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SYNTHESIS OF NITROGENOUS SUGARS

by

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

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PREFACE

In this thesis a brief account is given of the significance of certain amino sugars as constituents of antibiotics, and the more important methods that are available for the synthesis of amino sugars are reviewed. Studies undertaken with the intent to contribute to the chemistry of nitrogenous sugar synthesis are then described and their results are discussed.

The candidate wishes to express his heart-felt gratitude to his research supervisor, Professor H. H. Baer, for his keen interest in the problem, his stimulating guidance and valuable instructions and his firm determination to develop in the candidate a true scientific attitude for research.

Finally, the candidate wishes to thank the Canadian Commonwealth Scholarship Committee for the award of a scholarship.

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ABSTRACT

The nitromethane cyclization of L'-methoxy-diglycolic aldehyde was shown to furnish methyl 3-nitro-3-deoxy-α-L-arabino-pyranoside and methyl 3-nitro-3-deoxy-β-D-arabinopyranoside as coproducts of the previously obtained β-D-ribo isomer. The enantiomeric dialdehyde, D'-methoxy-diglycolic aldehyde, afforded the corresponding α-D- and β-L-arabino derivatives in addition to the main β-L-ribo isomer. Catalytic hydrogenation of the four new nitroglycosides gave the corresponding aminoglycoside hydrochlorides. Acid hydrolysis of methyl 3-amino-3-deoxy-β-D-arabinopyranoside hydrochloride and methyl 3-amino-3-deoxy-α-L-arabinopyranoside hydrochloride yielded the known 3-amino-3-deoxy-D-arabinose hydrochloride and the hitherto unknown 3-amino-3-deoxy-L-arabinose hydrochloride, respectively, as mutarotating β-forms.

The spontaneous epimerization, in aqueous solution, of aci-nitropentoside sodium salts was investigated and shown to lead to equilibria in which the erythro configuration predominates.

The results of this first part of the thesis have been published.*

The nitromethane cyclisation was extended to a disaccharidic dialdehyde leading to an aci-nitro condensation product (yield 58%). Deionization and catalytic hydrogenation of the aci-nitro salt mixture afforded a crystalline α-D-glucopyranosyl 4-amino-4-deoxy-β-D-heptulo-pyranoside hydrochloride that was subsequently converted to its crystalline N-acetate.

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* H. H. Baer and A. Ahammad, Can. J. Chem., 41, 2931 (1963).

The configuration of the nitrogenous heptulose moiety of the above disaccharides was partially elucidated by degradative studies, in the course of which a number of new nitrogenous heptulose derivatives was obtained.

I. INTRODUCTION

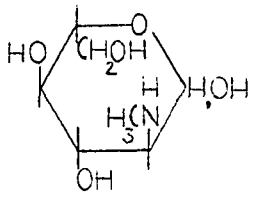
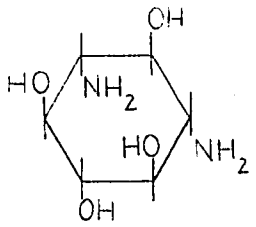
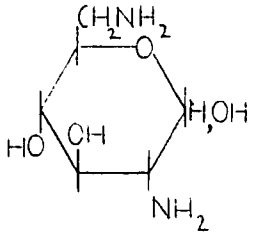
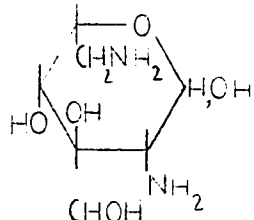
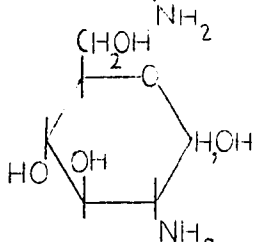
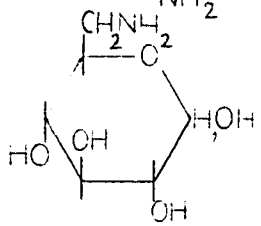
A. Amino Sugars as Constituents of Antibiotics

The development during the past two decades of the antibiotic drugs has profoundly influenced the science and practice of medicine. Waksman (1) has defined an antibiotic as a chemical substance produced by microorganisms, which is capable of inhibiting the growth and destroying bacteria and other microorganisms. The contributions that can be made by synthetic organic chemistry toward an advancement of antibiotics research are twofold. First, the elucidation of the structure of a new antibiotic often requires the synthesis of certain compounds of reference for comparison with and identification of fragments obtained in degradation studies. Secondly, the total chemical synthesis of an antibiotic may be attempted. Although such a synthesis will generally not be able to compete commercially with microbiological processes, it can nevertheless be a worthwhile project. Quite apart from the satisfaction that the chemist derives from accomplishing the synthesis of a natural product, he may in pursuit of such work succeed in synthesing substances of antibiotic character not provided by nature. Structurally modified, synthetic antibiotics could be of pharmacological value, for instance in the combat of resistant strains of bacteria. Compounds which are closely related to antibiotics in their structures, but which lack antibacterial activity, might prove valuable as comparative substrates in investigations of the modes of drug action.

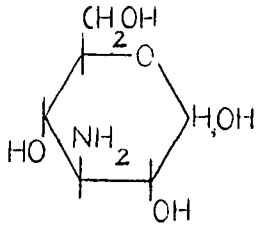
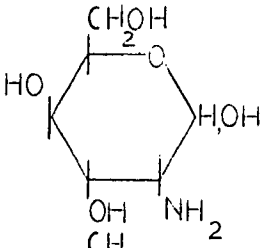
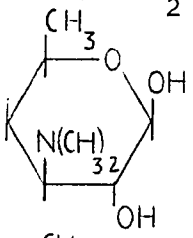
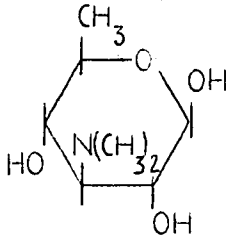
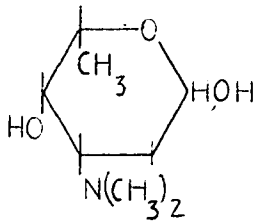
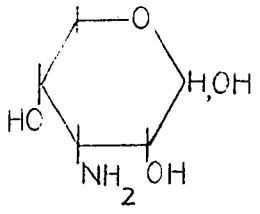
Many antibiotics have been found to contain carbohydrate moieties (2, 3). Of special importance among these carbohydrate moieties are certain amino sugars of unusual structures which have not been encountered elsewhere in nature. In Table I are given these novel amino sugars together with the antibiotics from which they are derived.

Table I

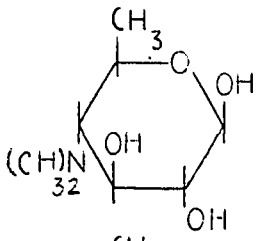
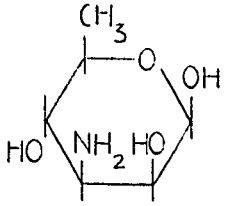
Unusual Amino Sugars Found in Antibiotic Substances

Amino Sugar Present	Structure	Antibiotic
2-Deoxy-2-methylamino-L-glucose		streptomycin; hydroxy-streptomycin; dihydroxy-streptomycin
Streptamine		"
Neosamine C (Paromose II)		neomycin A; neomycin C; paromomycin II
Neosamine B (Paromose I)		neomycin B; paromomycin I
2-Amino-2-deoxy-D-glucose		paramomycin I; paromomycin II; racemomycin O
6-Amino-6-deoxy-D-glucose		kanamycin

(Table I - continued)

Amino Sugar Present	Structure	Antibiotic
Kanosamine		kanamycin
2-Amino-2-deoxy-D-glucose		streptothricin
Desosamine (Picrocin)		erythromycin; picromycin; methymycin; narbomycin; oleandomycin
Mycaminose		carbomycin (magnamycin); leucomycins; foromacidins (spiramycins)
Rhodosamine		rhodomycin; pyrromycin
3-Amino-3-deoxy-D-ribose		puromycin

(Table I - continued)

Amino Sugar Present	Structure	Antibiotic
Amosamine		amicetin
Mycosamine		nystatin; amphotericin B; pimaricin; candidin; rimocidin

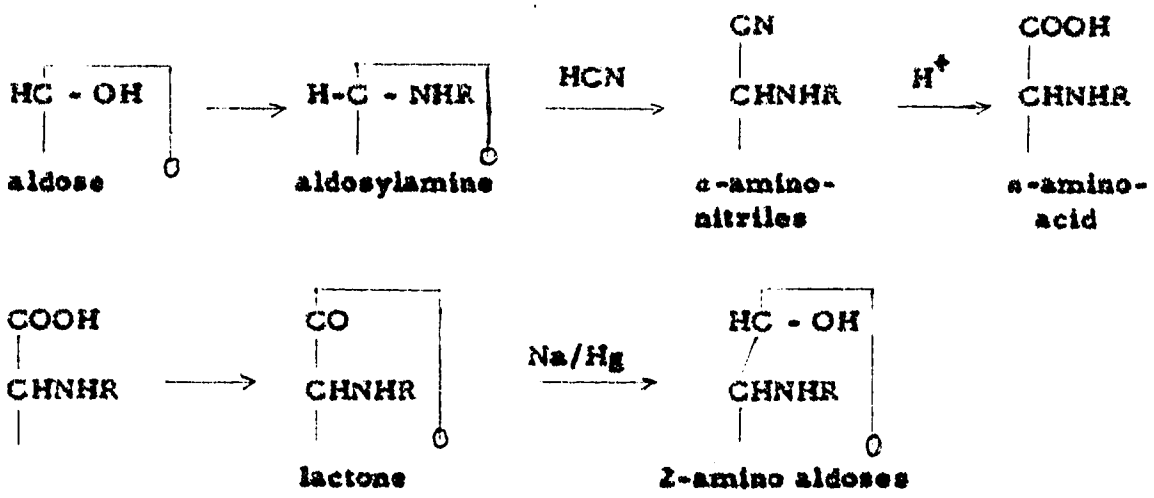
In contrast to the rare amino sugars of Table I, many of which carry an amine function at C-3, the more familiar 2-amino sugars, D-glucosamine and D-galactosamine, occur widely in nature. They are distributed not only in microorganisms but form common components of mucopolysaccharides, glycoproteins, gangliosides and other substances throughout the animal kingdom (4). A simple D-glucosamine disaccharide that shows antibiotic activity is worth mentioning here. It is α,α-trehalosamine (α-D-glucopyranosyl 2-amino-2-deoxy-α-D-glucopyranoside) and has been found in culture filtrates of a strain of streptomyces (5).

B. Methods for the Synthesis of Amino Sugars

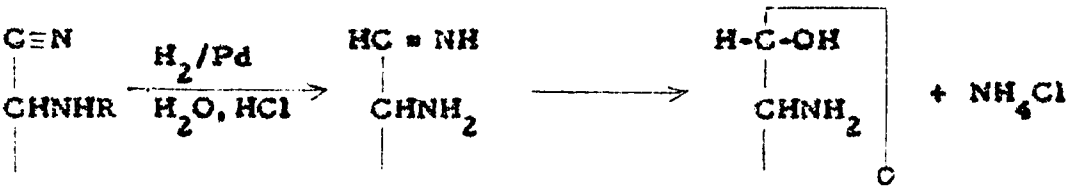
Considerable work has been done in recent years toward the synthesis of amino sugars in general and the components of antibiotics in particular. Several general methods have been developed which will be briefly surveyed in this section. The literature quoted here is intended to illustrate more important examples rather than to be exhaustive.

1. The Cyanohydrin Synthesis via Aldosylamines

Reaction of aldoses with ammonia or amines produces aldosylamines to which hydrogen cyanide can be added so that a mixture of epimeric α-amino nitriles is formed. Fischer and Leuchs (6) who introduced this method for the first synthesis of an amino sugar, namely D-glucosamine from D-arabinose, hydrolyzed the amino nitrile to the corresponding α-aminoglyconic acid which was then converted into its lactone, and the lactone was reduced with sodium amalgam to give the 2-amino sugar containing one more carbon than the starting aldose. The original reaction sequence, which is depicted below, was



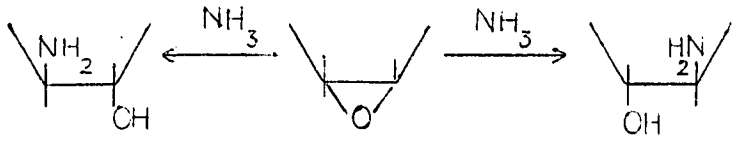
cumbersome and afforded poor yields and impure products, particularly in the last three steps. A great improvement, however, was achieved by Kuhn and Kirschenlohr (7, 8, 9) who introduced what was called "catalytic hemihydrogenation of aminonitriles". The aminonitrile is thereby directly converted under mild conditions into the amino sugar.



The Kuhn method advantageously allows the use of benzylamine ($R = CH_2C_6H_5$) or aniline ($R = C_6H_5$), instead of the less suitable ammonia, in the generation of the aldosylamine when unsubstituted amino sugars are desired, since the residues R are removed in these cases concurrently with the "hemihydrogenation" of the nitrile function. An additional advantage is the requirement in the final step of only a stoichiometric amount of acid, applied in dilute form at room temperature, which contrasts with a need for vigorous acid treatment in the older Fischer-Leuchs procedure. Hence, it has become possible now to utilise the method for the synthesis not only of amino monosaccharides (7, 8, 9, 10, 11, 12) but also of (acid-sensitive) amino disaccharides (13).

2. Syntheses Involving Ring Opening in Sugar Epoxides by the Action of Ammonia

Sugar epoxides react with ammonia to give two epimeric amino sugars according to the following reaction sequence:



The amino and the hydroxyl groups formed in these reactions are trans related and the proportion of each isomer formed depends on the structure and stereochemistry of the parent epoxide. The Fürst-Plattner rule (14) predicts the configuration of the major product and is applicable to rigid, six-membered ring systems. It states that epoxides tend to open with the new groups formed in axial dispositions. The more rigid the pyranoid ring is, the more effective is this steric control in the opening of the epoxide ring. The desired control may be achieved by limiting the flexibility of the pyranoid ring. Thus, epoxy derivatives of bicyclic systems such as benzylidene or 1,6-anhydro sugars are especially suitable starting materials for these syntheses.

The method has been employed as early as 25 years ago. Thus, derivatives of 2-amino-2-deoxy-D-altrose, 3-amino-3-deoxy-D-glucose, 3-amino-3-deoxy-D-altrose, 2-amino-2-deoxy-D-glucose and 2-amino-2-deoxy-1,6-anhydro-β-D-galactose were obtained (15,16,17). In this connection it is interesting to note that in the course of these investigations the first rigorous proofs of configuration of the then long-known D-glucosamine and D-galactosamine were provided.

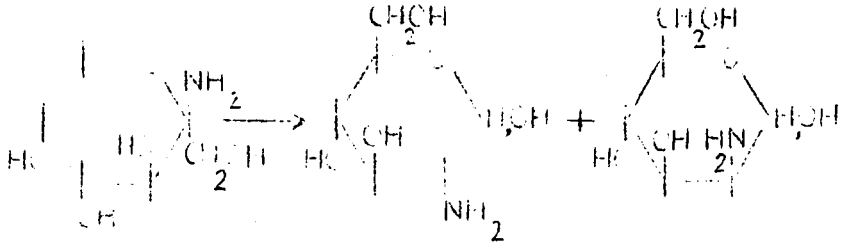
More recently, and of particular importance with view to the chemistry of antibiotics, the ammonia-epoxide method has been used

by B. R. Baker and co-workers (18, 19, 20) for the synthesis of 3-amino-3-deoxy-pentoses, especially of 3-amino-3-deoxy-D-ribose which is a constituent of puromycin. Similarly, Foster et al. (21) have synthesized mycaminose, the carbohydrate component of magnamycin, from methyl 2, 3-anhydro-α-D-allopyranoside and dimethylamine. Also, R. W. Jeanloz and co-workers (22, 23) have synthesized several amino sugar derivatives in this fashion, and Overend and Vaughan (24) have summarized other examples of related reactions.

Sugar epoxide rings may also be opened by the action of sodium azide, and reduction of the azido sugars so produced yields the corresponding amino sugar derivatives (25).

3. Syntheses Involving Intramolecular Rearrangements of Glycosylamines

A ketose in which the lactol hydroxyl is replaced by an amino group is known as a ketosylamine. The most common example is D-fructosylamine. When a ketosylamine is treated with organic acids such as benzoic, succinic or oxalic acids, it undergoes a rearrangement to give an epimeric mixture of 2-amino-2-deoxy-aldoses. This reaction, referred to as



D-fructosylamine epimeric amino aldoses

Heyns rearrangement (26, 27, 28, 29), is akin to the conversion of aldosylamines into 1-amino-1-deoxy-ketoses known as Amadori rearrangement. The ratio of the isomers obtained in the Heyns rearrangement is dependent upon the configuration of the ketosylamine. Thus, D-lyxo-hexulosylamine

(D-tagatosylamine) is rearranged to give mainly 2-amino-2-deoxy-D-galactose and a little 2-amino-2-deoxy-D-talose, whereas L-xylo-hexulosylamine (L-sorbosylamine) is rearranged to give approximately equal amounts of 2-amino-2-deoxy-L-gulose and 2-amino-2-deoxy-L-idose. D-Arabino-hexulosylamine (D-fructosylamine) and D-ribo-hexulosylamine (D-psicosylamine) are also rearranged, the former giving mainly 2-amino-2-deoxy-D-glucose and a little 2-amino-2-deoxy-D-mannose, the latter giving 2-amino-2-deoxy-D-allose and 2-amino-2-deoxy-D-altrose in the ratio of 2 to 1. The tendency to undergo rearrangement decreases as follows: D-lyxo-hexulosylamine $\rangle$ D-arabino-hexulosylamine and D-ribo-hexusylamine $\rangle$ L-xylo-hexulosylamine.

Carson (30, 31, 32) has shown that N-alkyl substituted ketosylamines can be similarly rearranged to give N-alkylamine aldoses.

4. Displacement Reactions

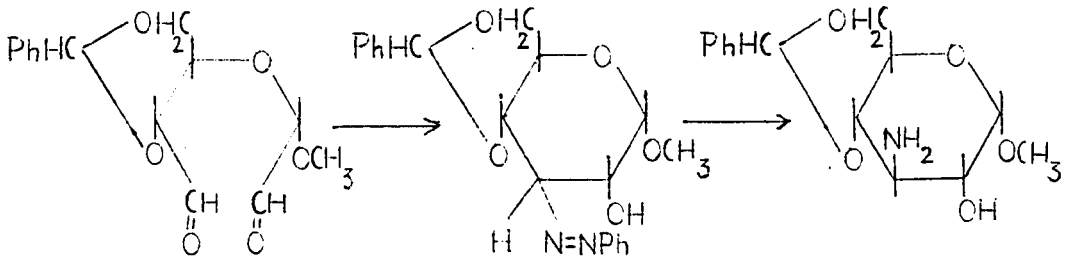
Direct displacement of a tosyloxy group from suitable sugar derivatives has occasionally been used for the synthesis of amino sugars. Thus, ammonolysis of 1, 2:5, 6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose gives a product which was originally believed (33, 34) to be 1, 2:5, 6-di-O-isopropylidene-3-amino-3-deoxy-α-D-glucofuranose. However, it has been shown later on (35, 36) that the ammonolysis proceeds with inversion at carbon atom 3 to form 1, 2:5, 6-di-O-isopropylidene-3-amino-3-deoxy-α-D-allofuranose.

