo	4.37	5.21	5.74	5.10	6.59	5.67	5.94	6.46
27	β-D-manno	4.40	4.94	6.14	5.88	6.41	5.64	6.13	6.42

D. Reaction of N-Bromoacetamide with Nitroolefins

N-Bromoacetamide (NBA) is well-known as a brominating agent and was applied as such for syntheses of α-bromonitro sugars as discussed in Part II of this thesis.

Generally less familiar is the reaction of N-bromoamides with unsaturated hydrocarbons. According to a review by R.S. Neale (70), N-bromoamides fail to add to unsaturated bonds. An exception is the addition of NBA to cyclohexene or styrene on photolysis in carbon tetrachloride (71). Apparently disproportionation occurs to give N,N-dibromoacetamide which undergoes rapid addition to cyclohexene to produce compounds of structure 28 and 29. The trans-2-acetamido-cyclohexyl bromide 30 was isolated only as a by-product in a yield of 1%.



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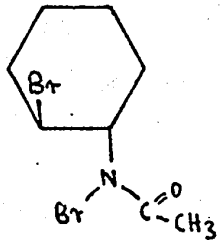

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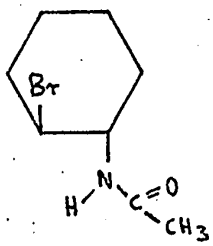
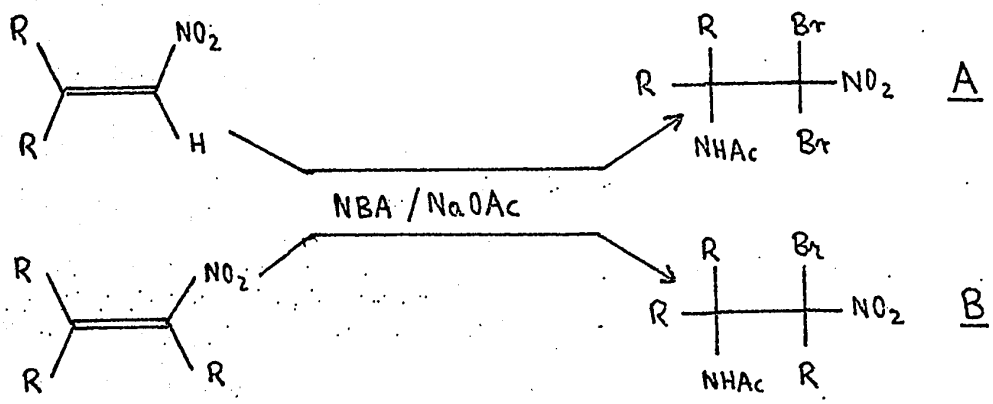


30

In the course of the present research it was observed that NBA reacts smoothly with nitroolefins in the presence of sodium acetate. Light is not required. All the nitroolefins so far investigated added NBA readily across the double bond to form α-bromonitro-β-acetamido products in high yields. If the reaction is performed on nitroolefins that possess an α-hydrogen atom, the latter is replaced by bromine during the reaction, and α,α-dibromo-β-acetamido products are formed.

The reaction can be presented schematically as follows:



As will be discussed later on, the presence of sodium acetate seems to be essential, but catalytic amounts only are needed. In the absence of sodium acetate no addition products of structure A or B have been observed. Depending upon the amount of sodium acetate used, various proportions of α-bromo-nitro-β-acetoxy compounds were isolated as by-products. Apparently they arise from competitive attack of acetate ion at the electrophilic β-carbon of the polarized carbon-carbon double bond.

The preparative importance of the NBA addition lies mainly in a high stereoselectivity. As will be outlined in subsequent sections, this feature has permitted the synthesis of various nitrogenous carbohydrates not readily accessible otherwise.

i) Reaction of NBA with β-nitrostyrene

When β-nitrostyrene (7), which was chosen as a model compound, was allowed to react with NBA in the presence of a catalytic amount of sodium acetate, crystalline 1,1-dibromo-1-nitro-2-acetamido-2-phenylethane (31) was obtained in a

yield of 88%. Unreacted starting material was recovered in a yield of 8%. The structure of 31 was supported by elemental analysis and spectral data. The i.r. spectrum of 31 showed bands (cm^{-1}) at 3310 (m, NH), at 1660 (s, amide I), at 1570 (s, NO_2), and at 1520 (s, amide II). The n.m.r. spectrum exhibited a 5-proton narrow multiplet at 2.64τ for the aromatic protons, a 1-proton doublet at 3.70τ with a splitting of 10 Hz for the benzylic proton and a 3-proton singlet at 7.97τ for the acetamido group. The doublet character of the signal at 3.70τ resulted from vicinal coupling with the amido proton, and when this proton was exchanged with D_2O the doublet collapsed to a singlet.

$$\phi\text{-}CH{=}CHNO_2 \xrightarrow[NaOAc]{NBA} \phi\text{-}\underset{\underset{NHAc}{|}}{CH}\text{-}CBr_2NO_2 \xrightarrow{NaBH_4} \phi\text{-}\underset{\underset{NHAc}{|}}{CH}\text{-}CH_2NO_2$$

7 31 32

The dibromonitro compound 31 was further characterized by its conversion into the known (72) 1-nitro-2-acetamido-2-phenylethane (32) by reductive removal of the bromine with sodium borohydride (Iffland method).

ii) Reaction of NBA with 3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-xylo-hex-5-enofuranose (6)

When nitroolefin 6 was allowed to react with NBA, a solid material consisting of three products was obtained (Reaction Scheme L, Route A). Column chromatography of the

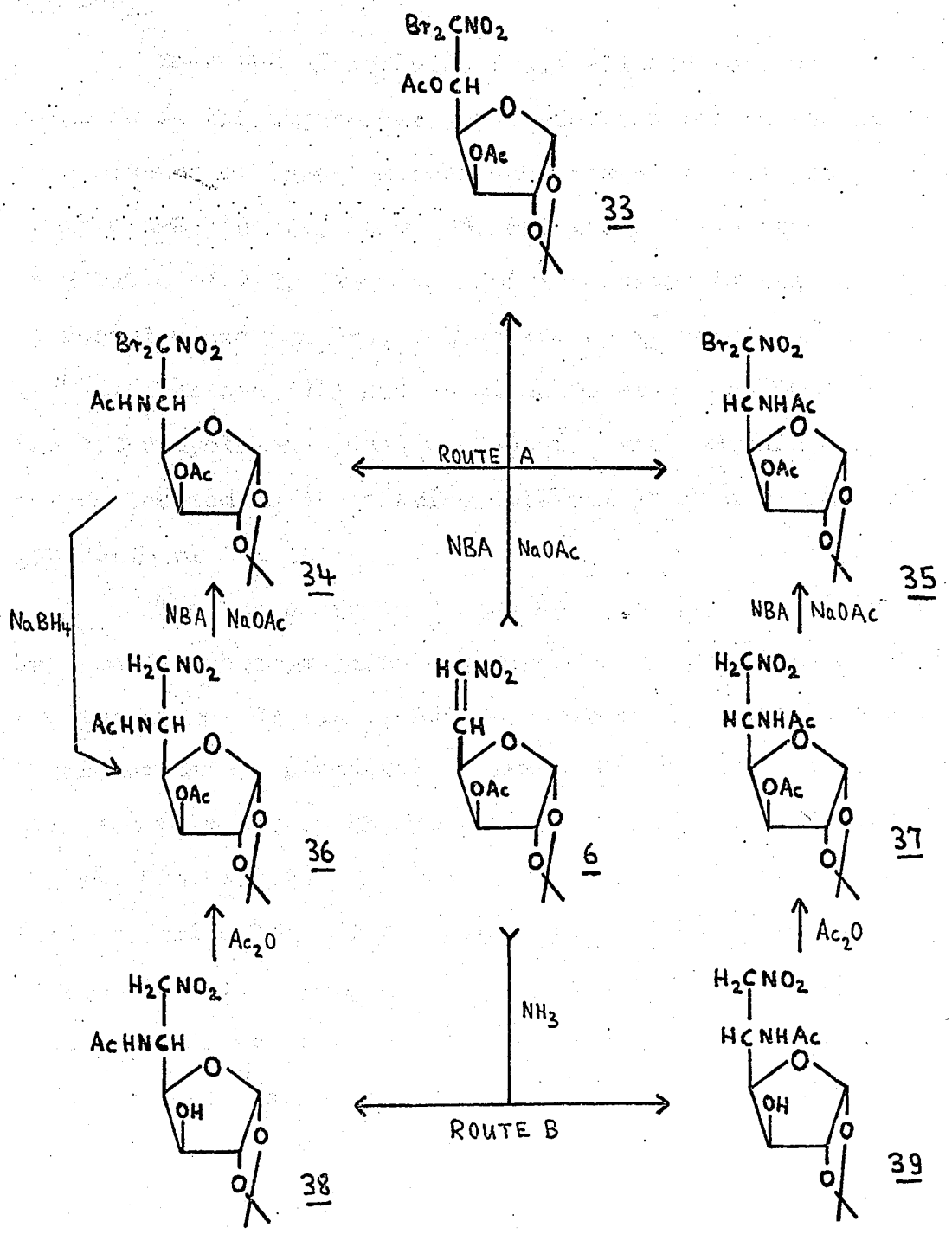
crude material afforded pure 3,5-di-O-acetyl-6,6-dibromo-5,6-dideoxy-1,2-O-isopropylidene-6-nitro- α-D-glucofuranose (33) as a by-product in a yield of 5%. The main fraction consisted of a mixture of 5-acetamido-3-O-acetyl-6,6-dibromo-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose (34) and the corresponding β-L-idofuranose isomer (35). From this mixture, pure 34 was crystallized in 77% yield, and repeated recrystallizations of the mother liquor material gave 35 in 9% yield. Based on optical rotation measurements the composition of the mixture was 81.5% of 34 and 15.5% of 35, and a similar ratio (80-85% of 34 and 15-20% of 35) was deduced by n.m.r. spectroscopy. The latter estimation was made possible by integration (at 250 Hz sweep width) of the H-5 signals—— a triplet at 4.45 τ for 34 and a doublet at 4.52 τ for 35.

The constitutions of the three reaction products were ascertained by spectroscopic data and, for 34 and 35 only, by elemental analysis. The i.r. spectrum of the α-D-gluco acetamido derivative 34 showed absorption bands (cm^{-1}) at 3370 (NH), at 1720 (s, O-acetyl), at 1685 (s, amide I), at 1580 (s, NO_2), and at 1520 (s, amide II). The β-L-ido isomer 35 exhibited absorption bands at 3275 (m, NH) at 1750 (s, O-acetyl), at 1670 (s, amide I), at 1580 (s, NO_2), and at 1525 (s, amide II). The di-O-acetyl compound 33 showed absorption bands at 1760 and 1740 (s, two O-acetyls) and at 1590 (s, NO_2). The n.m.r. spectra of all three products showed two 3-proton singlets between 8.54 and 8.75 τ corresponding to the methyl groups of the isopropylidene function, and two 3-proton singlets

between 7.87 and 8.03 τ caused by N-and/or 0-acetyl groups. More detailed n.m.r. data are given in Table VIII, p. 123.

Since no elemental analysis was obtained for the di-0-acetyl compound 33 a mass spectrum was recorded. The highest reliable peak appeared at m/e = 396, most likely resulting from a loss of one bromine atom, a hydrogen atom and a methyl group from the molecular ion (m/e = 491). A very strong peak with an isotopic pattern typical of a compound containing two bromine atoms was observed around m/e = 475, corresponding to a loss of a methyl from the molecular ion. For comparison, a mass spectrum of the acetamido compound 34 was recorded. Again there was a strong peak around m/e = 475 with an isotopic pattern of a dibromo compound. The highest reliable peak appeared at m/e = 395 corresponding to a loss of one bromine atom, a hydrogen atom and a methyl group from the molecular ion (m/e = 490). The fragmentation pattern was quite similar for the two analogs 33 and 34.

Reaction Scheme L



The acetamido compounds 34 and 35 were further characterized by an independent synthesis (Reaction Scheme L, Route B).

When the nitroolefin 6 was allowed to react with ammmonia in tetrahydrofuran, the addition led to the formation of a mixture of 5-acetamido-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose (38) and its β-L-ido isomer (39) in a ratio of 2:3. Ammonia addition evidently was followed by acetyl migration from O-3 to the newly formed amino group at C-5. Paulsen (23) made similar observations when he treated the 1,2-O-cyclohexylidene analog of 6 with ammonia and obtained the corresponding 5-acetamido derivatives in a D-gluco to L-ido ratio of 3 : 1.

The two products 38 and 39 were obtained in pure form by a column chromatographic separation of the mixture. The β-L-ido isomer 39 was isolated in crystalline form and was characterized by elemental analysis and spectral data. The i.r. spectrum showed absorption bands (cm^{-1}) at 3380 and 3340 (m, OH, NH), at 1665 (s, amide I), at 1545 (s, NO_2), and at 1510 (s, amide II). The n.m.r. spectrum showed the presence of the acetamido group (3-proton singlet at 8.06τ) and the isopropylidene ring (two 3-proton singlets at 8.57τ and 8.73τ). More detailed n.m.r. data are tabulated in Table VIII. The α-D-gluco isomer 38 failed to crystallize and no elemental analysis was obtained. However, comparison of the spectral data with those of the β-L-ido isomer allowed a definite structural assignment. The i.r. spectrum (neat film) showed

absorption bands (cm^{-1}) at 3300 (m, NH, OH), at 1655 (s, amide I), at 1550 (s, NO_2), and at 1530 (s, amide II). The n.m.r. spectrum exhibited signals for the acetamido group (3-proton singlet at 7.99τ) and the isopropylidene function (two 3-proton singlets at 8.58τ and 8.72τ). More detailed n.m.r. data are shown in Table VIII. The assignment of the α-D-gluco and β-L-ido configuration, respectively, rests mainly on a comparison of their optical rotations ($[\alpha]_D + 5.4^\circ$ and $[\alpha]_D -32.8^\circ$) with the rotations measured by Paulsen (23) for the cyclohexylidene analogs ($[\alpha]_D \pm 23.8^\circ$ and $[\alpha]_D -29.3^\circ$, respectively). A more positive rotation of the α-D-gluco isomers appears to be a general rule for this class of compounds (73), which was obeyed by all the derivatives encountered in this investigation. The configurational assignment was also supported from dichroic studies which will be revealed in a special section.

The two nitro sugars 38 and 39 were acetylated with acetic anhydride in ether and pyridine to afford in good yields crystalline 5-acetamido-3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose 36 and crystalline 5-acetamido-3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-β-L-idofuranose (37). The i.r. spectra of both isomers showed absorption bands (cm^{-1}) in the region of 3250-3300 (m, NH), at 1750 (s, O-acetyl), at 1660 (s, amide I), at 1555 (s, NO_2), and at 1545 (s, amide II). The n.m.r. spectra showed in addition to the signals for the acetamido group and the isopropylidene group a new 3-proton singlet for the O-acetyl group at 7.93τ in the gluco isomer

and at 7.94τ in the ido isomer. More n.m.r. data are compiled in Table VIII.

Treatment of the acetylated compounds 36 and 37 with NBA in the presence of sodium acetate furnished the same dibromonitro sugars that were obtained by the addition of NBA to the nitroolefin 6 (Route A). Thus, the gluco acetate gave 5-acetamido-3-O-acetyl-6,6-dibromo-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose 34 in a yield of 85%. In a smilar fashion the ido acetate gave the corresponding brominated ido isomer 35 in a yield of 91%. The physical and spectral data of the two products agreed with those observed for the same products obtained via Route A. The structure of the β-L-ido isomer was further supported by elemental analysis.

When compound 34 was treated with sodium borohydride according to Iffland, reductive debromination led to the formation of compound 36, another proof of their interrelationship.

Inspection of the n.m.r. data compiled in Table VIII reveals a number of noteworthy facts. In all isopropylidene furanosides encountered (33 - 39), the methyl protons of the isopropylidene group have similar chemical shifts, namely one 3-proton singlet resonates at 8.71-8.75τ, while the other 3-proton singlet resonates at 8.54-8.58τ. The coupling constant between H-1 and H-2 on the one hand, and between H-2 and H-3 on the other hand appears to assume also a constant value. Since in all derivatives H-1 and H-2 appeared as doublets with the same splitting of 3.5-4.0 Hz, the splitting between

H-2 and H-3 must be zero. Thus one has to assume a dihedral angle of 90° for H-2 and H-3. The regularity of the $J_{1,2}$- and $J_{2,3}$-splitting demands a great conformational rigidity of the furanoside ring. This rigidity is also revealed by the coupling constants between H-3 and H-4, which could be measured and were found to be constant for compounds 33-37. A total spectral analysis was possible for the brominated compounds 33-35, since in these cases the H-6 protons are replaced by bromine and hence cannot interfere with the other protons. In addition to the other assignments, values for the $J_{4,5}$-coupling constant were deduced which in the ido isomer are equal to zero and amount to 10 Hz in the gluco isomer. Thus the ido isomer can be distinguished from the gluco isomer by the value of the $J_{4,5}$-coupling constant.

TABLE VIII

N.m.r. data of 6-nitro sugars (τ-values)

Compd.	Config.	isopropylidene	acetamido	O-acetyl	H-1	H-2	H-3	H-4	H-5
33	gluco	8.74/8.54		7.91/7.87	4.19(4)*	5.62(0)	4.69(3)	5.50(9)	3.87
34	gluco **	8.75/8.55	8.03	7.92	4.20(4)	5.64(0)	4.62(3)	5.53(10)	4.45
35	ido	8.71/8.54	7.99	7.97	4.07(4)	5.55(0)	4.68(3)	5.42(0)	4.52
36	gluco	8.73/8.55	8.08	7.93	4.10(4)	5.51(0)	4.66(3)		
37	ido	8.72/8.54	8.02	7.94	4.08(4)	5.49(0)	4.71(3)		
38	gluco	8.72/8.58	7.99		4.09(4)	5.45(0)			
39	ido **	8.73/8.57	8.06		4.10(4)	5.52(0)			

* Coupling constants in Hz are given in parentheses.

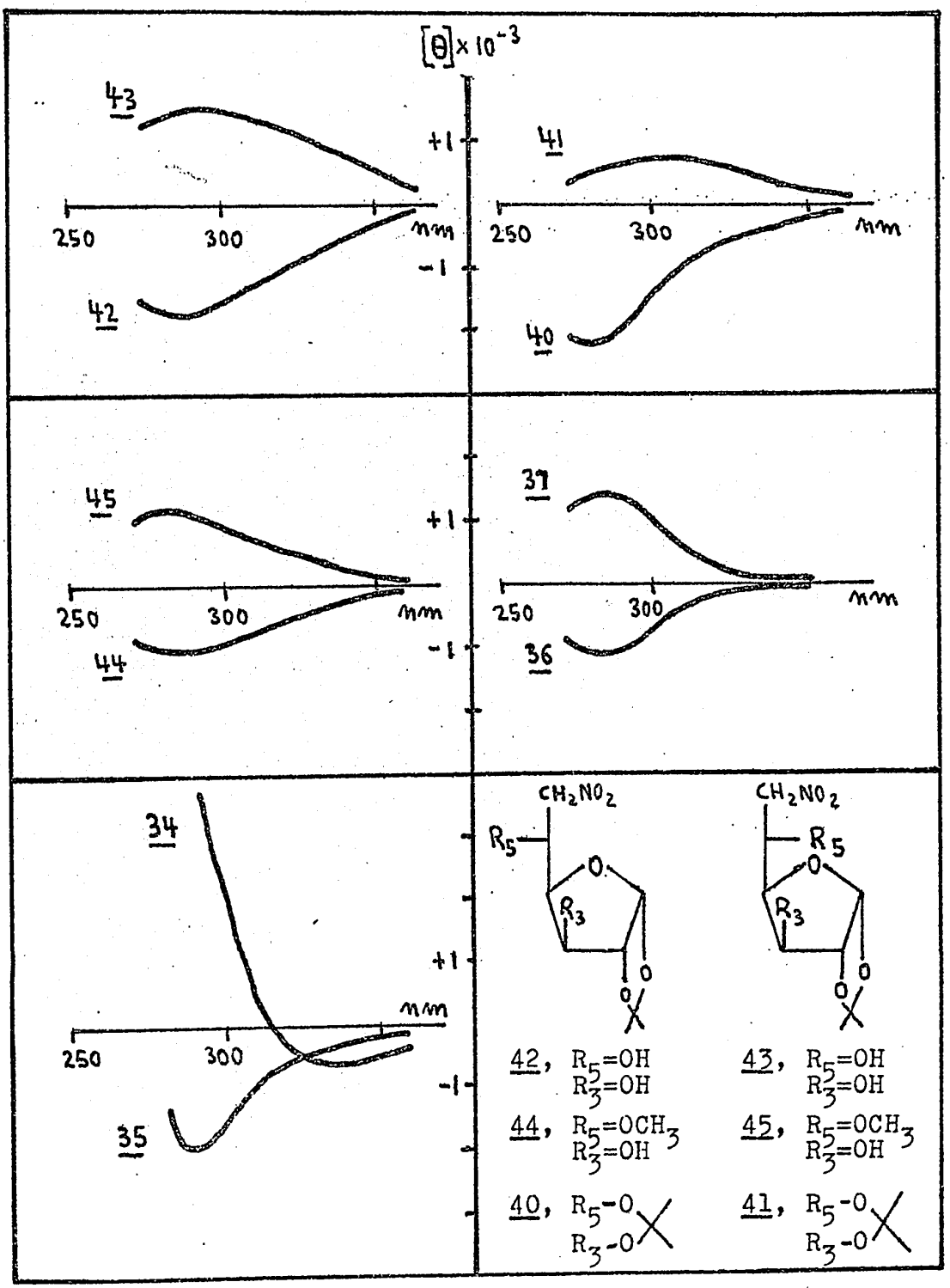
** In $CDCl_3$/DMSO-d_6, otherwise in $CDCl_3$.

Circular Dichroism of 6-Deoxy-6-nitro-hexofuranoses

In connection with the studies involving the addition of NBA and of ammonia to the 5,6-nitroolefin (6), C-5 epimeric pairs were isolated and the configurational assignment was based on comparing the optical rotation of the pair of epimers, the compounds with the D-gluco configuration (absolute configuration at C-5: R) having in each case the higher dextrorotation. As assignment of configuration at C-5 required the availability of both epimers, it was thought desirable to have a method at hand which would allow the direct configurational assignment of single epimers.

As mentioned before, Satoh and coworkers (44) studied the optical rotatory dispersion (o.r.d.) and the dichroic behavior of some epimeric pairs of acyclic C-nitro polyols. They found that the Cotton effect in these types of compounds depended solely on the absolute configuration of the carbon adjacent to the nitromethyl group. As a rule, 1-nitro-1-deoxy polyols having the R configuration at C-2 showed a negative Cotton effect, while those having the S configuration showed a positive Cotton effect. Similar observations were made with 6-nitro-6-deoxy hexofuranoses as discussed below. The c.d. curves are depicted in Figure XI on the next page, while the ellipticity values are compiled in Table XIX, p. 223.

