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APPROACHES TO THE SYNTHESIS OF ANTIBIOTICS AMINO SUGARS

by

Fawzy F. Z. Georges

A thesis submitted to the School of Graduate Studies in partial fulfilment of the requirements for the degree of Ph.D. in Chemistry

UNIVERSITY OF OTTAWA
OTTAWA, CANADA, 1976

In the name of the Father

and of the Son

and of the Holy Spirit

Amen.

To The Lord

JESUS

With Great

Admiration

And Good Hope to All Mankind

"There is excitement, adventure, and challenge,
and there can be great art, in organic synthesis."

R. B. Woodward
in Perspectives in Organic Chemistry

ACKNOWLEDGMENT

I gratefully acknowledge my indebtedness to Professor Hans H. Baer for his profound interest, guidance, encouragement and patience throughout the course of the research and during the preparation of this thesis.

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I also wish to thank my colleague and friend, Mr. Chukwuemeka B. Madumelu for his keen interest and fruitful exchange of views.

My deep appreciation goes to my wife for undertaking the task of reproducing the n.m.r. spectra, and for her moral support.

Finally, a special word of gratitude to my great mother for her support and constant encouragement.

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Part I

Methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-glucopyranoside (42), methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (44) and methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-arabino-hexopyranoside (38) reacted with N-bromosuccinimide in refluxing carbon tetrachloride in the presence of barium carbonate to give the corresponding 6-bromo-6-deoxy-4-O-benzoyl derivatives in yields of 56-80%. Whereas single products (43 and 45) were obtained from 42 and 44 respectively, the 2-deoxy sugar 38 in first experiments gave the expected α-glycoside 39 (64%) but also a second product which was revealed to be the β-glycoside 40 (16%). The formation of 40 was suppressed by an increased amount of acid scavenger. Attempted selective removal of the bromide functions with hydrogen in the presence of 10% palladium on carbon and base are discussed. These attempts proved unsuccessful except in one instance where 42 seemed to have successfully led to the desired product.

Part II

The reaction of nitro sugar derivatives having one or two free hydroxyl functions vicinal to the nitro group, with

methanesulfonyl chloride and triethylamine in ether or dichloromethane solution was investigated with a view to preparing methylsulfonyl esters and, by elimination, nitroolefins. Included was a simplified procedure for the preparation of methyl 6-deoxy-α-D-glucopyranoside from methyl α-D-glucopyranoside. The deoxy derivative served as the starting point for the sequential preparation of methyl 3,6-dideoxy-3-nitro-α-D-glucopyranoside (62), its 2,4-diacetate (64), and its 4-monoacetate (65) essentially according to procedures previously established in the L-series. The following compounds were used in the investigation: 2t-nitrocyclohexane-1r,3c-diol (53) as a model compound, and methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-glucopyranoside (42), its β-anomer (57), methyl 3,6-dideoxy-3-nitro-α-D-glucopyranoside (62), the 4-acetate (65) of 62, the 4-acetate (75) of the α-D-manno isomer, and the α-L-galacto isomer (23) of this 3,6-dideoxy series. Reactions generally proceeded with high yields and gave either isolable methanesulfonates, or nitroolefins (presumably by elimination from intermediary unstable methanesulfonates), or both types of product. The rate of mesylation in 62 was found to be considerably greater at position 4 than at position 2, so that upon interruption of the reaction after an appropriate period of time the 4-mono-O-mesyl derivative 70 could be isolated in 36% yield, with 60% of unchanged 62 being recoverable for re-use.

In addition, the following mesylates were isolated: the monomesylate (54) of 53, the 2-mesylates 56, 66, and 72 of 42, 65, and 23, respectively, and the 2,4-dimesylate (71) of 62. Acid de-O-acetylation of 66 gave the corresponding 2-mesylate 68. Some isolated esters were converted into olefins by refluxing with sodium bicarbonate in benzene. The nitroolefins obtained were 2-nitrocyclohex-2-ene-1-ol (55), the 2,3-unsaturated 4,6-O-benzylidene glycosides 47 and 58 from 42 and 57, respectively, and the 2,3-unsaturated 6-deoxy sugars 69 and 67 from 68 and 75, respectively. Unidentified olefins arose from 23. Both isomeric monomesylates 68 and 70 could be reductively dehydromesyloxylated in one step with sodium borohydride to give the respective deoxy derivatives 79 and 78.

Part III

The synthesis of 2,3,6-trideoxy-3-dimethylamino-D-arabino-hexose hydrochloride (84) (D-angolosamine, a constituent of the antibiotic, angolamycin) is described. Treatment of 68 or 69 with sodium borohydride produced methyl 2,3,6-trideoxy-3-nitro-α-D-arabino-hexopyranoside (79). Catalytic hydrogenation of 79 gave the corresponding 3-amino glycoside hydrochloride (82) which upon acid hydrolysis furnished 3-amino-2,3,6-trideoxy-D-arabino-hexose hydrochloride (83) (D-acosamine, the enantiomer of a component of the antibiotic, actinoidin). N,N-Dimethylation of 82 followed by hydrolysis

afforded the crystalline D-angolosamine.