Similarly, the displacement of tosyloxy groups by hydrazine has been found to be useful as a synthetic route to new and rare amino sugars, since the hydrazino derivatives are easily reduced to amine derivatives (37, 35, 36, 38, 39, 40, 41). Displacement of toxyloxy groups has also been accomplished by azide ion and the resulting azido sugar derivatives are readily reduced to amino sugar derivatives (25, 41). Like ammonolysis, the displacements with hydrazine and azide ion are attended with inversion.

5. Miscellaneous Reactions that have been employed less frequently

Of other special methods for the preparation of amino sugars mention may be made of the reduction of the oxime of methyl 3-oxo-β-D-glucopyranoside affording methyl 3-amino-3-deoxy-β-D-allo- and -glucopyranosides (42). Catalytic reduction with Adam's catalyst gives preferentially the allo derivative, while reduction with sodium amalgam gives the gluco and allo derivatives in comparable amounts.

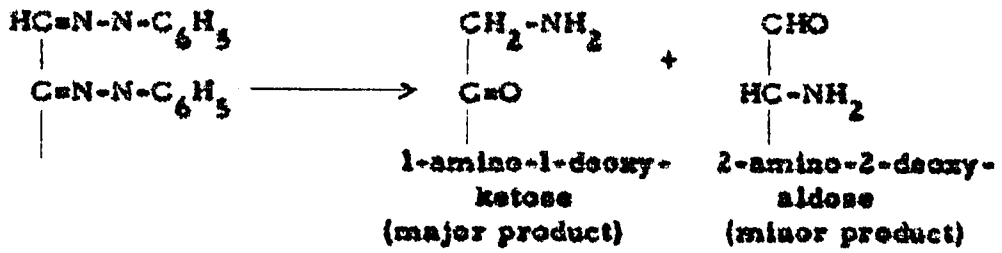
Reduction of phenylazo derivatives has served as a route to amino sugars. Guthrie (43) has prepared methyl 3-amino-4, 6-O-benzylidene-3-deoxy-α-D-glucoside by reduction of the corresponding 3-phenylazo derivative, the latter having been prepared from the periodate-oxidized methyl 4, 6-O-benzylidene-α-D-glucoside and phenylhydrazine.



3-phenylazo-3-deoxy-D-glucose (or-D-allose)-derivative

methyl 3-amino-4, 6-O-benzylidene-3-deoxy-α-D-glucose

The catalytic reduction of phenylosazones has occasionally been utilized to produce amino sugars (44, 45), but this method seems to be of little preparative value.

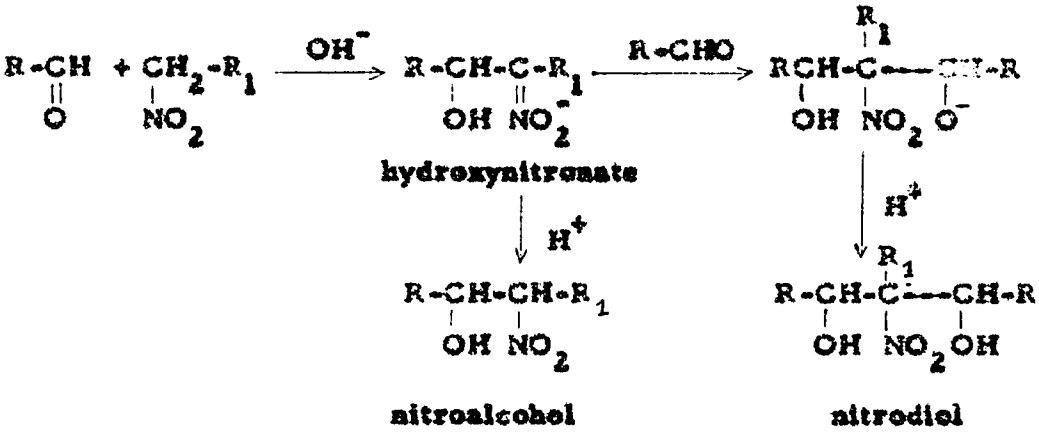


6. The Nitromethane Cyclization of Sugar Dialdehydes

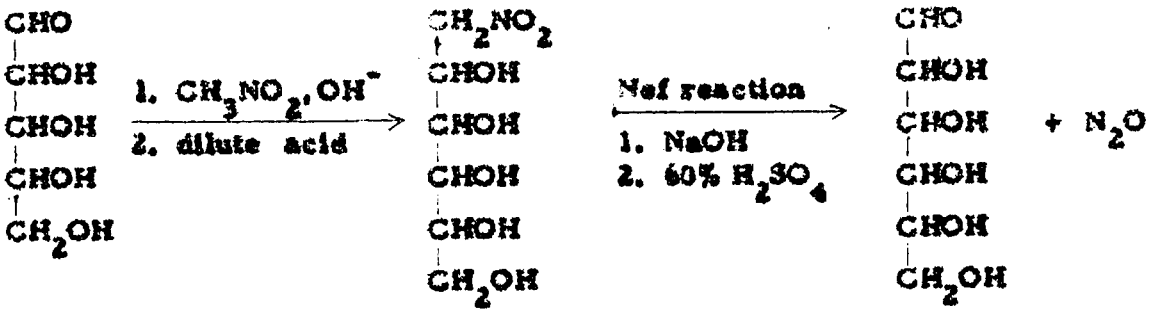
In 1958, Baer and Fischer (46) introduced a novel method for the synthesis of nitrogenous sugar derivatives consisting of the cyclization of sugar dialdehydes with nitromethane in the presence of basic catalysts. As it was the purpose of the present thesis to elaborate this method further, it will be discussed in greater detail in this section:

(a) General aspects of the reaction of nitroalkanes with aldehydes

In 1895, L. Henry (47) found that aldehydes undergo aldol-type addition reactions with primary or secondary nitroalkanes to afford nitroalcohols. The reaction takes place in alkaline medium, and in the case of primary nitroalkanes leads first to hydroxynitronates. From the hydroxynitronate, the nitroalcohol can be liberated by careful acidification, or alternatively a nitrodiol may arise by reaction with excess aldehyde.



The reaction has in subsequent years found widespread applications in aliphatic and aromatic* chemistry and has been reviewed in detail (48). It was introduced into carbohydrate chemistry by J. C. Sowden and H. O. L. Fischer (49) in 1944. These authors prepared nitrodeoxy-alditols from aldoses and nitromethane (or nitroethanol); they were, however, interested not so much in the obtained nitrogenous sugar derivatives as such, but subjected them to a Nef reaction, i. e., acidic elimination of the nitro group. The Sowden-Fischer procedure has thus become one of the foremost methods of lengthening the carbon chain in carbohydrates (50).



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

In similar fashion, Grosheintz and Fischer (51) condensed nitromethane with 1, 2-isopropylidene-D-xylodialdose and obtained, upon removal of the isopropylidene blocking group, 6-nitro-6-deoxy-D-glucose and -L-idose. They then observed that these 6-nitro aldoses under the influence of alkali undergo internal Henry reaction. That is to say, carbocyclic ring formation takes place and the products are stereoisomeric nitrodeoxy-inositols. Only recently have configurations been assigned to the various

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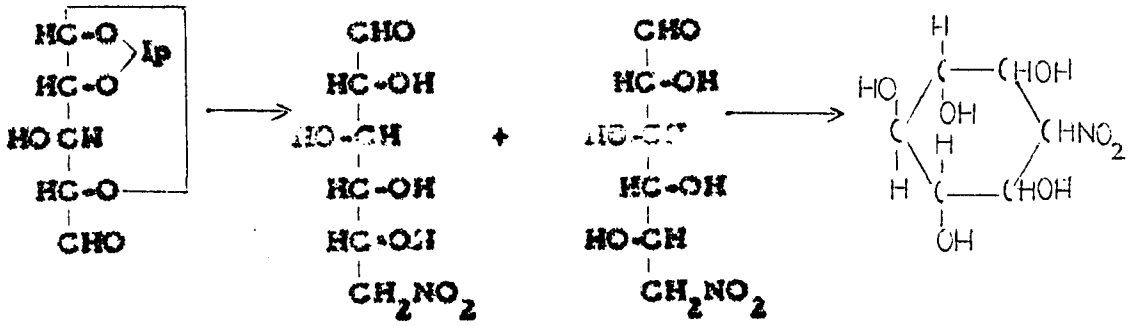
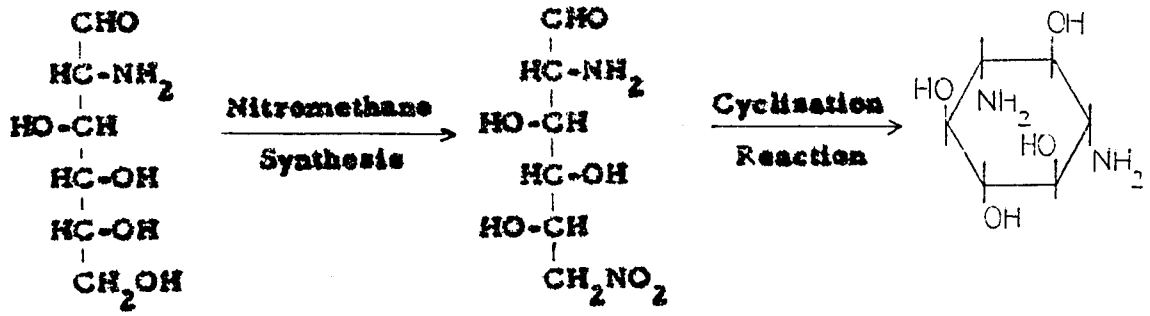
* The nitroalcohols formed from aromatic aldehydes dehydrate spontaneously to nitrostyrene derivatives.

stereoisomers obtained (52).



6-nitro-6-deoxy-D-glucose + L-idose → stereoisomeric nitrodeoxy-inositols

Adopting this principle of synthesis of the inositol ring, Wolfrom and co-workers (53) converted, through several steps, D-glucosamine into the 1, 3-diamino-1, 3-dideoxy-inositol, streptamine, a component of streptomycin. This work, which is depicted here schematically, represents the first utilization of the nitroalkane-aldehyde reaction for the synthesis of an antibiotic constituent.

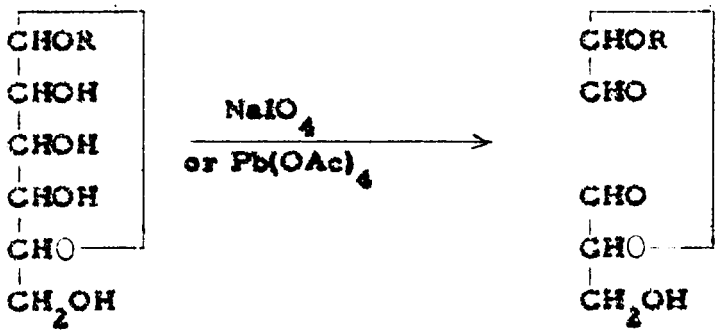


D-glucosamine → Streptamine

(b) Synthesis of 3-Nitro and 3-Amino Sugars

Being aware of the ease of formation of six-membered, carbocyclic rings in the above-described cyclisations, Baer and Fischer (46) presumed that it might be possible to synthesise nitrogen-containing pyranose sugars, too.

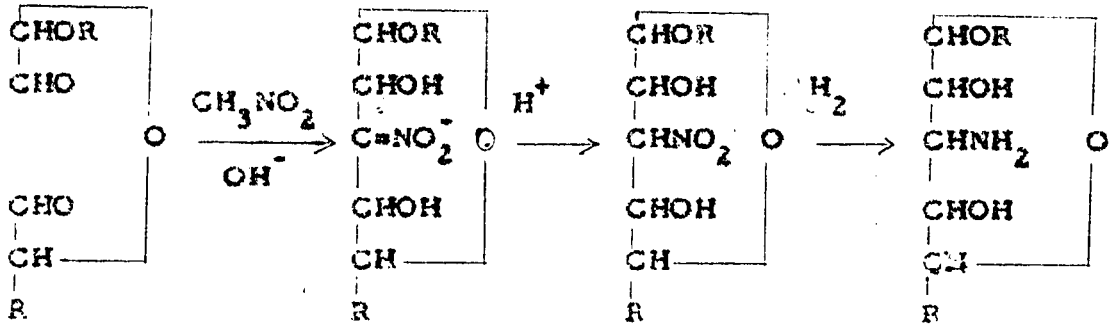
In view of the successful cyclisations leading to six-membered, carbocyclic rings (inositol derivatives), Baer and Fischer in 1958 began to investigate the possibility of condensing "sugar dialdehydes" with nitromethane, which should lead to nitrogenous pyranose derivatives (46). A "sugar dialdehyde" in this context, is the product of periodate or lead tetraacetate oxidation of a glycoside. These oxidations have been studied thoroughly and



have been reviewed in great detail (54, 55, 56). They usually are straightforward and proceed in high, often quantitative yields, so that the preparation of the starting materials presents no difficulties. The oxidised glycosides are represented in this discussion in their open-chain, true dialdehyde forms, although it is acknowledged that in aqueous and alcoholic solutions there exist equilibria with hydrated forms, hemiacetals and hemialdals (57). Under the alkaline conditions of the nitromethane reactions these equilibria are rapidly shifted so that the compounds do in fact behave like aldehydes.

Baer and Fischer found (46) that sugar dialdehydes easily react

with nitromethane by way of a twofold condensation, both aldehyde groups condensing with the same nitromethane molecule. That is to say, cyclisation occurs leading to pyranosides which carry nitrogen on the ring. 3-Nitro-3-deoxy-glycosides, a novel class of carbohydrate derivatives, have thus become available, and their reduction has opened a new route to 3-amino-3-deoxy sugars.



The method has proved to be of general applicability. Thus, nitro and amino pentoses, hexoses, 6-deoxyhexoses, 1,6-anhydrohexoses, and 2,7-anhydroheptuloses have been synthesised.

L'-Methoxy-diglycolic aldehyde (C), which arises from periodate oxidation of any methyl β-D- or α-L-pentopyranoside (A, B), was cyclised to give in 40% yield a crystalline aci-nitro glycoside salt subsequently shown to be methyl 3-aci-nitro-3-deoxy-β-D-erythro-pentopyranoside sodium (D). Acidification produced mainly methyl 3-nitro-3-deoxy-β-D-ribopyranoside (E); a small amount of its 3-epimer, methyl 3-nitro-3-deoxy-β-D-xylopyranoside (F) was also produced although it could not be isolated in pure form. Hydrogenation of E and F afforded the corresponding amino glycosides G and H, and hydrolysis, finally, of G led in good overall yield to 3-amino-3-deoxy-D-ribose (I). A similar reaction sequence was carried out with D'-methoxy-diglycolic aldehyde (J), the optical antipode of C arising from methyl α-D- or β-L-pentopyranosides, and furnished the enantiomorphs

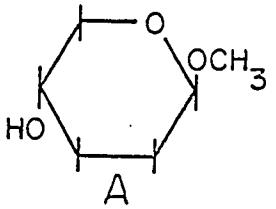
of compounds D-I (Chart 1) (46, 58).

In the α-hexoside series (Chart 2), similar experiments (59, 60, 61) using D'-methoxy-D-hydroxymethyldiglycolic aldehyde (B) obtained from methyl α-D-hexopyranosides (A) led to a non-crystalline mixture of methyl 3-aci-nitro-3-deoxy-hexopyranoside salts (C). Acidification and hydrogenation of this mixture gave crystalline methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (D) (31-36%) and the corresponding glucoside (ca 60%) (E, isolated as tetraacetate) as main products along with a small amount of methyl 3-amino-3-deoxy-α-D-talopyranoside (F). It was noted that, when prior to hydrogenation the nitronate mixture was allowed to stand in aqueous solution in the presence of a stoichiometric amount of alkali, a marked change in optical rotation took place. This mutarotation, which was quite unexpected to occur with glycosides, was shown (61) to be due to spontaneous epimerizations at the carbon atoms adjacent to the nitronate grouping. As a result the amounts of mannoside D and glucoside E found upon hydrogenation diminished sharply, taloside F became the main product (40%), and a new isomer, shown to have galacto configuration (G) was formed in addition.

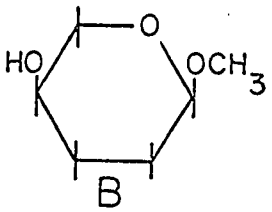
3-Amino-3-deoxy-D-mannose prepared in the above fashion was converted by a standard procedure into its 6-deoxy-derivative, which was identical with mycosamine (62).

In the β-hexoside series, the results of the nitromethane cyclization were, in principle, similar to those of the α-series. However, the ratio of stereoisomers formed differed, which showed that the anomeric carbon atom exerts a directing influence on the steric course of the reaction. Thus, L'-methoxy-D-hydroxymethyldiglycolic aldehyde (A) gave rise to three crystalline methyl 3-nitro-3-deoxy-β-D-hexopyranosides (B) having gluco, galacto and manno configuration, with the two former preponderating and the latter being a minor product (Chart 3). No talo derivative was found (63, 64).