Figure XI. - C.D. Curves of 6-nitro sugars



When the dichroic behavior of the epimeric pair of 5-deoxy-5-acetamido-6-deoxy-6-nitro hexofuranoses 36 and 37 was studied it was found that the isomer with the D-gluco configuration 36 (R configuration at C-5) showed a negative Cotton effect, while the isomer with the L-ido configuration 37 (S configuration at C-5) showed a positive Cotton effect. Substitution of the hydrogen atoms at C-6 by bromine reverses the absolute configuration at C-5 (because the "weights" of C-4 and C-6 according to the priority rules are interchanged) and the sign of the Cotton effect was reversed accordingly. Thus the epimer with D-gluco configuration 34 (S configuration at C-5) now showed a positive Cotton effect, while the epimer with L-ido configuration 35 (R configuration at C-5) showed a negative Cotton effect. Encouraged by these observations, the following known pairs of epimers were synthesized according to procedures given in the literature (73, 74) :

6-deoxy-1,2:3,5-di-0-isopropylidene-6-nitro-α-D-glucofuranose (40),

6-deoxy-1,2:3,5-di-0-isopropylidene-6-nitro-β-L-idofuranose (41),

6-deoxy-1,2-0-isopropylidene-6-nitro-α-D-glucofuranose (42),

6-deoxy-1,2-0-isopropylidene-6-nitro-β-L-idofuranose (43)[4],

6-deoxy-1,2-0-isopropylidene-5-0-methyl-6-nitro-α-D-glucofuranose (44)

6-deoxy-1,2-0-isopropylidene-5-0-methyl-6-nitro-β-L-idofuranose (45)

---

4. This known (74) compound was prepared by a selective cleavage of the 3,5-0-isopropylidene group of compound 41 with 80% acetic acid.

The dichroic behavior of these additional pairs of epimers was as expected in all cases, so that it appears that the following rules hold generally:

1. 6-Nitro-hexofuranoses which have at C-5 the R configuration show a negative Cotton effect, while those having the S configuration show a positive Cotton effect.
2. The sign of the Cotton effect is not affected by the nature of the C-5 substituent; replacement of the hydroxyl group by a methoxyl group, an acetamido group, or even involvement of the C-5 oxygen in a ketal ring does not change the dichroic behavior of a given epimer qualitatively, although quantitative changes are noticeable.

Since only one epimeric pair of 6,6 -dibromo-6-deoxy-6-nitro hexofuranoses was examined the rules cannot be applied with certainty in these cases, however they still seem to hold since the isomer having the absolute configuration R at C-5 showed a negative Cotton effect while the isomer with the S configuration showed a positive Cotton effect.

iii) Reaction of NBA with Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-D-hex-2-enopyranosides

As was seen in the preceding section, the addition reaction of NBA to carbohydrate nitroolefins may proceed with a certain degree of stereoselectivity. An even greater degree of selectivity than with compound 6 was found to exist when the nitroalkene moiety is incorporated in, rather than attached to, the glycoside ring. When 2,3-unsaturated nitro glycosides were allowed to react with NBA the stereochemistry was governed by their anomeric configuration. Single acetamido adducts were obtained (with one exception), and in each adduct the 2-acetamido group assumed an orientation trans to the glycosidic methoxyl group, i.e., in β-glycosides it was placed equatorially, and in α-glycosides, axially.

The configuration of the bromonitro function at C-3 could not be determined rigorously; however, it is tentatively assumed that the nitro group, in general, resides in the equatorial position. This assumption is supported by n.m.r. and c.d. data which are discussed in special sections on p. 148 and 152.

The nomenclature of the 3-bromo-3-deoxy-3-nitro derivatives follows the principle employed in Part II of this thesis, i.e., the bromine atom is regarded as the equivalent of the hydroxyl group on C-3 of the parent sugar.

The i.r. spectral data of all new compounds diseussed in this chapter are compiled in Table IX. The n.m.r. spectral data are listed in Tables X-XII.

TABLE IX

Infrared frequencies (cm^{-1}) in Nujol

Compound	OH/NH	Ester-C=O	Amide I	Amide II	NO_2
46	3260m,b		1660s,b	1530m,b	1560s
47		1760s			1570s
48	3300m,b		1665s,b	1540s,b	1550s
50	3520,3470,3300		1640s,b	1540s,b	
51	3300s	1745s	1640s,b	1545s,b	
52	3300m,b	1745s	1665s	1535s	1560s
54	3460m		1705s	1500s	1570s
55		1760s			1565s
56	3450m		1695s	1510s	1560s
57	3400,3200s,b		1655s	1540s,b	1560s
58	3400,3300s,b		1640s,b	1550,1510s,b	
61	3300w,b		1645s	1545m,b	1560s
62		1755s			1570s
63	3280s		1650s	1545	1545
64	3320w,b		1670s	1525s,b	1565s
65	3320w,b		1670s	1540m,b	1570s
66	3300s		1655s	1545	1545

Designations: b=broad; m=medium; s=strong; w=weak.

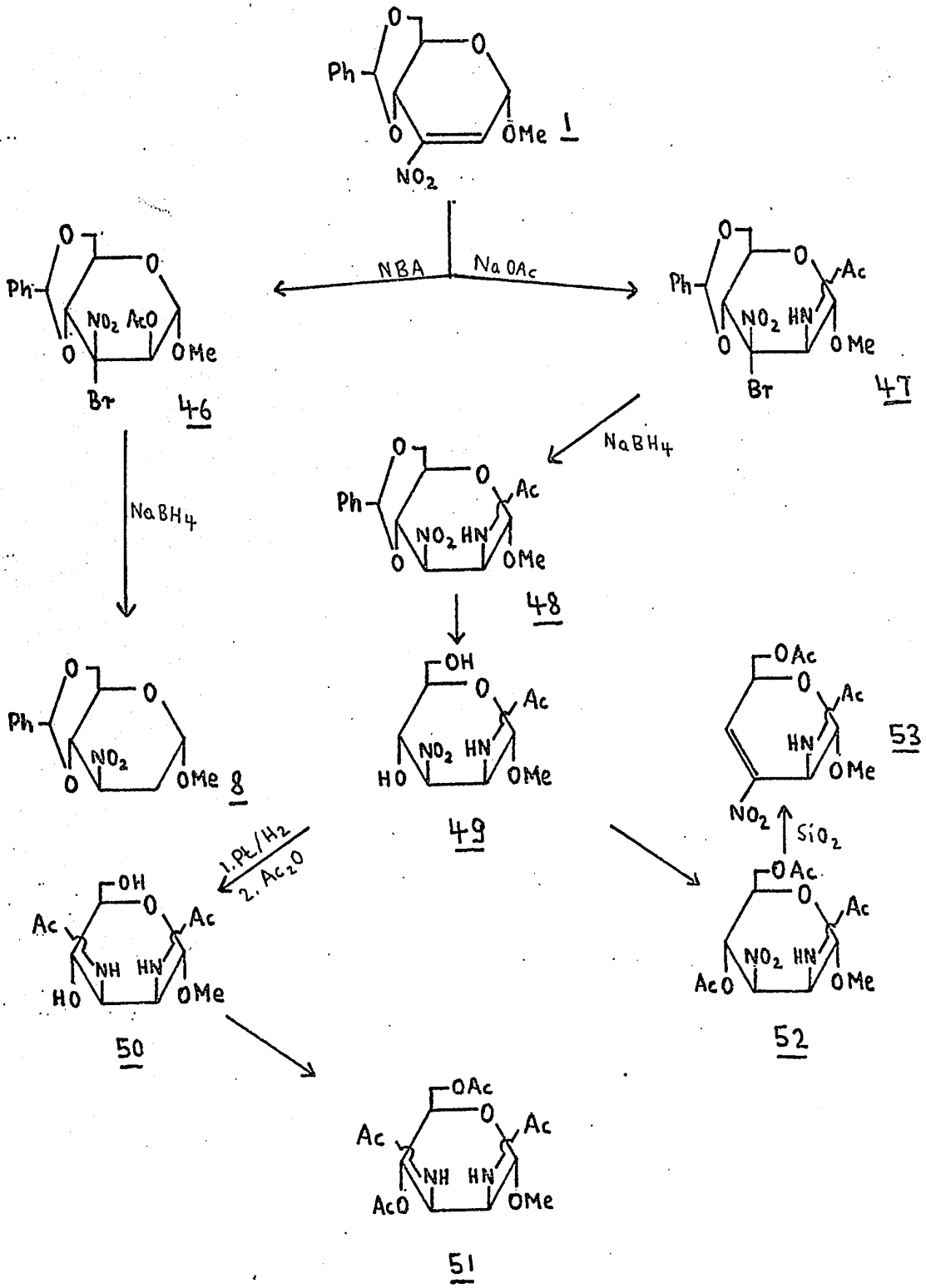
Derivatives of 2,3-Diamino-2,3-dideoxy-mannose

When methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-erythro-hex-2-enopyranoside (1) was treated with NBA in the presence of excess sodium acetate, a mixture of two products was obtained. Separation by column chromatography afforded methyl 2-acetamido-4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-α-D-altropyranoside (46) and its 2-O-acetyl analog (47) in a ratio of 2:1. The i.r. spectrum of the fast-moving material, obtained from the chromatographic separation, was superimposable on that of a sample isolated previously in a bromination reaction (Part II, Chapter D, compound 56) and thus proved the formation of 47. However, in an attempt to recrystallize some of the crude 47 from hot ethyl acetate it was reconverted into the starting nitroolefin 1. The ease of nitroolefin formation was also indicated by the ready formation of the 2,3-dideoxy-3-nitro glycoside 8 upon treatment of crude 47 with sodium borohydride. Compound 46 was characterized by elemental analysis and its spectral properties.

When the addition of NBA to nitroolefin 1 was catalyzed by a small amount of sodium acetate only, the amount of the 2-O-acetyl derivative 47 formed was diminished and the 2-acetamido compound 46 was obtained in a yield of 75%. The addition reaction gave the same result when it was performed in the dark, which proved that it is not a photochemical reaction. A radical mechanism therefore is unlikely. In the absence of sodium acetate compound 46 was not formed, and this fact clearly demonstrated the catalytic effect of the salt.

For a rigorous assignment of its configuration at C-2 compound 46 was converted into a compound of known configuration by a series of stereochemically unambiguous reactions (Reaction Scheme M).

Reaction Scheme M



First, reductive removal of the bromine atom by the Iffland method furnished methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-mannopyranoside (48). Compound 48 was obtained in a yield of 91% and by its physical and spectral properties proved to be identical with a product referred to as "by-product VI" by Baer and Rajabalee (28). These workers had obtained that compound in an amination of 1 and tentatively assumed the manno configuration without providing rigorous proof. To provide such proof, compound 48 was debenzylidenated with trifluoroacetic acid to yield methyl 2-acetamido-2,3-dideoxy-3-nitro-α-D-mannopyranoside (49). Although t.l.c. indicated the formation of a uniform product, it did not crystallize and was therefore characterized as its crystalline 4,6-diacetate (52) which was obtained by boron trifluoride-catalyzed acetylation.

Catalytic hydrogenation of compound 49 in 0.1 N hydrochloric acid followed by an N-acetylation furnished crystalline methyl 2,3-diacetamido-2,3-dideoxy-α-D-mannopyranoside (50). Peracetylation of 50 with acetic anhydride in pyridine gave known (75) methyl 2,3-diacetamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-mannopyranoside (51).

Since the reactions leading from 46 via 48, 49, and 50 to 51 did not involve C-2, the identification of 51 afforded proof for the C-2 configuration of the compounds in this series. Furthermore, C-3 was not involved in the conversions starting with 48, and consequently 48 and the products derived from it must possess the α-D-manno configuration. The chemical

proof was corroborated by n.m.r. data (Table X). Thus, in compounds 46, 48 and 52 the coupling constant $J_{1,2}$ was zero, affirming diequatorial arrangement of H-1 and H-2. The coupling constant $J_{2,3}$ was small also (zero in 52, and 4 Hz in 48), in accord with the assigned dispositions of H-2 and H-3. Furthermore, large coupling constants $J_{3,4}$ and $J_{4,5}$ (10 Hz) were found in compounds 51 and 52, as is expected for trans-diaxial arrangements of the protons at C-3, C-4 and C-5.

In summary, it may be stated that the NBA reaction has provided an easy and extremely stereoselective access to derivatives of methyl 2,3-diamino-2,3-dideoxy-α-D-mannopyranoside. In the addition of ammonia to 1, which was previously investigated (28), analogous products were obtained but a strong preference for the D-gluco configuration was observed. The two methods therefore complement each other very well.

Another benefit accrued from these studies. When compound 52 was refluxed in chloroform in the presence of silica gel it underwent dehydroacetylation to afford methyl 2-acetamido-6-O-acetyl-2,3,4-trideoxy-3-nitro-α-D-threo-hex-3-enopyranoside (53), the first Δ^3 -unsaturated derivative prepared in this series. Compound 53 was also obtained from methyl 2-acetamido-2,3-dideoxy-3-nitro-α-D-talopyranoside (57) and was characterized in that connection. As will be discussed later (p.140), the interrelation thereby established between two series of diamino sugars played a key role in the

configurational proof for α-D-talo derivatives. Moreover, it may be anticipated that 53 can serve as an intermediate for the synthesis of 2,3,4-triamino hexoses.

TABLE X

N.m.r. data of diaminomannose derivatives (τ-values)

Compound	PhCH	OCH_3	2-Ac	3-Ac	4-Ac	6-Ac	H-1	H-2	H-3	H-4
47	4.21	6.61	8.00				5.28(0)*	4.35(0)		
46	4.21	6.64	8.04				5.33(0)	4.69(0)		
	4.19**	6.68	8.19				5.30(0)	4.96(0)		5.19(8)
48	4.36	6.61	8.01				5.32(0)			
	4.32**	6.66	8.15				5.34(0)	4.94(4)		
52		6.60	8.02		7.91	7.98	5.31(0)	4.95(0)	4.95(10)	4.35(10)
51		6.63	8.00	8.13	7.96	7.96				5.14(10,10)

* Coupling constants in Hz are given in parentheses.

** In DMSO-d_6.

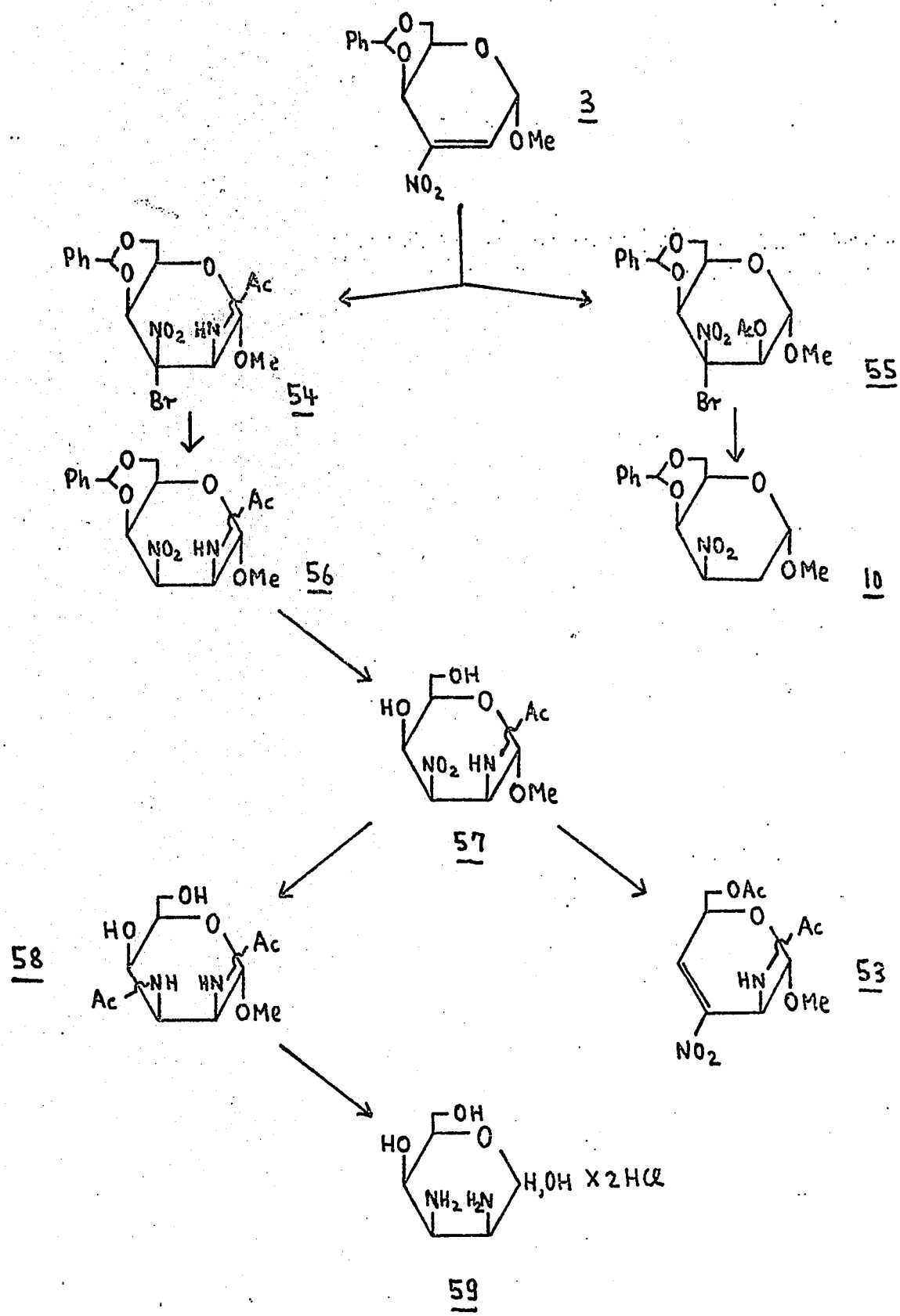
Derivatives of 2,3-Diamino-2,3-dideoxy-talose

Addition of NBA to methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-threo-hex-2-enopyranoside (3) gave a mixture of methyl 2-acetamido-4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-α-D-idopyranoside (54) and methyl 2-O-acetyl-4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-α-D-idopyranoside (55). By chromatographic separation compound 54 was isolated in a yield of 83%, while compound 55 was obtained in a yield of 15% (Reaction Scheme N). The structures of both compounds were ascertained by elemental analysis and their spectral properties. The n.m.r. data of 55 and 54 and its derivatives are listed in Table XI.

Reduction of the O-acetyl derivative 55 with sodium borohydride (Iffland method) led to formation of the known methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-lyxo-hexopyranoside (10). Since the same product was obtained (p. 97) in the reduction of the nitroolefin 3 with sodium borohydride, it may well be that 55, in reversal of its formation, reacts to give 3 which is then reduced to 10.

Reductive removal of the bromine from compound 54 produced methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-talopyranoside (56) in a yield of 84%. An ultraviolet spectrum of a 10^{-4} molar solution of 56 in 0.01 N alcoholic potassium hydroxide showed high-intensity absorption (ϵ, 21 200) at a wavelength of 250nm, indicating the D-talo configuration for compound 56 (see Part II, Chapter A).

Reaction Scheme N



Debenzylidenation of 56 with trifluoroacetic acid afforded crystalline methyl 2-acetamido-2,3-dideoxy-3-nitro-α-D-talopyranoside 57.

Catalytic hydrogenation with platinum in the presence of acetic anhydride (36) converted 57 into methyl 2,3-diacetamido-2,3-dideoxy-α-D-talopyranoside (58) in a yield of 69%.

The diacetamido glycoside 58 was hydrolyzed with refluxing half-concentrated hydrochloric acid. Work-up and decolorization with charcoal gave a colorless, hygroscopic syrup which resisted all attempts at crystallization. The syrup strongly reduced Fehling solution and its n.m.r. spectrum in D_2O showed neither methoxyl nor acetamido signals. Therefore the syrup presumably consisted of the expected 2,3-diamino-2,3-dideoxy-D-talose dihydrochloride (59).

N-Acetylation of the presumed diamino talose dihydrochloride also failed to give a crystalline derivative. The hygroscopic powder obtained gave a positive Fehling test, and its n.m.r. spectrum in D_2O showed no signals in the region of the glycosidic methoxyl resonance but strong signals in the region where acetamido groups are expected to resonate (76). An i.r. spectrum (neat film) showed strong absorption bands (cm^{-1}) at 3300 (OH,NH), 1650 (amide I) and at 1530 (amide II). The data agree with structure 60 of a diacetamido sugar. However, 59 and 60 were not characterized further.

Borontrifluoride-catalyzed acetylation of the nitro glycoside 57 with acetic anhydride gave, instead of the expected

4,6-diacetate, an unsaturated compound, namely, methyl 2-acetamido-6-O-acetyl-2,3,4-trideoxy-3-nitro-α-D-*threo*-hex-3-enopyranoside (53). The nitroolefinic structure of 53 was ascertained by its spectroscopic properties. Thus, 53 showed a strong i.r. absorption band at 1530 cm^{-1} which is typical of a nitro group attached to a carbon-carbon double bond. The n.m.r. spectrum exhibited signals at 2.64 τ (1-proton doublet, H-4, with $J_{4,5}$=2Hz), at 4.83 τ (1-proton doublet, H-2, with a coupling constant of 10 Hz; upon D_2O exchange this signal collapsed to give a singlet), at 5.12 τ (1-proton singlet, H-1), at 6.56 τ (3-proton singlet, OCH_3), and at 7.92 and 8.03 τ (two 3-proton singlets, 2-acetamido and 6-O-acetyl). The nitroolefin structure was also indicated by its u.v. absorption (λ_{max} 247 nm, ε 5000, in chloroform). Addition of excess methanolic sodium methoxide to a 10^{-4} molar solution of 53 caused an instantaneous bathochromic shift to 257 nm with increased intensity. A similar bathochromic shift involving a carbohydrate nitroolefin has been observed before (27) and was found to be the result of nucleophilic methoxylation at the olefinic bond.

As described earlier (p.134), the same 3,4-unsaturated nitroolefin was also formed from compound 52 by dehydro-acetylation. Since the α-D-*manno* configuration of compound 52 was established, the formation of the same 3,4-unsaturated nitroolefin from 57 proved the configuration at C-2 in the latter, and compounds 56 - 60 can therefore be assigned the α-D-*talo* configuration. Further support for this assignment

was derived from n.m.r. data of compound 56. A spectrum of 56 in DMSO-d_6 showed a 1-proton triplet at 4.47τ with a splitting of 3 Hz, a narrow 1-proton doublet at 4.96τ, a 2-proton singlet at 5.25τ, a 2-proton singlet at 5.80τ and a 1-proton singlet at 6.26τ. Although none of the signals could be definitely attributed to any specific proton, the total number of ring protons was accounted for, and since no signal showed a splitting larger than 3 Hz it follows that no vicinal, trans-diaxial protons were present in the molecule. This is in agreement with the α-D-talo configuration, although it does not rule out the α-D-ido configuration, with an axial nitro group, which is, however, highly unlikely.

In summary, the NBA reaction with nitroolefin 3 has opened an avenue to derivatives of 2,3-diamino-2,3-dideoxy-D-talose. No derivatives of this sugar have hitherto been described in the literature. Addition of ammonia to 3 has never been investigated but such addition to the β-anomer of 3 has led exclusively into the D-galacto series (27).

TABLE XI

N.m.r. data of diaminotalose derivatives (τ-values)

Compound	PhCH	OCH_3	2-Ac	6-Ac	H-1	H-2	H-4
55	4.41	6.59	8.03		5.08(0)*	4.27(0)	5.22(0)
54	4.37	6.60	8.31		5.17(0)	4.81(0)	5.17(0)
56	4.38	6.60	8.25		5.14(0)		5.14(0)
	4.24**	6.67	8.32		***		
57		6.64	8.09				
53		6.56	8.03	7.92	5.12(0)	4.83(0)	2.64(2)

* Coupling constants in Hz are given in parentheses.