Part IV

D-Ristosamine (2,3,6-trideoxy-3-amino-D-ribo-hexose hydrochloride) (93), the enantiomer of the constituent of the antibiotic, ristomycin, was synthesized in the following sequence:

Methyl 3,4,6-tri-O-acetyl-2-deoxy-β-D-arabino-hexopyranoside (88) was prepared from commercial 3,4,6-tri-O-acetyl-D-glucal (86) via the 2-chloromercuri glycoside 87 according to previously described procedures with minor work-up modifications. Deacetylation of 88 followed by benzylidenation led to 89 which was then mesylated to give the 3-mesylate 90. This was converted into the azide 91 by reaction with sodium azide in DMF which proceeded with inversion at C-3. The benzylidene acetal ring of 91 was then opened by N-bromosuccinimide to produce methyl 3-azido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-β-D-ribo-hexopyranoside (92). Part of this bromide was debenzoylated and catalytically hydrogenated in the presence of palladium on carbon. Acid hydrolysis of the product gave hygroscopic 93. Hydrogenation of 92 at 15 p.s.i. for 1 h (without prior debenzoylation) furnished methyl 3-benzamido-6-bromo-2,3,6-trideoxy-β-D-ribo-hexopyranoside (94). When the hydrogenation of 92 was performed at higher pressure (35 p.s.i.) and for an extended reaction time (3 h), the 6-deoxy-3-benzamido derivative 95

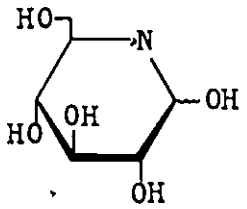
was produced, which upon acid hydrolysis afforded the known, crystalline N-benzoyl-D-ristosamine.

INTRODUCTION

An antibiotic substance is a chemical compound, elaborated by microorganisms, that inhibits the growth of other microorganisms or animal and plant tumors. The mechanism of action often involves interference with DNA, RNA or protein synthesis. From the viewpoint of clinical efficacy, the most prolific producers of antibiotics are the actinomycetes[1] (genus Actinomyces). The age of antibiotics began in the early 1940's, when the first patient was successfully treated with penicillin to combat bacterial infections. The occurrence of unique and unusual amino, deoxy, and branched-chain sugars in some of the antibiotics has stimulated a surge of interest in the distribution of such carbohydrates elsewhere in nature, and many have been found as components of bacterial cell walls, capsular materials, and other macromolecular substances.

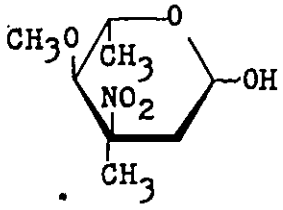
Amino sugars usually exist in antibiotics glycosidically linked to complex aglycones. On the other hand, certain amino sugars, either free or as simple derivatives, have been found recently as fermentation products and shown to possess antimicrobial activity. One notable case

is nojirimycin[2], an antibiotic elaborated by several strains of streptomyces and shown to be 5-amino-5-deoxy-D-glucopyranose (1), the only sugar so far detected in nature in which the ring oxygen is replaced by another hetero atom.



1

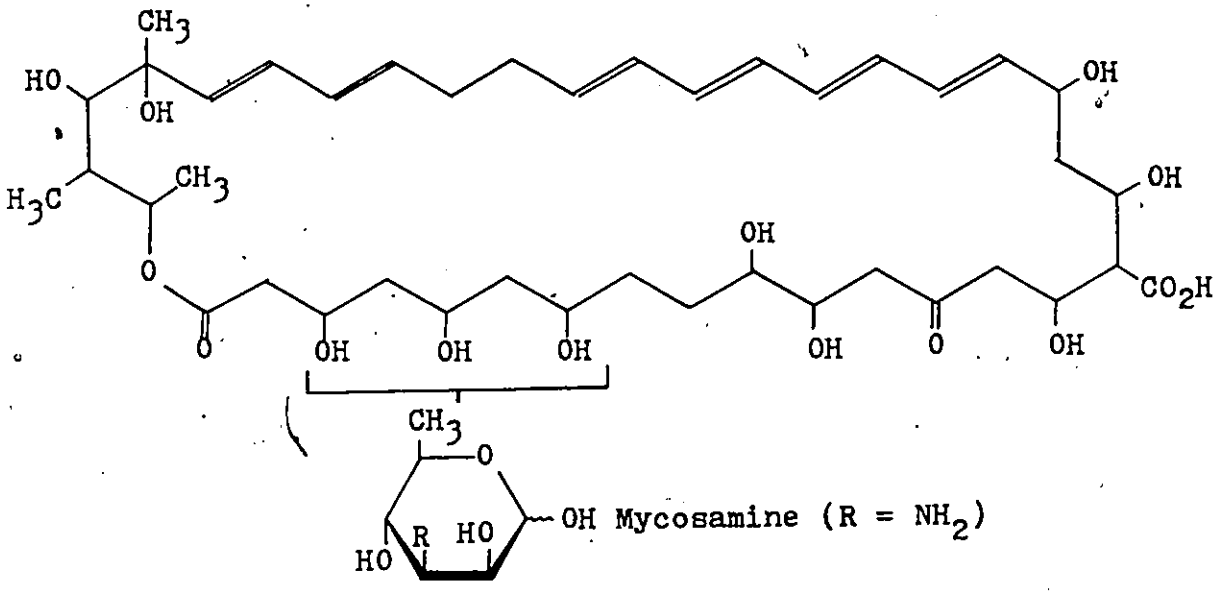
The search for new antibiotics has retained its momentum over the past years unearthing, as it progresses, several hitherto unknown amino sugars, and even one nitro sugar, namely evernitrose, which is 2,3,6-trideoxy-3-C-methyl-4-O-methyl-3-nitro-L-ribohexose (2)[3] and occurs in the complex, oligosaccharide-like antibiotics, everninomycin B and D.