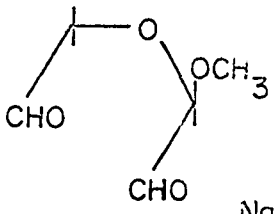
Chart I



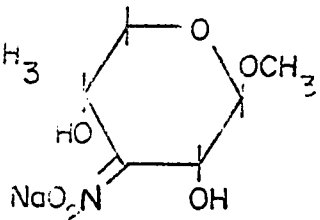
A



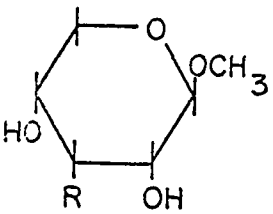
B



C

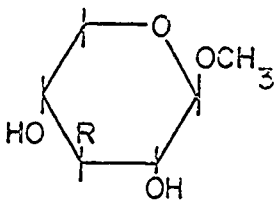


D



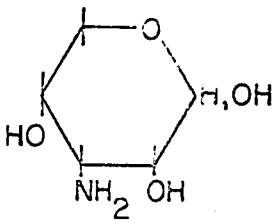
E, R = NO_2

G, R = NH_2

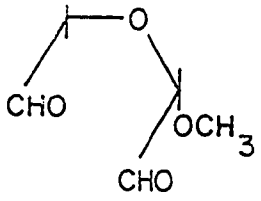


F, R = NO_2

H, R = NH_2



I



J

Chart 2

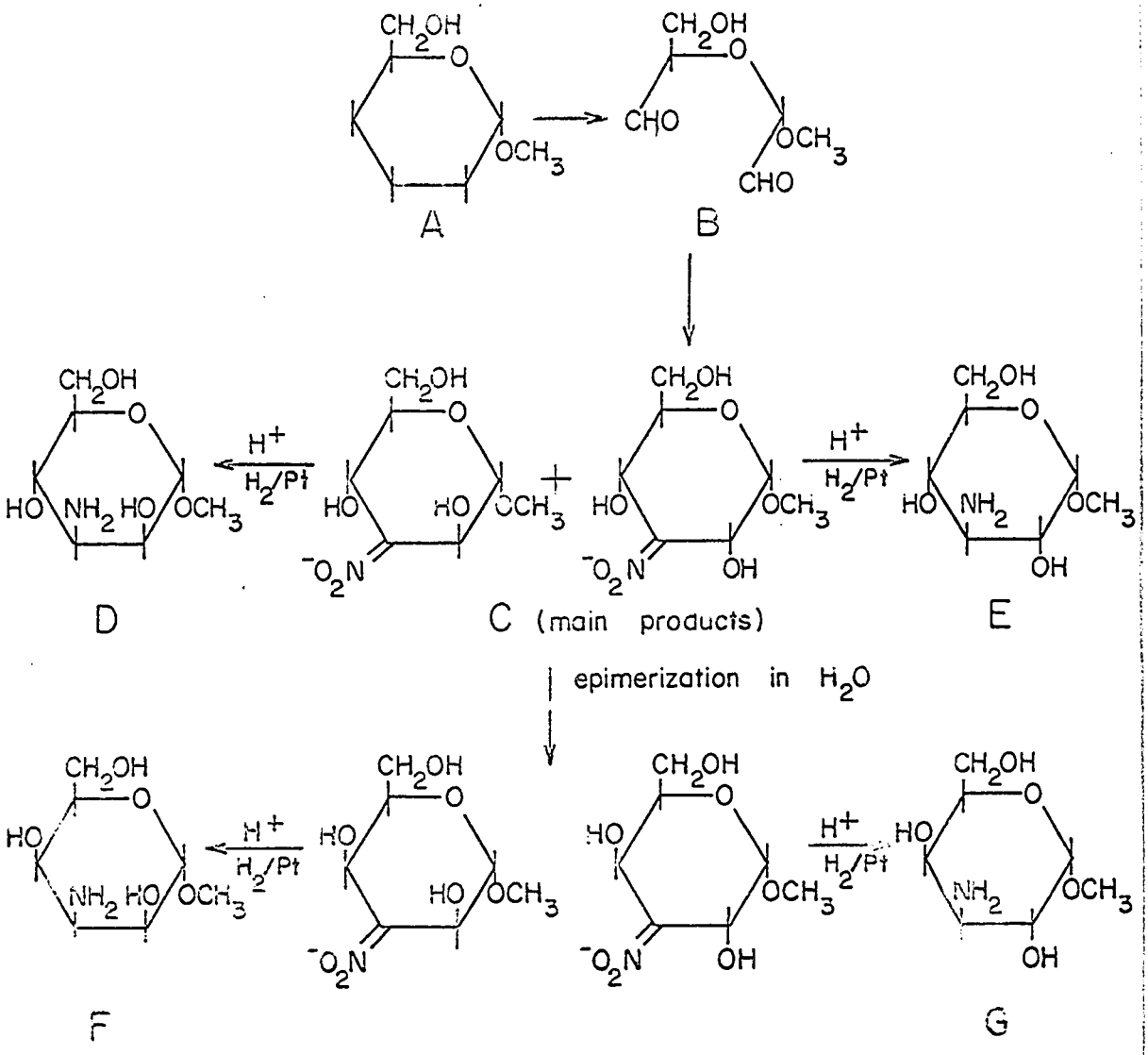
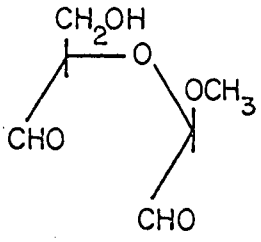
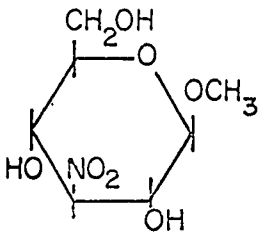


Chart 3

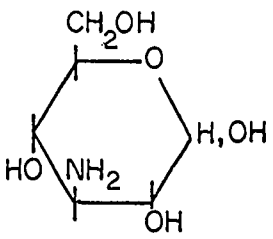


A



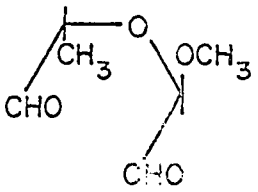
B

(+ galacto and manno isomers)

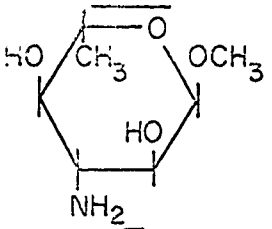


C

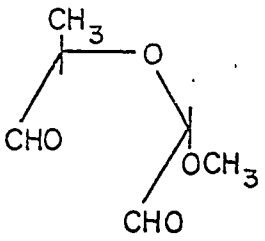
Kanosamine



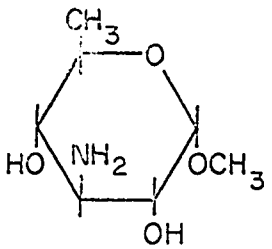
D



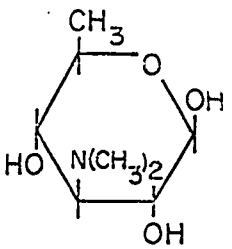
F



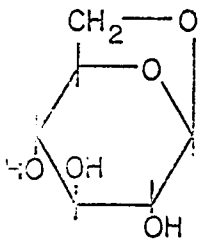
E



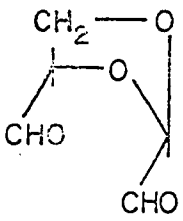
G



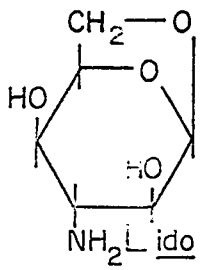
H Mycaminose



K

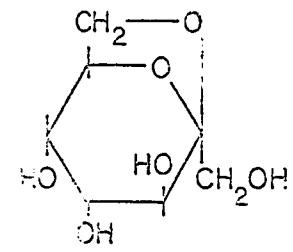


J

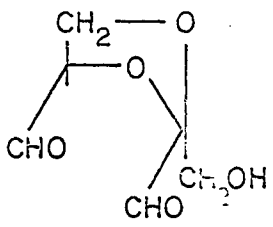


L ido

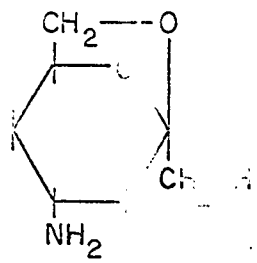
(+ altro and gulo isomers)



N



M



O

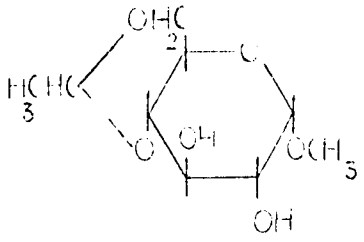
Since the nitro glucoside and its reduction product crystallized well in the β-series, this is the preferred method for the synthesis (64) of 3-amino-3-deoxy-D-glucose (C), a component of the antibiotic kanamycin.

The nitro β-glycosides also undergo mutual interconversion in aqueous, alkaline solution, with the gluco derivative being favored, but with much of the galacto and very little of the manno isomer being present in the equilibrium (65, 66).

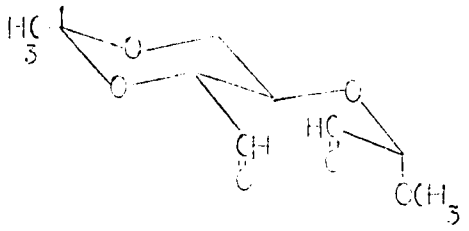
Analogous experiments performed with the dialdehyde D (from methyl α-L-rhamnopyranoside) and with its enantiomorph (E) afforded the L- and D-forms of methyl 3-amino-3-, 6-dideoxy-glucopyranoside (F and G, respectively). N, N-Dimethylation and acid hydrolysis of G gave mycaminose (H), the amino sugar moiety from magnamycin (67, 68, 69, 70).

The dialdehyde (J) obtainable from levoglucosan (K) also condensed readily with nitromethane and yielded a mixture of 3-nitro-3-deoxyhexosans and on subsequent hydrogenation, 3-amino-3-deoxy-hexosans (L) (71, 72). The products were shown to possess gulo, ido, and altro configuration. The homologous dialdehyde (M) derived from sedoheptulosan (N) afforded three crystalline 2, 7-anhydro-4-nitro-4-deoxy-β-D-heptulopyranoses and their corresponding amines (O) (73), which proved to be of the gulo, altro and allo configurations (74) (Chart 3).

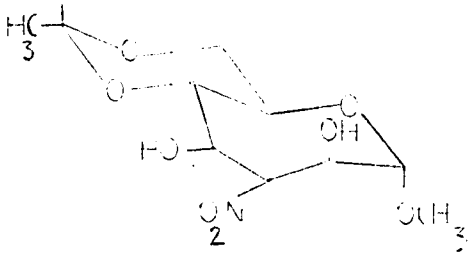
One example has been reported of the synthesis of an amino-deoxy-aldoheptose (75). The product (B) of periodate oxidation of methyl 4, 6-ethylidene-α-D-glucopyranoside (A) gave a methyl 5, 7-ethylidene-3-nitro-3-deoxy-heptoseptanoside (C) which upon hydrogenation, acid hydrolysis and N-acetylation afforded 3-acetamido-3-deoxy-D-glycero-D-mannoheptose (D);



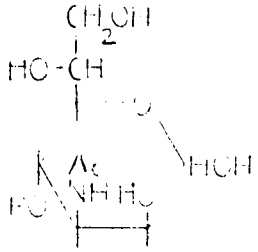
A



B



C



D

C. Specification of the Goals of the Present Thesis

In the light of the knowledge available at the time of undertaking this project about the nitromethane condensation with sugar dialdehydes as presented in the Introduction, it appeared to be of interest to investigate the following problems:

1. The nitromethane condensation with sugar dialdehydes does not proceed in a stereospecific way, although a notable stereoselectivity is always observed. In the cyclization of the dialdehydes derived from the pentosides only the nitrogenous derivatives of ribose and xylose are described. All these arise only from the 3-aci-nitro-3-deoxy-erythro-nitronates. It was, therefore, desirable to investigate this condensation in more detail, especially with respect to whether and to which extent, stereoisomers of the erythronitronates were formed.

2. It is known that in the hexose series and also in the pentose series glycoside nitronates in aqueous solution undergo spontaneous epimerizations. It appeared interesting to study this epimerization in the pentose series.

3. With a view of the growing importance of antibiotics, it seemed desirable to widen the scope of the nitromethane cyclization. To this end, it appeared quite interesting to condense with nitromethane the disaccharide dialdehyde that is readily available from sucrose, in order to prepare nitrogenous disaccharides and nitrogenous derivatives of heptuloses.

II. DISCUSSION

A. Cyclization of L'-Methoxy- and D'-Methoxy-diglycolic Aldehydes

In the cyclization (58), with nitromethane and sodium methoxide, of L'-methoxydiglycolic aldehyde (I) a methyl aci-nitrodeoxy pentoside sodium salt had been isolated in crystalline condition in a yield of about 40%. This salt had been shown to possess formula II and must therefore be denoted as methyl 3-aci-nitro-3-deoxy-β-D-erythro-pentopyranoside sodium.* It is seen that in the cyclization of I leading to the nitronate II there have been generated two asymmetric centers, at C-2 and C-4. Therefore, it had to be expected that stereoisomers of II should also be formed in this reaction. The three possible stereoisomers of II which might arise are the corresponding α-L-threo (III), β-D-threo (IV), and α-L-erythro (V) 3-deoxypentose derivatives. A study was undertaken in order to find out which of these isomers, if any, are co-products in this cyclization.

When dialdehyde I is cyclized with nitromethane, the α-L-threo and β-D-threo forms of methyl 3-aci-nitro-3-deoxypentopyranoside sodium (III and IV, respectively) indeed occur in the reaction mixture as minor components beside the chief product, β-D-erythro salt II. Although the salts III and IV could not be isolated as such, their presence was indicated by the isolation of two new, free nitroglycosides that arose upon deionization of the nitronate mixture. Thus, methyl 3-nitro-3-deoxy-α-L-arabinopyranoside (VI), originating from III and methyl 3-nitro-3-deoxy-β-D-arabinopyranoside (VII), arising from IV, were obtained by fractional

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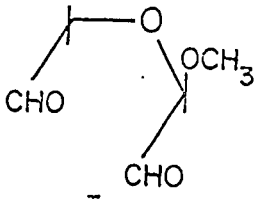
* This notation replaces the older nomenclature, methyl 3-aci-nitro-3-deoxy-β-D-ribopyranoside sodium, which was used in reference 58.

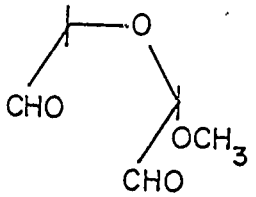
crystallization in yields of approximately 5% each.

The course of the cyclisation with nitromethane of I in methanol was followed by paper chromatography. It was found that even at 0° the dialdehyde disappeared within about 10 minutes. Already, after 3 minutes, the three nitronates II, III, and IV were present, as was revealed by chromatographic detection of the corresponding free nitroglycosides following deionization. There appeared to be a preponderance of IV during the first few minutes of the reaction, but the final pattern, with II as the chief product, was largely established after 15 minutes; and small changes, if any, in the proportions of II, III, and IV in solution occurred thereafter over a period of 48 hours. The salt II began to crystallize out after an induction period of 10 to 15 minutes, a circumstance which evidently furthered its formation.

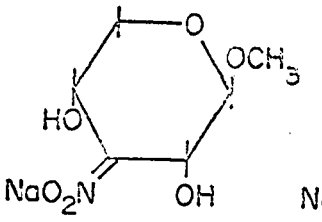
The new crystalline nitroglycosides VI and VII were hydrogenated to furnish the corresponding aminoglycosides, which crystallized as hydrochlorides: methyl 3-amino-3-deoxy-α-L-arabino-pyranoside hydrochloride (VIII) and methyl 3-amino-3-deoxy-β-D-arabino-pyranoside hydrochloride (IX). Proof of the structure and configurations of VIII and IX was afforded by acid hydrolysis yielding reducing amino sugars. Glycoside IX gave 3-amino-3-deoxy-D-arabinose hydrochloride (XI), which crystallized as upward-mutarotating β-form ($[\alpha]_D$ - 147° → -113°). This sugar had been described by Baker, Schaub, and Williams (20), although these authors did not record a mutarotation. Glycoside VIII afforded the hitherto unknown enantiomorph of XI, namely 3-amino-3-deoxy-L- arabinose hydrochloride (X). Belonging to the L-series and exhibiting downward mutarotation ($[\alpha]_D$ + 145° → + 110°), the crystalline compound has to be designated as the β-form.



I

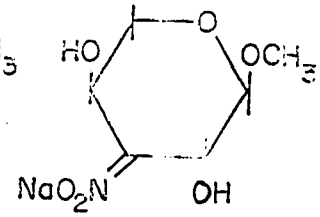


XII

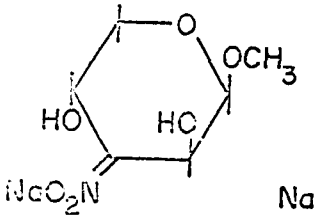


II

β-D-erythro

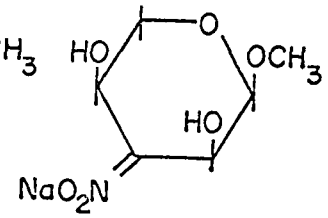


α-L-threo



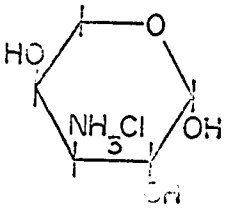
IV

β-D-threo

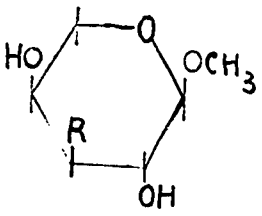


V

α-L-erythro

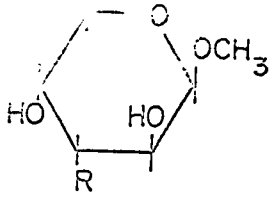


X



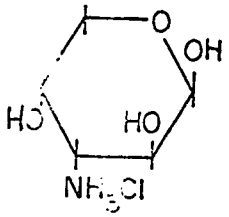
VI, R=NO$_2$

VIII, R=NH$_3$Cl

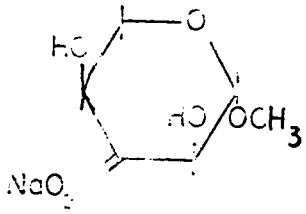


VII, R = NO$_2$

IX, R= NH$_3$Cl

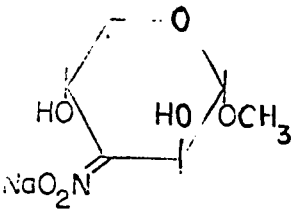


XI



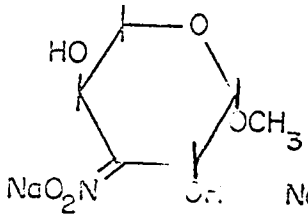
XIII

β-L-erythro



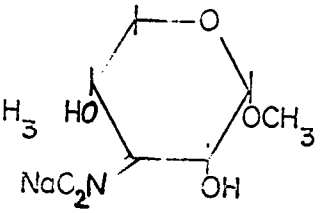
XIV

α-D-threo



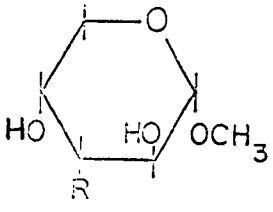
XV

β-L-threo



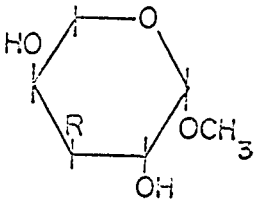
XVI

α-D-erythro



XVII, R = NO$_2$

XIX, R=NH$_3$Cl



XVIII, R = NO$_2$

XX, R = NH$_3$Cl

There had also been described (58) a parallel nitromethane condensation using D'-methoxy-diglycolic aldehyde (XII; i.e., the enantiomorph of I) and, accordingly, furnishing methyl 3-aci-nitro-3-deoxy-β-L-erythro-pentopyranoside sodium (XIII; i.e. the enantiomorph of II). Obviously, then, the α-D-threo salt XIV and the β-L-threo salt XV, being enantiomorphs of III and IV, respectively, had to be expected to arise as co-products in this parallel case. This has, in fact, proved true since the corresponding free nitroglycosides, methyl 3-nitro-3-deoxy-α-D-arabinopyranoside (XVII) and methyl 3-nitro-3-deoxy -β-L-arabino-pyranoside (XVIII) have been isolated. Hydrogenation furnished methyl 3-amino-3-deoxy-α-D-arabinopyranoside hydrochloride (XIX) and methyl 3-amino-3-deoxy-β-L-arabinopyranoside hydrochloride (XX), respectively. The physical constants of the new glycosides are shown in Table II.

The compounds obey Hudson's rule of isorotation. Thus, the value of A for the molecular rotational contribution of the glycosidic carbon atom in a pair of nitro anomers, e.g. VI and XVIII, is 18,596; the value is 17,695 for the corresponding amino derivatives VIII and XX, and 18,711 for the nitrogen-free, parent methyl α- and β-L-arabino-pyranosides (76). The values B for the cores of the molecules are +35,114 for the pair of nitroglycosides VI:XVIII; +22,625 for the pair of amines VIII: XX; and +21,501 for the anomeric methyl L-arabinopyranosides (Table III). The latter set of figures exemplifies anew that substitution of an amino group for a hydroxyl group in glycosides has little influence upon the optical rotation (65, 72*, 73**). Introduction of a nitro group, on the other hand, can produce a considerable change in the molecular

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* Further literature in support of this rule is cited there.