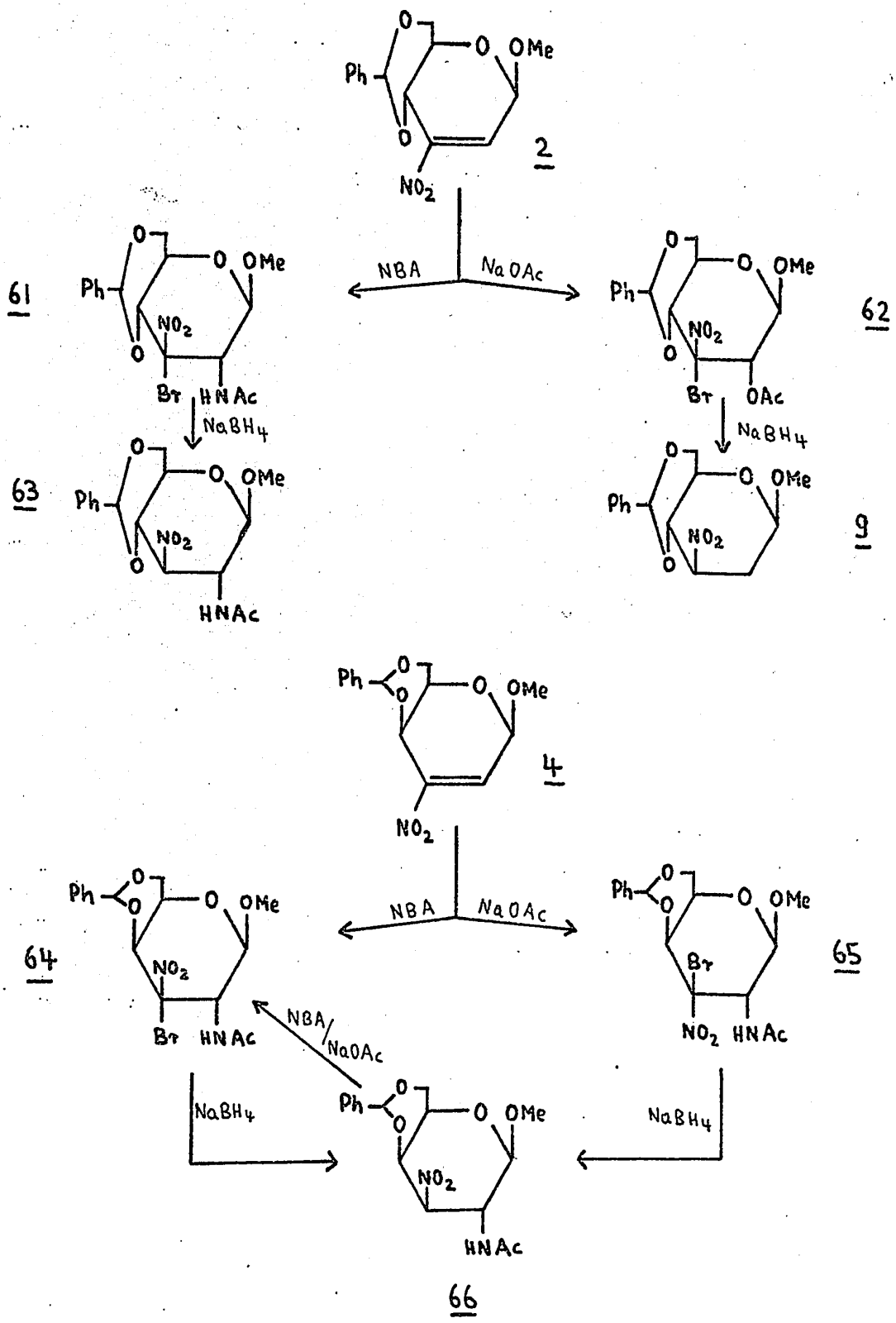
** In DMSO-d_6.

*** No individual protons could be assigned. The spectrum exhibited two 2-proton singlets, two 1-proton singlets , and a narrow 1-proton multiplet.

Synthesis of Methyl 2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (63)

Addition of NBA to methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-erythro-hex-2-enopyranoside (2) in the presence of excess sodium acetate led to the formation of a mixture of methyl 2-acetamido-4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-β-D-allopyranoside (61) and methyl 2-O-acetyl-4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-β-D-allopyranoside (62) in a ratio of 2:1 (Reaction Scheme O). The two products were obtained in an analytically pure state by column chromatography of the mixture. Inspection of the n.m.r. spectra of both bromo-nitro compounds 61 and 62 clearly proved the substituents at C-2 to be equatorially oriented, since a large coupling constant $J_{1,2}$ of 8 Hz required a trans-diaxial arrangement for H-1 and H-2. Other n.m.r. data are listed in Table XII.

Reaction Scheme O



Treatment of the 2-O-acetyl derivative 62 with sodium borohydride furnished the known methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-arabino-hexopyranoside (9). An intermediacy of nitroolefin 2 is assumed in the formation of this 2-deoxy sugar.

Reductive removal of the bromine (Iffland method) from the 2-acetamido compound 61 gave in high yield the known (25) methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (63).

Synthesis of Methyl 2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-galactopyranoside (66)

The addition reaction of NBA with methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-threo-hex-2-enopyranoside (4) in the presence of a catalytic amount of sodium acetate gave a 1:1 mixture of methyl 2-acetamido-4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-β-D-galactopyranoside (65) and its β-D-gulo isomer (64) (Reaction Scheme O). The two isomers were separated by column chromatography and obtained in yields of 45% each. In its n.m.r. spectrum, either product exhibited an anomeric proton doublet with $J_{1,2}$=9 Hz, indicating that H-1 and H-2 must be trans-diaxial and therefore proving that the 2-acetamido group is equatorially oriented. Consequently, the stereoisomerism of 64 and 65 must be due to the C-3 configuration. A definite decision as to which product had the galacto and which the gulo configuration could not be made, but a speculative assignment will be offered in connection with a

more detailed discussion of n.m.r. data (p.148) and dichroic data (p.152).

Reductive removal of the bromine with sodium borohydride from both 64 and 65 afforded the same, known (27) methyl-2-acetamido-4,6-0-benzylidene-2,3-dideoxy-3-nitro-β-D-galactopyranoside (66).

When compound 66 was treated with NBA in the presence of sodium acetate, it underwent bromination at C-3 and the bromonitro compound 64 was obtained in a yield of 80%. There was chromatographic evidence (t.l.c.) for the formation of only minute traces of isomer 65 in this reaction. This result tends to indicate that the configurational assignment made for C-3 in 64 and 65 was the correct one, since it appears reasonable to expect a compound with axial bromine (i.e. 64) to arise from this bromination.

TABLE XII

N.m.r. data of NBA-adducts of β-D-nitroolefins (τ-values)

Compound	PhCH	OCH_3	2-Ac	H-1	H-2	H-4
62	4.39	6.51	7.93	5.37(8)*	4.47(8)	6.12(7)
61	4.38	6.54	8.02	5.49(8)	4.97(8)	
63	4.27**	6.63	8.22	5.37(9)	4.99(9,10)	
64	4.32	6.56	7.93	5.38(8)	4.93(8)	5.32(1)
	4.14**	6.65	8.11			5.22(0)
65	4.28**	6.61	8.15	5.52(8)	5.08(8)	5.09(0)
66	4.35**	6.64	8.24			

* Coupling constants in Hz are given in parentheses.

** In DMSO-d_6.

N.m.r. Data of Acetamidonitro Sugars

It has been demonstrated by Lemieux et al. (77) and further elaborated by others (78) that the chemical shifts of the methyl proton signals of acetoxy or acetamido groups on six-membered rings depend on the axial or equatorial orientation of these substituents. The shifts are often, but not always, independent of the presence of other groups in the molecule. The table below summarizes the results (τ-values) recorded in the literature (77, 78).

Substituent	Configuration	$CDCl_3$	DMSO-d_6
$-O-\overset{\overset{O}{\|}}{C}-CH_3$	axial	7.75-7.80-7.90	
	equatorial	7.88-8.03	
$-NH-\overset{\overset{O}{\|}}{C}-CH_3$	axial	7.92-8.04	8.07-8.14
	equatorial	8.03-8.12	8.20-8.30

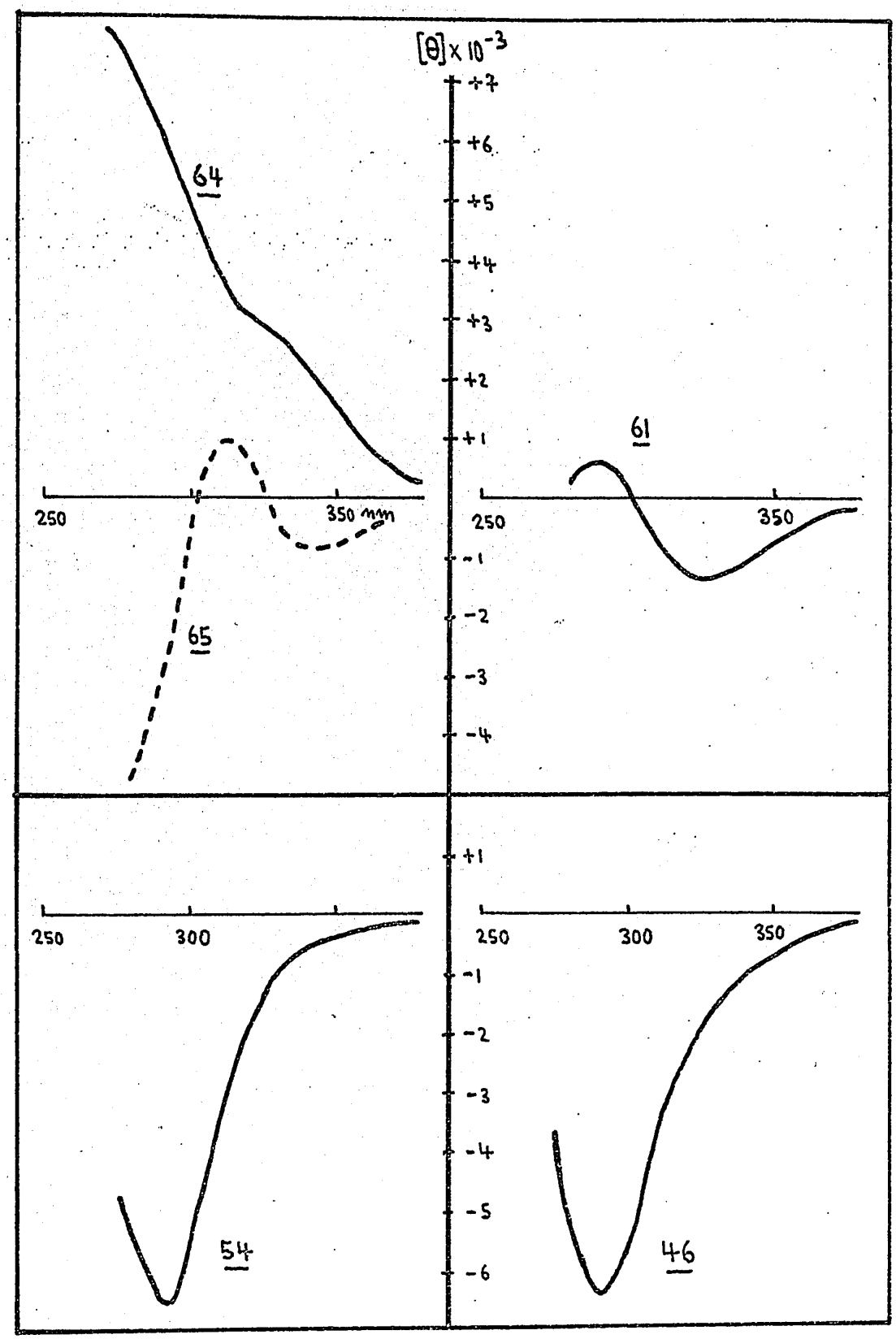
When the spectra of the O-acetyl and N-acetyl derivatives described in this chapter were examined, deviations from the tabulated ranges were observed in certain cases. Although the signals for compounds 47 - 51 and 62 - 63, as well as for compounds 64 - 66 appear within the expected ranges, a large deviation was observed for compounds 54 - 57. Thus the methyl proton signals of the axial acetamido group in

compounds 54 and 56 occurred upfield even of the range normally characteristic for equatorial acetamido groups. In the debenzylidenated compound 57 the deviation was not so large; however, the signal for the axial acetamido group still appeared in the region normally associated with equatorial acetamido groups. Since it is believed that the configuration of compounds 54 - 57 was well established in this work, these compounds present exceptions to the rules which in most cases offer a surprisingly accurate means for configurational and conformational assignments.

The n.m.r. data allow also comparisons between brominated and nonbrominated acetamidonitro sugars. It is seen that there are no significant differences in chemical shifts of the anomeric methoxyl group between brominated and nonbrominated derivatives. The same holds for the chemical shift of the benzylidene methine proton signals when compound 54 is compared with compound 56, while in all other cases the methine proton signal of the brominated products appears downfield. The downfield shift is significant in compound 46 (compared with 48). It is also significant for one, but not the other, of the two C-3 epimeric products obtained from 4 when comparison is made with the nonbrominated compound 66. The limited data available suggest that, in the bromo derivatives, a downfield shift of the benzylidene methine signal occurs when the bromine atom at C-3 and the oxygen at C-4 are in a cis arrangement. On this basis, provisional configurations have been allocated to 64 and 65, with due reservations.

Inspection of molecular models indicates that in such cis structures there is a parallel arrangement of the C-Br bond and one of the unshared electron orbitals of the oxygen at C-4, and this might be responsible for the observed shifts. A similar observation was discussed for the halonitro sugars in Part II, Chapter D.

Figure XII. - C.D. Curves of acetamidobromonitro sugars



Circular Dichroism of Acetamidobromonitro Sugars

Inspection of the c.d. curves in Figure XII shows some similarities to the curves measured for the bromonitro sugars (Figures VII and VIII) as discussed in Part II, Chapter D. Thus, compound 46 with the D-altro configuration showed a strong negative Cotton effect quite similar to that of the bromonitro sugars with D-altro configuration (Part II, compounds 49 and 56). A strong negative Cotton effect was also shown by the acetamido derivative with D-ido configuration 54, which again is paralleled by the dichroic behavior of the bromonitro sugar of the same configuration (Part II, compound 26). A correlation can also be seen for the bromonitro sugars with D-gulo and D-galacto configurations. Thus, the c.d. of 64 showed a strong positive Cotton effect paralleling that of the D-gulo bromonitro sugars obtained as normal products in Part II. Compound 65, which is assumed to carry its nitro group in the axial position, gave rise to a c.d. curve quite similar to that of the abnormal product in Part II to which the D-galacto configuration was assigned. The c.d. curve for compound 61 showed maxima of much smaller magnitude and was different from the curve of the bromonitro sugar with D-allo configuration encountered in Part II.

In summary, one can conclude that the configurational assignments of the acetamidobromonitro sugars, which were derived by chemical means and n.m.r. spectroscopic data, are consistent with the dichroic behavior of these compounds.

E X P E R I M E N T A L

General Remarks

Melting points were determined in capillaries with an electrically heated aluminum block apparatus and are uncorrected.

Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter at room temperature, and circular dichroism (c.d.) curves were recorded with a Jasco ORD/UV-5 instrument for solutions in dioxane.

Unless otherwise stated, infrared (i.r.) spectra were obtained from Nujol mulls by use of a Beckman-IR 20 spectrophotometer. The absorption intensities are recorded as strong (s), medium (m), weak (w), and broad (b), and frequency maxima are expressed in wavenumbers (cm^{-1}).

The nuclear magnetic resonance (n.m.r.) spectra were obtained on a Varian HA-100 spectrometer from chloroform-d solutions containing tetramethylsilane as internal standard, unless stated otherwise.

Ultraviolet (u.v.) spectra were measured with a Perkin-Elmer spectrophotometer, model 202.

Mass spectra were determined with a Hitachi-Perkin-Elmer R.M.U. 6D spectrometer at an ionization potential of 70 e.V.

Thin layer chromatography (t.l.c.) was performed on Silical Gel G (E. Merck AG, Darmstadt, Germany). The spots

were detected by spraying with a 1% ceric sulfate solution in 10% sulfuric acid. The solvent systems used for the irrigation of the t.l.c. plates were as follows:

Solvent A:	Carbon tetrachloride:ethyl acetate	7:3
Solvent B:	Carbon tetrachloride:ethyl acetate	4:3
Solvent C:	petroleum ether:ethyl acetate	2:3
Solvent D:	petroleum ether:ethyl acetate	3:2
Solvent E:	benzene:ethyl acetate	1:10
Solvent F:	benzene:methanol	9:1
Solvent G:	chloroform:acetone	7:3
Solvent H:	chloroform:methanol	4:1

Column chromatography was carried out with Silica Gel 0.05-0.20 mm (E. Merck AG, Darmstadt, Germany) as adsorbent.

Paper chromatography was performed by the descending technique using Whatman No. 1 paper with the system, ethyl acetate - pyridine - water - acetic acid (5:5:3:1) according to Fischer and Dörfel (79). The spots were made visible by spraying with ninhydrin and R_{GN}-values refer to the mobility relative to D-glucosamine hydrochloride.

All evaporations were carried out <u>in vacuo</u> at a bath temperature of 35-40°. All solid materials were dried in a desiccator <u>in vacuo</u> over phosphorus pentoxide.

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

Cation exchange resin refers to Rexyn 101 ($H^{\oplus}$) (Fisher Scientific Comp., Fair Lawn, New Jersey, USA), and anion exchange resin refers to Dowex 1-X8 ($OH^{\ominus}$) (J.T. Baker, Chem. Comp., Phillipsburg, New Jersey, USA).

Several reaction procedures are recurring throughout this thesis and they are therefore described here in a general way.

i. Debenzylidenation with Trifluoroacetic Acid (80)

The benzylidene nitro sugar (1 mmole) was stirred with 90% trifluoroacetic acid (6 ml) at room temperature. The reaction was readily monitored by t.l.c. and usually was completed after 30 minutes. The reaction mixture was then diluted with water (10 ml) and evaporated. Successive evaporations with water and ethanol usually furnished a colorless, syrupy, debenzylidenated product of high purity.

ii. Acetylation with Acetyl chloride and Triethylamine (51)

Triethylamine (1.93 ml, 13.8 mmole) in anhydrous ether (30 ml) was chilled in an ice water bath, and acetyl chloride (1.04 ml, 14.7 mmole) was added with magnetic stirring. A voluminous white precipitate of triethylammonium chloride occurred. After 5 minutes a solution of the nitro sugar (0.5-1.0 mmole) in dry methylene chloride (5 ml) was added and the reaction mixture was stirred for 30 minutes at 0^{o}. The mixture was then agitated with cold water, and after phase separation, the aqueous layer was extracted twice with ether. The combined ether solution and extract was washed three times with water, dried over sodium sulfate and evaporated giving usually pure, acetylated products in yields over 80%.

iii. Reductive Removal of Bromine from α-Bromonitro Sugars

The reductive removal of bromine in α-bromonitro compounds with sodium borohydride was pioneered by Iffland et al. (57) and below is referred to as Iffland method. Sodium borohydride was added to a solution of the bromonitro compound in ethanol. The amounts of reagents used are specified in the descriptions of individual experiments. The reaction mixture was stirred for about 30 minutes at room temperature and then slightly acidified with 10% aqueous acetic acid and diluted with water. The solution was concentrated by partial evaporation in order to remove most of the ethanol. Usually, a white precipitate separated. This precipitate was filtered off, washed with cold water and dried. The debrominated product so obtained normally was analytically pure after one recrystallization.

PART I

PREPARATION OF 3-NITRO SUGARS AND DERIVATIVES THEREOF

N.m.r.-Spectroscopic Analysis of 4,6-O-Benzylidene Nitro Sugars

Crystalline 4,6-O-benzylidene-3-deoxy-3-nitro-hexopyranosides 3-6 and 19-21 were prepared as described in subsequent sections. To test the quantitative n.m.r.-spectroscopic assay, mixtures containing three components in varying proportions were made by accurate weighing of pure crystalline samples. The n.m.r. spectra (100 MHz) were taken from approximately 10% solutions at a sweep width of 100 Hz and a sweep offset of 500 Hz. The methine proton peaks were identified by comparison of their τ-values with those in the spectra of individual isomers (compare Table I, p.15). The component ratios were determined by averaging three integrations for each methine signal and expressing each intensity in terms of percent of the sum of intensities. The results for four such mixtures, I-IV, are recorded in Table XIII. As can be seen, single integrations of a given signal deviated 1-2% from the average value, and the latter deviated 1-4% from the expected value.

In the same way were determined the unknown component ratios of mixtures A (from nitromethane cyclization of 2 followed by benzylidenation) and B (from nitromethane cyclization of 2 with subsequent epimeric equilibration followed by benzylidenation). The results are shown in Table XIII also.

TABLE XIII

Analysis of acetal mixtures by m.m.r. spectroscopy

Mixture	Composition: Compounds	Composition: Ratio	PhCH signals: τ- Values*	PhCH signals: Intensity ratios
I	3, 4, 5	16.7:49.8:33.5	4.34 4.41 4.48	19.0:48.2:32.8
II	3, 4, 5	33.3:14.5:52.2	4.34 4.41 4.49	29.6:15.1:55.3
III	21, 4, 5	28.9:42.6:28.5	4.32 4.41 4.48	27.3:41.8:30.9
IV	21, 4, 19	39.7:25.1:35.2	4.33 4.41 4.48	35.3:27.5:37.2
A	3, 4, 5, 6		4.34 4.42 4.49†	37.1:11.8:51.1†
			(4.24 4.33‡ 4.40)	42.0:49.2‡:8.8
B	3, 4, 5, 6		4.34 4.42 4.49†	15.5:52.6:31.9†

* In $CDCl_3$ except for the set in parentheses, which refers to DMSO-d_6.

I-IV Standards made by mixing weighed amounts of crystalline compounds.

A Mixture from nitromethane cyclization of 2 (see text).

B Mixture from nitromethane cyclization followed by epimeric equilibration (see text).

† 5 + 6

‡ 4 + 5

Separation of α-Glycoside Acetals

(a) Preparation of nitro glycoside and acetal mixtures

Preparation of the dialdehyde 2, its cyclization with nitromethane in methanol solution containing sodium methoxide, and deionization of the product to give a mixture (A) of nitro glycosides was performed as previously described (31), with the minor modification of allowing a reaction time of 45 rather than 25 minutes. The same applies to the preparation of the mixture (B) of epimerized glycosides (31). Benzylidenation of mixtures A and B with benzaldehyde and zinc chloride had previously given small yields of the crystalline α-D-gluco acetal 5 (21) and α-D-talo acetal 4 (20), respectively. For the present studies, benzylidenated mixtures were prepared as previously described, but the syrups obtained were used for n.m.r. spectroscopy and column chromatography without prior removal of crystallizable components.

T.l.c. was employed throughout the subsequent separation procedures to examine fractions and check the purity of products. Using solvent A as irrigating solvent, compound 3 moved fastest, closely followed by 5 and 4; compound 6 moved rather more slowly.

(b) Chromatography of benzylidenated mixture A

Crude, benzylidenated mixture A, obtained as a syrup (21.5 g) from 2 (0.068 mole, from 13.2 g of methyl α-D-glucopyranoside) was placed on a column (6.5 x 60 cm) containing 800 g of silica gel. Elution was performed with carbon tetrachloride/ethyl acetate mixtures of compositions (v/v) 7:3 (fractions 1 - 30), 1:1 (fractions 31 - 39), and 2:3 (fractions 40 - 80), the

fractions being 75 ml in volume. All fractions were inspected by t.l.c., and the residues obtained after appropriate pooling and evaporation were examined by n.m.r. spectroscopy. Fractions 1 - 15 were free from carbohydrates but contained benzaldehyde (6.76 g). Fractions 16 - 21 yielded pure 3 (2.22 g). Fractions 22 - 30, 31 - 36, 37 - 39, 40 - 50, and 51 contained 4.49, 1.46, 0.43, 1.29 and 0.68 g of mixtures of 3, 4, and 5. Fractions 52 - 63 and 75 - 80 were blank, and fractions 64 - 74 gave pure 6 (1.00 g). Thus the total, overall yield of nitro glycoside acetals was 11.57 g (54.7% of the theoretical based on starting methyl α-D-glucopyranoside). Individual yields, calculated by summation of pure fractions and spectroscopically-determined proportions of components in mixed fractions, were the following: 3, 4.86 g (22.9%); 4, 0.94 g (4.4%); 5, 4.77 g (22.5%), and 6, 1.00 g (4.7%).

When the column chromatography was performed with half the above glycoside load and with a carbon tetrachloride/ethyl acetate mixture of constant composition (7:3), a somewhat better separation of the more mobile compounds, 3, 5, and 4 took place and parts of each were eluted as pure fractions, in that order, with mixed fractions occurring in between. However, the solvent was unsatisfactory for elution of slow-moving 6.

(c) Chromatography of benzylidenated mixture B

A crude syrup (21.8 g) resulting from benzylidenation of a mixture (B) of epimerized nitro glycosides obtained from 2 was chromatographed. The technique detailed in (b) was used except that the eluant composition was carbon tetrachloride/

ethyl acetate in the ratios 4:3, 1:1, and 2:3 for fractions 1 - 24, 25 - 30, and 31 - 50, respectively. Fractions 1 - 10 contained benzaldehyde (5.6 g). Fractions 11 - 15 and 17 - 18 consisted of mixtures of 3 (1.20 g) and 5 (0.80 g), and of 5 (0.30 g) and 4 (0.55 g), respectively, the product ratios being determined from n.m.r. spectra. Fractions 16, 19 - 30, and 31 - 50 yielded virtually pure 5 (0.47 g), 4 (3.48 g), and 6 (1.03 g), respectively. Hence the total yield of nitro glycoside acetals was 7.83 g. Since the ratios of individual acetals were very similar before and after chromatography it appears that recovery was essentially complete. The weight deficit is attributed to benzaldehyde (5.6 g) and residual solvent in the starting syrup.

Methyl 4,6-O-Benzylidene-3-deoxy-3-nitro-α-D-mannopyranoside (3)

Compound 3 as obtained from a chromatographic column was recrystallized for analysis from chloroform/petroleum ether; m.p. 138-139°, $[\alpha]_D$ +27.7° (c, 0.8 in chloroform). The compound showed characteristic i.r. bands at 3400 (m,b, OH) and at 1560 (s, NO_2)

Analysis for $C_{14}H_{17}NO_7$ (311.3)

Calcd: C, 54.01; H, 5.51; N, 4.50.

Found: C, 53.96, H, 5.56; N, 4.59.

Methyl 3-Deoxy-3-nitro-α-D-mannopyranoside (7)

The acetal 3 (300 mg) was debenzylidenated by treatment with trifluoroacetic acid at room temperature for 15 minutes. Completion of the reaction was ascertained by t.l.c. (solvent A). Work-up afforded a syrupy material (206 mg, 96.0%) which could be crystallized from tetrahydrofuran/ether (184 mg) to

have a melting point of 113-115° and $[\alpha]_D$ +44.5° (c, 0.9 in water). The i.r. spectrum exhibited bands at 3540 (s) and 3340 (s,b, OH), and at 1545 (s, NO_2).

Analysis for $C_7H_{13}NO_7$ (223.2)

Calcd: C, 37.67; H, 5.87; N, 6.28.

Found: C, 37.79; H, 5.93; N, 6.35.

A sample of 7 (100 mg) was dissolved in water (8 ml) and 0.1 N hydrochloric acid (5 ml). Platinum catalyst (prehydrogenated from 50 mg of PtO_2) was added to this solution and the mixture was hydrogenated overnight. Filtration and evaporation of the solution followed by recrystallization of the residue from 95% ethanol at 4° furnished methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (10) (84 mg, 81.5%) in two batches, with melting points of 234-236° (dec.) and 232-235° (dec.), $[\alpha]_D$ +57.5° (c, 0.3 in water). Reported: $[\alpha]_D$ +60° in water (30, 42) and decomposition at about 205° (30), 221-223° (31), 210-240° (42). Evidently the melting behavior is not very characteristic, it being probably influenced by traces of impurities and the mode of heating. A sample at hand from previous work in this laboratory melted with decomposition at 230-231° and caused no depression when admixed to new 10. The i.r. spectra were identical also.

Methyl 4,6-O-Benzylidene-3-deoxy-3-nitro-α-D-talo pyranoside (4)

Compound 4 collected from the column melted at 177-178° and showed $[\alpha]_D$+66.8° (c, 1.1 in chloroform); reported (20): m.p. 175°, $[\alpha]_D$ +68° (in chloroform). The i.r. spectrum was identical with that of an authentic sample.

Methyl 3-Deoxy-3-nitro-α-D-talopyranoside (8)

The acetal 4 (200 mg) was debenzylidenated with trifluoroacetic acid during 20 minutes at room temperature. The syrupy product (117 mg, 82.0%) was crystallized from chloroform to give 8 (93 mg) melting at 86-87°; $[\alpha]_D$ +87.5° (c, 0.9 in water). The i.r. spectrum showed bands at 3240 (s,b, OH) and at 1550 (s, NO_2).

Analysis for $C_7H_{13}NO_7$ (223.2)

Calcd: C, 37.67; H, 5.87; N, 6.28.

Found: C, 37.46; H, 6.08; N, 6.12.

A sample of 8 (40 mg) was catalytically hydrogenated for 3 hours in water (3 ml) and 0.1 N hydrochloric acid (2 ml), in the presence of platinum catalyst (from 70 mg PtO_2). Upon recrystallization of the product from 99% ethanol by slow addition of ethyl acetate, methyl 3-amino-3-deoxy-α-D-talopyranoside hydrochloride (11) was obtained in a yield of 99%, m.p. 187-188° (dec.), $[\alpha]_D$ +88.3° (c, 0.3 in water). Identity with an authentic sample was established by a mixture melting point (186-188°, dec.), comparison of i.r. spectra, and paper chromatography (31).

Methyl 4,6-O-Benzylidene-3-deoxy-3-nitro-α-D-glucopyranoside (5)

Compound 5 collected from a column showed a melting point of 166-167° and $[\alpha]_D$ +86.5° (c, 0.7 in ethanol). Reported (21): m.p. 167°, $[\alpha]_D$ +87.2° (in ethanol). The i.r. spectrum was also identical with that of an authentic sample.

Methyl 4,6-O-Benzylidene-3-deoxy-3-nitro-α-D-galactopyranoside (6)

Compound 6 collected by column chromatography was

recrystallized for analysis from ethyl acetate/petroleum ether to give a material melting at 166-167°; $[\alpha]_D$ +205° (c, 0.5 in chloroform). The i.r. spectrum exhibited bands at 3460 (m,b, OH) and at 1550 (s , NO_2).

Analysis for $C_{14}H_{17}NO_7$ (311.3)

Calcd: C, 54.01; H, 5.51; N, 4.50.

Found: C, 53.83, H, 5.51; N, 4.41.

Methyl 3-Deoxy-3-nitro-α-D-galactopyranoside (9)

The acetal 6 (94 mg) was debenzylidenated with trifluoroacetic acid during 30 minutes at room temperature. Crystallization of the syrupy product (67 mg) from chloroform afforded 9 (32 mg) with a melting point of 145-146°; $[\alpha]_D$ +209° (c, 0.4 in water). The remainder of 9 (35 mg) was recovered as a syrup. The material showed i.r. bands at 3400 (m) and 3200 (m, b, OH), and at 1550 (s, NO_2).

Analysis for $C_7H_{13}NO_7$ (223.2)

Calcd: C, 37.67; H, 5.87; N, 6.28.

Found: C, 37.92; H, 6.02; N, 6.16.

Methyl 3-Amino-3-deoxy-α-D-galactopyranoside hydrochloride (12)

Syrupy 9 (35 mg) was dissolved in water (5 ml) and 0.1 N hydrochloric acid (2 ml), and was hydrogenated for 3 hours in the presence of platinum catalyst (from 50 mg PtO_2). Evaporation of the filtrate followed by two co-evaporations with ethanol gave crystalline 12 (34 mg) which upon re-crystallization from ethanol melted with decomposition at 219-221° and had $[\alpha]_D$ +146.5° (c, o.2 in water). The i.r. spectrum of 12 showed bands at 3350 (m) with 2 shoulders at 3400 and 3420

(OH and NH_2).

Analysis for $C_7H_{16}ClNO_5$ (229.7)

Calcd: C, 36.61; H, 7.02; Cl, 15.44.

Found: C, 36.76; H, 6.79; Cl, 15.71.

In agreement with the earlier observation on amorphous 12, the mobility of the compound in paper chromatography (31) was lower than that of its isomers 10 and 11.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-α-D-threo-hex-2-enopyranoside (13)

A mixture of the acetal 6 (100 mg), anhydrous sodium acetate (200 mg), and acetic anhydride (2 ml) was heated on a steam bath for 30 minutes with continuous swirling. The mixture was then poured into ice water (50 ml) which caused a white crystalline material to precipitate. The product, which was collected by filtration, washed well with cold water and dried, weighed 86 mg (91.0%) and melted at 175-177°. Recrystallization from ethyl acetate/petroleum ether raised the melting point to 182-184°. Reported (20): m.p. 185-186°. An i.r. spectrum was identical with that of 13 from the earlier work (20).

In like manner but with a reaction time of 15 minutes, 13 was obtained in 83% yield starting from the isomeric acetal 4. The formation of nitro olefins is discussed in more detail in Part III, Chapter A.

Separation of β-Glycoside Acetals

The preparation of dialdehyde 15 and its cyclization with nitromethane to give the nitro β-glycosides 16, 17 and 18 has been described (39 - 41a) as has the benzylidenation of these glycosides, individually as pure compounds and in mixtures recovered from mother liquors (41b ; 21).

(a) Fractional crystallization

Mother liquors that remained when upon nitromethane cyclization of 15 the bulk of crystallizable β-D-glucoside 16 had been collected (15) were evaporated, and the residue was benzylidenated. From the mixture of acetals so produced, the β-D-galacto isomer 20 can be obtained by fractional crystallization from ethanol in which it is the least soluble component. However, 6-8 recrystallizations are needed to achieve high purity. A more convenient procedure is to dissolve the mixture in a small amount of acetone and then to add chloroform, which causes precipitation of a material highly enriched in 20. One subsequent recrystallization of the precipitate from ethanol usually is sufficient to give reasonably pure 20, m.p. 229-231° (decomp.). Reported (21): m.p. 230-231° (decomp.). This procedure is probably the most convenient one for the preparation of larger quantities of 20, as it renders unnecessary the use of isolated, crystalline 17 for benzylidenation.

The acetone/chloroform mother liquor from the above separation procedure is strongly enriched in the β-D-manno compound 21, but purification of the latter by continued fractional crystallization could not be achieved. If pure 21 is desired without

having to start with pure 18 and without resorting to chromatography, one may benzylidenate nitromethane cyclization mixtures from which the bulk of both 16 and 17 have been removed (21, 40). However, column chromatography proved advantageous for isolating 21.

(b) Column chromatography

The following example describes the separation of an acetal mixture containing mainly 20 and 21 (the latter preponderating) as well as a small proportion of 19. The mixture (10 g) and a few grams of silica gel were intimately mixed by two co-evaporations with acetone in a rotary evaporator, and the dry mass was then placed on a column (4.5 x 65 cm) containing 500 g of silica gel. Elution was performed with chloroform/acetone (7:3, v/v) at a rate of about 17 ml per 10 min. The eluate was inspected at intervals by t.l.c., and the fractions were suitably combined. The first 800 ml (approximately) of effluent was blank (it may be recyled). The following 300 ml contained β-D-manno derivative 21 which was obtained by evaporation and was recrystallized from ethanol to give a very pure product (5.23 g), m.p. 202°, $[\alpha]_D$-112° (c, 1.2 in ethanol). Reported (21): m.p. 196°, $[\alpha]_D$-107°. The next 60 ml of effluent yielded impure 21 (1.05 g, m.p. 189°) that contained some 19. Continued elution with about 500 ml of solvent furnished the β-D-galacto derivative 20 (3.23 g) which emerged after a few blank fractions (or, in similar runs, with slight overlapping). Upon recrystallization from ethanol it showed m.p. 232°, $[\alpha]_D$ +25° (c, 1 in dimethylformamide).

(c) Nitronate formation

A mixture (1 g) containing mainly 20 and 21 along with a small proportion of 19 was dissolved in chloroform (40 ml), and an ethanolic, N potassium hydroxide solution (3.5 ml) was added. A voluminous precipitate occurred within 5 min. and t.l.c. of the reaction mixture, performed after 10 min. with a neutralized sample, indicated absence of 21 and presence of both 19 and 20. The reaction mixture was then shaken with 40 ml of water in which the precipitate dissolved. After phase separation the aqueous layer was extracted twice with chloroform which was combined with the organic phase. Excess acetone was then added to the aqueous phase and the solution was at once deionized with an acidic cation exchange resin. The filtrate was concentrated to remove most of the acetone, whereby the β-D-galacto isomer 20 crystallized in chromatographically pure form (131 mg). The aforementioned chloroform phase was washed twice with water, dried over sodium sulfate, and evaporated to give chromatographically pure β-D-gluco isomer 19 (710 mg). The products were identified by their i.r. spectra and physical constants.

TABLE XIV

Circular dichroism of 4,6-O-benzylidene acetals of 3-nitro sugars

Compound	Extrema		[θ] at a given λ (in nm)				
	λ(in nm)	[θ]	270	290	310	330	360
3	284	3280	2570	3100	2020	1180	170
21	282	3217	2502	3016	1586	827	0
4	293	830	474	810	691	395	59
5	279	945	735	470	-893	-840	-184
	315	-1000					
19	281	-1085	-940	-960	-310	-146	0
6	274	150	105	-170	-927	-800	-127
	316	-970					
20	276	347	301	0	-761	-670	-139
	311	-763					

PART II

INVESTIGATIONS CONCERNING THE NITRONATE FORMATION IN PARTIALLY BLOCKED 3-NITROHEXOSES

A. Ultraviolet Spectra of Glycoside Nitronates

The nitro glycosides used in the U.V. studies were prepared as described in Part I and Part III, Chapters B and D. Compounds 14 and 17 were previously synthesized according to references (28) and (26), respectively. For the measurement of U.V. absorptions accurately weighed samples (about 3.6 mg) of the nitro glycosides were dissolved in 10 ml of 99% ethanol. Aliquots were withdrawn and their volumes were made up to 10 ml with 0.01 or 0.001 N ethanolic potassium hydroxide solution as specified (Table II p. 44), to give solutions with a concentration of 10^{-4} M in nitro compound. The spectra were measured using 1-cm cells, with the reference cell containing ethanolic potassium hydroxide of the same normality. The results are compiled in Table II and absorption curves are depicted in Figures III - VI.

B. Mechanism of the manno ⟶ gluco Epimerization

Treatment of β-D-mannoside 7 with potassium hydroxide

The nitro sugar 7 (62 mg) was dissolved in 0.1 N ethanolic potassium hydroxide (20 ml). After standing for 10 minutes at 25° the solution was deionized by cation exchange, filtered, and evaporated to give a solid that was recrystallized from methanol/water. The product (55 mg, 89%) melted at 180-181°. The i.r. spectrum of the product was identical with that of an authentic sample of the β-D-glucoside 5. Reported (19): m.p. 181-182°.

Treatment of α-D-mannoside 6 with potassium hydroxide

The nitro sugar 6 was treated with base as described above for 7 and furnished the α-D-glucoside 4 (81.0%) with a melting point of 165-166°, $[\alpha]_D$ +82.1° (c, 0.6 in methanol). Reported (21): melting point 167°, $[\alpha]_D$ +82.0°. The i.r. spectrum of the product was also identical to that of authentic 4 (21).

Treatment of β-D-mannoside with sodium methoxide

The nitro sugar 7 (62 mg) was dissolved in 0.1 N methanolic sodium methoxide (20 ml). After standing at 25° for 2.5 hours the solution was deionized and evaporated to give 57 mg (92%) of crystals which on recrystallization from methanol/water furnished β-D-glucoside 5 (53 mg, 85.3%). The melting point of 180-181° and the i.r. spectrum proved the identity of the product with an authentic sample of 5.

Treatment of β-D-erythro olefin 18 with sodium methoxide

The nitro olefin 18 (58.6 mg) was dissolved in 0.1 N methanolic sodium methoxide (20 ml) to which one equivalent of water was added so as to simulate the conditions that would obtain upon dehydration of 7. After a reaction time of 2.5 hours at room temperature the reaction mixture was deionized by cation exchange and evaporated to give a crystalline residue. Recrystallization from ethanol afforded methyl 4,6-O-benzylidene-3-deoxy-2-O-methyl-3-nitro-β-D-glucopyranoside (19) (58 mg, 96.7%) with a melting point of 185°; reported (24), 186°.

The i.r. spectrum as well as the n.m.r. spectrum were identical to those of an authentic sample (24).

Treatment of β-D-mannoside 7 with sodium methoxide in the presence of thiobenzyl alcohol

Thiobenzyl alcohol (0.2 ml) was mixed with 0.1 N methanolic sodium methoxide (33 ml). After 15 minutes the nitro sugar 7 (103 mg) was added and the reaction mixture was stirred at room temperature. According to t.l.c. (solvent A) 7 was completely converted into 5 after 30 minutes, and work-up after 60 minutes yielded recrystallized β-D-glucoside 5 (89 mg, 86.4%), with a melting point of 179-181°. The i.r. spectrum of the product proved its identity with an authentic sample of 5. There was no evidence for formation of the known (24) benzylthio derivative 20.

Treatment of 2-O-acetyl-β-D-mannoside 21 with potassium hydroxide

To an ice cold solution of the nitro sugar acetate 21 (70.5 mg) in methanol (5 ml) was added a 0.2 N methanolic potassium hydroxide solution (20 ml). T.l.c. (solvent B) revealed that the reaction was complete after 2 minutes. Work-up by deionization and evaporation after 25 minutes furnished the crystalline 2-O-methyl ether 19 (57 mg, 88.1%) with a melting point of 184-185°. An undepressed mixture melting point and the i.r. spectrum proved the identity of the product with an authentic sample.

C. Acetylations with Acetyl Chloride and Triethylamine

Methyl 2-O-Acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-galactopyranoside (22)

The nitro galactoside 3 (206 mg) was dissolved in methylene chloride (10 ml) and acetylated with acetyl chloride (1.04 ml) in the presence of triethylamine (1.93 ml). After completion of the reaction, the mixture was agitated with water, whereupon the main part of the product (160 mg) separated as crystals which were collected, washed with cold water and dried. They melted at 149-151°. An additional crop of crystals (43 mg, m.p. 146-148°) was obtained by extractive work-up as described in the general acetylation procedure. Thus the total yield of 22 amounted to 87%. The i.r. spectrum of the product was identical with that of an authentic sample (50).

Methyl 2-O-Acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-mannopyranoside (21)

The nitro mannoside 7 (206 mg) was dissolved in methylene chloride (4 ml) and acetylated as described above for 3. Extractive work-up afforded crystalline 21 (223 mg, 95%). Upon recrystallization from chloroform/petroleum ether the material (194 mg) showed a melting point of 162-163°, $[\alpha]_D$ -88.7° (c, 0.5 in chloroform). The melting point of 21 recrystallized from ethanol/water had been reported as 136-137° (21), and no optical rotation had been recorded.

Because of the melting point discrepancy the earlier acetylation method (21) was repeated but the product was recrystallized from chloroform/petroleum ether. The product (yield 79%, m.p. 159-160°) was identical with 21 prepared by the new method according to an undepressed mixture melting point, the i.r. spectrum, and the n.m.r. spectrum. The n.m.r. data (in τ-values): 2.60 (5-proton multiplet, phenyl), 4.13 (1-proton doublet, H-2, with $J_{2,3} = 3.5$ Hz, $J_{1,2} = 0$ Hz), 4.33 (1-proton singlet, methine proton), 5.20 (1-proton quartet, H-3, with $J_{2,3} = 3.5$ and $J_{3,4} = 10.5$), 5.48 (sharp singlet, H-1, overlapped by H-6, 6-multiplet), 6.05 (symmetrical 1-proton triplet, H-4, J = 10.5 Hz), 6.50 (3-proton singlet, OCH_3, overlapping with H-5 multiplet), 7.89 (3-proton singlet, O-acetyl).

Methyl 2-O-Acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-α-D-mannopyranoside (23)

The nitro mannoside 6 (206 mg) was dissolved in methylene chloride (6 ml) and acetylated as described above for 7. Extractive work-up afforded a syrupy material which was dissolved in ethanol and precipitated with water as an amorphous powder (201 mg, 86%) with a rotation of $[\alpha]_D + 4.5°$ (c, 0.6 in chloroform). The i.r. spectrum showed characteristic bands at 1745 (s, O-acetyl) and at 1560 (s, NO_2). The n.m.r. spectrum showed signals (τ-values) centered at 2.66 (5-proton multiplet, phenyl), at 4.33 (1-proton singlet, methine proton), at 4.47 (1-proton quartet, H-2, with $J_{1,2} = 2$ Hz

and $J_{2,3}$=4 Hz), at 5.03 (1-proton quartet, H-3, with $J_{2,3}$=4 Hz and $J_{3,4}$=10 Hz), at 5.26 (1-proton doublet, H-1, with $J_{1,2}$=2 Hz), at 6.62 (3-proton singlet, OCH_3), and at 7.94 (3-proton singlet, O-acetyl). The signals for the remaining protons were not assignable.

Analysis for $C_{16}H_{19}NO_8$ (353.30)

Calcd: C, 54.40; H, 5.42; N, 3.97.

Found: C, 54.56; H, 5.29; N, 3.97.

Methyl 2-O-Acetyl-3-(O-acetyl-aci-nitro)-4,6-O-benzylidene-3-deoxy-α-D-lyxo-hexopyranoside (25)

The nitro taloside 1 (103 mg) in methylene chloride (3 ml) was acetylated with triethylamine (0.97 ml) and acetyl chloride (0.52 ml). Extractive work-up gave a crystalline material (120 mg, 92%) which was homogeneous on t.l.c. (solvent B). Recrystallization from ethyl acetate gave a first crop of 25 (29 mg) melting at 136-137° and upon addition of petroleum ether to the mother liquor, a second crop (83.5 mg) melting at 132-135°. The i.r. and u.v. data are reported in the discussion. The n.m.r. spectrum exhibited signals (τ-values) at 2.5-2.7 (5-proton multiplet, phenyl), 4.35 (overlapping signals with 2-proton intensity assigned to H-2 and the methine proton), 4.9-6.2 (a complex pattern of signals corresponding to 5 ring protons), 6.62 (3-proton singlet, OCH_3), and 7.83 and 7.96 (3-proton singlets, O-acetyl).