** In reference 73, tentative configurational assignments for two new amino sugars were based on this rule. They have now been confirmed by nuclear magnetic resonance studies (74).

Table II

Physical data of the new glycosides

Compound	Configuration	m. p.	$[\alpha]_D$ in water
Nitro:			
VI	α-L-arabino	180-182°	+85.5°
XVII	α-D-arabino	179-180°	-86.0°
XVIII	β-L-arabino	179-180°	+278°
VII	β-D-arabino	178-180°	-278°
Amino:		m. p. (decomp)	
VIII	α-L-arabino	164-165°	+24.7°
XIX	α-D-arabino	165°	(-24.7)*
XX	β-L-arabino	180-183°	+202°
IX	β-D-arabino	181-183°	-205°

* By reversal of the sign of rotation of the enantiomorph (VIII). The amount of substance available was insufficient for measurement of the rotation.

Table III

Values for the molecular rotational contribution of the glycosidic carbon atom (A) and core of the molecule (B) of the new glycosides.

Compound	$[M]_D$	A	B
Methyl 3-nitro-3-deoxy-α-L-arabinoside (VI)	+16, 518	18, 596	+35, 114
Methyl 3-nitro-3-deoxy-β-L-arabinoside (XVIII)	+53, 709		
Methyl 3-amino-3-deoxy-α-L-arabinoside hydrochloride (VIII)	+ 4, 930	17, 695	+22, 625
Methyl 3-amino-3-deoxy-β-L-arabinoside hydrochloride (XX)	+40, 319		
Methyl α-L-arabinoside	+ 2, 790	18, 711	+21, 501
Methyl β-L-arabinoside	+40, 212		

$$A = \frac{1}{2}\left\{[M]_D \text{ for } \alpha\text{-anomer} - [M]_D \text{ for } \beta\text{-anomer}\right\}$$

$$B = \frac{1}{2}\left\{[M]_D \text{ for } \alpha\text{-anomer} + [M]_D \text{ for } \beta\text{-anomer}\right\}$$

rotation, as is seen in the present case and in various earlier examples (65, 73).

B. Partial Epimerization of Methyl 3-aci-Nitro-3-deoxy-Pentopyranoside Sodium Salts

The β-D-erythro nitronate II had been found (58) to exhibit, in aqueous solution, an unexpected and, at the same time, unexplained mutarotation (Fig. 1). The new nitroarabinosides, methyl-3-nitro-3-deoxy-α-L-arabinopyranoside (VI) and methyl 3-nitro-3-deoxy-β-D-arabinopyranoside (VII), have been converted into their respective sodium nitronates, III and IV, by the addition of equivalent amounts of sodium hydroxide in water. Immediately there commenced mutarotations leading to the same final $[\alpha]_D$ value. Deionization at this point and chromatographic inspection of the resulting solutions, directly as well as following hydrogenation to the amine stage, indicated that equilibrations had taken place; identical chromatographic patterns were obtained regardless of which was the starting compound. In the equilibrium the levorotatory β-D-erythro salt II greatly predominated. On account of the rotation value of the equilibrated solution the remainder was judged to consist largely of the dextrorotatory α-L-threo salt III. It was in fact possible to isolate the crystalline product of deionization of III, methyl 3-nitro-3-deoxy-α-L-arabinopyranoside (VI), in a yield of 6% from an equilibrated solution of II. An estimate based on the initial rotations of II and III and on the final rotation would indicate a ratio of 85:15 of the two salts, which was consistent with the chromatographic picture. This calculation neglects a possible participation in the equilibrium of the strongly levorotatory β-D-threo salt IV; however, since no evidence for its presence was found, it could have been present in negligible amount only. The apparent failure of IV to play a significant part in the composition of the epimerization

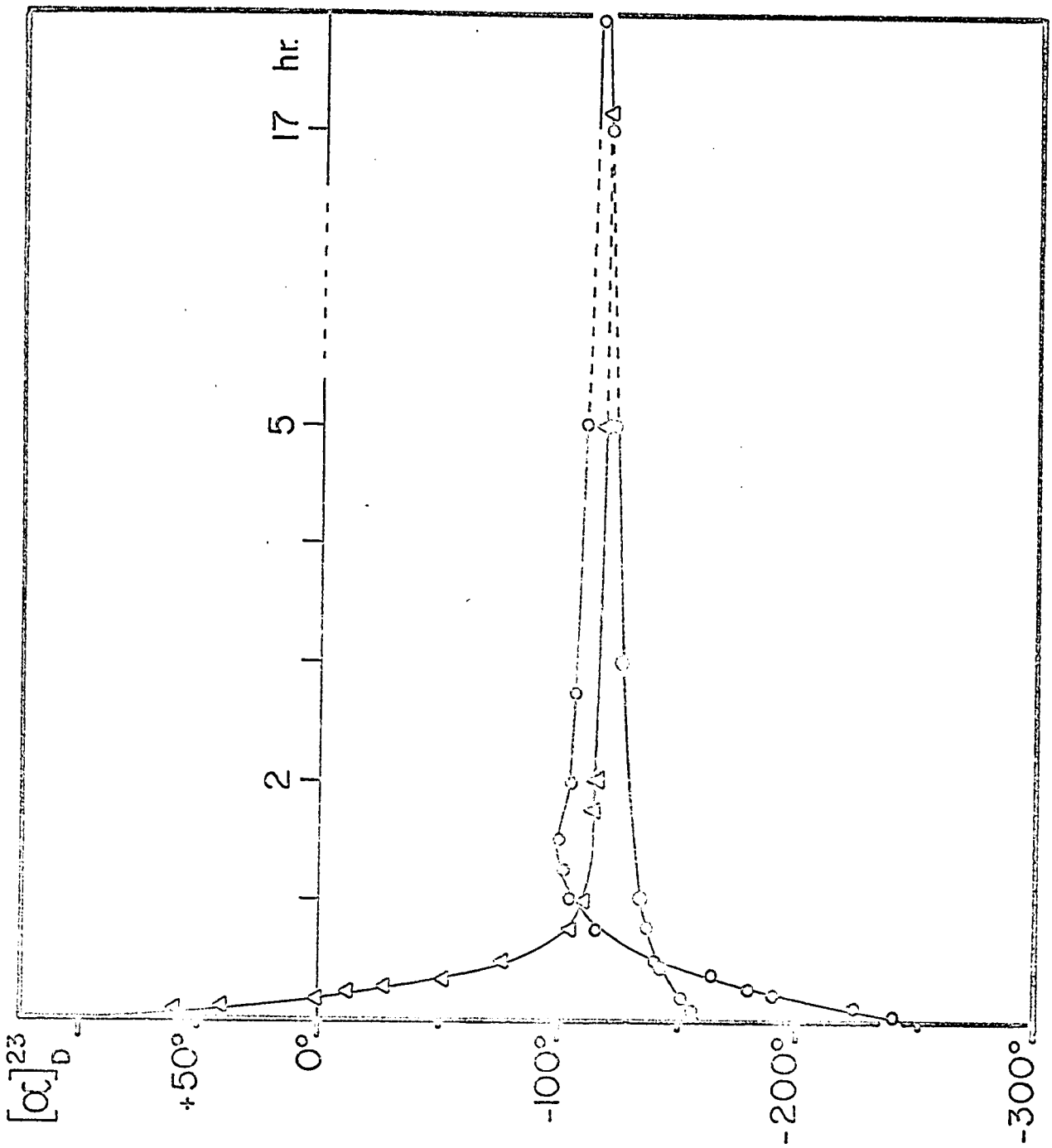
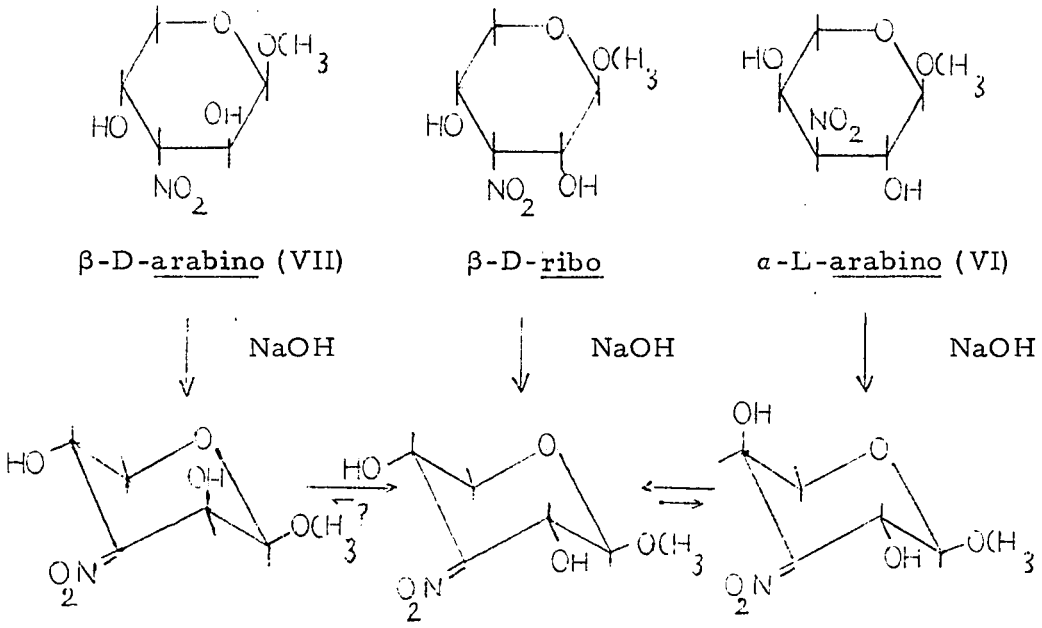
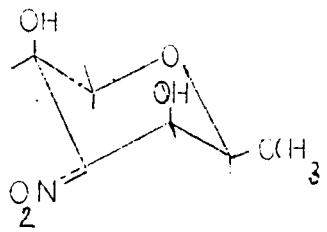


Fig. 1. The mutarotations of the nitrones II (○), III (△), and IV (○) in water.

equilibrium in water is not necessarily inconsistent with the fact that in a kinetically controlled condensation reaction in methanolic medium it does arise to an appreciable extent. The spontaneous epimerisation may be represented by the following scheme:

Methyl 3-nitro-3-deoxy-**pentopyranosides**



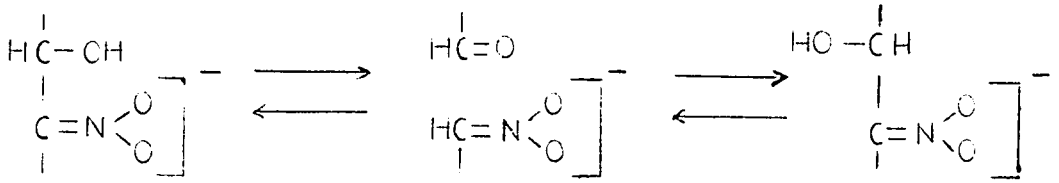


V

As for the fourth possible isomer, the α-L-*erythro* salt V, no sign of its formation has thus far been observed either in cyclization or in epimerization experiments. The present results, then, lead to the conclusion that the thermodynamic stabilities of the *aci*-nitro salts decrease in the order II > III > IV > V. In this connection it is worth mentioning that the same order of thermodynamic stabilities has been established for the *aci*-nitro-β-D-hexopyranoside sodium salts (66). In that series, the β-D-*erythro*, α-L-*threo*, and β-D-*threo* configurations of the pentoside nitronates have their counterparts in the nitronates arising from the 3-nitro-3-deoxy-hexopyranosides with β-D-*gluco*, β-D-*galacto*, and β-D-*manno* configurations, respectively.

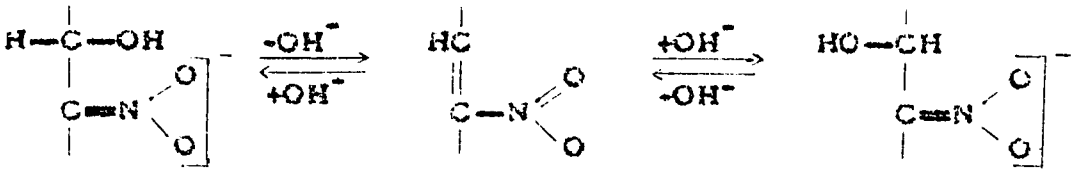
The conclusion drawn above about the stability of the *aci*-nitro pentopyranoside sodium salts is also consistent with conformational considerations. The β-D-*erythro* isomer II should be the most stable and hence favored one, since it is unique in having all the three variable substituents in equatorial positions in the C-1 chair conformation. Furthermore, it is known from similar condensationsthat in the more favored isomer the hydroxyl group of a newly formed asymmetric carbon atom tends to assume *trans* position to the substituent on the adjacent original asymmetric center (77, 78). This line of thought gives some additional support to favoring stabilization of β-D-*erythro* isomer II and suggests the α-L-*threo* isomer III as a second choice.

Two possible mechanisms may be discussed for the epimerization reaction. The first one, suggested without experimental proof by Grosheintz and Fischer (79) to explain the interconversion of stereoisomeric nitrodeoxyinositols, involves a reversal of the Henry condensation:

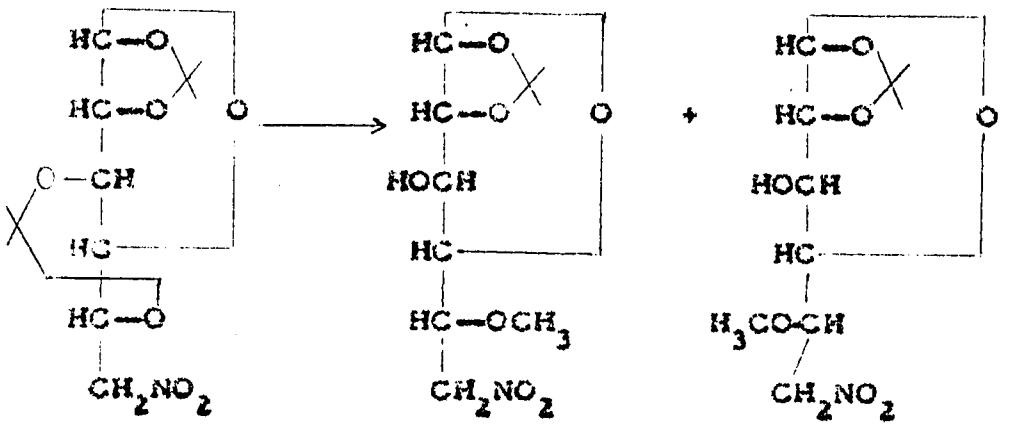


Lichtenthaler (80), in a detailed study leading to the stereochemical elucidation of Grosheints and Fischer's nitroinositols, rejected this mechanism on the grounds of his failure to detect by paper chromatography any reaction intermediates arising from the proposed C-C cleavage. However, the apparent absence of such intermediates can hardly be considered as convincing evidence against the mechanism, since they need not and probably would not occur in amounts sufficient for chromatographic detection.

A second mechanism calls for the intermediate formation of a nitroolefin:



Although no direct proof is available for this mechanism either, it is supported by occurrence of epimerization in a case where reverse Henry condensation is precluded. 1, 2:3, 5-Diisopropylidene-6-nitro-6-deoxy-D-glucofuranose rapidly loses its 3, 5-acetone group through the action of dilute, methanolic alkali at room temperature, and forms a mixture of C-5 epimeric methyl ethers, 1, 2-isopropylidene-5-O-methyl-6-nitro-6-deoxy-D-glucofuranose and -L-idofuranose (81). The formation of a nitroolefin intermediate has been demonstrated by U. V. spectroscopy:



C. Cyclisation of a Dialdehyde Obtained from Sucrose by Partial Lead Tetraacetate Oxidation

An extension of the nitromethane cyclisation to disaccharides was undertaken in view of the fact that a simple nitrogenous disaccharide, α,α-trehalosamine, had been found in nature and had been shown to possess antibiotic properties (5). It was contemplated that the dialdehyde XXI, which according to Perlin and Mitra (82) is readily obtained from sucrose by partial lead tetraacetate oxidation, should give rise to disaccharides of the general structure XXIII. This structure is related to trehalosamine, although the nitrogen function is in a different position and the nitrogenous moiety is a heptulose rather than a hexose. Apart from any potential biological usefulness, such structure would in itself be of interest since it would represent the first oligosaccharide containing a nitrogenous seven-carbon sugar, and it would contribute to the knowledge of nitro- and amino-heptuloses, a class of sugars of which some members have only been synthesised very recently (73).

Dialdehyde XXI was cyclised with nitromethane in the presence of sodium methoxide in methanol, and a mixture of aci-nitro

disaccharide sodium salts (XXII) was obtained in a yield of 58%. As can be seen by inspecting formulas XXI and XXII the glucose ring of sucrose is involved neither in the production of XXI nor in the cyclization to XXII. Also, the stereochemistry at carbons 2 and 5 of the ketose moiety may be presumed to remain unchanged in the sequence of reactions.* Therefore, the aci-nitro disaccharide sodium salts XXII should be designated as α-D-glucopyranosyl 4-aci-nitro-4-deoxy-β-D-heptulopyranoside sodium salts. Deionization of this salt mixture gave an amorphous mixture of the corresponding nitro disaccharides, α-D-glucopyranosyl 4-nitro-4-deoxy-β-D-heptulopyranosides (XXIII). Paper chromatography revealed the presence of two nitro components in similar quantities.

Catalytic reduction of the nitro disaccharide mixture afforded a pure, crystalline amino disaccharide hydrochloride, α-D-glucopyranosyl 4-amino-4-deoxy-β-D-heptulopyranoside hydrochloride XXIV, in a yield of 23% (based on starting sucrose). N-acetylation (83) of XXIV yielded the corresponding α-D-glucopyranosyl 4-acetamido-4-deoxy-β-D-heptulopyranoside XXV in crystalline state.

Whereas the structures of the new disaccharides followed from the mode of synthesis, the configurations at C-3, C-4 and C-5 remained to be established. Attempts were, therefore, made to elucidate these configurations. In the pursuit of this end, several nitrogenous heptulose derivatives were obtained following acid degradation of the disaccharides, and were used for further studies intended to clarify the configurational questions.

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* There has been no evidence for epimerization at the corresponding carbon atoms in all the nitromethane cyclizations investigated previously.

Amino disaccharide hydrochloride XXIV was hydrolyzed with 2N hydrochloric acid to give D-glucose and a reducing 4-amino-4-deoxy-D-heptulose hydrochloride (XXVI). D-Glucose was detected by paper chromatography, and the nitrogenous fragment was isolated with the help of a cation exchange resin. The 4-amino-4-deoxy-D-heptulose was converted into its crystalline N-acetate, 4-acetamido-4-deoxy-D-heptulose (XXVII). The yield of XXVII based on XXIV was 45%. Since XXVII exhibited a downward mutarotation ($[\alpha]_D$ + 66° ⟶ + 55°) and belonged to the D-series, it was assigned an α-anomeric configuration.