Analysis for $C_{18}H_{21}NO_9$ (395.4)

Calcd: C, 54.65; H, 5.35; N, 3.54.

Found: C, 54.61; H, 5.18; N, 3.64.

When a sample of 25 (100 mg) was chromatographed over a silica gel column with solvent B as eluent, only a single compound was recovered (63 mg, 85.2%) which proved to be methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-*threo*-hex-2-enopyranoside (24), with a melting point of 187-188° (reported (20), 185-186°). The i.r. spectrum was superimposable on that of an authentic sample (20).

D. Synthesis and Reactions of δ-Halonitro Sugars

In all synthetic work in this connection essentially two bromination methods were employed. In one method, termed direct bromination, bromine was added to an alkaline solution of the nitro glycoside, i.e., to a solution containing preformed nitronate. In the other method, N-bromoacetamide (NBA) was used as bromine source in the presence of sodium acetate. In both methods the reaction mixtures were worked up either by precipitation or by extraction, depending on the solubility of the products. The two procedures referred to as "precipitative work-up" or "extractive work-up" in the description of individual experiments are therefore given in general terms below.

Precipitative work-up

The alcoholic reaction mixtures were diluted with water. Partial evaporation of the alcohol by concentration of the mixtures under reduced pressure usually afforded a highly pure and crystalline precipitate, which was filtered off, washed with cold water, and dried.

Extractive work-up

The alcoholic reaction mixtures were diluted with water and most of the alcohol was evaporated under reduced pressure. The halonitro sugars were extracted from the remaining aqueous solution with three portions of chloroform. The chloroform extract was washed twice with water and then dried over anhydrous sodium sulfate. Evaporation of the chloroform usually afforded highly pure reaction products.

Spectral data

The n.m.r. data of compounds synthesized in this Part II, Chapter D are listed in Tables IV and V. The c.d. data are compiled in Table XIV, and the c.d. curves are depicted in Figure VII and VIII.

Methyl 4,6-O-Benzylidene-3-bromo-3-deoxy-3-nitro-α-D-idopyranoside (26)

Direct bromination. —— To an ice cold solution of the α-D-taloside 1 (103 mg) in methanol (15 ml) was added 0.1 N aqueous sodium hydroxide (3.7 ml). After stirring the solution for 5 minutes, bromine was added dropwise until the reaction mixture remained slightly yellow. Extractive work-up after another 5 minutes of stirring gave a white solid (104 mg) which upon recrystallization from chloroform/n-pentane afforded the bromonitro sugar 26 (96 mg, 73.9%) with a melting point of 126-128°. Another recrystallization from the same solvents raised the melting point to 129-130°, $[\alpha]_D$ +45.5° (c, 0.6 in chloroform). The i.r. spectrum showed characteristic bands at 3550 and 3490 (W, OH) and at 1565 (s, NO_2).

Analysis for $C_{14}H_{16}BrNO_7$ (390.20)

Calcd: C, 43.14; H, 4.13; Br, 20.46.

Found: C, 43.26; H, 4.17; Br, 20.83.

Bromination with NBA. —— A solution of 1 (200 mg) in methanol (20 ml) was stirred with a saturated, aqueous solution of sodium acetate (2 ml) and NBA (100 mg) for 30 minutes at room temperature. Extractive work-up afforded the bromonitro

sugar 26 (235 mg, 93.6%) melting at 127-129°. A mixture melting point with the material obtained by the direct bromination method remained undepressed. A comparison of the i.r. spectra of the two products confirmed their identity also.

Methyl 4,6-O-Benzylidene-3-chloro-3-deoxy-3-nitro-α-D-idopyranoside (27)

To an ice cold solution of α-D-taloside 1 (124 mg) in methanol (30 ml) was added a 5% aqueous solution of sodium hypochlorite (reagentgrade; Matheson, Coleman and Bell). Inspection by t.l.c. (solvent B) after 5 and 15 minutes showed the presence of only one faster moving material. The reaction mixture was therefore neutralized with 10% aqueous acetic acid and worked up by precipitation. The solid so obtained was recrystallized from ethanol/water to furnish 27 (117 mg, 84.8%) with a melting point of 104-105° and $[\alpha]_D$ +48.3° (c, 0.7 in chloroform). The i.r. spectrum indicated the presence of the nitro group and the hydroxyl group by bands at 1570 (s) and 3480 (m).

Analysis for $C_{14}H_{16}ClNO_7$ (345.74)

Calcd: C, 48.70; H, 4.65; Cl, 10.27.

Found: C, 48.80; H, 4.86; Cl, 10.40.

Methyl 2,3-Anhydro-4,6-O-benzylidene-3-nitro-α-D-talopyranoside (28)

By alkaline chlorination of 1. —— A solution of nitro sugar 1 (62 mg) in methanol (15 ml) was stirred at room temperature with commercial Javex household bleach (0.6 ml). After 15 minutes t.l.c. with solvent B showed a single, faster moving spot (presumably 27), which was replaced by a less fast-moving spot after a reaction time of 35 minutes. Precipitative work-up and recrystallization from ethanol/water gave the nitro epoxide 28 (50 mg, 81.2%) with a melting point of 214-216°. The same nitro epoxide was obtained by alkaline peroxidation of a nitroolefinic sugar as described in Part III of this thesis (see compound 22, m.p. 215-216°). Comparison of the i.r. and n.m.r. spectra of the two products confirmed also their identity.

From the bromonitro sugar 26. —— The bromonitro sugar 26 (35 mg) was dissolved in methanol (10 ml) and stirred with aqueous N sodium hydroxide for 15 minutes at room temperature, whereby a white solid separated. Dilution with water and partial evaporation of the methanol afforded the nitro epoxide 28 (24.8 mg, 89.8%) melting at 214-215°. An i.r. spectrum proved its identity with the product obtained by the chlorination method.

Regeneration of methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-talopyranoside (1)

Reduction of the bromonitro sugar 26 (200 mg) in an ice cold solution of ethanol (40 ml) with sodium borohydride (80 mg) according to the Iffland method gave, after

5 minutes, the nitro sugar 1 (128 mg, 80.0%) melting at 174-175°. The i.r. spectrum proved the identity of the product with known 1. T.l.c. inspection (solvent B) of the reaction mixture revealed that besides the major spot corresponding to 1, there were traces of a spot having the same R_f-value as the nitro epoxide 28.

Methyl 4,6-O-Benzylidene-3-bromo-3-deoxy-3-nitro-β-D-gulopyranoside (29)

Direct bromination.—— To an ice cold suspension of the β-D-galactoside 3 (311 mg) in ethanol (40 ml) was added an aqueous N solution of sodium hydroxide (11 ml). After stirring for 4 minutes a clear solution was obtained to which bromine was added dropwise until a slight yellow color persisted. Stirring in the ice bath was continued for another 15 minutes and was then followed by precipitative work-up. The solid material so obtained (281mg, 72.2%) had a melting point of 75-78° and $[\alpha]_D$ +31.6° (c, 0.6 in chloroform). The i.r. spectrum indicated the presence of an OH group (3450 m,b) and an NO_2 group (1565 s).

Analysis for $C_{14}H_{16}BrNO_7$ (390.20)

Calcd: C, 43.14; H, 4.13; Br, 20.46; N, 3.59.

Found: C, 43.03; H, 4.24; Br, 20.38; N, 3.80.

Bromination with NBA.——A solution of nitro sugar 3 (186 mg) in methanol (20 ml) and a saturated, aqueous solution of sodium acetate (2 ml) and NBA (100 mg) were mixed, and the mixture was refluxed for 1 hour and then worked up using the precipitative method. The bromonitro sugar 29 (161 mg, 69.0%) so obtained melted at 77-79°. A comparison of the i.r. spectrum with that of the material isolated in the direct bromination proved the identity of the two products.

Methyl 2,4,6-Tri-O-acetyl-3-bromo-3-deoxy-3-nitro-β-D-gulopyranoside (31)

The bromonitro sugar 29 (140 mg) was debenzylidenated by treatment with trifluoroacetic acid (4.5 ml) and water (0.5 ml) for 15 minutes. The syrupy product (100 mg) so obtained failed to crystallize and was therefore acetylated with acetic anhydride (3 ml) in the presence of a few drops of boron trifluoride etherate. The acetylation mixture was stirred at room temperature for 20 minutes and then poured into ice water (30 ml). A white crystalline material was obtained after trituration for 20 minutes. The solid was filtered off, washed with cold water, and dried to give 31 (103 mg, 72.3%) melting at 107-108°. Recrystallization from ethyl acetate/petroleum ether raised the melting point to 112-113°; $[\alpha]_D$ +25.0° (c, 0.5 in chloroform). The i.r. spectrum showed characteristic bands at 1740 and 1765 (s, O-acetyl) and at 1570 (s, NO_2).

Analysis for $C_{13}H_{18}BrNO_{10}$ (428.21)

Calcd: C, 36.48; H, 4.24; Br, 18.67; N, 3.27.

Found: C, 36.60; H, 4.31; Br, 18.69; N, 3.32.

Reactions of methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-gulopyranoside (29)

Debromination of 29 with sodium borohydride.—— The bromonitro sugar 29 (100 mg) was treated with sodium borohydride (50 mg) in ethanolic solution according to Iffland. Work-up afforded 3 (71 mg, 89%) which after recrystallization from ethanol/water

melted at 232°. A mixture melting point with authentic 3 and comparison of i.r. spectra confirmed the identity of the product.

Debromination of 29 with potassium hydroxide.—— The bromonitro sugar 29 (50 mg) was dissolved in ethanol (2 ml), an aqueous N solution of potassium hydroxide was added, and the mixture was stirred for 30 minutes at room temperature. Inspection by t.l.c. (solvent D) revealed that no 29 was left and that a product with the same mobility as 3 was formed. The reaction mixture was therefore diluted with ethanol (10 ml) and rapidly deionized with cation exchange resin. The solution so obtained gave a positive test for bromine with potassium iodide/starch, indicating that hypobromous acid was originally present and hence that bromine must have been removed from the sugar as positive bromonium ion. Evaporation of the solution and recrystallization of the residue from ethanol/water afforded 3 (24 mg, 61.8%) melting at 230-232° and giving an undepressed mixture melting point with authentic 3.

Debromination of 29 with sodium methoxide.—— A methanolic solution (5 ml) of bromonitro sugar 29 (80 mg) was refluxed in the presence of a methanolic 0.1 N solution of sodium methoxide (2 ml) for 20 minutes. T.l.c. inspection (solvent D) of the reaction mixture revealed that a major product with very low mobility was formed and that some starting material was left. When the reaction mixture was diluted with water a solid material (16 mg) separated which was

identified as unreacted 29 by t.l.c. and its i.r. spectrum. The major, slow-moving product was not identified. A smell of benzaldehyde in the reaction mixture indicated debenzylidenation.

Methyl 2-O-Acetyl-4,6-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-gulopyranoside (32)

A solution of the β-D-galactoside acetate 22 (115 mg) in methanol (10 ml) was stirred for 1 hour at room temperature with a saturated, aqueous solution of sodium acetate (1 ml) and NBA (50 mg). Precipitative work-up gave a solid (128 mg) which was recrystallized from ethanol/water to furnish 32 (116 mg, 87.5%) with a melting point of 178-180° and $[\alpha]_D$ +4.7° (c, 0.4 in chloroform). Characteristic i.r. bands were observed at 1765 (s, O-acetyl) and 1570 (s, NO_2). Mass spectral and n.m.r. data were also in agreement with the assigned structure. The mass spectrum exhibited peaks around m/e= 430 with an isotopic distribution pattern typical of a monobromo derivative. Peaks with weak intensities were observed at m/e= 352 (corresponding to a loss of Br from the molecular ion) and at m/e 325 (corresponding to a loss of benzaldehyde from the molecular ion).

Methyl 4,6-O-Benzylidene-3-chloro-3-deoxy-3-nitro-β-D-gulopyranoside (33)

To a solution of nitro sugar 3 (62 mg) in ethanol (15 ml) was added a 5% aqueous solution of sodium hypochlorite (0.6 ml) and the mixture was stirred at room temperature. T.l.c. inspection (solvent C) after 10 minutes revealed that

no 3 was left and an uniform, faster moving product was formed. The reaction mixture was stirred for another 15 minutes and then worked up by a combination of the precipitative method (12 mg) and the extractive method (60 mg). Recrystallization of the combined solids from ethyl acetate/petroleum ether afforded crystalline 33 (58 mg, 76%) with a melting point of 166-167° and $[\alpha]_D$+35.1° (c, 0.7 in chloroform). Characteristic i.r. bands were observed at 3480 (m, OH) and at 1570 (s, NO_2).

Analysis for $C_{14}H_{16}ClNO_7$ (345.74)

Calcd: C, 48.70; H, 4.65; Cl, 10.27.

Found: C, 48.62, H, 4.78; Cl, 10.26.

An identical material was obtained in a similar yield when the reaction was performed with a Javex solution.

Methyl 2,4,6-Tri-O-acetyl-3-chloro-3-deoxy-3-nitro-β-D-gulopyranoside (35)

The chloronitro sugar 33 (200 mg) was debenzylidenated with trifluoroacetic acid (5.0 ml) during 20 minutes at room temperature. The syrupy residue (145 mg) failed to crystallize and was therefore acetylated with acetic anhydride (5 ml) catalyzed by boron trifluoride etherate during 20 minutes. The acetylation mixture was poured into ice water which caused separation of an oil. The oil was extracted into chloroform (3x10 ml). The chloroform extract was washed twice with a cold, saturated sodium bicarbonate solution (5 ml) and twice with water (5 ml). It was then dried over anhydrous sodium sulfate and evaporated to give the acetate 35 as a syrup.

Crystalline 35 was obtained from chloroform/n-pentane. It melted at 91-92° and showed $[\alpha]_D$ -6.3° (c, 0.6 in chloroform). Characteristic i.r. bands were observed at 1765 and 1745 (s, O-acetyl) and at 1575 (s, NO_2).

Analysis for $C_{13}H_{18}ClNO_{10}$ (383.75)

Calcd: C, 40.72; H, 4.73; Cl, 9.25.

Found: C, 40.77; H, 4.71; Cl, 9.48.

Methyl 4,6-O-Benzylidene-3-bromo-3-deoxy-3-nitro-α-D-gulopyranoside (36) and -α-D-galactopyranoside (37)

Direct bromination. — A solution of the α-D-galactoside 2 (311 mg) in ethanol (40 ml) was stirred in an ice bath for 5 minutes with aqueous 0.1N sodium hydroxide (11 ml). Then bromine was added dropwise until the reaction mixture remained slightly yellow. After stirring the reaction mixture for another 15 minutes it was worked up precipitatively to afford a white solid material (355 mg, 91%). According to t.l.c. (solvent B) there was no starting material left but two new, faster moving products were formed in an estimated ratio of 1:1. A 60 MHz n.m.r. spectrum of the mixture in $CDCl_3$ exhibited two sharp methine proton singlets at 4.30τ and 4.48τ with an integration ratio of 45.55. The solid material was chromatographed on a column (absorbent: 20 g of silica gel, eluent: solvent C). A clean separation was achieved and afforded a fast fraction of 37 (130 mg, 33.4%) which melted at 66°, $[\alpha]_D$ + 160.3° (c, 0.5 in chloroform).

Analysis for $C_{14}H_{16}Br\ N\ O_7$, (390.20)

Calcd: C, 43.14; H, 4.13; Br, 20.46.

Found: C, 43.27; H, 4.15; Br, 20.72.

The slow fraction furnished upon evaporation crystalline 36 (190 mg, 48.7%), which melted at 118-120° and had a rotation of $[\alpha]_D$ + 108.0° (c, 0.8 in chloroform).

Analysis for $C_{14}H_{16}Br\ N\ O_7$, (390.20)

Calcd: C, 43.14; H, 4.13; Br, 20.46.

Found: C, 42.85; H, 4.22; Br, 20.45.

The spectral properties of the two isomers were in accord with the structural assignments (i.r. for 37: 3540 (m, OH) and 1560 (s, NO_2); for 36: 3510 (m, b, OH) 1560 (s, NO_2).

Bromination with NBA. — A solution of nitro sugar 2 (93 mg) in methanol (10 ml) was stirred at room temperature with a saturated, aqueous solution of sodium acetate (1 ml) and NBA (50 mg). There was no starting material left after 30 minutes and the reaction mixture was worked up by the precipitative method. The solid material so obtained showed two spots on t.l.c. (solvent C) and exhibited two methine proton signals at 4.30 τ and 4.48 τ with an intensity ratio of 15:85. The two products were separated by column chromatography as described in the preceding paragraph. The pure isomeric products obtained (37: 12.5 mg, 10.8%; 36: 82 mg, 70.8%) were identical with the respective products obtained by the direct bromination as indicated by their melting points (37, 65-67°; 36, 119-120°), t.l.c. mobilities and i.r. spectra.

Reactions of methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-gulopyranoside (36) and -α-D-galactopyranoside (37)

Debromination with sodium borohydride. — Bromonitro compound 36 (170 mg) was dissolved in ethanol (35 ml) and reduced at room temperature with sodium borohydride (80 mg) according to Iffland. Work-up after a reaction time of 10 minutes and recrystallization from ethylacetate/ petroleum ether afforded (131 mg, 96.8%) of methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-galactopyranoside (2) with a melting point of 165-167°.

The i.r. and n.m.r. spectra were identical with those of an authentic sample. In an analogous manner the bromine was reductively removed from the isomeric bromonitro compound 37 (20 mg). Again 2 (12 mg, 75%) was obtained and characterized by its melting point (165-166°) and its i.r. spectrum.

Debromination with sodium hydroxide. — Bromonitro compound 37 (95 mg) was dissolved in methanol (30 ml) and stirred with an alcoholic N solution of sodium hydroxide (1 ml). T.l.c. inspection (solvent D) after 5 hours showed the slow generation of a new product having the same mobility as a reference sample of methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-α-D-talopyranoside (28). After 10 hours, t.l.c. indicated near completion of the reaction. The reaction mixture was therefore diluted with water and the methanol was evaporated to give crystalline 28 (54.1 mg, 79.5%) with a melting point of 208-210° and $[\alpha]_D$ +89.0° (c, 0.5 in chloroform). Reported values for 28 (compound 22, Part III, Chapter C); m.p. 215-216° and $[\alpha]_D$ +91.8° (in chloroform). The identity of the product with 28 was further confirmed by its i.r. spectrum. Treatment of the isomeric bromonitro sugar 36 with base under comparable conditions gave no 28 and only starting material 36 was recovered even after a prolonged reaction time of 20 hours.

However, after treatment of isomer 36 (30 mg) with a methanolic solution (5 ml) of 0.1 N sodium methoxide (1 ml) at reflux temperature for 20 minutes, t.l.c. (solvent C) indicated the formation of a major product with very low mobility, and a minor product with the same mobility as 28.

The reaction mixture was diluted with water, and upon evaporation a precipitate separated. This precipitate was filtered off, washed with cold water and dried to give 28 (6 mg, 28%) with a m.p. of 213-215°. The i.r. spectrum of the material proved its identity with the previously obtained epoxynitro sugar 28.

Methyl 4,6-O-Benzylidene-3-chloro-3-deoxy-3-nitro-α-D-gulopyranoside (38)

A methanolic solution (15 ml) of nitro sugar 2 (120 mg) was stirred at room temperature with Javex (1 ml). T.l.c. inspection (solvent D) after 1 hour indicated that a new, uniform product of higher mobility than 2 was formed. Extractive work-up furnished the crystalline chloronitro compound 38 (123 mg, 92.4%), which after recrystallization from ethanol/water melted at 121-122°; $[\alpha]_D$ +143.9° (c, 0.4 in chloroform). The compound showed characteristic i.r. bands at 3540 (m, OH) and 1570 (s, NO_2).

Analysis for $C_{14}H_{16}ClNO_7$, (345.74)

Calcd: C, 48.70; H, 4.65; Cl, 10.27.

Found: C, 48.53; H, 4.77; Cl, 10.13.

Methyl 4,6-O-Benzylidene-3-bromo-2,3-dideoxy-3-nitro-α-D-xylo-hexopyranoside (39) and -α-D-lyxo-hexopyranoside (40)

A solution of the 2,3-dideoxy-3-nitro glycoside 8 (200 mg) in ethanol (30 ml) was stirred for 5 minutes with aqueous 0.1 N sodium hydroxide (6.8 ml). Then bromine was added dropwise until a slightly yellowish color was maintained in the reaction mixture. Stirring was continued for another 10 minutes and was followed by precipitative work-up. The crude material so obtained (220 mg, 97.8%) showed two spots on t.l.c. (solvent A), both with a higher mobility than the starting material. A 60 MHz n.m.r. spectrum in $CDCl_3$ exhibited two methine proton signals at 4.28τ and 4.41τ with an intensity ratio of 25:75. The two products were separated by column chromatography (adsorbent: 20 g silica gel, eluent: solvent A). The faster moving product 40 (47 mg, 20.9%) melted at 105-106° and had a rotation of $[\alpha]_D$ +140.5° (c, 0.3 in chloroform). A characteristic i.r. band was observed at 1565 (s, NO_2). The product was further characterized by mass spectrometric analysis as described in the Discussion, Part II. The more slowly moving product 39 (156 mg, 69.3%) was recrystallized from chloroform/n-pentane and melted at 103-104°; $[\alpha]_D$ +112.5° (c, 0.4 in chloroform). A characteristic i.r. band was observed at 1565 (s, NO_2). The product was further characterized by mass spectrometry.

Analysis for $C_{14}H_{16}BrNO_6$ (374.20)

Calcd: C, 45.05; H, 4.31; Br, 21.35.

Found: C, 45.02, H, 4.14; Br, 21.63.

Bromination with NBA. — A solution of nitro sugar 8 (60 mg) in methanol (5 ml) was allowed to react at room temperature, for 30 minutes, with NBA (30 mg) in the presence of a saturated, aqueous solution of sodium acetate (0.5 ml). Precipitative work-up afforded a crude material whose 60 MHz n.m.r. spectrum in $CDCl_3$ exhibited two methine proton signals at 4.27 τ and 4.41 τ with an intensity ratio of 22:78. The spectra of the crude materials obtained by the direct bromination method and the NBA method were superimposable. Since t.l.c. (solvent A) also suggested identity of the two materials, the mixture obtained by the NBA method was characterized no further.

Methyl 4,6-O-Benzylidene-3-chloro-2,3-dideoxy-3-nitro-α-D-xylo-hexopyranoside (41) and -α-D-lyxo-hexopyranoside (42)

A solution of nitro sugar 8 (250 mg) in methanol (30 ml) was stirred at room temperature for 2 hours with Javex (2 ml). Inspection by t.l.c. (solvent D) indicated the formation of a major product and a faster moving, minor product. Work-up by extraction furnished a syrupy material (240 mg, 85.5%) whose n.m.r. spectrum in $CDCl_3$ exhibited two methine proton signals at 4.28 τ and 4.42 τ with an intensity ratio of 14:86. The two products were separated by column chromatography (adsorbent: 20 g silica gel, eluent: Solvent D).

The fast-moving product 42 (35 mg, 12.5%) was crystallized from ethanol/water and melted at 122-123°; $[\alpha]_D$ +126° (c, 0.6 in chloroform). A characteristic i.r. band was located at

1570 (s, NO_2). The product was further characterized by mass spectrometric analysis, which is described in the Discussion, Part II. The slow-moving product 41 (188 mg, 66.9%) was crystallized from ethanol/water and melted at 101-102°; $[\alpha]_D$ +128° (c, 0.5 in chloroform). A characteristic i.r. band at 1565 (s) indicated the presence of a nitro group. The product was further characterized by mass spectrometry.

Analysis for $C_{14}H_{16}ClNO_6$ (329.74)

Calcd: C, 51.10; H, 4.89; Cl, 10.77.

Found: C, 51.04; H, 4.83; Cl, 10.79.

Methyl 4,6-O-Benzylidene-3-bromo-2,3-dideoxy-3-nitro-β-D-xylo-hexopyranoside (43)

A methanolic solution (5 ml) of nitro sugar 9 (60 mg) was brominated at room temperature with NBA (30 mg) in the presence of a saturated, aqueous solution of sodium acetate (0.5 ml). The reaction was complete after 15 minutes (t.l.c.), and precipitative work-up gave an amorphous powder of 43 (65 mg, 96.2%) with $[\alpha]_D$ + 22.0° (c, 0.5 in chloroform). The i.r. spectrum showed a characteristic band at 1565 (s, NO_2).

Analysis for $C_{14}H_{16}BrNO_6$ (374.20)

Calcd: C, 45.05; H, 4.31; Br, 21.35.

Found: C, 45.03; H, 4.12; Br, 21.35.

Methyl 4,6-O-Benzylidene-3-chloro-2,3-dideoxy-3-nitro-β-D-xylo-hexopyranoside (44)

Nitro sugar 9 (177 mg) was dissolved in methanol (45 ml) and the solution was stirred at room temperature with Javex (1.8 ml). The reaction was monitored by t.l.c. (solvent D) which indicated completion of the reaction after 10 minutes. Stirring was continued for another 10 minutes and the reaction was worked up by the extractive method. The syrupy material so obtained was dissolved in ethanol, and addition of water precipitated a solid (182 mg, 91.8%)which melted at 48-49°, $[\alpha]_D$ +18.2° (c, 0.7 in chloroform). A characteristic i.r. band was observed at 1565 (s, NO_2).

Analysis for $C_{14}H_{16}ClNO_6$ (329.74)

Calcd: C, 51.10; H, 4.89; Cl, 10.77.

Found: C, 51.06; H, 4.8 ; Cl, 10.82.

Methyl 4,6-Di-O-acetyl-3-chloro-2,3-dideoxy-3-nitro-β-D-xylo-hexopyranoside (46)

The chloronitro sugar 44 (330 mg) was debenzylidenated with trifluoroacetic acid (6.0 ml) during 1 hour at room temperature. The reaction mixture was then worked up and furnished a colorless syrupy material (220 mg) which failed to crystallize. The syrup was therefore acetylated with acetic anhydride (5 ml) in the presence of a catalytic amount of boron trifluoride etherate. After standing for 20 minutes at room temperature the acetylation mixture was poured onto ice water, whereby oily droplets separated. The oily material was extracted with chloroform (3x10 ml) and the chloroform extract was washed twice with a saturated, aqueous solution of sodium hydrogen carbonate (5 ml) and twice with water (5 ml). After drying over sodium sulfate the chloroform solution was evaporated and afforded a syrup which gave the acetate 46 by crystallization from cyclohexane. Compound 46 (192 mg, 64.7%) melted at 90-91°; $[\alpha]_D$ +27.5° (c, 0.5 in chloroform). The i.r. spectrum showed characteristic bands at 1745 with a shoulder at 1760 (s, O-acetyl), and at 1570 (s, NO_2).

Analysis for $C_{11}H_{16}ClNO_8$ (325.71

Calcd: C, 40.60; H, 4.95; Cl, 10.86.

Found: C, 40.76; H, 5.05; Cl, 10.81.

Methyl 2-O-Acetyl-4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-allopyranoside (48)

The nitro glucoside acetate 47 (200 mg) was dissolved in methanol (20 ml) and brominated at room temperature with NBA (100 mg) in the presence of a saturated, aqueous solution of sodium acetate (2 ml). Precipitative work-up after a reaction time of 3 hours gave a solid material (234 mg, 95.5%). Recrystallization from ethyl acetate/petroleum ether afforded pure 48 (197 mg) with a melting point of 223-225°. A mixture melting point with a sample obtained in an independent synthesis (Part III, Chapter D), (compound 62) remained undepressed. The i.r. and n.m.r. spectra were also identical.

Epoxide formation from 48

To a solution of compound 48 (52 mg) in methanol (5 ml) was added a 0.1 N methanolic solution of sodium methoxide (2.4 ml). The reaction mixture was heated to reflux for 30 minutes and then cooled and deionized with cation exchange resin. The solution, smelling slightly of benzaldehyde, was diluted with water, and most of the methanol was removed by evaporation. A white, solid precipitate of methyl 2,3-anhydro-4,6-benzylidene-3-nitro-β-D-mannopyranoside 50 (15 mg, 40.5%) was obtained with a melting point of 178-180°. A sample prepared from the altro isomer (49), (p.198), had a melting point of 182-183°. T.l.c., i.r., and n.m.r. further proved the identity of 50 with the epoxide described later.

Methyl 2-O-Acetyl-4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-altropyranoside (49)

The nitro mannoside acetate 21 (150 mg) was dissolved in methanol (15 ml) and brominated with NBA (75 mg) in the presence of a saturated, aqueous solution of sodium acetate (0.5 ml). Stirring for 1 hour at room temperature was followed by precipitative work-up, which afforded crude 49 (174 mg, 95%) with a melting point of 140-142° and $[\alpha]_D$ -76.2° (c, 0.5 in chloroform). Recrystallization from ethanol/water raised the melting point to 152-153° and the rotation to $[\alpha]_D$-80.8° (c, 1.3 in chloroform). The i.r. spectrum of 49 showed characteristic bands at 1775 (s, O-acetyl) and at 1565 (s, NO_2).

Analysis for $C_{16}H_{18}BrNO_8$ (432.25)

Calcd: C, 44.50; H, 4.20; Br, 18.45.

Found: C, 44.43; H, 4.30; Br, 18.64.

Treatment of compound 49 with base at elevated temperature: Epoxide formation.—— To a solution of compound 49 (64.8 mg) in methanol (5 ml) was added a methanolic 0.1 N solution of sodium methoxide (3 ml). The reaction mixture was heated to reflux for 30 minutes, then cooled and deionized with ion exchange resin. The neutral solution, in which a smell of benzaldehyde was noticeable, was diluted with water and the methanol was largely evaporated. A white, solid material separated and was filtered off, washed with cold water and dried (17 mg, 36.7%). The melting point (179-180°), t.l.c.,

and the i.r. spectrum proved that the product was identical with the epoxide 50 previously obtained from 48. Recrystallization of the product from ethyl acetate/petroleum ether gave analytically pure 50, with a melting point of 182-183° and $[\alpha]_D$-68.4° (c, 0.6 in chloroform). The characterization of epoxide 50 by its spectral and dichroic properties is discussed in connection with the alkaline epoxidation of carbohydrate nitroolefins (Part III, Chapter C, compound 27).

Analysis for $C_{14}H_{15}NO_7$ (309.3)

Calcd: C, 54.45; H, 4.89; N, 4.53.

Found: C, 54.63; H, 5.08; N, 4.32.

Treatment of compound 49 with base at room temperature: Formation of "mixture A" —— A solution of 49 (64.8 mg) in methanol (5 ml) was stirred with 0.1 N methanolic sodium methoxide (3 ml). After 30 minutes, inspection by t.l.c. (solvent C) revealed the formation of a seemingly uniform product with slower mobility than the starting material. The reaction mixture was therefore deionized with ion exchange resin and diluted with water. Evaporation of the methanol furnished a white solid (48 mg, 82.3%) with a rotation of $[\alpha]_D$-38.2°(c,0.5 in chloroform). The n.m.r. spectrum (60 MHz) of this material in $CDCl_3$ exhibited two methine proton signals at 4.22 τ and 4.41 τ in an intensity ratio of 20:80, indicating the presence of two compounds. Furthermore, the n.m.r. spectrum was superimposable on that of "mixture A" encountered in the bromination of 7 and described later on. Since neither of the two products could be isolated in a pure state, the mixture was acetylated using the acetyl chloride

triethylamine method. The solid acetate mixture obtained was recrystallized twice from ethyl acetate/petroleum ether to give a single product that proved to be methyl 2-O-acetyl-4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-allopyranoside (48) (34.5 mg, 65%), melting at 223-225°. The identity of the product with 48 described earlier was confirmed by comparison of i.r. and n.m.r. spectra and by t.l.c. (solvent A).

Treatment of compound 49 with base at 0°

A solution of 49 (64.8 mg) in methanol (5 ml) was stirred in an ice bath with an 0.1 N methanolic solution of sodium methoxide (1.5 ml, 1 equivalent). T.l.c. inspection (solvent C) after 1 hour revealed that some starting material was left, but the major spot had the same mobility as the mixture obtained in the base treatment at room temperature. Deionization with ion exchange resin and precipitative work-up led to the isolation of a solid material (52 mg) which was passed through a chromatographic column (adsorbent: 10 g silica gel, eluent: solvent C). A small amount (5 mg) of fast-moving product was eluted first and proved to be unreacted starting material 49 as shown by its melting point (149-151°) and its i.r. spectrum. The more slowly moving product (37 mg) was uniform on t.l.c., however a 60 MHz n.m.r. spectrum in $CDCl_3$ exhibited two methine proton signals at 4.22 τ and 4.42 τ in an intensity ratio of 15:85. The n.m.r. spectrum was identical with that of the mixture obtained above in the base treatment at room temperature.

Methyl 4,6-O-Benzylidene-3-bromo-3-deoxy-3-nitro-β-D-allopyranoside 51 and -β-D-altropyranoside 52 (mixture A)

Bromination of nitro mannoside 7 with NBA.—— The nitro sugar 7 (415 mg) was brominated in methanolic solution (40 ml) with NBA (200 mg) in the presence of a saturated, aqueous solution of sodium acetate (4 ml). Refluxing for 1 hour followed by precipitative work-up gave a white solid material (507 mg, 97.5%), "mixture A" with $[\alpha]_D$ -35.5° (c, 0.6 in chloroform), which on t.l.c. inspection with various developing systems showed a single spot only. However, a 60 MHz n.m.r. spectrum in $CDCl_3$ exhibited two methine proton signals at 4.42τ and 4.23τ in an intensity ratio of 80:20, indicative of the presence of 51 and 52. The i.r. spectrum showed characteristic bands at 3440 (m,b, OH), and at 1565 (s, NO_2). All attempts to separate the two products failed and therefore they could not be characterized in a pure state. A similar mixture (superimposable n.m.r. spectrum) was obtained when the bromination was carried out at room temperature for 5 hours.

Bromination of nitro mannoside 7 with NBS.—— To a solution of nitro sugar 7 (103 mg) in methanol (10 ml) was added N-bromosuccinimide (71 mg) and a saturated, aqueous solution of sodium acetate (1 ml). The reaction mixture was refluxed for 1 hour and worked up precipitatively to afford a white solid material (106 mg). The n.m.r. spectrum of this material in $CDCl_3$ was superimposable on that of "mixture A".

Direct bromination of nitro mannoside 7.—— A solution of nitro sugar 7 (311 mg) in methanol (25 ml) was stirred in an ice bath for 10 minutes with aqueous, 0.1 N sodium hydroxide (12.5 ml). Then bromine was added dropwise until the reaction mixture remained slightly yellow. Continued stirring for another 10 minutes in the ice bath was followed by precipitative work-up to give a white solid material (319 mg). A 60 MHz n.m.r. spectrum of this material in $CDCl_3$ exhibited four signals in the region where methine protons resonate (4.23τ, 4.32τ, 4.42τ, and 4.49τ), indicating the presence of four products in an intensity ratio of 5:10:35:50. T.l.c. using solvent A showed one major spot with the same mobility as that of the nitro glucoside 5, one slightly faster moving spot, and a weak, slow-moving spot having the same mobility as the starting material 7. The mixture was placed on a column (adsorbent: 20 g silica gel, eluent: solvent A) and eluted. All fractions were examined by t.l.c. and pooled accordingly. A fast-moving material (120 mg) was isolated first. It appeared uniform on t.l.c. and had a rotation of $[\alpha]_D$-39.8° (c, 0.9 in chloroform). Its n.m.r. spectrum showed only two methine proton signals, at 4.23τ and 4.42τ (intensity ratio, 15:85). The spectrum was superimposable with that of "mixture A". After discarding some intermediate mixed fractions, a homogeneous product (93 mg) was isolated which had the same t.l.c. mobility as 5. Its identity as pure 5 was established by an undepressed mixture melting point (180-181°) and by comparison of the n.m.r. spectrum with that of an authentic sample. A subsequent,

chromatographically uniform fraction furnished upon evaporation 19 mg of starting material 7 whose identity was established by an undepressed mixture melting point (194-196°) and its i.r. spectrum. As a result of this separation the methine proton signals of the original mixture were assigned in the following way: 4.23τ to 52, 4.32τ to 7, 4.42τ to 51, and 4.49τ to 5 (see also Part I for chemical shifts of methine protons). Mixed fractions eluted between the fractions yielding "mixture A", 5, and 7 were discarded.

Bromination of nitro glucoside 5 with NBA.—— Nitro sugar 5 (415 mg) was brominated in methanolic solution (40 ml) with NBA (620 mg) in the presence of a saturated, aqueous solution of sodium acetate (4 ml). After 1 hour, only traces of starting material were left and mainly a faster moving product was formed according to t.l.c. (solvent A). The picture did not change during another 5 hours of refluxing. Precipitative work-up furnished a crude material ("mixture B", 457 mg) which still contained traces of starting material. A 60 MHz n.m.r. spectrum in $CDCl_3$ exhibited three signals in the methine proton region (4.22τ, 4.41τ and 4.48τ) in an intensity ratio of 15:75:10. Except for some minor signals the n.m.r. spectrum was almost identical with that obtained from "mixture A". Similarly the i.r. spectrum proved to be almost identical with that of "mixture A" and showed characteristic bands at 3440 (m,b, OH), and 1565 (s, NO_2). The rotation of the material was $[\alpha]_D$ -41.2° (c, 0.4 in chloroform). In accord with previous assignments the methine proton signals were attributed to 52

(4.22 τ), to 51 (4.41 τ), and to unreacted 5 (4.48 τ).

Methyl 2-O-Acetyl-4,6-benzylidene-3-bromo-3-deoxy-3-nitro-β-D-allopyranoside (48) and -β-D-altropyranoside (49)

A solution of "mixture A" (150 mg) in methylene chloride (6 ml) was acetylated with acetyl chloride (1.04 ml) and triethylamine (1.93 ml). Work-up gave a solid residue which showed two spots on t.l.c. (solvent A), the major spot being the faster moving one. The n.m.r. spectrum exhibited signals in the region of 4.10-4.20 τ (corresponding to the methine proton and H-2 of 49) and in the region of 4.30-4.50 τ (corresponding to the methine proton and H-2 of 48) in an intensity ratio of 20:80. The mixture was placed on a column for chromatographic separation (adsorbent: 20 g silica gel; eluent: solvent A). Evaporation of the fractions containing the fast-moving product furnished 48 (117 mg, 70.5%), with a melting point of 222-224°. The i.r. spectrum proved to be identical with that of compound 48 obtained previously. The slow-moving material (24.5 mg, 14.8%) melted at 149-151° and was identified with previously prepared 49 by comparison of i.r. spectra.

Methyl 2,3-Anhydro-4,6-benzylidene-3-nitro-β-D-mannopyranoside (50)

Treatment of "mixture A" with base: Epoxide formation.—— A solution of"mixture A" (60 mg) in methanol (5 ml) and 0.1 N methanolic sodium methoxide (1.5 ml) was heated to reflux. The reaction mixture was cooled after 30 minutes and diluted with water. Evaporation of the methanol afforded a precipitate

of 50 (40 mg, 84.2%) melting at 181-183°. The i.r. spectrum confirmed the identity of this material with the epoxide 50 obtained previously upon base treatment of the bromonitro sugar acetates 48 and 49.

Treatment of "mixture B" with base: Epoxide formation.—— A solution of "mixture B" (117 mg) in methanol (10 ml) and 0.1 N methanolic sodium methoxide (3 ml) was heated to reflux. Work-up as above after a reaction time of 30 minutes afforded crystalline 50 (65 mg, 77.8%) melting at 181-182°. The identity of the material with compound 50 obtained previously was established by its i.r. spectrum.

Methyl 4,6-O-Benzylidene-3-bromo-2,3-dideoxy-3-nitro-β-D-ribo-hexopyranoside (53)

A methanolic solution (20 ml) of the 2,3-dideoxy-3-nitro glycoside 11 (200 mg) was refluxed in the presence of NBA (150 mg) and a saturated aqueous solution of sodium acetate (2 ml). Precipitative work-up after 1 hour afforded the bromonitro sugar 53 (222 mg, 87.3%) as an amorphous powder with a rotation of $[\alpha]_D$ -26.2° (c, 0.6 in chloroform). The i.r. spectrum showed characteristic band at 1560 (s, NO_2).

Analysis for $C_{14}H_{16}BrNO_6$ (274.20)

Calcd: C, 45.05; H, 4.31; Br, 21.35.

Found: C, 45.19; H, 4.23; Br, 21.31.

Attempted Bromination of the Nitro Glucoside 4 with NBA

To a solution of 4 (311 mg) in methanol (30 ml) was added NBA (150 mg) and a saturated, aqueous solution of sodium acetate (3 ml). The reaction mixture was heated to reflux, but even after a reaction time of 10 hours there was no t.l.c. evidence for product formation. Precipitative work-up afforded a white solid material (242 mg, 77.8%) melting at 166-167°. The n.m.r. spectrum was identical to that of the starting material 4.

Attempted Bromination of the Nitro Glucoside Acetate 54 with NBA

A solution of 54 (100 mg) in methanol (10 ml) was stirred with NBA (50 mg) and a saturated aqueous solution of sodium acetate (1 ml) for 3.5 hours at room temperature. There was no evidence of product formation, and upon work-up the starting material 54, melting point (196-197°) was recovered to 96%.

Bromination of the Nitro Mannoside 6 with NBA

To a solution of 6 (200 mg) in methanol (20 ml) was added NBA (400 mg) and a saturated aqueous solution of sodium acetate (2 ml). The mixture was heated to reflux and the reaction was monitored by t.l.c. (solvent C). The pattern observed after 3 hours remained essentially unchanged after 4 hours. The reaction mixture was then worked up precipitatively. A white solid material (213 mg) was obtained which showed two spots, the slower one having a similar mobility as the starting material 6. In the i.r. spectrum, the absorption band corresponding to the asymmetric stretching vibration of

the nitro group was split, one peak being at 1565 and the other at 1555 cm^{-1}. The higher absorption band being most likely caused by a α-bromo-substituted nitro group, this suggested that bromination had occurred at least partially. A 60 MHz n.m.r. spectrum in $CDCl_3$ exhibited four signals in the methine proton region at 4.24, 4.34 and 4.43, and 4.48τ in an intensity ratio of 33 : 42 : 25 (The signals at 4.34 and 4.43τ integrated together to give a value of 42%, however the signal at 4.43τ made by far the greater contribution). No attempt to separate the products was undertaken, but the presence of brominated products was confirmed when treatment of the mixture (80 mg) with a boiling solution of sodium methoxide (2 ml) for 20 minutes afforded pure methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-α-D-mannopyranoside (55). The yield was 51% after two recrystallizations from ethanol. The same epoxynitro sugar was obtained and identified in another connection (compound 20, Part III, Chapter C), and the two products were proved to be identical by their undepressed mixture melting point of 171-173° and by identical i.r. spectra.

In accord with previous assignments one can tentatively attribute the methine proton signal at 4.24τ to methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-altropyranoside (57) that at 4.34τ to starting material 6, that at 4.43τ to methyl 4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-allopyranoside (58), and that at 4.48τ to 4 (epimerized starting material).

Methyl 2-O-Acetyl-4,6-O-benzylidene-3-bromo-3-deoxy-3-nitro-α-D-altropyranoside (56)

The α-D-mannoside acetate 23 (100 mg) was brominated in methanolic solution (10 ml) with NBA (50 mg) in the presence of a saturated aqueous solution of sodium acetate (1 ml). Precipitative work-up after a reaction time of 2 hours at room temperature afforded a white solid material (103 mg, 84.5%) with a melting point of 152-153° and a rotation of $[\alpha]_D$ 12.3° (c, 1.2 in chloroform). The i.r. spectrum showed characteristic bands at 1760 (s, O-acetyl), and at 1570 (s, NO_2). N.m.r. spectral data were in accord with the structural assignment. The microanalytical data obtained were not wholly satisfactory although they did indicate the presence of 93% of the expected amount of bromine in the sample. Instability of the compound resulting in loss of bromine during storage and purification for analysis might be an explanation.

Analysis for $C_{16}H_{18}BrNO_8$ (432.25)

Calcd: C, 44.50; H, 4.20; Br, 18.45.

Found: C, 45.97; H, 4.57; Br, 17.12.

Treatment of 56 with base at elevated temperature: Epoxide formation.—— To a solution of 56 (64.8 mg) in methanol (5 ml) was added a 0.1 N methanolic solution of sodium methoxide (3 ml). The mixture was kept under reflux for 30 minutes and then cooled to room temperature. On dilution with water a voluminous precipitate separated which was filtered off, washed with cold water and dried to furnish the epoxynitro sugar 55 (38 mg, 82%), with a melting point of 173-174°. The i.r. spectrum was identical with that of 55 previously obtained.

Treatment of 56 with base at room temperature: Deacetylation accompanied by epimerization. — A solution of 56 (86.4 mg) in methanol (10 ml) and 0.1 N methanolic sodium methoxide (4 ml) was kept at room temperature. Inspection by t.l.c. (solvent A) after 1 hour revealed the formation of a seemingly uniform, more slowly moving product. Precipitative work-up after a reaction time of 3 hours afforded a white solid ("mixture C", 71 mg, 91%). The i.r. spectrum showed bands at 3380 (m, OH) and at 1560 (s, NO_2); there was no absorption in the region characteristic for an O-acetyl group. The 60 MHz n.m.r. spectrum exhibited two methine proton signals at 4.24τ and at 4.43τ in an intensity ratio of 40 : 60. They were tentatively assigned to 57 and 58, respectively. The spectrum showed also two signals for glycosidic methoxyl groups at 6.55 and 6.61τ, the lower-field signal being more intense. All attempts to separate the two products failed.

Acetylation of "mixture C". — A solution of "mixture C" (150 mg) in methylene chloride (10 ml) was acetylated with acetyl chloride (1.04 ml) and triethylamine (1.93 ml). Work-up afforded a solid material (153 mg) which seemed homogeneous on t.l.c. with various developing systems and had the same mobility as the acetate 56. The n.m.r. spectrum showed a complex pattern in the methine proton region which was due to overlap of the methine proton signals and the signals for H-2. The spectrum showed however two distinct acetyl signals at 7.88τ and 7.97τ with an intensity ratio of 65 : 35 and a total integration value corresponding to three protons. All attempts to separate

the two products failed. The signals at 7.88τ and 7.97τ were tentatively assigned to the O-acetyl group of methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-α-D-allopyranoside and to the α-D-altro isomer 56, respectively.