Methanolysis of the mixture of nitro disaccharides (XXIII) with 2% hydrogen chloride in methanol (w/v) yielded methyl α-D-glucopyranoside and methyl 4-nitro-4-deoxy-α-D-heptulopyranoside (XXIX). The latter was obtained in crystalline condition through purification via a dibenzylidene derivative, methyl 1, 3:5, 7-di-O-benzylidene-4-nitro-4-deoxy-α-D-heptulopyranoside (XXVIII), which was obtained in a yield of 16% based on sucrose. Gentle hydrolytic removal (84) of the benzylidene groups from XXVIII afforded XXIX in a yield of 77%. Catalytic reduction of XXIX gave chromatographically pure methyl 4-amino-4-deoxy-α-D-heptuloside hydrochloride (XXX) in a yield of 61%.

The α-configuration at the anomeric center of XXX (and hence XXVIII - XXIX and of all compounds derived from XXX) follows from a comparison of the molecular rotation of XXX with that of the disaccharide XXIV. The disaccharide XXIV ($[M]_D$ + 42,054) may be regarded as an α-D-glucopyranoside whose "aglycon" is the β-heptulopyranosyl residue. If the aglycon were optically inactive, the molecular rotation of the disaccharide should be similar to that of methyl α-D-glucopyranoside ($[M]_D$ + 30,691). The difference between the latter value and

the observed value is + 11, 363 and may serve as an approximate measure of the rotational contribution of the "aglycon", i.e., of the β-heptulopyranosyl residue. Now, the methyl heptuloside XXX has a much higher molecular dextrorotation ($[M]_D$ + 25, 613), and as the compound belongs to the D-series it is, therefore, judged to be the α-anomer. The data are shown in Table IV.

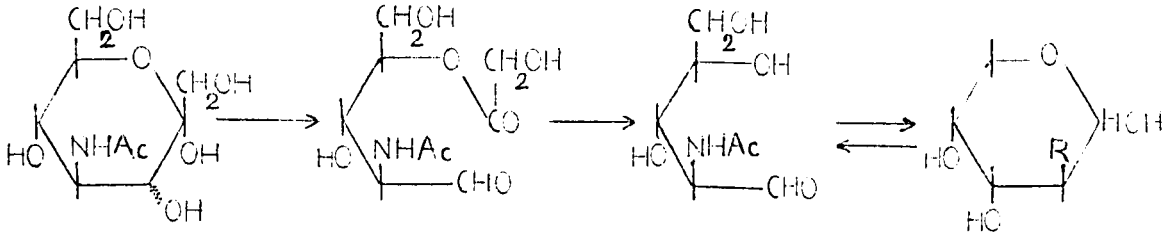
Table IV

Compound	$[\alpha]_D$	Mol. wt.	$[M]_D$
Disaccharide XXIV	+103.2	407.5	+42,054 (X)
Methyl α-D-glucopyranoside	+158.2	194	+30,691 (Y)
Methyl heptuloside XXX	+ 98.7	259.5	+25,613

X - Y = contribution of β-heptuloside residue.

Methanolysis of the amino disaccharide hydrochloride XXIV with 5% hydrogen chloride in methanol (w/v) gave crystalline methyl α-D-glucopyranoside and the same methyl 4-amino-4-deoxy-α-D-heptulopyranoside hydrochloride (XXX) that had been previously obtained by hydrogenation of the nitroheptuloside XXIX. The amino-glycoside XXX was further characterised as its 1, 3, 4, 5, 7-pentaacetyl derivative XXXI; and it was shown, moreover, that hydrolytic removal of the glycosidic methyl group followed by N-acetylation led, in 68% yield, to the same 4-acetamido-4-deoxy-D-heptulose (XXVII) which had been prepared before by direct hydrolysis and N-acetylation from the amino disaccharide hydrochloride XXIV.

In order to establish the configurations at carbons 4 and 5 the reducing N-acetate, 4-acetamido-4-deoxy-D-heptulose XXVII, was partially degraded with lead tetraacetate. The procedure used was that developed by Perlin and Brice (85) who demonstrated that ketoses are cleaved by a limited amount of oxidant preferentially between the reducing center and the adjacent ring carbon (and not the adjacent hydroxymethyl group). The Perlin degradation thus results in the removal of the two top carbons of the ketose chain producing a lower aldose. It represents one of the few useful methods of controlled ketose degradation. In our case, the acetamido heptulose XXVII gave rise to known 2-acetamido-2-deoxy-D-arabinose (86) and, upon acid hydrolysis, 2-amino-2-deoxy-D-arabinose hydrochloride (86). The degradation products were identified with authentic samples by rotation, infrared spectroscopy, melting point and chromatography.



XXVII

R = NHAc (N-Acetyl-D-arabinosamine)

R = NH_3Cl (D-Arabinosamine hydrochloride)

Since C-2, C-3 and C-4 of D-arabinosamine correspond to C-4, C-5 and C-6 of the heptulose, the only configuration remaining unknown in the

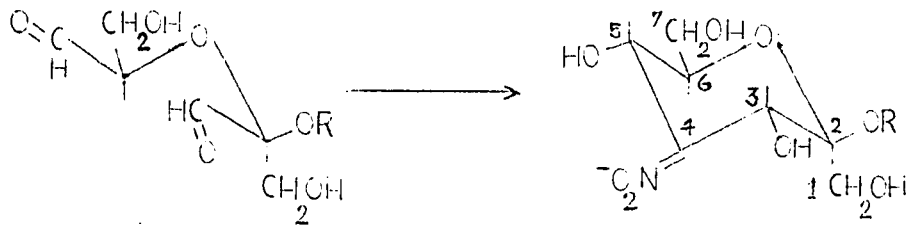
latter was that at C-3. In order to solve this last problem, it was attempted to make use of the solvolysis of a methanesulfonyl derivative.

It is known that in cyclohexane and pyranoside rings sulfonyloxy groups situated trans to a vicinal acetoxy or acylamido group may undergo facile solvolysis involving participation of the neighboring group (87, 88). Under the same conditions, a cis sulfonyloxy group undergoes replacement at a much slower rate if at all (89). Baker and co-workers (90, 19) have introduced this reaction into carbohydrate chemistry using sodium acetate in refluxing 95% aqueous 2-methoxyethanol or ethanol as reagents. Since under these conditions the solvolysis of a trans sulfonyloxy group is attended with inversion, this method has found frequent applications for stereochemical transformations in amino sugars, for preparative purposes (18, 20, 91, 92, 93, 23) as well as, sometimes, for the determination of unknown configurations (72, 94).

The aminoglycoside hydrochloride XXX was, therefore, converted into crystalline methyl 4-acetamido-4-deoxy-1, 3, 5, 7-tetra-O-mesyl-α-D-heptulopyranoside (XXXIII) via the amorphous N-acetate XXXII (overall yield, 61%). Solvolysis of the tetramesyl derivative XXXIII with sodium acetate in refluxing 2-ethoxyethanol during two days, followed by acetylation of the product, gave a crystalline derivative which was revealed by analysis to have retained two mesyl groups. Unfortunately, this result does not allow a definitive conclusion to be drawn regarding the configuration at C-3, for it might be explained in terms of either configuration. According to Oldham and Rutherford's rule (95), which has been appraised at length by Tipson (96), a primary sulfonyloxy adjacent to the glycosidic center in keto sugars (i. e., at C-1) is extremely resistant to displacement, while a primary sulfonyloxy at the ultimate carbon is relatively easily displaced. Secondary sulfonyloxy groups are stable unless their solvolysis proceeds through anchimeric assistance. Applying the Oldham-Rutherford-Tipson rule,

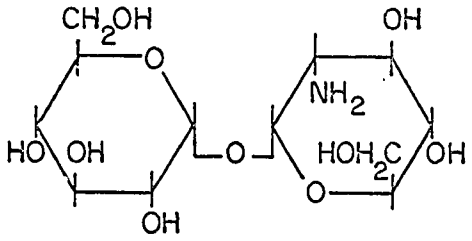
and taking into consideration the established trans relationship between C-4 and C-5 which should provide for anchimeric assistance, one would have to conclude that solvolysis has occurred at C-5 and C-7. The acetylated product would then be a methyl 5, 7-di-O-acetyl-4-acetamido-4-deoxy-1, 3-di-O-mesyl-α-D-heptulopyranoside (XXXIV), and the failure of the C-3 mesyloxy group to solvolyze would tend to indicate a 3, 4 cis orientation and hence D-manno configuration of the starting sugar. On the other hand, cases have been reported in which solvolysis in trans sulfonyloxy-acylamido sugars proceed very sluggishly (72) or not at all (97), probably because of steric hindrance. The D-gluco configuration of XXXIII cannot be ruled out, therefore. In fact, the gluco configuration would seem more likely to be formed in the cyclization of dialdehyde XXI, for conformational reasons to be now discussed.

As was mentioned earlier, in the more favorable isomers arising from nitromethane condensations the hydroxyl group at a newly created asymmetric carbon tends to be oriented trans with respect to the substituent on the adjacent, original asymmetric center. Hence, it is quite justifiable to expect that the hydroxyl group at C-3 in the seven-carbon sugar moiety of the disaccharide XXII should place itself in equatorial position in order to have trans relationship to the β-glycosidic, equatorial α-D-glucopyranosyl group. An axial hydroxyl at C-3 would introduce considerable conformational instability because of Reeves "Δ2 effect" (98), a condition present when a hydroxyl-to-carbon bond bisects the O-C-O angle in a pyranose derivative. Moreover, the aci-nitro substituent probably forces the molecule into a somewhat distorted chair form in which an axial hydroxyl, at C-3, would be moved toward some degree of eclipsing with the glycosidic oxygen.

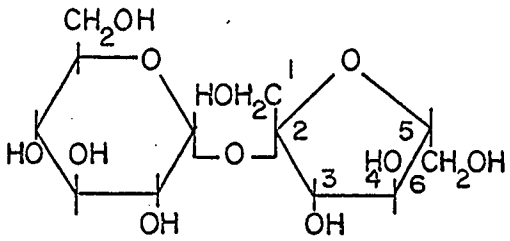


dialdehyde XXI

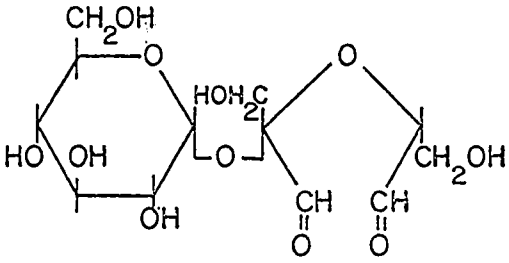
R = α-D-glucopyranosyl



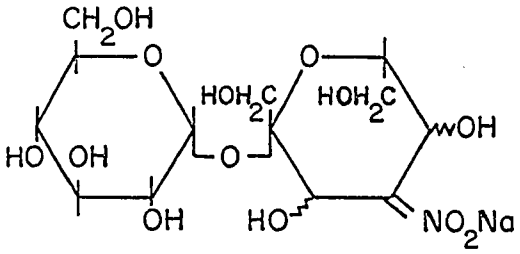
trehalosamine



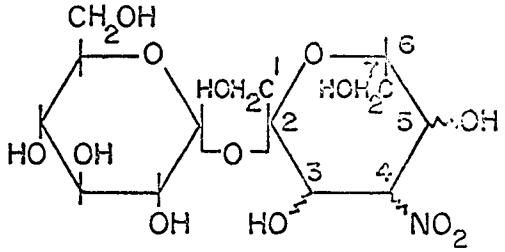
sucrose



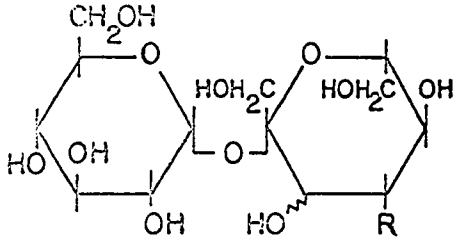
XXI



XXII

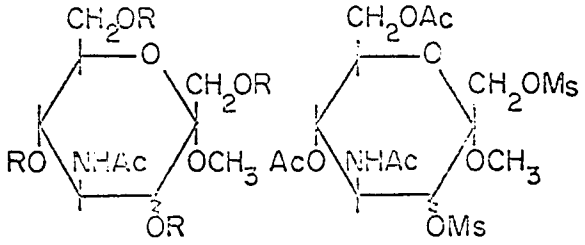


XXIII



XXIV, R = NH_3Cl

XXV, R = NHAc

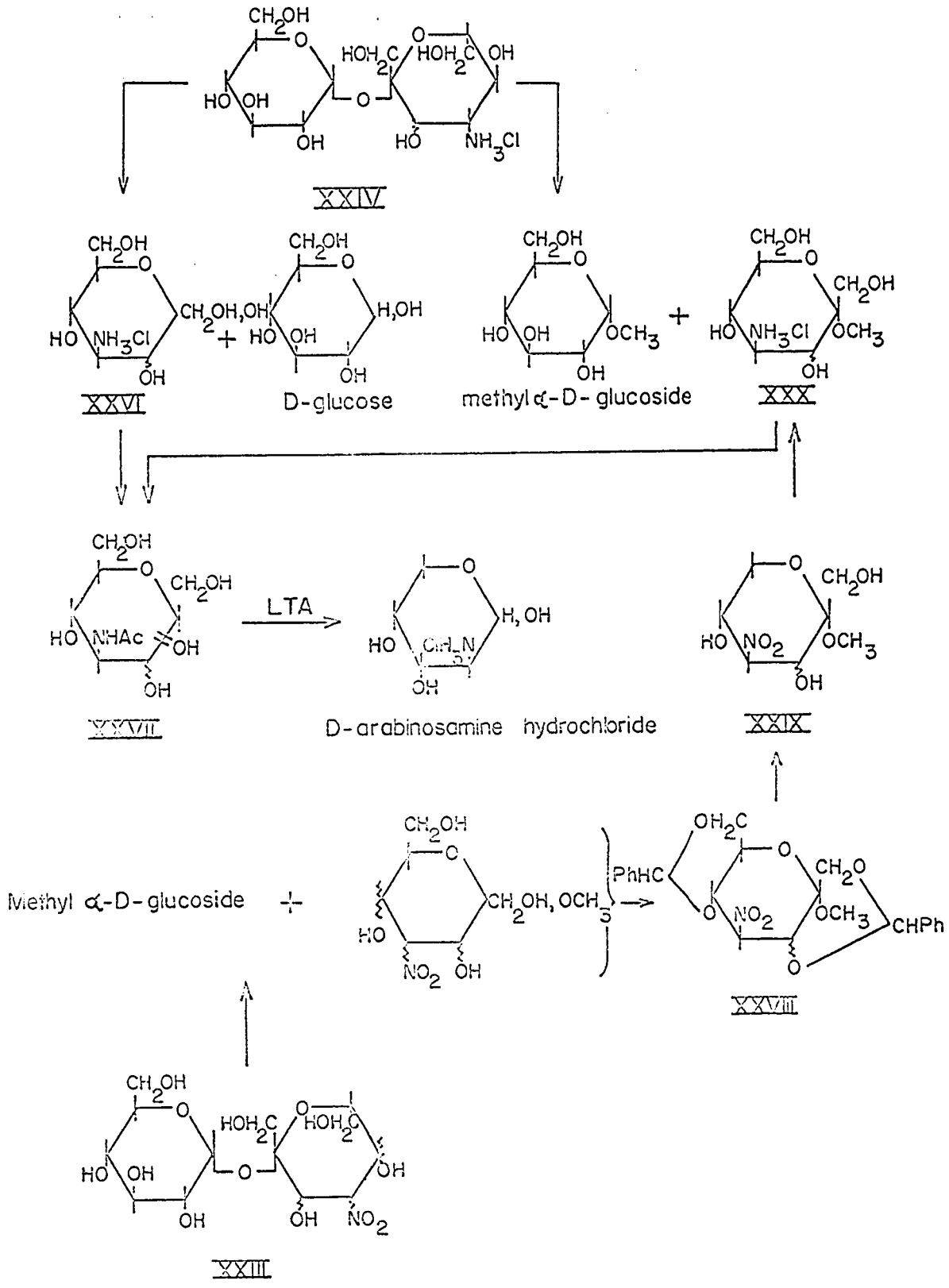


XXXI, R = Ac

XXXII, R = H

XXXIII, R = Ms

XXXIV


XXIV
XXVI
D-glucose
methyl α-D-glucoside
XXX
LTA
XXVII
D-arabinosamine hydrochloride
XXIX
Methyl α-D-glucoside
XXVIII
XXIII

III. EXPERIMENTAL

The melting points were determined in an aluminium block apparatus. All evaporations were done in vacuo at 35-40° (bath temperature) unless otherwise indicated. Paper chromatography was performed by the descending technique on Whatman No. 1 paper. The nitro compounds were irrigatedwith 1-butanol-acetic acid-water (4:1:5, v/v, upper layer) and made visible by spraying with alkali (1 part N NaOH + 4 parts methanol + 5 parts 1-butanol) and inspection under an ultraviolet lamp. The amino compounds were irrigated with pyridine-ethyl acetate-acetic acid-water (5:5:1:3, v/v , with pyridine-ethyl acetate-water, 11:40:6, v/v, in the bottom of the tank) and indicated with ninhydrin. R_{gm} = speed relative to glucosamine hydrochloride. The N-acetamido compounds were irrigated with 1-butanol-pyridine-water (60:40:30, v/v, with the same solvent system in the bottom of the tank) and detected according to Pan and Dutcher (199). Infrared spectra were taken in nujol mull on Perkin-Elmer Infracord spectrophotometer Model 137.

Preparation of L'-Methoxy-diglycolic Aldehyde (I)

L'-Methoxy-diglycolic aldehyde (I) was made according to Jackson and Hudson (100). Sodium metaperiodate (42.8 g) was dissolved with mild heating in 300 ml of water. After cooling to 5° there was added, with swirling and irrespective of some reappearing crystals, 16.4 g of solid methyl β-D-xylopyranoside (m.p. 154 - 155°, $[\alpha]_D$ - 65.6°) in small portions in the course of about 10 minutes. The reaction was then allowed to proceed at room temperature whereby the periodate having separated initially redissolved soon. About 30 minutes after the beginning of the oxidation, neutralisation of the formic acid being formed was started by cautious, portionwise addition of 1M sodium bicarbonate

solution (90 ml). After 2 hours the oxidation was complete as indicated by a negative potassium iodide-starch test performed with a withdrawn portion that had been mixed with excess bicarbonate.

A precipitate, consisting of sodium iodate that appeared during the reaction, was filtered off, and the dialdehyde solution was then concentrated. Ethanol (100 ml) was added, precipitated sodium iodate was filtered off, and the solution was concentrated again. This process was repeated until no more alcohol-insoluble, inorganic material separated.

Condensation of Dialdehyde I with Nitromethane. Paper Chromatographic Study of the Cyclization Reaction

(a) L'Methoxy-diglycolic aldehyde prepared from 1.64 g of methyl β-D-xylopyranoside was dissolved in 10 ml of absolute methanol and chilled in ice-bath. Nitromethane (0.56 ml) and precooled sodium methoxide solution (7.6 ml; concentration, 3 g of sodium per 100 ml) were added and the volume was swiftly made up to 30 ml with ice-cold methanol. Aliquots (3 ml) of the reaction mixture were withdrawn after 3, 8, 15, 30 and 60 minutes and after 3, 7, 24 and 48 hours. The aliquots were immediately deionized by swirling with excess Amberlite IR-120(H^+) and by passage through a short column of additional, fresh resin. The resin used had been pre-washed with methanol and was washed with several small portions of methanol afterwards. The deionized filtrates were brought to equal volumes of 25 ml and inspected by paper chromatography. The results were as follows:

Reaction time	R_f - values	Reaction time	R_f - values
3 min	(0.64)-0.68, 0.81	3 hrs	0.64-0.68, 0.81
8	0.64 -0.68, 0.81	7	0.64-0.68, 0.80
15	0.64 -0.69, 0.81	24	0.64-0.68, 0.80
30	0.64 -0.69, 0.80	48	0.64-0.68, 0.80
60	0.64 -0.68, 0.80		

In the R_f 0.6-0.7 region there appeared poorly resolved double spots corresponding to VI and VII. The spots around R_f 0.80 were considerably stronger; they appeared to have weak front haloes (R_f 0.83) and were identical with those given by nitroriboside containing a little nitroxyloside obtained by deionization of pure β-D-erythro salt II (58).