Treatment of "mixture C" with base at elevated temperature.—— A solution of "mixture C" (60 mg) in methanol (5 ml) and 0.1 N methanolic sodium methoxide (1.5 ml) was heated to reflux. The reaction mixture was cooled after 30 minutes and diluted with water, whereby a voluminous precipitate separated. Filtration and washing with cold water afforded the epoxynitro sugar 55 (36 mg, 75.8%), with a melting point of 172-173°. An undepressed mixture melting point and i.r. spectra proved the identity of the product with previously-obtained 55.

TABLE XV

Circular dichroism of α-halonitro sugars and some precursors

Compound	Extrema		[θ] at a given λ (in nm)				
	λ (in nm)	[θ]	270	290	310	330	360
26	292	-4220		-4130	-2430	-590	-90
27	290	-3233	-1850	-3230	-1400	-240	0
29	288	6438	3980	6330	3640	2040	620
33	279	3667	3110	3130	1070	690	200
36	287	2800	1850	2770	2020	1490	390
37	290 329	-1810 2640		-1810	550	2635	1120
38	278	1658	1550	1110	410	380	80
8	281 317	496 -427	325	305	-370	-325	-100
39	285	1892	1670	1830	1410	1120	310
40	293	4600	1000	4520	3440	1880	510
41	275	1328	1220	960	520	480	175
42	288	2903	1600	2855	1600	800	170
9	280 319	851 -354	710	620	-270	-280	-50
43	287	4920	3140	4690	2750	1740	555
44	282	2916	2590	2570	1150	780	220
47	287	740	400	710	150	0	0
48	270 320	-795 -631	-795	-630	-610	-540	-160
22	280	2638	2240	2370	1150	690	115
49	291	-4830	-2300	-4785	-2990	-1470	-370
6	292	-4935	-1930	-4870	-3360	-1660	-450
11	293	721	370	690	585	370	70
53	289	-2436	-1410	-2420	-1440	-500	-110

PART III

SYNTHESIS AND REACTIONS OF NITROOLEFINS

A. Synthesis of Nitroolefins

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-hex-2-enopyranosides

i) α-D-threo Isomer 3.—— A mixture of methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-galactopyranoside (180 mg), anhydrous sodium acetate (360 mg) and acetic anhydride (5 ml) was heated on a steam bath for 30 minutes with frequent swirling. The reaction mixture was then cooled to room temperature and poured into 30 ml of ice water. The white precipitate was filtered off, washed with cold water, and dried. Recrystallization from ethyl acetate/petroleum ether afforded the nitroolefin 3 (148 mg, 87.2%) with a melting point of 183-184°. Reported (20): m.p. 185-186°. The i.r. spectrum of 3 was identical with that of an authentic sample prepared (20) from methyl 4, 6-O-benzylidene-3-deoxy-3-nitro-α-D-talopyranoside. When the improved method of olefin preparation was applied to the taloside just mentioned, 3 was obtained in a yield of 83%.

ii) β-D-threo Isomer 4.—— Compound 4 was obtained in 95% yield from methyl 4,6-O-benzylidene-3-deoxy-3-nitro-β-D-galactopyranoside by the method used above. It had a melting point of 154-155°, $[\alpha]_D$ -47.5° (c, 0.7 in DMF), and its i.r. spectrum was identical with that of an authentic sample for which $[\alpha]_D$ -47.8° had been recorded (21).

iii) β-L-threo Isomer 5.—— This compound was obtained in an analogous fashion from methyl 4,6-O-benzylidene-3-deoxy-3-nitro-β-L-galactopyranoside in a yield of 93.5%, m.p. 159-161°, $[\alpha]_D$+47.1 (c, 1.1. in DMF).

iv) α-D-erythro Isomer 1.—— This compound was prepared by dehydroacetylation of methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-α-D-glucopyranoside as reported in the literature (20).

Found: m.p. 182-183°, $[\alpha]_D$-92.5° (c, 0.7 in ethyl acetate).

Reported: m.p. 183°, $[\alpha]_D$-93° .

v) β-D-erythro Isomer 2.—— This compound was prepared by dehydroacetylation of methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside according to the literature (19).

Found: m.p. 143-144°, $[\alpha]_D$-187° (c, 0.6 in chloroform).

Reported: m.p. 144-145°, $[\alpha]_D$-192.5°.

3-O-Acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-xylo-hexofuranos-5-ene (6)

This nitroolefin was prepared from a mixture of 6-deoxy-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose and its β-L-ido isomer (74) by consecutive acetylation and Schmidt-Rutz reaction as reported in the literature (22). The nitroolefin was obtained in a yield of 63% and the physical data (m.p. 108-110°, $[\alpha]_D$+6.8° (c, 0.8 in chloroform) were in agreement with reported values.

β-Nitrostyrene (7)

β-Nitrostyrene (m.p. 57°) was prepared from benzaldehyde and nitromethane according to the literature (60).

B. Reduction of Methyl 4,6-0-Benzylidene-2,3-dideoxy-3-nitro-D-hex-2-enopyranosides

General Procedure for Reduction with Sodium Borohydride

To a solution of a given nitroolefinic sugar (100 mg) in ethanol (10 ml) was added a solution of sodium borohydride (50 mg) in ethanol (5 ml). The reaction mixture was stirred at room temperature for a specified time (Table XVI). To remove the sodium ions the reaction mixture was then stirred with cation exchange resin for ten minutes, after which the resin was filtered off and washed several times with ethanol. The combined filtrate and washings were evaporated to dryness. Repeated evaporations with methanol afforded in all cases a crystalline residue which upon recrystallization from ethyl acetate/petroleum ether gave pure products. Yields and physical constants found and reported for the four stereoisomeric methyl 4,6-0-benzylidene-2,3-dideoxy-3-nitrohexopyranosides are summarized in Table XVI.

TABLE XVI

Reductions with sodium borohydride

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-	Reaction time (hours)	Yield (%)	m.p. (°C)	$[\alpha]_D$	Reported m.p. (°C)	Reported $[\alpha]_D$	Reference
α-D-arabino-hexopyranoside (8)	2	91	108-110	+67*	112	+67	(20)
β-D-arabino-hexopyranoside (9)	3	87	149-150	-96*	149	-96	(19)
α-D-lyxo-hexopyranoside (10)	1	81	108-109	+155**	108		(20)
β-D-lyxo-hexopyranoside (11)	1	89	177-179	+22**	176	+15	(81)

* Optical rotation measured in chloroform.

** Optical rotation measured in dimethylformamide.

General Procedure for Reduction with Zinc and Acetic Acid

To a solution of a given nitroolefinic sugar (293 mg) in ether (30 ml) were added zinc dust (600 mg) and 25% aqueous acetic acid (1.5 ml). The reaction mixture was refluxed for 1-2 hours and the insoluble material was then removed by filtration. The filtrate was evaporated several times with added methanol to yield a crystalline residue. Recrystallization from ethyl acetate/petroleum ether afforded the desired oximino products in a pure state. Yields, physical and microanalytical data are recorded in Table XVII.

TABLE XVII

Reductions with zinc and acetic acid

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-oximino-	Yield (%)	m.p. (^{0}C)	$[\alpha]_D$ ($CHCl_3$)	Reported m.p. (^{0}C)	Reported $[\alpha]_D$ ($CHCl_3$)	Reference
-D-erythro-hexopyranoside (12)	88	197-199	+171	203	+172	(20)
-D-erythro-hexopyranoside (13) *	87	233	-16.4			
-D-threo-hexopyranoside (14)	86	220-221	+248	220	+257	(82)
-D-threo-hexopyranoside (15) **	81	215-216	-61.5			

Analysis for $C_{14}H_{17}NO_7$ (279.3) Calcd: C, 60.21; H, 6.14; N, 5.02.

* Found: C, 60.40; H, 6.19; N, 5.07.

** Found: C, 60.12; H, 6.09; N, 4.92.

Methyl 3-Acetoximino-4,6-O-benzylidene-2,3-dideoxy-β-D-erythro-hexopyranoside (16)

To a solution of oxime 13 (100 mg) in pyridine (2 ml) was added acetic anhydride (1 ml). After standing overnight at room temperature the reaction mixture was poured into 30 ml ice water, whereby a white, solid material separated. The solid was filtered off, washed with cold water, and dried. Recrystallization from ethanol gave the acetoximino compound 16 (107 mg, 93.1%) with a melting point of 216° and $[\alpha]_D$-15.6° (c, 1.2 in chloroform).

Analysis for $C_{16}H_{19}NO_6$ (321.3)

Calcd: C, 59.80; H, 5.92; N, 4.36.

Found: C, 59.72; H, 5.99; N, 4.21.

Methyl 3-Acetoximino-4,6-O-benzylidene-2,3-dideoxy-β-D threo-hexopyranoside (17)

The procedure described for the preparation of the acetoximino compound 16 was followed exactly. In this manner the oxime 15 afforded the acetoximino derivative 17 in a yield of 78.1%, with a melting point of 163-164° and an optical rotation of $[\alpha]_D$+83.8° (c, 0.4 in chloroform).

Analysis for $C_{16}H_{19}NO_6$ (321.3)

Calcd: C, 59.80; H, 5.92; N, 4.36.

Found: C, 59.78; H, 6.08; N, 4.37.

Methyl 4,6-O-Benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose (18)

A solution of oxime 12 (200 mg) in ethanol (10 ml) was stirred at room temperature with a mixture of levulinic acid (4 ml) and 0.1 N hydrochloric acid (1 ml) for four hours. The reaction mixture was then diluted with water (25 ml) and the ethanol was distilled off in vacuo. The remaining aqueous solution was then extracted three times with chloroform (20 ml). The combined chloroform extracts were washed twice with saturated sodium bicarbonate solution (10 ml) and twice with water (10 ml). The washed chloroform solution was dried with anhydrous sodium sulfate and evaporated to give a crystalline residue. The residue was recrystallized from 2-propanol to yield the known oxo sugar 18 (142 mg, 77.6%) with a melting point of 176-177° and $[\alpha]_D$ +155° (c, 0.7 in ethyl acetate).
Flaherty et al. (65) reported m.p. 177-178°, $[\alpha]_D$ +159° (ethyl acetate).
Rosenthal et al. (65) reported m.p. 174-176°.

Methyl 4,6-O-Benzylidene-2-deoxy-β-D-erythro-hexopyranosid-3-ulose (19)

Oxime 13 was subjected to the deoximation method described above for oxime 12. The oxo sugar 19 was obtained in a yield of 98.8% with a melting point of 193-195° and $[\alpha]_D$ -51.5° (c, 1.0 in chloroform). After recrystallization from 2-propanol the melting point was 194-195°.

Analysis for $C_{14}H_{16}O_5$ (264.3)

Calcd: C, 63.62; H, 6.10.

Found: C, 63.46; H, 6.30.

C. Alkaline Epoxidation of Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-D-hex-2-enopyranosides with Hydrogen Peroxide

General Procedure

To a solution of a given nitroolefinic sugar (200 mg) in ethanol (20 ml) was added 1 ml of aqueous, 30% hydrogen peroxide (reagent grade), and the pH of the mixture was adjusted to 8-9 by adding a few drops of N sodium hydroxide solution. The reaction mixture was stirred at room temperature for a specified time (Table XVII) during which the epoxide began to crystallize, usually at an early stage. Completion of the reaction was checked by t.l.c. using solvent C as developing system. The white, crystalline precipitate was removed by filtration, washed with a small amount of cold water (for 20 and 21) or cold ethanol (for 22, 24 and 26), and dried in a desiccator. By adding some water to the mother liquor and concentrating the solution under diminished pressure, second crops were obtained of 20 and 22, whereas the mother liquors of sparingly soluble 24 and 26 furnished the more soluble 23 and 25, respectively, which constituted the major reaction products. The products so obtained gave single spots on t.l.c. and had reasonably sharp melting points which were raised a

few degrees only, by recrystallization from 95% ethanol. Yields, physical constants, and microanalytical data for the epoxides are given in Table XVIII.

TABLE XVIII

α-Epoxynitro sugars

Compound	Reaction time (min)	Yield (%)	Melting point (°C)	$[\alpha]_D^{25}$ in $CHCl_3$ (c,0.5-0.8) (degrees)	Anal.Found for $C_{14}H_{15}NO_7$ (309.3)* C	H	N
Methyl 2,3-anhydro-4,6-O-genzylidene-3-C-nitro							
-α-D-mannopyranoside (20)	90	77	173-174	+51.2	54.52	4.75	4.35
-β-D-allopyranoside (21)	30	89	204-205	-98.8	54.69	5.03	4.36
-α-D-talopyranoside (22)	40	84	215-216	+91.8	54.64	4.83	4.73
-β-D-gulopyranoside (23)	50	67.5	154-155	-62.1	54.56	5.05	4.34
-β-D-talopyranoside (24)	50	13	241-243(dec.)	-31.2**	54.42	4.87	
-β-L-gulopyranoside (25)	45	64	154-156	+62.7			
-β-L-talopyranoside (26)	45	11	239-241(dec.)				
-β-D-mannopyranoside (27)			182-183	-68.4	54.63	5.08	4.32

* Analysis Calcd. for $C_{14}H_{15}NO_7$: C, 54.45; H, 4.89; N, 4.53.

** In dimethylformamide.

TABLE XIX

Circular dichroism of epoxynitro sugars

Compound	Extrema		[θ] at a given λ (in nm)				
	λ (in nm)	[θ]	270	290	310	330	360
20	276	-1444	-1295	-600	2365	1820	270
	313	2465					
21	279	6335	5350	5110	-353	-1160	-317
	323	-1214					
22	279	-4641	-4010	-3210	2070	2240	460
	319	2503					
23	284	1146	930	1130	1610	1720	550
	321	1844					
24	281	-4381	-3580	-3390	1460	1810	400
	320	2025					
25	283	-1757	-1480	-1690	-1640	-1810	-690
	321	-1886					
26	280	5560	4480	4080	-1660	-2090	-534
	320	-2334					
27	275	-1125	-1040	375	1920	1310	150
	312	1937					

D. Reaction of N-Bromoacetamide with Nitroolefins

i) Reaction of N-Bromoacetamide with β-Nitrostyrene (7)

1,1-Dibromo-1-nitro-2-acetamido-2-phenylethane (31)

To a solution of β-nitrostyrene 7 (149 mg) in acetone (10 ml) were added N-bromoacetamide (NBA) (207 mg) and sodium acetate (10 mg). The reaction mixture was stirred at room temperature for 5 hours, after which t.l.c. (solvent A) showed a major, more slowly moving spot and only traces of the starting compound 7 . The reaction mixture was diluted with water (20 ml), and most of the acetone was distilled off under reduced pressure. The white solid material which precipitated was filtered off, washed with cold water, and dried. The contamination in the solid, which according to t.l.c. consisted of traces of starting material, was removed by passage through a short column (adsorbent: 20 g silica gel, eluent: solvent A). A fast-moving, minor fraction contained unreacted β-nitrostyrene (12 mg, 8%) with a melting point of 57-58°. The slow-moving major fraction consisted of 31 (324 mg, 88.5%) with a melting point of 129-130° (dec.). Recrystallization from ethanol/water did not alter the melting point.

Analysis for $C_{10}H_{10}N_2O_3Br_2$ (366.0)

Calcd: C, 32.80; H, 2.73; N, 7.68; Br, 43.70.

Found: C, 32.85; H, 2.89; N, 7.64; Br, 43.55.

1-Nitro-2-acetamido-2-phenylethane (32)

A solution of 31 (200 mg) in ethanol (20 ml) was stirred in an ice bath with sodium borohydride (100 mg). According to t.l.c. (solvent B) no starting material was left after 15 minutes. The reaction mixture was slightly acidified with aqueous 10% acetic acid and diluted with water (20 ml). Evaporation of the ethanol gave a whitish solid precipitate. Recrystallization from ethyl acetate/petroleum ether gave pure 32 (102 mg, 89.5%) melting at 137-138°. Stefanovic et al. (72) reported a melting point of 138°.

ii) Reaction of N-bromoacetamide with 3-O-Acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-xylo-hex-5-enofuranose (6)

5-Acetamido-3-O-acetyl-6,6-dibromo-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose (34) and the corresponding β-L-idofuranose isomer (35)

Route A.—— A solution of nitroolefin 6 (273 mg) in acetone (20 ml) containing NBA (300 mg) and sodium acetate (10 mg) was stirred for 90 minutes after which time t.l.c. (solvent E) showed that the reaction was almost complete. However, stirring was continued overnight. The reaction mixture was then diluted with water (20 ml), and the acetone was largely evaporated. A white solid precipitated and was filtered off, washed with cold water and dried to give 466 mg of a crude material. This crude solid showed three spots on t.l.c. (solvent E), namely, one minor fast-moving spot, one minor slow-moving spot and one major spot with medium mobility.

Column chromatography (adsorbent: 20 g silica gel, eluent: solvent E) of the crude material gave two fractions. A small, fast-moving fraction gave 24 mg (5.4%) of 3,5-di-O-acetyl-6,6-dibromo-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose (33), which after recrystallization from ethanol/water had a melting point of 136-138° and an optical rotation of $[\alpha]_D$+15.4° (c, 0.3 in methanol). The major fraction (419 mg, 94.6%) consisted of a mixture of 34 and 35 and showed an optical rotation of $[\alpha]_D$+32.1° (c, 0.7 in methanol). Recrystallization from ethyl acetate/petroleum ether afforded pure 34 (323 mg, 77%) with a melting point of 193-194° and $[\alpha]_D$+51.3° (c, 0.6 in methanol).

Analysis for $C_{13}H_{18}N_2O_8Br_2$ (490.1)

Calcd: C, 31.85; H, 3.70; Br, 32.60.

Found: C, 32.04; H, 3.86; Br, 32.33.

The residue obtained by evaporation of the mother liquor was repeatedly recrystallized from ethyl acetate/petroleum ether to give pure 35 (29 mg) melting at 158-160°.

Route B. —— To a solution of 5-acetamido-3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-β-L-idofuranose (37) (110 mg) in methanol (10 ml) were added NBA (100 mg) and a saturated aqueous solution of sodium acetate (1 ml). The reaction mixture was stirred for 1 hour at room temperature and then diluted with water (10 ml). A white precipitate separated when the solution was partially evaporated. The precipitate was collected, washed with cold water, and dried. Recrystallization from ethyl acetate/petroleum ether furnished

35 (148 mg, 91%) melting at 160-161° with $[\alpha]_D$-53.6° (c, 0.6 in methanol).

Analysis for $C_{13}H_{18}N_2O_8Br_2$ (490.1)

Calcd: C, 31.85; H, 3.70; Br, 32.60.

Found: C, 32.09; H, 3.87; Br, 32.37.

Bromination of 5-acetamido-3-O-acetyl-5,6-dideoxy-1, 2-O-isopropylidene-6-nitro-α-D-glucofuranose (36) in an analogous fashion afforded the corresponding α-D-gluco isomer 34 (138 mg, 85%) with a melting point of 191-192° and $[\alpha]_D$ +52.0° (c, 0.4 in methanol).

5-Acetamido-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose (38) and -β-L-idofuranose (39)

A solution of nitroolefin 6 (273 mg) in tetrahydrofuran (20 ml) was stirred with aqueous, concentrated ammonia solution (5 ml). After 15 minutes t.l.c. (solvent F) showed that no starting material was left and that two new, more slowly moving products were formed. Dilution of the reaction mixture with water (20 ml) and evaporation, followed by several coevaporations with ethanol, gave a crystalline residue. Column chromatography (adsorbent: 20 g silical gel, eluent: solvent F) gave two fractions. The fast fraction gave 34 (115 mg, 39.7%) which failed to crystallize and was obtained on drying as a brittle glass showing $[\alpha]_D$+5.4° (c, 0.7 in methanol). The slower fraction furnished 39 (163 mg, 56.2%) as crystals which upon recrystallization from ethyl acetate/petroleum ether melted at 179-180° and showed $[\alpha]_D$-32.8° (c, 0.3 in methanol).

Analysis for $C_{11}H_{18}N_2O_7$ (290.3)

Calcd: C, 45.51; H, 6.25; N, 9.65.

Found: C, 45.43; H, 6.38; N, 9.69.

5-Acetamido-3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-glucofuranose (36)

Method a.—— To a suspension of 38 (490 mg) in ether (15 ml) were added acetic anhydride (6 ml) and pyridine (12 ml). The reaction mixture was evaporated after standing overnight in a refrigerator. Several coevaporations with ethanol gave a syrupy residue that crystallized from ethyl acetate/n-pentane. Recrystallization from the same solvents furnished analytically pure 36 with a melting point of 86-88° and $[\alpha]_D$ +12.6° (c, 0.7 in methanol).

Analysis for $C_{13}H_{20}N_2O_8$ (332.3)

Calcd: C, 46.98; H, 6.07; N, 8.43.

Found: C, 46.86; H, 6.19; N, 8.25.

Method b.—— To a solution of 34 (100 mg) in ethanol (10 ml) was added sodium borohydride (50 mg). The reaction mixture was stirred for 15 minutes, after which time t.l.c. (solvent E) indicated that no starting material was left. The reaction mixture was slightly acidified with aqueous 10% acetic acid and then diluted with water (15 ml). Evaporation of most of the ethanol gave a white precipitate which was filtered off, washed with cold water, and dried. Recrystallization from ethyl acetate/n-pentane gave pure 36 (61 mg, 90%) melting at 87-88°.

5-Acetamido-3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-β-L-idofuranose (37)

Compound 39 (160 mg) was acetylated as described above for 38. Analytically pure 37 (183 mg, 91.8%) was obtained from ethyl acetate/n-pentane. It melted at 119-120° and had an optical rotation of $[\alpha]_D$-33.4° (c, 0.7 in methanol).

Analysis for $C_{13}H_{20}N_2O_8$ (332.3)

Calcd: C, 46.98; H, 6.07; N, 8.43.

Found: C, 46.85; H, 6.17; N, 8.55.

TABLE XX

Circular dichroism of 6-nitro sugars

	Extrema		[θ] at a given λ (in nm)				
Compound	λ (in nm)	[θ]	270	290	310	330	360
34	332	-682		3710	250	-630	-330
35	290	-2060		-2060	-890	-330	-140
36	283	-1182	-990	-1080	-320	-40	0
37	282	1352	1130	1220	365	40	0
40	277	-2289	-2160	-1910	-830	-445	-80
41	307	647	270	510	630	440	85
42	283	-1888	-1640	-1785	-1280	-835	-150
43	284	1326	1125	1290	1190	840	150
44	283	-1024	-870	-970	-730	-490	-100
45	280	1150	1045	1015	660	430	75

iii) Reaction of N-Bromoacetamide with Methyl 4,6-Benzylidene-2,3-dideoxy-3-nitro-α-D-erythro-hex-2-enopyranoside (1)

Methyl 2-Acetamido-4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-α-D-altropyranoside (46) and its 2-O-acetyl analog (47)

a) With excess sodium acetate. —— A solution of nitroolefin 1 (293 mg) in acetone (20 ml) was vigorously stirred with a solution of NBA (200 mg) in aqueous, saturated sodium acetate (15 ml). After 7 hours, water (30 ml) was added to the reaction mixture and the acetone was evaporated. A white precipitate separated and was filtered off and washed with cold water. Drying afforded 425 mg of a white solid, which showed two spots on t.l.c. (solvent G). The two products were separated by column chromatography (adsorbent: 20 g Silica gel, eluent: solvent G).