(b) L'-Methoxy-diglycolic aldehyde prepared from 0.82 g of methyl β-D-xylopyranoside was condensed as described under (a) with 0.28 ml nitromethane in 8 ml methanol in the presence of 3.8 ml of sodium methoxide solution. The reaction mixture (15 ml) was divided into 3-ml fractions after intervals of 5 min, 15 min, 1 hr, 4 hr, and 24 hr. Each fraction was deionized as described, evaporated and then hydrogenated catalytically. The hydrogenations were done at ordinary temperature and pressure in 10 ml of N/10 hydrochloric acid with 200 mg of platinum oxide. The excess acid was removed with Amberlite IR-45(OH^-) and the solutions were evaporated. Paper chromatography of the residues of evaporation revealed complex patterns. The R_{gm} - values of the main components are given in the accompanying table. Additional, slow-moving products (R_{gm} 1 and below) were present in small amounts in all the fractions.

Reaction time	R_{gm} - values
5 min	1.73, 1.99 (faint), 2.16
15	1.73, 1.99 (faint), 2.16
60	1.73, 1.99 (faint), 2.16
4 hr	1.70, 1.99 (faint), 2.16
24	1.70, 1.99 (faint), 2.16

The spot R_{gm} 2.16 was identified as methyl 3-amino-3-deoxy-β-D-ribopyranoside hydrochloride and the spot R_{gm} 1.99 as methyl 3-amino-3-deoxy-β-D-xylopyranoside hydrochloride by co-chromatography of authentic samples (58).

Methyl 3-Nitro-3-deoxy-α-L-arabinopyranoside (VI) and Methyl 3-Nitro-3-deoxy-β-D-arabinopyranoside (VII)

L'Methoxy-diglycolic aldehyde (I) was prepared from 8.2 g (0.05 mole) of methyl β-D-xylopyranoside, and was dissolved in 75 ml of methanol. Nitromethane (2.8 ml, 1 molar equivalent) was added and the solution was chilled in an ice-bath. With swirling, 38.5 ml of a chilled, methanolic sodium methoxide solution (containing 3 g of sodium per 100 ml) was dropped in at a moderately rapid rate. After 15 minutes the reaction mixture was deionised, with efficient magnetic stirring at 0°, by addition of 75 ml of Amberlite IR-120(H^+) which had been previously washed with methanol. The solution was decanted from the resin and, to ensure complete deionisation, slowly passed over a column which contained another 25 ml of fresh Amberlite. The first batch of resin was washed repeatedly with methanol and the washings were also passed through the column. The colorless effluent was evaporated with two successive

additions of ethanol. The residue was then taken up in about 10 ml of dichloromethane. Upon seeding with VI* and scratching with a glass rod, crystallisation occurred and was allowed to proceed at room temperature for 1 hour. The crystals were isolated and washed with ice-cold dichloromethane; yield, 391 mg; $[\alpha]_D^{23}$ + 83.7° (c, 1.05 in water). Recrystallisation from ethyl acetate afforded rectangular platelets of m.p. 180-182° and $[\alpha]_D^{23}$ + 85.5° (c, 1.1 in water). The product was chromatographically uniform (R_f 0.64) methyl 3-nitro-3-deoxy-α-L-arabinopyranoside (VI). Anal. Calc. for $C_6H_{11}O_6N$ (193.2): C, 37.31; H, 5.74; N, 7.25. Found: C, 37.25; H, 5.63; N, 7.27.

From the above dichloromethane mother liquor a second crop of crystals separated in the course of 24 hours at 0°. This material (379 mg; $[\alpha]_D^{23}$ - 149°) was revealed by paper chromatography to be a mixture giving a double spot (R_f 0.64 - 0.68) corresponding to the two nitroarabinosides VI and VII, and a weaker spot (R_f 0.80) corresponding to methyl 3-nitro-3-deoxy-β-D-ribopyranoside.

Now petroleum ether (b.p. 30-60°) was added dropwise to the mother liquor to incipient cloudiness. Upon standing overnight in a refrigerator the solution deposited crystals, the amount of which could be augmented by careful addition of carbon tetrachloride and by keeping the flask first at room temperature, then at 4° for 24 hours. The crystals were isolated and washed with ice-cold dichloromethane; yield, 325 mg, m.p. 160-167°, $[\alpha]_D^{23}$ - 218° (c, 1.1 in water). After one recrystallization from ethyl acetate the product was not yet chromatographically uniform but showed two spots of R_f 0.68 and R_f 0.80. A pure product, methyl 3-nitro-3-deoxy-β-D-arabinopyranoside (VII), was obtained after three recrystallisations from 1-propanol. It had m.p. 178-180°, R_f 0.69, and $[\alpha]_D^{23}$ - 278° (c, 0.5 in water). Anal. Calc. for $C_6H_{11}O_6N$ (193.2): C, 37.31; H, 5.74; N, 7.25. Found: C, 37.58; H, 5.89; N, 7.16.

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* The seed crystals were obtained in a preliminary experiment described at the end of this Section (page 49).

With a theoretical yield of 9.66 g, the combined nitroglycosides isolated up to this stage amounted to 11.3%. Clearly, the bulk of reaction products was still contained in the mother liquor. Chromatography showed the presence of both methyl 3-nitro-3-deoxy-α-L-arabinopyranoside (VI) and methyl 3-nitro-3-deoxy-β-D-arabinopyranoside (VII), with the latter being in preponderance. The chief component, however, was the β-D-ribo isomer (R_f 0.80). An additional weak spot (R_f 0.83) was judged on the basis of previous experience to be due to the β-D-xylo isomer (58).

Preliminary Experiments

Seed Crystals of Methyl 3-Nitro-3-deoxy-α-L-arabinopyranoside (VI) and Methyl 3-Nitro-3-deoxy-β-D-arabinopyranoside (VII)

An experiment conducted in the same way as described above, except for a reaction time of 50 rather than 15 minutes, gave essentially the same results. The dialdehyde I (from 16.4 g of methyl β-D-xyloside) in a solution of 150 ml of absolute methanol was condensed with 5.6 ml of nitromethane in the presence of 77 ml of sodium methoxide solution at ice-bath temperature. The reaction mixture was allowed to stand at 0° for 50 minutes during which time it turned slightly yellow and began to deposit an aci-nitro sodium salt. The entire reaction mixture was then deionised with excess Amberlite IR-120(H^+). The colorless, deionised solution was concentrated to a thick sirup that was evaporated twice with ethanol and once with ether. The sirup, which retained some solvent, was left for several days in an unevacuated desiccator over concentrated sulphuric acid. Crystallisation occurred during this period but remained incomplete. The crystals were isolated by trituration of the material with ether in an ice-salt bath, washed with cold ether and

after drying weighed 800 mg. This product was impure methyl 3-nitro-3-deoxy-α-L-arabinopyranoside (VI) showing m. p. 160-167° and $[\alpha]_D^{23}$ + 64.3° (c, 1 in water). Two recrystallisations from hot ethyl acetate afforded rectangular platelets of pure VI having m. p. 180°, $[\alpha]_D^{23}$ + 84.9° (c, 1 in water) and R_f 0.64.

The above ethereal mother liquor was evaporated to a syrup which was left for a few days in a desiccator containing sulphuric acid. A second crop of crystals was thereby deposited. These crystals were taken up in ice-cold ethyl acetate, isolated, and washed with an ice-cold ethyl acetate-ether mixture (1:1). The dry material weighed 1 g and showed m. p. 162-168° and $[\alpha]_D^{23}$ - 222.8° (c, 1 in water). Paper chromatography revealed this material to be a mixture of methyl 3-nitro-3-deoxy-β-D-arabinopyranoside (VII) and methyl 3-nitro-3-deoxy-β-D-ribopyranoside corresponding to R_f values of 0.68 and 0.80, respectively.

When in a further experiment the reaction was interrupted by deionization after 3 minutes, no VI could be isolated but only a levorotatory mixture ($[\alpha]_D$ - 222°) of VII and the β-D-ribo isomer was obtained.

Methyl 3-Nitro-3-Deoxy-α-D-arabinopyranoside (XVII) and Methyl 3-Nitro 3-deoxy-β-L-arabinopyranoside (XVIII)

D-Methoxy-diglycolic aldehyde (XII) was prepared from 2.46 g of methyl α-D-xylopyranoside in exactly the same manner as described for the enantiomorph I. It was cyclised with nitromethane (0.825 ml) at ice-bath temperature in 23 ml methanol in the presence of 11.5 ml sodium methoxide solution (3 g of sodium in 100 ml methanol). After 15 minutes the reaction mixture was deionized by adding 23 ml of methanol-washed Amberlite IR-120(H^+). The solution was decanted and passed through a small column of Amberlite (20 ml). The resin used for

deionization was repeatedly washed with methanol and the washings were also passed through the column. The deionized solution was evaporated to a sirup which was further evaporated with two successive additions of ethanol and then taken up in a small amount of dichloromethane. Carbon tetrachloride was added drop by drop to incipient cloudiness. Upon cooling in an ice-bath and scratching with a glass rod crystallization occurred. The crystals were isolated and washed with ice-cold dichloromethane. The yield of crude XVII was 140 mg. It showed m.p. 178-179° and $[\alpha]_D^{23}$ - 78° (c, 1 in water) after one, and m.p. 179-180°, $[\alpha]_D^{23}$ - 86° (c, 1 in water) and R_f 0.64 after a second recrystallization from ethyl acetate. Anal. Calc. for $C_6H_{11}O_6N$ (193.2): C, 37.31; H, 5.74; N, 7.25. Found: C, 37.11; H, 5.64; N, 7.09.

The mother liquor furnished 268 mg of a crystalline product ($[\alpha]_D^{23}$ + 228.5) on standing overnight in a refrigerator. It was methyl 3-nitro-3-deoxy-β-L-arabinopyranoside (XVIII) accompanied by β-L-ribo isomer. Several recrystallizations, first from ethyl acetate, then from 1-propanol, afforded pure XVIII with m.p. 179-180°, R_f 0.69 and $[\alpha]_D^{23}$ + 278° (c, 0.5 in water). Anal. Calc. for $C_6H_{11}O_6N$ (193.2): C, 37.31; H, 5.74; N, 7.25. Found: C, 37.07; H, 5.68; N, 7.17.

The infrared spectra of the two isomeric glycosides XVII and XVIII showed marked differences in the 1200 - 700 cm^{-1} region, but they were, as expected, identical with those of the two enantiomorphs VI and VII respectively.

Methyl 3-Amino-3-deoxy-α-L-arabinopyranoside Hydrochloride (VIII)

A sample of 200 mg of the nitroarabinoside VI in 5 ml of water was hydrogenated with a platinum catalyst (200 mg of PtO_2, prehydrogenated) in the presence of 11 ml of N/10 hydrochloric acid. The hydrogen uptake was 77 ml at 23° and 757 mm Hg. After filtration and removal of excess acid with Amberlite IR-45(OH^-) to pH 6, the solution was evaporated leaving a colorless sirup which was crystallized from ethanol-ethyl acetate. The yield of colorless needles of methyl 3-amino-

3-deoxy-α-L-arabinopyranoside hydrochloride (VIII) showing $[\alpha]_D^{23}$ + 21.5 (c, 0.5 in water) and m.p. 167-169° (decomp) was 160 mg (77.5%). For analysis, the product was recrystallised from ethanol-ethyl acetate and then exhibited m.p. 164-165° (decomp), $[\alpha]_D^{23}$ + 24.7° (c, 1 in water) and R_{gm} 1.70. Anal. Calc. for $C_6H_{14}O_4NCl$ (199.6): C, 36.09; H, 7.07; N, 7.02. Found: C, 36.51; H, 7.37; N, 6.8.

Methyl 3-Amino-3-deoxy-β-D-arabinopyranoside Hydrochloride (IX)

Platinum dioxide (300 mg) was prehydrogenated in 16.5 ml of N/10 hydrochloric acid. A solution of 300 mg of the nitro-arabinopyranoside (VII) in 5 ml of water was then introduced. The hydrogen uptake was 101 ml in about 70 minutes. The catalyst was filtered off and the excess acid was removed by treatment with Amberlite IR-45(OH^-) to a pH of about 6. The solution was evaporated to a sirup that was further evaporated with two successive additions of ethanol. A colorless sirup was obtained that crystallized from ethanol containing a few drops of ethyl acetate. The yield of IX was 150 mg and the product showed m.p. 177 - 178° (decomp). The product was recrystallised from ethanol with addition of a little ethyl acetate giving colorless needles of m.p. 181 - 183° (decomp), $[\alpha]_D^{23}$ -205° (c, 0.5 in water) and R_{gm} 1.76. Anal. Calc. for $C_6H_{14}O_4NCl$ (199.6): C, 36.09; H, 7.06; N, 7.02. Found: C, 35.65; H, 7.09; N, 6.86.

Methyl 3-Amino-3-deoxy-α-D-arabinopyranoside Hydrochloride (XIX)

A sample of 14 mg of the nitroarabinoside XVII in 3 ml of water was hydrogenated with the use of 20 mg of platinum dioxide in the presence of 0.72 ml of N/10 hydrochloric acid. The hydrogenation product was isolated analogously to methyl 3-amino-3-deoxy-α-L-arabinopyranoside hydrochloride (VIII). The yield was 7 mg of colorless needles of

methyl 3-amino-3-deoxy-α-D-arabinopyranoside hydrochloride (XIX). The product was confirmed, by its melting point of 165° (decomp) and by its infrared spectrum, to be the enantiomorph of VIII.

Methyl 3-Amino-3-deoxy-β-L-arabinopyranoside Hydrochloride (XX)

Nitroarabinoside XVIII (75 mg) in water (5 ml) was hydrogenated with 80 mg of platinum dioxide in the presence of 3.9 ml N/10 hydrochloric acid. The hydrogen uptake was 28 ml (23°, 763 mm Hg) after 1 hour. The reaction mixture was worked up as described above for methyl 3-amino-3-deoxy-α-L-arabinopyranoside hydrochloride (VIII) and methyl 3-amino-3-deoxy-β-D-arabinopyranoside hydrochloride (IX). The product was crystallized from ethanol and a little ethyl acetate affording 46 mg of crystals of methyl 3-amino-3-deoxy-β-L-arabinopyranoside hydrochloride (XX), which showed $[\alpha]_D^{23}$ + 202° (c, 0.5 in water). Although this was in good agreement with the expected value, the melting point of 150-151° did not match that of the enantiomorph IX and could not be raised by simple recrystallization. There were noticeable, although slight, differences in the infrared spectra in nujol mull of IX and XX, too. These discrepancies were resolved, however, when XX was recrystallized, from ethanol - ethyl acetate, with inoculation of the supersaturated solution with a trace of the antipode (IX). The crystals so obtained melted at 180-183° (decomp) and gave an infrared spectrum identical with that of IX. It appears, therefore, that these aminoglycosides are capable of existing in different crystal modifications.

3-Amino-3-deoxy-β-L-arabinose Hydrochloride (X)

A sample of 104.3 mg of methyl 3-amino-3-deoxy-α-L-arabinopyranoside hydrochloride (VIII) in 10 ml of 2N hydrochloric acid was heated in a sealed container for 19 hours at 95-98°. After cooling,

the absolute rotation of the yellowish solution, α_D + 2.06° in a 2-dm tube, corresponded to a specific rotation of + 106.5° for the free sugar. The solution was decolorized with activated carbon and evaporated repeatedly with water to remove excess hydrochloric acid, and the remaining sirup was crystallized by trituration with 1 ml of glacial acetic acid. There could be isolated 80 mg (83%) of 3-amino-3-deoxy-β-L-arabinose hydrochloride (X) whose infrared spectrum was identical with that of the known enantiomorph (see next section). The product decomposed on heating at 150°. It exhibited $[\alpha]_D^{23}$ + 145° (2.5 minutes) ⟶ + 110° (20 minutes, final; c, 0.5 in water). On the grounds of this downward mutarotation, β-configuration was assigned to the crystalline sugar.

3-Amino-3-deoxy-β-D-arabinose Hydrochloride (XI)

A sample of 146 mg of methyl 3-amino-3-deoxy-β-D-arabinoside hydrochloride (IX) was hydrolyzed as described in the preceding section. The hydrolysate showed α_D -2.77° in a 2-dm tube, which corresponded to $[\alpha]_D^{23}$ - 101.8° for the free sugar (XI). Of the latter, an amount of 83 mg could be isolated as crystals showing decomposition at about 150°. The upward mutarotation, $[\alpha]_D^{23}$ - 147.4° (2 minutes) ⟶ - 113° (20 minutes, final; c, 0.5 in water) allowed the assignment to XI of β-configuration. The equilibrium rotation value of 3-amino-3-deoxy-β-D-arabinose hydrochloride (XI) agreed well with that given in the literature ($[\alpha]_D$ - 112°, in water), although a mutarotation had not been recorded previously (20).

The Partial Epimerization of Methyl 3-aci-Nitro-3-deoxy-pentopyranoside Sodium Salts

β-D-erythro Salt II

A sample of 1.231 g of II (58) was dissolved in 100 ml of

carbon dioxide-free water at 22°. After 17 hours the mutarotation had reached a final value of $[\alpha]_D^{23}$ - 117.9 (Fig. 1). The solution was then deionised with 25 ml of Amberlite IR-120(H^+) and evaporated leaving a colorless, sirupy residue that was evaporated twice with dichloromethane, and finally taken up in a small amount of dichloromethane. Upon scratching with a glass rod, crystallisation of methyl 3-nitro-3-deoxy-α-L-arabinopyranoside (VI) occurred and was allowed to proceed in a refrigerator for 1 hour. The isolated material was washed with ice-cold dichloromethane and amounted to 59 mg; $[\alpha]_D^{22}$ + 70.8° (c, 0.5 in water). In a parallel experiment the yield was 66 mg; $[\alpha]_D^{23}$ + 73.4°. Upon recrystallisation from ethyl acetate the product showed m.p. 180°, $[\alpha]_D^{23}$ + 85.5° (c, 0.5 in water) and R_f 0.64. Identity with methyl 3-nitro-3-deoxy-α-L-arabinopyranoside (VI) was confirmed by a comparison of the infrared spectra as well as by a mixed melting point that was undepressed.