The fast-moving compound 47 (145 mg, 33.5%) had a melting point of 152-153° and $[\alpha]_D$+10.5° (c, 0.6 in chloroform). An i.r. spectrum showed strong absorptions at 1760 (s, O-acetyl) and at 1570 (s, NO_2). Recrystallization from hot ethyl acetate converted 47 into a different product melting at 181-182° and showing $[\alpha]_D$-97.5° (c, 0.8 in chloroform). Its i.r. spectrum lacked carbonyl absorption, and the band for the nitro group now appeared at 1525, in the region typical for nitroalkenes. The product was identified as 1.

The slow-moving compound eluted from the column was 46 (270 mg, 62.5%). Upon recrystallization from ethanol/water it had a melting point of 127-129° and $[\alpha]_D$+46.1° (c. 1.3 in chloroform).

Analysis for $C_{16}H_{19}N_2O_7Br$ (431.3)

Calcd: C, 44.60; H, 4.44; N, 6.51; Br, 18.50.

Found: C, 44.32; H, 4.59; N, 6.63; Br, 18.68.

b) With a catalytic amount of sodium acetate.—— To a solution of nitroolefin 1 (50 mg) in acetone (4 ml) were added NBA (35 mg) and sodium acetate (2 mg). After stirring for 2 hours and work-up as performed above a white solid was obtained. Inspection by t.l.c. (solvent G) revealed that only traces of the 2-O-acetyl compound 47 were formed. Twofold recrystallization of the crude product from ethyl acetate/petroleum ether furnished pure 46 (56.5 mg, 76%) with a melting point of 125-126°.

An identical run was performed under exclusion of light; the same result was obtained. However, in an experiment omitting sodium acetate no 46 was formed.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-α-D-arabino-hexopyranoside (8)

Sodium borohydride (30 mg) was added to a solution of 47 (100 mg) in ethanol (20 ml). The reaction mixture was stirred in an ice bath for 1 hour and then acidified with 10% aqueous acetic acid. Water (20 ml) was added, and upon partial evaporation of the ethanol a white precipitate was obtained. Recrystallization from ethanol/water afforded 8 (59.5 mg, 87.3%) melting at 109-110°. A mixture melting point with an authentic sample of 8 remained undepressed. An i.r. spectrum ascertained the identity of this product with 8 obtained previously.

Methyl 2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-mannopyranoside (48)

A solution of 46 (150 mg) in ethanol (10 ml) was stirred at with sodium borohydride (150 mg) at room temperature for 1 hour. Acidification with 10% aqueous acetic acid, dilution with water (20 ml), and partial evaporation of the mixture produced a white precipitate which was collected, washed with cold water, and dried. Recrystallization from chloroform/n-pentane gave 48 (112 mg, 91.2%) with a melting point of 121-123° and $[\alpha]_D$+14.8° (c, 1.1 in chloroform). An i.r. spectrum proved its identity with the product referred to as "by-product VI" by Baer and Rajabalee (28) who recorded microanalytical and physical data (mp 123-125°, $[\alpha]_D$+16.0° (c, 0.8 in chloroform).

Methyl 2-Acetamido-2,3-dideoxy-3-nitro-α-D-mannopyranoside (49)

Debenzylidenation of 48 (600 mg) with trifluoroacetic acid at room temperature for 30 minutes gave a syrupy product. It gave a single, slow-moving spot on t.l.c. (solvent G). All attempts at crystallization failed, and the product was not analyzed but used in syrupy form for the preparation of derivatives.

Methyl 2,3-Diacetamido-2,3-dideoxy-α-D-mannopyranoside (50)

A hydrogenation of syrupy 49 at normal pressure with platinum oxide as catalyst failed and therefore the material was subjected to a hydrogenation under moderately increased pressure.

To a solution of 49 (300 mg) in water (50 ml) and 0.1 N hydrochloric acid (11.6 ml) was added platinum oxide (200 mg). The hydrogenation mixture was shaken for 2.5 days at 25° under a hydrogen pressure of 4 atm. The catalyst was removed, the filtrate was evaporated, and several portions of added ethanol were evaporated from the residue. For N-acetylation the syrupy residue was dissolved in water (10 ml) and methanol (1 ml), acetic anhydride (0.5 ml) and Dowex 1-X8 (carbonate form) were added, and the reaction mixture was stirred for 90 minutes at room temperature. Filtration and evaporation afforded a colorless syrup which was crystallized from ethanol/water. Analytically pure 50 (243 mg, 77.3%) was obtained with a melting point of 248-250° and $[\alpha]_D$+4.8° (c, 0.4 in water).

Analysis for $C_{11}H_{20}N_2O_6$ (276.3)

Calcd: C, 47.82; H, 7.30; N, 10.14.

Found: C, 47.55; H, 7.43; N, 9.97.

Methyl 2,3-Diacetamido-4,6-di-O-acetyl-2,3-dideoxy-α-D-mannopyranoside (51)

The diacetamido compound 50 (100 mg) was acetylated in pyridine (4 ml) with acetic anhydride (1 ml). After standing overnight at room temperature the reaction mixture was evaporated with several additions of toluene and ethanol. Crystallization of the residue from benzene/petroleum ether furnished the fully acetylated compound 51 (109 mg, 83.4%) with a melting point of 199-201° and $[\alpha]_D$+84.0° (c, 0.5 in chloroform).

Guthrie and Murphy (75) reported a melting point of 200-202° and $[\alpha]_D$+89.2° (c, 0.9 in chloroform).

Methyl 2-Acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-nitro-α-D-mannopyranoside (52)

The syrupy compound 49 (100 mg) was acetylated with acetic anhydride (3 ml) by use of several drops of boron trifluoride etherate as a catalyst. After a reaction time of 30 minutes the reaction mixture was poured into ice water to give an amorphous precipitate which was filtered off, washed with cold water, and dried. The product was purified by precipitation with petroleum ether from ethyl acetate solution. The product so obtained was analytically pure and had $[\alpha]_D$+38.2° (c, 0.5 in chloroform).

Analysis for $C_{13}H_{20}N_2O_9$ (348.3)

Calcd: C, 44.83; H, 5.79; N, 8.05.

Found: C, 44.75; H, 5.89; N, 8.19.

Methyl 2-Acetamido-6-O-acetyl-2,3,4-trideoxy-3-nitro-α-D-threo-hex-3-enopyranoside (53)

A solution of fully acetylated 52 (30 mg) in chloroform (10 ml) was refluxed in the presence of silica gel (30 mg for column chromatography) for 1 hour. The silica gel was filtered off after cooling of the reaction mixture, and the filtrate was evaporated leaving a syrupy residue. Crystallization from ethyl acetate/petroleum ether afforded 53 (15 mg) melting at 162-163°. The spectral

properties (i.r. and n.m.r.) were identical to those of 53 isolated in the talo series, for which an elemental analysis was obtained.

iv) Reaction of N-Bromoacetamide with Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-α-D-threo-hex-2-enopyranoside (3)

Methyl 2-Acetamido-4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-α-D-idopyranoside (54) and its 2-O-acetyl analog (55)

Nitroolefin 3 (200 mg) was dissolved in acetone (16 ml) and added to a solution of NBA (200 mg) and sodium acetate (10 mg) in water (10 ml). The reaction mixture was stirred at room temperature for 2.5 hours. A whitish precipitate began to separate during the first hour. The mixture was then diluted with water (25 ml) and the acetone was evaporated. Additional amounts of the white precipitate separated. The product was filtered off, washed with cold water, and dried (295 mg). T.l.c. (solvent G) revealed that the precipitate consisted of at least two, easily separable compounds. Column chromatography (adsorbent: 20 g silical gel, eluent: solvent G) gave two fractions, both of which afforded crystalline products upon evaporation.

The fast-moving product proved to be 55 (46 mg, 15.6%) with a melting point of 225-226° and $[\alpha]_D$+31.5° (c, 0.5 in chloroform).

Analysis for $C_{16}H_{18}NO_8Br$ (432.3)

Calcd: C, 44.50; H, 4.20; Br, 18.45.

Found: C, 44.63; H, 4.01; Br, 18.74.

The slow-moving product proved to be 54 (245 mg, 83.1%) melting at 175-176° and having an optical rotation of $[\alpha]_D$+19.1° (c, 0.6 in chloroform).

Analysis for $C_{16}H_{19}N_2O_7Br$ (431.3)

Calcd: C, 44.60; H, 4.44; Br, 18.50.

Found: C, 44.74; H, 4.56; Br, 18.37.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-α-D-lyxo-hexopyranoside (10)

To a cold solution of the 2-O-acetyl derivative 55 (165 mg) in ethanol (30 ml) was added sodium borohydride (40 mg). According to t.l.c. (solvent A), no starting material was left after a reaction time of 20 minutes. Therefore the mixture was acidified with 10% aqueous acetic acid and then diluted with water (50 ml). Evaporation of the ethanol gave a white solid which was filtered off, washed with water, and dried to give 10 (95 mg, 84.0%) melting at 103-104°. A mixture melting point with an authentic sample (20) remained undepressed. An i.r. spectrum of the material proved its identity with previously-obtained 10.

Methyl 2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-talopyranoside (56)

The bromonitro sugar 54 (80 mg) was dissolved in ethanol (10 ml) and the solution was stirred in an ice bath with sodium borohydride (20 mg) for 10 minutes. Inspection by t.l.c. (solvent G) revealed that the reaction was completed after 5 minutes. The reaction mixture was acidified with 10% aqueous acetic acid and diluted with water (20 ml). Upon evaporation of the ethanol a white precipitate separated which was filtered off, washed with cold water and dried.

Recrystallization from chloroform/petroleum ether gave analytically pure 56 (55 mg, 84.3%) with a melting point of 205° and $[\alpha]_D$+55.3° (c, 0.8 in chloroform).

Analysis for $C_{16}H_{20}N_2O_7$ (352.3)

Calcd: C, 54.54; H, 5.72; N, 7.95.

Found: C, 54.39; H, 5.74; N, 7.80.

Methyl 2-Acetamido-2,3-dideoxy-3-nitro-α-D-talopyranoside (57)

Debenzylidenation of 56 (220 mg) was effected by treating it with trifluoroacetic acid at room temperature. After 30 minutes some water was added and the reaction mixture was evaporated, and several portions of added ethanol were evaporated from the residue. The syrupy residue so obtained crystallized upon trituration with ether to give 57 (153 mg, 92.7%) with a melting point of 119-120°. Recrystallization from chloroform/ether furnished a material with a melting point of 120-121° and $[\alpha]_D$+52.5° (c, 0.6 in water).

Analysis for $C_9H_{16}N_2O_7$ (264.2)

Calcd: C, 40.90; H, 6.10; N, 10.60.

Found: C, 40.95; H, 5.94; N, 10.77.

Methyl 2,3-Diacetamido-2,3-dideoxy-α-D-talopyranoside (58)

A solution of the nitro compound 57 (400 mg) in methanol (40 ml) was hydrogenated in the presence of acetic anhydride (2.4 ml), with prereduced platinum oxide (400 mg) as catalyst at normal pressure and room temperature. Uptake of hydrogen ceased after 5 hours. The catalyst was filtered off and the filtrate evaporated to give a syrupy residue which crystallized

from ethanol/ether. Purification over a small silica gel column (eluent: solvent H) and recrystallization from ether gave the diacetamido compound 58 (289 mg, 69.1%) with a melting point of 218-219° and $[\alpha]_D$+11.8° (c, 0.8 in water). Analysis for $C_{11}H_{20}N_2O_6$ (276.3)

Calcd: C, 47.82; H, 7.30; N, 10.14.

Found: C, 47.68; H, 7.29; N, 9.98.

2,3-Diamino-2,3-dideoxy-D-talose dihydrochloride (59)

The diacetamido compound 58 (150 mg) was hydrolyzed by refluxing with half-concentrated hydrochloric acid (15 ml) during a period of 16 hours. The resulting, dark brown solution was evaporated, and this was followed by several co-evaporations with water (until the smell of hydrochloric acid was no longer noticeable). The remaining, dark syrup was taken up in water and decolorized with acid-washed activated charcoal. Evaporation of the colorless solution gave a strongly hygroscopic syrup which could not be crystallized. The syrup strongly reduced Fehling solution and an n.m.r. spectrum (60 MHz) in deuterium oxide showed neither a methoxy signal nor acetamido signals. In paper chromatography using the Fischer-Dörfel system a ninhydrine-positive spot with $R_{GN} \simeq 0.86$ was detected. No further characterization of the product was attempted, but in view of the disappearance of the n.m.r. signals mentioned above, and of the positive ninhydrin reaction one can assume that hydrolysis of 58 was successful and that the product was 59.

2,3-Diacetamido-2,3-dideoxy-D-talose (60)

The syrupy, hygroscopic material 59 (50 mg) was N-acetylated by the usual method (83). Work-up gave a syrupy material, which was purified by column chromatography (adsorbent: 20 g silical gel, eluent: chloroform: methanol/ 1:1). A hygroscopic product (35 mg) was obtained which gave a single spot on t.l.c. but was not crystallizable. This material reduced Fehling solution and an n.m.r. spectrum (60 MHz) in D_2O showed strong signals in the region for acetamido groups. An i.r. spectrum (film) showed also strong signals at 1650 and 1530 cm^{-1} characteristic for acetamido groups. The product, therefore, was presumed to be the diacetamido sugar 60.

Methyl 2-Acetamido-6-O-acetyl-2,3,4-trideoxy-3-nitro-α-D-threo-hex-3-enopyranoside (53)

The nitro sugar 57 (100 mg) was acetylated with acetic anhydride (3 ml) and boron trifluoride etherate (3 drops) during 25 minutes at room temperature. The reaction mixture was then poured into ice water whereby a solid product separated, the solid was filtered off, washed with water and dried to give 53 (93 mg, 85.3%) with a melting point of 159-161°. After recrystallization from ethyl acetate/petroleum ether the product had a melting point of 162-163° and $[\alpha]_D$ +82.5° (c, 0.5 in chloroform).

Analysis for $C_{11}H_{16}N_2O_7$ (288.3)

Calcd: C, 45.85; H, 5.59; N, 9.71.

Found: C, 45.72; H, 5.64; N, 9.91.

The compound absorbed ultraviolet light: λ_{max} 247 nm (ϵ 5 000) in chloroform. Upon addition of 0.1 N methanolic sodium methoxide solution (0.1 ml) to 3 ml of both the sample (10^{-4} molar) and the reference cell the signal shifted to λ_{max} 257 nm and the absorbance increased to a value of 10 100.

v) Reaction of N-Bromoacetamide with Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-β-D-hex-2-enopyranosides.

Methyl 2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-3-bromo-β-D-allopyranoside (61) and its 2-O-acetyl analog (62)

The β-D-erythro nitroolefin 2 (293 mg) was dissolved in acetone (20 ml) and added to a solution of NBA (200 mg) in saturated, aqueous sodium acetate (15 ml). After being stirred for 5 hours at room temperature the reaction mixture was diluted with water (20 ml). Evaporation of the acetone gave a white precipitate which was filtered off, washed with cold water, and dried. The crude material (393 mg) showed on t.l.c. (solvent G) the presence of two easily separable compounds. Column chromatography (adsorbent: 20 g silical gel, eluent: solvent G) resulted in the isolation of the two compounds, 61 and 62.

The fast-moving product proved to be 62 which after recrystallization from ethanol/water had a melting point of 224-225° and $[\alpha]_D$-69.3° (c, 0.9 in chloroform).

Analysis for $C_{16}H_{18}NO_8Br$ (432.3)

Calcd: C, 44.50; H, 4.20; N, 3.24; Br, 18.45.

Found: C, 44.58; H, 4.28; N, 3.09; Br, 18.70.

The slow-moving product proved to be 61 (237 mg, 54.9%) which after recrystallization from ethyl acetate/petroleum ether had a melting point of 205-206° and $[\alpha]_D$-70.0° in (c, 0.4 in chloroform).

Analysis for $C_{16}H_{19}N_2O_7Br$ (431.3)

Calcd: C, 44.60; H, 4.44; N, 6.51; Br, 18.50.

Found: C, 44.67; H, 4.56; N, 6.32; Br, 18.78.

Methyl 2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (63)

The bromonitro sugar 61 (50 mg) was reductively debrominated with sodium borohydride (50 mg) in ethanol (10 ml) by the Iffland method. Work-up after 30 minutes at room temperature furnished compound 63 (36 mg, 88.2%) melting at 309-311°. Baer and Neilson (25) reported a melting point of 310-311°. The i.r. and n.m.r. spectra were identical with those of an authentic sample (25).

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-β-D-arabino-hexopyranoside (9)

The bromonitro compound 62 (100 mg) was debrominated with sodium borohydride (50 mg) in ethanol (20 ml) by the Iffland method. Work-up after 1 hour at room temperature afforded 9 (65 mg, 95.6%) with a melting point of 144-146°. A mixture melting point with an authentic sample (19) remained undepressed. The i.r. spectrum of the material ascertained its identity with previously-obtained 9 .

Methyl 2-Acetamido-4,6-O-benzylidene-3-bromo-2,3-dideoxy-3-nitro-β-D-gulopyranoside (64) and its β-D-galacto isomer (65)

To a solution of the β-D-threo nitroolefin 4 (293 mg) in acetone (20 ml) was added NBA (300 mg) and sodium acetate (10 mg). The reaction mixture was stirred overnight

at room temperature. T.l.c. inspection (solvent G) indicated that two new, more slowly moving products were formed in about equal proportions. The reaction mixture was therefore diluted with water (30 ml). Evaporation of the acetone gave a white precipitate which was filtered off, washed with cold water, and dried. The two products in the crude material (411 mg) were separated by column chromatography (adsorbent: 20 g silica gel, eluent: solvent G).

The fast-moving product proved to be 65 (196 mg, 45.5%), which after recrystallization from ethyl acetate/petroleum ether had a melting point of 188-189° (dec.) and $[\alpha]_D$ +86.6° (c, 0.9 in chloroform).

Analysis for $C_{16}H_{19}N_2O_7Br$ (431.1)

Calcd: C, 44.60; H, 4.44; N, 6.51; Br, 18.50.

Found: C, 44.90; H, 4.62; N, 6.38; Br, 18.33.

The slow-moving product proved to be 64 (187 mg, 43.4%), which after recrystallization from ethanol had a melting point of 190-191° and $[\alpha]_D$ -20.5° (c, 0.4 in dimethylformamide).

Analysis for $C_{16}H_{19}N_2O_7Br$ (431.3)

Calcd: C, 44.60; H, 4.44; N, 6.51; Br, 18.50.

Found: C, 44.43; H, 4.59; N, 6.36; Br, 18.38.

The slow-moving isomer 64 was also obtained by bromination of 66 with NBA. A solution of 66 (40 mg) in acetone (15 ml) was stirred at room temperature with NBA (40 mg) and a saturated, aqueous solution of sodium acetate (1 ml). Inspection by t.l.c. (solvent G) after 10 minutes revealed that

no more starting material was left and that only a single, faster moving product, with the same R_f-value as 64, was formed, Dilution with water (20 ml) and evaporation of the acetone gave a white precipitate that was filtered off, washed with cold water, and dried. Recrystallization from ethanol gave 64 (39.5 mg, 80.5%) melting at 188-191°. A mixture melting point with 64 obtained previously remained undepressed. The i.r. spectrum of the product established its identity with compound 64 isolated previously.

Methyl 2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-galactopyranoside (66)

a) From bromonitro compound 64.—— The bromine in 64 (64 mg) was reductively removed by the Iffland method in ethanolic solution (10 ml) with sodium borohydride (15 mg). The known compound 66 (51 mg, 97.2%) was obtained, which after recrystallization from nitromethane melted at 288-289° (dec.), $[\alpha]_D$+34.5° (c, 0.5 in diamethylformamide).

Baer and Ong (27) reported a melting point of 285° and $[\alpha]_D$+26.9° (dimethylformamide). The i.r. spectra proved the identity of 66 with an authentic sample (27).

b) From bromonitro compound 65.—— Bromonitro compound 65 was treated exactly as described above for compound 64. The product so obtained (50 mg, 95.3%) was recrystallized from nitromethane and then melted at 289° (dec.), $[\alpha]_D$+36.7° (c, 0.4 in dimethylformamide). The identity of the product with 66 was established by its i.r. spectrum.

TABLE XXI

Circular dichroism of acetamidobromonitro sugars

Compound	Extrema λ (in nm)	Extrema [θ]	[θ] at a given λ (in nm) 270	290	310	330	360
46	291	-6370		-6300	-3660	-1420	-410
54	292	-6517		-6510	-3660	-1000	-230
61	291 325	645 -1330		640	- 700	-1290	-430
64			7770	5920	3540	2650	885
65	310 344	915 - 887		-2950	915	- 510	-560

CLAIMS TO ORIGINAL RESEARCH

The following results in this thesis are claimed to be original.

Part I

1. The distinction of stereoisomeric methyl 4,6-O-benzylidene-3-deoxy-3-nitro-D-hexopyranosides by the chemical shifts of their benzylidene methine protons.
2. The application of the method in claim 1 in the re-investigation of the epimeric distribution in which methyl-3-deoxy-3-nitro-α-D-hexopyranosides arise, firstly, in the nitromethane cyclization, and secondly, in their base-catalyzed configurational equilibration via nitronates.
3. The separation of stereoisomeric methyl 4,6-O-benzylidene-3-deoxy-3-nitro-D-hexopyranosides by column chromatography and by the method involving their differential reactivities towards alkali.
4. Six new compounds were isolated and characterized in this connection.

Part II

1. The distinction of stereoisomeric methyl 4,6-O-benzylidene-3-deoxy-3-nitro-D-hexopyranosides, methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-D-hexopyranosides, and methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-D-hexopyranosides by their differential ultraviolet absorptions in dilute

alkaline solution, and correlation of this differential behavior with stereochemical features of the molecules.

2. The detection of a facile manno ⟶ gluco epimerization in the methyl 4,6-O-benzylidene-3-deoxy-3-nitro-D-hexopyranoside series and postulation of a retrograde Henry mechanism for this epimerization.
3. The acetylation of methyl 4,6-O-benzylidene-3-deoxy-3-nitro-D-hexopyranosides with acetyl chloride and triethlamine, leading in one case to the formation of the first stable, crystalline nitronic acid-acetic acid mixed anhydride.
4. The chlorination and bromination of nitro glycosides leading to the formation of a new class of carbohydrate derivatives, namely, α-halonitro glycosides.
5. The study of reactions of α-halonitro glycosides, with special attention paid to the formation of epoxynitro glycosides, another new class of carbohydrate derivatives.
6. The study of circular dichroism and magnetic resonance in α-halonitro glycosides.
7. Twenty-six new compounds were synthesized in this connection.

Part III

1. A procedural improvement for the preparation of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-D-threo-hex-2-enopyranosides.

2. The selective reduction of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-D-hex-2-enopyranosides with sodium borohydride, affording saturated 3-nitro glycosides.
3. The selective reduction of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-D-hex-2-enopyranosides with zinc and acetic acid, affording 2-deoxy-3-oximino glycosides.
4. The formation of epoxynitro glycosides by epoxidation of methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-D-hex-2-enopyranosides with alkaline hydrogen peroxide.
5. The study of the differential dichroic and n.m.r. spectroscopic behavior of epoxynitro glycosides.
6. The addition reaction of N-bromoacetamide to nitroolefins.
7. Application of the NBA reaction to 2,3-unsaturated 3-nitro glycosides, providing a stereoselective route to various 2,3-diamino-2,3-dideoxy sugars.
8. The study of circular dichroism in 6-deoxy-6-nitro-hexofuranoses.
9. Thirty-five new compounds were synthesized in this connection.

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