Paper chromatography of the mother liquor revealed the presence of some residual nitroarabinoside VI (R_f 0.64) besides a large amount of methyl 3-nitro-3-deoxy-β-D-ribopyranoside (R_f 0.80). There was also a little of the slightly faster moving xylo isomer (R_f 0.83). This pattern of composition was confirmed when the corresponding amino glycosides obtained after hydrogenation of the mother liquor were chromatographed. Paper chromatography revealed the presence of methyl 3-amino-3-deoxy-α-L-arabinopyranoside hydrochloride (VIII) (R_{gm} 1.70) and a small amount of methyl 3-amino-3-deoxy-β-D-xylopyranoside hydrochloride (R_{gm} 1.96) besides a large amount of methyl 3-amino-3-deoxy-β-D-ribopyranoside hydrochloride (R_{gm} 2.16). In addition to these, traces of several slow-moving as well as fast-moving, ninhydrin-positive by-products were detected. The chief component of the hydrogenated mother liquor was isolated in crystalline form and

identified as methyl 3-amino-3-deoxy-β-D-ribopyranoside hydrochloride (58); it had m.p. 167 - 168° (decomp) and $[\alpha]_D^{23}$ - 119° (c, in water) after one recrystallisation from 95% ethanol.

An attempt to improve the yield of methyl 3-nitro-3-deoxy-α-L-arabinopyranoside (VI) by refluxing the β-D-erythro salt II in 90% aqueous tetrahydrofuran for 4 hours or 8 hours was not successful.

α-L-threo Salt III

To a sample of 38.75 mg of methyl 3-nitro-3-deoxy-α-L-arabinopyranoside (VI) there was added 2 ml of N/10 sodium hydroxide solution, and the volume of the solution was made up to 5 ml by the addition of carbon dioxide-free water. Thus, 43.16 mg of the sodium salt III was present. The mutarotation was measured in a 2-dm tube and was found to be $[\alpha]_D^{23}$ + 57.9° (3 min.) → + 39.4° (5 min.) → + 0.58 (10 min.) → -25.0° (15 min.) → - 109.0° (60 min.) → - 116.4° (5 hours, constant) (Fig. 1). After deionisation, the same chromatographic pattern of nitro compounds, and after hydrogenation, the same pattern of amino compounds were observed as in the partial epimerisation of the β-D-erythro salt II.

β-D-threo Salt IV

To a sample of 14.78 mg. of methyl 3-nitro-3-deoxy-β-D-arabinopyranoside (VII) there was added 0.77 ml of N/10 sodium hydroxide solution and water to make up a volume of 3 ml. Thus, 16.45 mg of the β-D-threo salt IV was present. Mutarotation readings were taken with a 2-dm tube and are represented in Fig. 1. $[\alpha]_D^{23}$ - 239° (3 min.) → - 205° (9 min.) → - 181° (15 min.) → - 136° (30 min.) → - 116.6° (45 min.) → - 104.8° (60 min.) → - 100.3° (90 min.) → - 104° (2 hours) → - 115.1° (18 hours, constant). The chromatograms obtained after deionisation as well as after hydrogenation of the equilibrated

solution showed the same patterns as those obtained from β-D-*erythro* salt II and α-L-*threo* salt III.

Partial Oxidation of Sucrose with Lead Tetraacetate to Dialdehyde (XXI)

Dialdehyde XXI was prepared (82) by oxidation of sucrose with one equivalent of lead tetraacetate. Sucrose (10 g, 29.2 mmoles) was dissolved in 500 ml of water and to the solution was added 500 ml of glacial acetic acid. With vigorous stirring of the solution, 12.4 g of lead tetraacetate (28.0 mmoles) was added, and the oxidation was allowed to proceed for half an hour at room temperature. Divalent lead was removed by adding excess of Rexyn RG 50 (H^+) (about 130 ml). The filtrate was concentrated and most of the remaining acetic acid and water was removed by several codistillations with ethanol and toluene. The dialdehyde was obtained as a white solid.

α-D-Glucopyranosyl 4-*aci*-Nitro-4-deoxy-β-D-heptulopyranoside Sodium Salts (XXII)

The above dialdehyde XXI was dissolved in 85 ml of absolute methanol and the solution was chilled in an ice-bath. Under magnetic stirring there was added 1.6 ml of nitromethane and 23 ml of methanolic sodium methoxide (3 g of sodium per 100 ml of methanol). The amounts of reagents added corresponded to one equivalent each, as calculated for a quantitative production of dialdehyde from sucrose. Yellowish-white, powdery material began to separate after about 15 minutes. Stirring and ice cooling was continued for 45 minutes. Thereafter, the flask was transferred into a refrigerator and kept there for 4 more hours. The salt XXII was collected on a Büchner funnel, washed quickly with ice-cold methanol and immediately transferred to a desiccator. The

dried product weighed 7.2 g and showed $[\alpha]_D$ + 46.9° (c, 1 in water). Unless proper care was taken in isolating the sodium salt XXII, it tended to absorb moisture and ultimately became sirupy. However, once it was washed and dried, it was fairly stable and could be stored in a desiccator. On heating it became brown around 100° and foamed at 119-120°. Anal. Calc. for $C_{13}H_{22}O_{13}NNa$ (423.3): N, 3.31; Na, 5.43. Found: N, 3.26; Na, 5.39.

α-D-Glucopyranosyl 4-Nitro-4-deoxy-β-D-heptulopyranosides (XXIII)

Sodium salt XXII (5 g) was suspended in about 100 ml of absolute methanol and the suspension was treated with excess methanol-washed Rexyn RG 50 (H^+) (50 ml) at ice-bath temperature. The slightly yellow-colored filtrate was evaporated to a sirup that was further evaporated with two successive additions of ethanol to give a colorless hygroscopic product, $[\alpha]_D$ + 73.4° (c, 1 in water). The material sintered around 60° and foamed at 85°. Paper chromatography revealed the presence of two components (R_f 0.23 and 0.30) presumed to be isomeric nitrodisaccharides (XXIII).

α-D-Glucopyranosyl 4-Amino-4-deoxy-β-D-heptulopyranoside Hydrochloride (XXIV)

A sample of 1.26 g of the nitrodisaccharide mixture XXIII in 5 ml of water was hydrogenated with a platinum catalyst (1 g of platinum dioxide, prehydrogenated) in the presence of 31 ml of N/10 hydrochloric acid. The hydrogen uptake was 186 ml at room temperature in about 3.5 hours. The catalyst was filtered off and the solution was evaporated to give a sirup. The excess acid was removed by evaporating several times with water. Finally, the sirup was evaporated twice with ethanol to give a white solid product which was crystallised from methanol-ethyl acetate with addition of a few drops of water. The yield was 500 mg. For

recrystallization the product (XXIV) was dissolved in the minimum amount of water and glacial acetic acid was added dropwise until the solution became turbid. Recrystallized XXIV had m.p. 197° (decomp), $[\alpha]_D$ + 103.2° (c, 0.5 in water) and R_{gm} 0.88. Anal. Calc. for $C_{13}H_{26}O_{11}NCl$ (407.5): C, 38.31; H, 6.45; N, 3.43; Cl, 8.71. Found: C, 38.36; H, 6.58; N, 3.63; Cl, 8.62.

α-D-Glucopyranosyl 4-Acetamido-4-deoxy-β-D-heptulopyranoside (XXV)

Acetamido disaccharide XXV was prepared from 314 mg of the aminodisaccharide hydrochloride XXIV dissolved in 4.5 ml of water and 0.6 ml of methanol. To the ice-cold, magnetically stirred solution there was added 3 ml of Dowex-1 (CO_3^{--}) and 0.1 ml of acetic anhydride. After 90 minutes the resin was filtered off and washed well with water, and the combined filtrate and washings were stirred briefly with 2 ml of Dowex 50W-X8 (H^+). The filtered, colorless solution was evaporated to a sirup which was evaporated again with ethanol to give an amorphous solid. The product was crystallized from ethanol (2 ml) and a few drops of ethyl acetate; yield, 30 mg; m.p. 151-152°, $[\alpha]_D$ + 83.8° (c, 0.5 in water). The product was chromatographically uniform (R_f 0.32) α-D-glucopyranosyl 4-acetamido-4-deoxy-β-D-heptulopyranoside (XXV). Anal. Calc. for $C_{15}H_{27}O_{12}N$ (413.4): C, 43.57; H, 6.58; N, 3.39. Found: C, 43.52; H, 6.71; N, 3.23.

Hydrolysis of Amino Disaccharide Hydrochloride XXIV. 4-Acetamido-4-deoxy-D-heptulose (XXVII) and D-Glucose

To determine optimal conditions for the hydrolysis of the amino disaccharide hydrochloride XXIV, a 1% solution of the compound in 2N hydrochloric acid was heated on a steam-bath and samples for chromatography were withdrawn from time to time. Absence of XXIV on the chromatograms was noted after 20 minutes of hydrolysis.

A sample of 535 mg of disaccharide XXIV was hydrolyzed with 50 ml of 2N hydrochloric acid by heating on a steam-bath for 50 minutes. The slightly yellow hydrolysate (which reduced Fehling solution strongly) was evaporated, the excess acid being removed by evaporation with several additions of water. The sirup obtained was taken up in 4 ml of water and poured onto a narrow cation exchange column that contained 22 ml of Rexyn RG 50 (H^+) and therefore would retain the amino sugar but would let neutral glucose pass through. The column was eluted with 250 ml of water at a rate of 30 drops per minute. Evaporation of this eluate furnished a sirupy residue weighing 210 mg after dehydration with absolute alcohol and drying in high vacuum. The material gave a negative ninhydrin test and was indistinguishable from glucose on paper chromatograms sprayed with aniline hydrogen phthalate.

Elution of the ion exchange column was then continued using 250 ml of N hydrochloric acid. The colorless, ninhydrin-positive eluate was brought to a sirup and residual acid was removed by several evaporations with water. Finally, the sirup was evaporated with ethanol to give an amorphous powder (310 mg) of 4-amino-4-deoxy-D-heptulose hydrochloride (XXVI). Since attempts at crystallization were unsuccessful, the product was N-acetylated. This was done by stirring the solution of the compound, in 8 ml of water and 1 ml of methanol at 0°, with 9 ml of Dowex-1 (CO_3^{--}) and 0.176 ml of acetic anhydride. After 90 minutes the anion exchange resin was filtered off and the solution stirred briefly with 3.5 ml of Dowex-50W (H^+). The filtrate was evaporated to a sirup that was evaporated twice with ethanol. There was obtained from ethanol (2 ml) and ethyl acetate (a few drops) 150 mg of crystalline 4-acetamido-4-deoxy-D-heptulose (XXVII). It was recrystallized from ethanol; m.p. 171-172° (decomp), $[\alpha]_D$ + 66.0 (3 minutes) ⟶ + 55.0° (45 minutes, final; c, 3.5 in water) and R_f 0.48. Anal. Calc. for

$C_9H_{17}O_7N$ (251.2): C, 43.02; H, 6.77; N, 5.58. Found: C, 43.10; H, 6.91; N, 5.70.

4-Acetamido-4-deoxy-D-heptulose (XXVII) reduced Fehling and Benedict solutions, but did not respond to the α-naphthoresorcinol test in which (nitrogen-free) ketoses usually produce a red color.

Methanolysis of Nitro Disaccharide XXIII. Methyl 4-Nitro-4-deoxy-D-heptulopyranoside (XXIX) and Methyl α-D-Glucopyranoside

A sample of 4.3 g of α-D-glucopyranosyl 4-nitro-4-deoxy-β-D-heptulopyranosides (XXIII) was refluxed for 3.5 hours in 400 ml of methanolic hydrogen chloride solution (2 g of hydrogen chloride in 100 ml of absolute methanol). The dark brown solution was treated with activated carbon whereby it became pale yellow; it was then evaporated with additions of water in the end. The brown sirup obtained was dissolved in 100 ml of water and treated with 40 ml of Amberlite IR-45 (OH^-) to adjust the pH to about 5. The resin was filtered off and washed well with water. The solution was evaporated to a sirup which was freed from water by two evaporations with ethanol and finally taken up in a small amount of hot ethanol. Upon addition of a little ethyl acetate and cooling in a refrigerator there crystallized 0.9 g of methyl α-D-glucopyranoside. After recrystallization from ethanol it had m.p. 166° and $[\alpha]_D$ + 158.8° (c, 1 in water), in very good agreement with the literature (10).

Methyl 1,3:5,7-di-O-benzylidene-4-nitro-4-deoxy-D-heptulopyranoside (XXVIII). - The mother liquor from which the crude methyl α-D-glucopyranoside had separated was evaporated to a sirup (3 g) which could not be crystallized. Zinc chloride (3.6 g) and benzaldehyde (15 ml)

were added and the mixture was stirred at room temperature for 24 hours. Thereafter, water (40 ml) and petroleum ether (20 ml, b.p. 30-60°) were added and the heterogeneous mixture was stirred for 15 minutes. This treatment resulted in the separation of a semi-crystalline mass which was collected and washed twice with water and twice with petroleum ether. The crude product was dried in the air and then recrystallized from chloroform giving the dibenzylidene derivative XXVIII as fine needles (1.0 g) of m.p. 285-286°. The dibenzylidene derivative was soluble in hot chloroform, hot dimethyl formamide and hot dioxane but only sparingly soluble in hot ethanol. Solubility in cold solvents was very slight. Anal. Calc. for $C_{22}H_{23}NO_8$ (429.4): C, 61.53; H, 5.36; N, 3.26. Found: C, 61.45; H, 5.52; N, 3.18.

Methyl-4-Nitro-4-deoxy-D-heptulopyranoside (XXIX). - Dibenzylidene derivative XXVIII (3.05 g) in 450 ml of methanol-water (4:1, V/V) was refluxed and magnetically stirred with 18 g of Dowex 50W-X8 (H^+) for 44 hours. The resin was filtered off and the filtrate evaporated to give a crystalline residue which was freed from the last traces of water by two evaporations with ethanol. Recyrstallisation from ethyl acetate afforded 1.39 g of the debenzylidenated derivative XXIX, m.p. 157-158°, $[\alpha]_D$ + 101.9° (c, 0.5 in water). Anal. Calc. for $C_8H_{15}O_8N$ (253.2): C, 37.95; H, 5.93; N, 5.53. Found: C, 38.19; H, 6.00; N, 5.60.

Methyl 4-Amino-4-deoxy-D-heptulopyranoside Hydrochloride (XXX)

A sample of 1.127 g of the nitroglycoside XXIX in 5 ml of water was hydrogenated with 0.60 g of prehydrogenated platinum oxide in the presence of 45 ml of N/10 hydrochloric acid. The hydrogen uptake at room temperature was 300 ml. The catalyst was filtered off

and the filtrate was treated with Amberlite IR-45 (OH^-) to adjust the pH to about 5. Evaporation of the filtrate yielded a sirup that was twice evaporated with ethanol to give a crystalline residue. Recrystallization from ethanol-ethyl acetate, with a few drops of water added, afforded needles of XXX (700 mg) having m.p. 170-172° (decomp), $[\alpha]_D$ + 98.7° (c, 0.5 in water) and R_{gm} 1.15. Anal. Calc. for $C_8H_{18}O_6NCl$ (259.5): C, 36.99; H, 6.93; N, 5.39. Found: C, 37.20; H, 6.93; N, 5.19.

Methanolysis of α-D-Glucopyranosyl 4-Amino-4-deoxy-β-D-heptulopyranoside Hydrochloride (XXIV), Methyl 4-Amino-4-deoxy-D-heptulopyranoside Hydrochloride (XXX) and Methyl α-D-Glucopyranoside

A sample of 240 mg of the amino disaccharide hydrochloride XXIV was refluxed with 20 ml of methanolic hydrogen chloride (5 g hydrogen chloride per 100 ml of methanol) for 7.75 hours. The brown solution was evaporated to a sirup that was evaporated several times with water. The sirup was then dissolved in 25 ml of water, the solution decolorized with activated charcoal and brought to a sirup again. After dehydration with absolute ethanol, addition of ethyl acetate to the ethanolic solution, and seeding with XXX previously obtained, there crystallized 25 mg of methyl 4-amino-4-deoxy-α-D-heptulopyranoside hydrochloride (XXX) as needles of m.p. 173-174° (decomp), $[\alpha]_D$ + 98.0° (c, 0.5 in water) and R_{gm} 1.15. The product was confirmed to be identical with XXX from the previous experiment by an undepressed mixed melting point and by infrared spectroscopy.

The mother liquor, on standing in a refrigerator, deposited a second crop of crystals (30 mg); m.p. 158-160° (decomp), $[\alpha]_D$ + 126.5° (c, 0.5 in water). The product was chromatographically

uniform (R_{gm} 1.18). Its infrared spectrum was slightly different from that of the first crop. Possibly, it was XXX accompanied by methyl α-D-glucopyranoside. However, it was not investigated further.

To the mother liquor from the second crop a few more drops of ethyl acetate were added. On standing in a refrigerator, crystals (20 mg) melting at 161-162° were deposited. Recrystallization from ethanol afforded needles of pure methyl α-D-glucopyranoside of m.p. 166° and $[\alpha]_D$ + 158.0° (c, 0.5 in water).

Methyl 4-Acetamido-4-deoxy-1, 3, 5, 7-tetra-O-acetyl-D-heptulopyranoside (XXXI)

Aminoheptuloside hydrochloride XXX (250 mg) was acetylated in 5 ml of pyridine with 2 ml of acetic anhydride by allowing the reaction mixutre to stand for 24 hours at room temperature. After decomposition of the excess acetic anhydride, by adding 40 g of crushed ice, the reaction mixture was extracted four times with 15 ml of chloroform. The combined extracts after drying over anhydrous sodium sulfate were evaporated, the last traces of pyridine being removed by codistillation with toluene. The pentaacetate XXXI was obtained as a gel from ethanol; drying in a high vacuum afforded 140 mg of a microcrystalline powder having m.p. 191-192°, R_f 0.86 and $[\alpha]_D$ + 75.1° (c, 0.5 in chloroform). Anal. Calc. for $C_{18}H_{27}NO_{11}$ (433.4): C, 49.88; H, 6.28; N, 3.24. Found: C, 49.85; H, 6.37; N, 3.19.

4-Acetamido-4-deoxy-D-heptulose (XXVII) from Methyl 4-Amino-4-deoxy-D-heptuloside Hydrochloride (XXX)

A preliminary hydrolysis of the aminoheptuloside hydrochloride XXX was done by heating a 1% solution in 2 N hydrochloric acid on a steam-bath. Fractions were withdrawn after 15, 45, 60, 120 and

210 minutes. (Some decomposition was noted after 180 minutes). Paper chromatography of the various fractions revealed that the aminoglycoside XXX (R_{gm} 1.15) was largely hydrolyzed already after 15 minutes since its spot on the chromatograms was replaced by a new spot of R_{gm} 0.95 in all the fractions.

Methyl aminoheptuloside XXX (842 mg) was heated with 2 N hydrochloric acid (85 ml) on a steam-bath for one hour. The slightly yellow colored solution was evaporated, the acid being removed by several evaporations with water. After evaporating two times with ethanol, 4-amino-4-deoxy-D-heptulose hydrochloride (XXVI) was obtained as an amorphous powder which was N-acetylated by stirring at 0° in solution (19 ml of water and 2.25 ml of methanol) in the presence of 21 ml of Dowex-1 (CO_3^{--}) and 0.42 ml of acetic anhydride. The resin was filtered off after 90 minutes and the filtrate stirred for a short while with 8 ml of Dowex-50W (H^+). The clear solution was brought to dryness, and the residue was crystallized from 5 ml of ethanol with addition of a small amount of ethyl acetate. The acetamido sugar isolated (550 mg) melted at 173-175° (decomp) and exhibited $[\alpha]_D$ + 66.6° (3 minutes) ⟶ + 53° (45 minutes, final; c, 0.5 in water) and R_f 0.48. The product was confirmed by mixed-melting point determination and by infrared spectroscopy to be identical with 4-acetamido-4-deoxy-D-heptulose XXVII obtained by hydrolysis followed by N-acetylation of the aminodisaccharide (XXIV).

Degradation of 4-Acetamido-4-deoxy-D-heptulose (XXVII) to D-Arabinosamine Hydrochloride

Acetamidoheptulose XXVII (249 mg) was dissolved in 2.1 ml of water, and 120 ml of glacial acetic acid was added. To the stirred

solution there was added 444 mg (one equivalent) of finely powdered lead tetraacetate. After 15 minutes a 10% solution of oxalic acid in glacial acetic acid was added dropwise until no more lead oxalate precipitated, and the stirring was continued for another 30 minutes. The precipitated lead oxalate was filtered off and washed with glacial acetic acid. The filtrate was evaporated with several additions of water in order to remove most of the acetic acid. The residue was then dissolved in about 20 ml of water and the solution stirred briefly with 12 ml of Dowex-1 (HCO_3^-). The resin was filtered off and washed, and the colorless filtrate was brought to a volume of 15 ml. The solution was treated with 120 mg of sodium bicarbonate at 50° for 30 minutes and then deionized with Dowex 50W-X8 (H^+). Evaporation furnished a colorless sirup that gave a positive Morgan-Elson test for 2-acetamido sugars and had the same chromatographic speed as an authentic sample of 2-acetamido-2-deoxy-D-arabinose.

The above sirup was hydrolyzed with 21 ml of 0.3 N hydrochloric acid by heating on a steam-bath for 2 hours. The hydrolysate was evaporated to dryness and the product taken up in a small amount of methanol. A few drops of ethanol were added and the solution was allowed to stand in the open air for slow crystallization. Crystalline arabinosamine hydrochloride (68 mg) was collected and washed with ethanol. Melting point, 155-156° (decomp) and rotation, $[\alpha]_D$ - 123.1° (c, 0.5 in water) were in agreement with the literature values (m.p. 154-157° (decomp), $[\alpha]_D$ - 124°) (86). The identity with 2-amino-2-deoxy-D-arabinose hydrochloride was confirmed further by its mixed melting point of 155-156° (decomp) with authentic 2-amino-2-deoxy-D-arabinose hydrochloride. Infrared spectrum and chromatographic movement (R_{gm} 1.08) were also identical with those of an authentic specimen.

Methyl 4-Acetamido-4-deoxy-D-heptulopyranoside (XXXII)

A sample of 495 mg of the aminoheptuloside hydrochloride XXX dissolved in 11.2 ml of water and 1.5 ml of methanol was N-acetylated by stirring with 12.5 ml of Dowex-1 (CO_3^{--}) and 0.25 ml of acetic anhydride at ice-bath temperature. After 90 minutes the anion exchange resin was filtered off and the solution stirred briefly with 5 ml of Dowex-50W (H^+). The filtrate was evaporated giving a sirup which on evaporation twice with ethanol afforded an amorphous product, presumably the N-acetyl glycoside XXXII. It was used directly for the following experiment since it could not be obtained in crystalline condition.

Methyl 4-Acetamido-4-deoxy-1, 3, 5, 7-tetra-O-mesyl-D-heptulopyranoside (XXXIII)

The above amorphous acetamide XXXII was dissolved in 6 ml of pyridine and chilled to 0°. Methanesulphonyl chloride (1.25 ml) was added slowly with stirring. The reaction mixture was stirred for 30 more minutes and then left overnight in a refrigerator. The excess methanesulphonyl chloride was decomposed by adding 25 g of crushed ice and the mixture was left at 0° for 3 hours, during which time the tetramesylate XXXIII separated in crystalline form. The product was collected and washed with water; yield, 667 mg, m.p. 185-186°. Tetramesylate XXXIII was difficultly soluble in the common organic solvents but was fairly soluble in hot 2-methoxyethanol and 2-ethoxyethanol. Anal. Calc. for $C_{14}H_{27}NO_{15}S_4$ (577.6): C, 29.12; H, 4.68; N, 2.43; S, 22.18. Found: C, 28.97; H, 4.84; N, 2.37; S, 22.24.

Solvolysis of the Tetramesylate XXXIII

Tetramesyl derivative XXXIII (616 mg) was solvolyzed for 45 hours in refluxing 95% 2-ethoxyethanol (10 ml) in the presence of

900 mg of anhydrous sodium acetate. The dark brown solution deposited on cooling sodium mesylate (300 mg) which was filtered off. The filtrate was evaporated affording a colored, semi-solid mass that was dried in vacuo and subsequently acetylated by heating for 1 hour on a steam-bath with 10 ml of pyridine and 2.5 ml of acetic anhydride. After decomposition of excess acetic anhydride with ice, the mixture was extracted four times with 15 ml of chloroform. The combined extracts were dried over anhydrous sodium sulphate and then treated with activated charcoal. The solution was evaporated, residual pyridine being removed by evaporating twice with toluene. Colorless rectangles crystallized from ethanol in a yield of 345 mg. Recrystallization from ethanol afforded beautiful rectangles of m.p. 237-238°, $[\alpha]_D$ + 88.8° (c, 0.6 in chloroform), and R_f 0.84, which analysed correctly for a dimesyldiacetyl derivative of XXXII. Anal. Calc. for $C_{16}H_{27}O_{13}NS_2$ (505.7): C, 38.02; H, 5.35; S, 12.68. Found: C, 38.20; H, 5.56; S, 12.65.

From the considerations made in the Discussion, the product may tentatively be assigned structure XXXIV. When it was subjected to renewed solvolysis (4 days) followed by acetylation under conditions similar to those described in the preceding paragraph, only starting material was isolated.

CLAIMS TO ORIGINAL RESEARCH

1. The alkali-catalyzed nitromethane cyclization of L'-methoxy-diglycolic aldehyde was investigated with respect to by-products that may be formed in addition to the known main product (methyl 3-aci-nitro-3-deoxy-β-D-erythro-pentopyranoside sodium). It was established that about 5% each of the corresponding α-L-threo and β-D-threo salts are formed.

2. Analogous experiments were carried out with D'-methoxy-diglycolic aldehyde giving rise to the enantiomeric compounds, namely the corresponding α-D-threo and β-L-threo salts.

3. If was shown that aci-nitro pentoside salts in aqueous solution undergo spontaneous epimerizations at carbons 2 and 4.

4. In the course of these investigations the following new compounds were isolated in crystalline condition:

   (a) Methyl 3-nitro-3-deoxy-α-L-arabinopyranoside
   (b) Methyl 3-nitro-3-deoxy-α-D-arabinopyranoside
   (c) Methyl 3-nitro-3-deoxy-β-D-arabinopyranoside
   (d) Methyl 3-nitro-3-deoxy-β-L-arabinopyranoside
   (e) Methyl 3-amino-3-deoxy-α-L-arabinopyranoside hydrochloride
   (f) Methyl 3-amino-3-deoxy-α-D-arabinopyranoside hydrochloride
   (g) Methyl 3-amino-3-deoxy-β-D-arabinopyranoside hydrochloride
   (h) Methyl 3-amino-3-deoxy-β-L-arabinopyranoside hydrochloride
   (i) 3-Amino-3-deoxy-L-arabinose hydrochloride.

5. The nitromethane cyclization was extended for the first time to a disaccharidic dialdehyde. This afforded a novel type of nitrogenous disaccharide, i.e., trehalose - type disaccharides consisting of glucose

and nitrogenous heptulose. The following crystalline disaccharide derivatives were prepared:

(a) α-D-Glucopyranosyl 4-aci-nitro-4-deoxy-β-D-heptulopyranoside sodium salts

(b) α-D-Glucopyranosyl 4-amino-4-deoxy-β-D-heptulopyranoside hydrochloride

(c) α-D-Glucopyranosyl 4-acetamido-4-deoxy-β-D-heptulopyranoside

6. Degradative studies were undertaken which resulted in a partial elucidation of the configuration of the heptulose moiety in the above disaccharides. The following crystalline, new compounds were thereby obtained:

(a) 1, 3:5, 7-Di-O-benzylidene-4-nitro-4-deoxy-α-D-heptulopyranoside

(b) Methyl 4-nitro-4-deoxy-α-D-heptulopyranoside

(c) Methyl 4-amino-4-deoxy-α-D-heptulopyranoside hydrochloride

(d) Methyl 4-acetamido-4-deoxy-1, 3, 5, 7-tetra-O-acetyl-α-D-heptulopyranoside

(e) 4-Acetamido-4-dooxy-D-heptulose

(f) Methyl 4-acetamido-4-deoxy-1, 3, 5, 7-tetra-O-mesyl-α-D-heptulopyranoside

(g) A di-O-mesyl-di-O-acetyl derivative, probably methyl 5, 7-di-O-acetyl-4-acetamido-4-deoxy-1, 3-di-O-mesyl-α-D-heptulopyranoside.

REFERENCES

1. Alfred Burger, Medicinal Chemistry, Vol II, Interscience Publishers, Inc., New York (1951).
2. James D. Dutcher, Advances Carbohydrate Chem., 18, 259 (1963).
3. Kenneth L. Rinehart, Jr., The Neomycins and Related Antibiotics, John Wiley Sons, Inc., New York (1964).
4. For reviews see: H. H. Baer, Fortschr. Chem. Forsch., 3, 822 (1958); A. B. Foster and D. Horton, Advances Carbohydrate Chem., 14, 213 (1959); R. Kuhn, Angew. Chem., 72, 805 (1960).
5. F. Arcamone and F. Bizioli, Gazz. Chim. Ital., 87, 896 (1957).
6. E. Fischer and H. Leuche, Ber., 36, 24 (1903).
7. R. Kuhn and W. Kirschenlohr, Angew. Chem., 67, 786 (1955).
8. R. Kuhn and W. Kirschenlohr, Ann., 600, 115 (1956).
9. R. Kuhn and W. Kirschenlohr, Ann., 600, 126 (1956).
10. R. Kuhn and W. Bister, Ann., 602, 217 (1957).
11. R. Kuhn and H. Fischer, Ann., 612, 65 (1958).
12. R. Kuhn, H. J. Leppelmann and H. Fischer, Ann., 620, 15 (1959).
13. R. Kuhn and W. Kirschenlohr, Ann., 600, 135 (1956).
14. A. Fürst and P. A. Plattner, Intern. Congr. Pure and Appl. Chem., 13th Congr., 409 (1951); J. Colloid Sci., Suppl. No. 1 (1954).
15. A. B. Foster, M. Stacey and S. V. Vardheim, Nature, 180, 247 (1957); Acta Chem. Scand., 12, 1605 (1958).
16. W. N. Haworth, W. H. G. Lake and S. Peat, J. Chem. Soc., 271 (1939).

17. S.P. James, F. Smith, M. Stacey and L.F. Wiggins, J. Chem. Soc., 625 (1946).

18. B.R. Baker and R.E. Schaub, J. Org. Chem., 19, 646 (1954).

19. B.R. Baker and R.E. Schaub, J. Am. Chem. Soc., 75, 3864 (1953).

20. B.R. Baker, R.E. Schaub and J.H. Williams, J. Am. Chem. Soc., 77, 7 (1955).

21. A.B. Foster, T.D. Inch, J. Lehmann, M. Stacey and J.M. Webber, J. Chem. Soc., 2116 (1962).

22. R.W. Jeanloz, D.M. Schmid and P.J. Stoffyn, J. Am. Chem. Soc., 79, 2586 (1956).

23. R.W. Jeanloz, Z.T. Glazer and D.A. Jeanloz, J. Org. Chem., 26, 532 (1961).

24. W.G. Overend and G. Vaughan, Chem. and Ind. (London), 995 (1955).

25. R.D. Guthrie and D. Murphy, J. Chem. Soc., 5288 (1963).

26. K. Heyns and W. Koch, Z. Naturforsch. 7b, 486 (1952).

27. K. Heyns and K.H. Meinecke, Chem. Ber., 86, 1453 (1953).

28. K. Heyns, R. Eichstedt and K.H. Meinecke, Chem. Ber., 88, 1551 (1955).

29. K. Heyns, H. Paulsen, R. Eichstedt and M. Rolle, Chem. Ber., 90, 2039 (1957).

30. J.F. Carson, J. Am. Chem. Soc., 77, 1881 (1955).

31. J.F. Carson, J. Am. Chem. Soc., 77, 5957 (1955).

32. J.F. Carson, J. Am. Chem. Soc., 78, 3728 (1956).

33. K. Freudenberg, O. Burkhart and E. Braun, Ber., 59, 714 (1926).

34. S. Peat and L.F. Wiggins, J. Chem. Soc., 1810 (1930).

35. R.U. Lemieux and P. Chu, J. Am. Chem. Soc., 80, 4745 (1958).

36. B. Coxon and L. Hough, J. Chem. Soc., 1643 (1961).

37. K. Freudenberg and O. Brauns, Ber., 55, 3233 (1922).

38. M.L. Wolfrom, F. Shafizadeh and R.K. Armstrong, J. Am. Chem. Soc., 80, 4665 (1958).

39. M.L. Wolfrom, F. Shafizadeh, R.K. Armstrong and T.M. Shen Han, J. Am. Chem. Soc., 81, 3716 (1959).

40. W. Roth and W. Pigman, J. Org. Chem., 26, 2455 (1961).

41. M.L. Wolfrom, J. Bernsmann and D. Horton, J. Org. Chem., 27, 4505 (1962).

42. B. Lindberg and O. Theander, Acta Chem. Scand., 13, 1226 (1959).

43. R.D. Guthrie, Proc. Chem. Soc. (London), 387, (1960); Advances Carbohydrate Chem., 16, 105 (1961).

44. K. Maurer and B. Schiedt, Ber., 68, 2187 (1935).

45. R. Kuhn and W. Kirschenlohr, Ber., 87, 1547 (1954).

46. H.H. Baer and H.O.L. Fischer, Proc. nat. Acad. Sci. U.S.A., 44, 991 (1958).

47. L. Henry, Compt. Rend., 120, 1265 (1895); 121, 210 (1895).

48. B.M. Vanderbilt and H.B. Hass, Ind. Eng. Chem., 32, 34 (1940); H.B. Hass and R.F. Riley, Chem. Rev., 32, 373 (1943).

49. J.C. Sowden and H.O.L. Fischer, J. Am. Chem. Soc., 66, 1312 (1944).

50. J.C. Sowden, Advances Carbohydrate Chem., 6, 291 (1951).

51. J.M. Grosheintz and H.O.L. Fisher, J. Am. Chem. Soc., 70, 1476, 1479 (1948).

52. F.W. Lichtenthaler, Angew. Chem., 75, 93 (1963); Angew. Chem. internat. Edit. 1, 662 (1962).

53. M.L. Wolfrom, S.M. Olin and W.J. Polglase, J. Am. Chem. Soc., 72, 1724 (1950).

54. E.L. Jackson, Org. Reactions, 2, 341 (1944).

55. J.M. Bobbitt, Advancees Carbohydrate Chem., 11, 1 (1956).

56. A.S. Perlin, Advances Carbohydrate Chem., 14, 9 (1959).

57. R.D. Guthrie, Advances Carbohydrate Chem., 16, 105 (1961).

58. H.H. Baer and H.O.L. Fischer, J. Am. Chem. Soc., 81, 5184 (1959).

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

60. H.H. Baer, Angew. Chem., 73, 532 (1961).

61. H.H. Baer, J. Am. Chem. Soc., 84, 83 (1962).

62. M.H. von Saltza, J. Reid, J.D. Dutcher and O. Wintersteiner, J. Am. Chem. Soc., 83, 2785 (1961).

63. H.H. Baer, Chem. Ber., 93, 2865 (1960).

64. H.H. Baer, J. Am. Chem. Soc., 83, 1882 (1961).

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

66. H.H. Baer and F. Kienzle, Unpublished Results.

67. A.C. Richardson, Proc. Chem. Soc. (London), 255 (1960).

68. A.C. Richardson and K.A. McLauchlan, J. Chem. Soc. (London), 2499 (1962).

69. A.C. Richardson, Proc. Chem. Soc. (London), 430 (1961).

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

71. A.C. Richardson and H.O.L. Fischer, Proc. Chem. Soc. (London), 341 (1960).

72. A.C. Richardson and H.O.L. Fischer, J. Am. Chem. Soc., 83, 1132 (1961).

73. H.H. Baer, J. Org. Chem., 28, 1287 (1963).

74. H.H. Baer, L.D. Hall and F. Kienzle, J. Org. Chem., 29, 2014 (1964).

75. G. Baschang, Liebig's Ann. Chem., 663, 167 (1963).

76. J.K. Dale and C.S. Hudson, J. Am. Chem. Soc., 52, 2534 (1930).

77. J.C. Sowden and R. Schaffer, J. Am. Chem. Soc., 73, 4662 (1951).

78. R. Kuhn, W. Bister and H. Fischer, Liebig's Ann. Chem., 617, 109 (1958).

79. J.M. Grosheintz and H.O.L. Fischer, J. Am. Chem. Soc., 70 1479 (1948).

80. F. Lichtenthaler, Chem. Ber., 94, 3071 (1961).

81. H.O.L. Fischer and H.H. Baer, Liebig's Ann. Chem., 619, 53 (1958).

82. A.K. Mitra and A.S. Perlin, Can. J. Chem., 37, 2047 (1959).

83. S. Roseman and J. Ludowieg, J. Am. Chem. Soc., 76, 301 (1954).

84. J. Honeyman and T.C. Stening, J. Chem. Soc., 537 (1958).

85. A.S. Perlin and C. Brice, Can. J. Chem., 34, 541 (1956).

86. R. Kuhn and G. Baschang, Ann., 628, 193 (1959).

87. S. Winstein, et al., J. Am. Chem. Soc., 64, 2796 (1942); 70, 812 (1948); 72, 2311, 4669 (1950); 74, 5584 (1952).

88. G.E. McCasland, R.K. Carter and H.E. Clark, J. Am. Chem. Soc., 71, 637 (1949).

89. S. Winstein, E. Grunwald, R.E. Buckles and C. Hanson, J. Am. Chem. Soc., 70, 816 (1948).

90. B.R. Baker, R.E. Schaub, J.P. Joseph and J.H. Williams, J. Am. Chem. Soc., 76, 4044 (1954).

91. R.W. Jeanloz, J. Am. Chem. Soc., 79, 2591 (1957).

92. Z. Tarasiejska and R.W. Jeanloz, J. Am. Chem. Soc., 79, 2660 (1957).

93. R.W. Jeanloz, J. Am. Chem. Soc., 81, 1956 (1959).

94. H.H. Baer and T. Neilson, Can. J. Chem., (in press).

95. J.W.H. Oldham and J.K. Rutherford, J. Am. Chem. Soc., 54, 366 (1932).

96. R.S. Tipson, Advances Carbohydrate Chem., 8, 107 (1953).

97. Z. Tarasiejska and R.W. Jeanloz, J. Am. Chem. Soc., 79, 4215 (1957).

98. R.E. Reeves, Advances Carbohydrate Chem., 6, 107 (1951).

99. S.C. Pan and J.D. Dutcher, Anal. Chem., 28, 836 (1956).

100. E.L. Jackson and C.S. Hudson, J. Am. Chem. Soc., 59, 994 (1937); 63, 1229 (1941).

101. E. Fischer, Ber., 26, 2406 (1893).