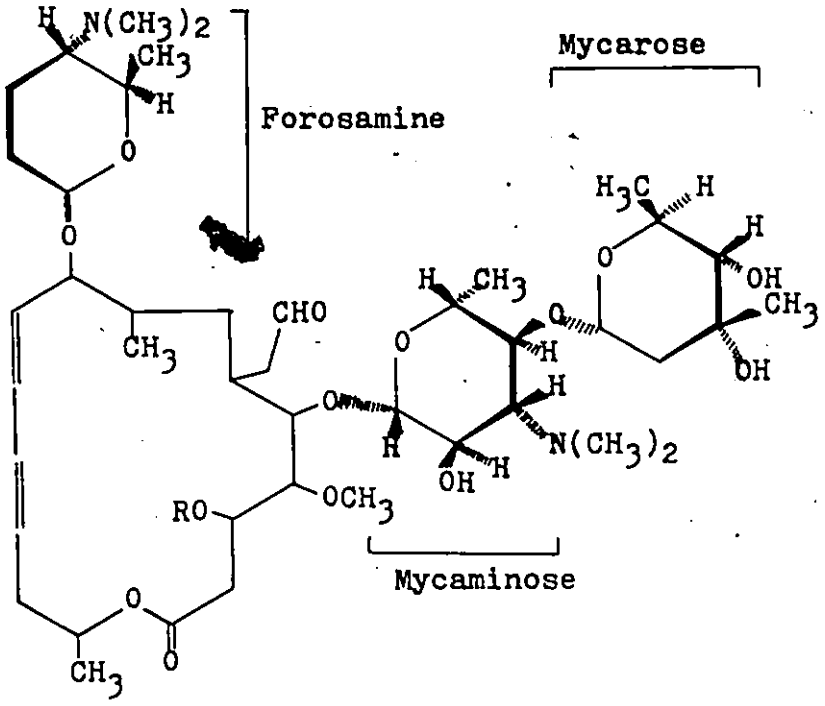
2

Hanessian and Haskell[4] (1970) divided antibiotics containing sugars into five main groups based on their overall common structural relationships, namely:

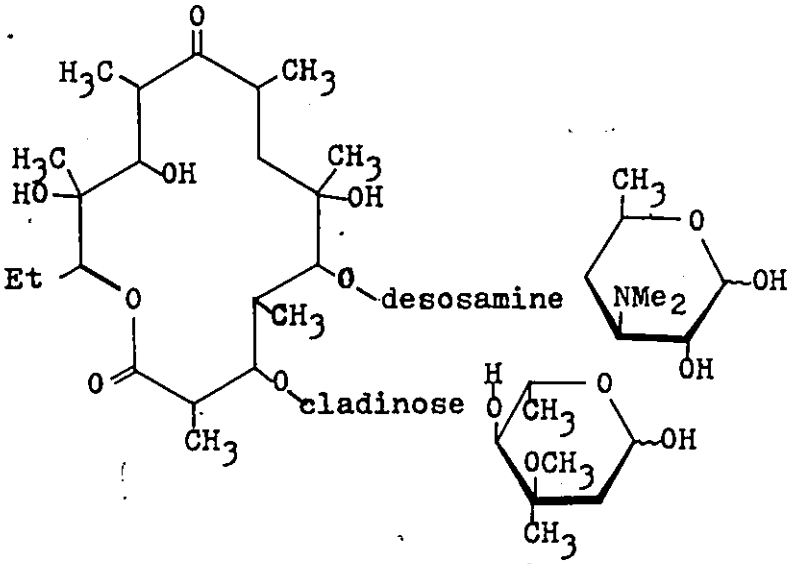
(i) The macrolides, e.g. nystatin (3), spiramycin (4) and erythromycin (5). Several members of this family of antibiotics are active primarily against gram positive organisms and are important chemotherapeutic substances. Also to this group belongs angolamycin (6) which inhibits the growth of some strains of Staphylococcus isolated from clinical sources[5] and which are resistant to erythromycin alone or both erythromycin and oleandomycin. It is also active against Clostridium tetani and Mycoplasma pneumoniae Mac. The antibiotic is produced by actinomycetes[6] and by Streptomyces eurythermus[7].



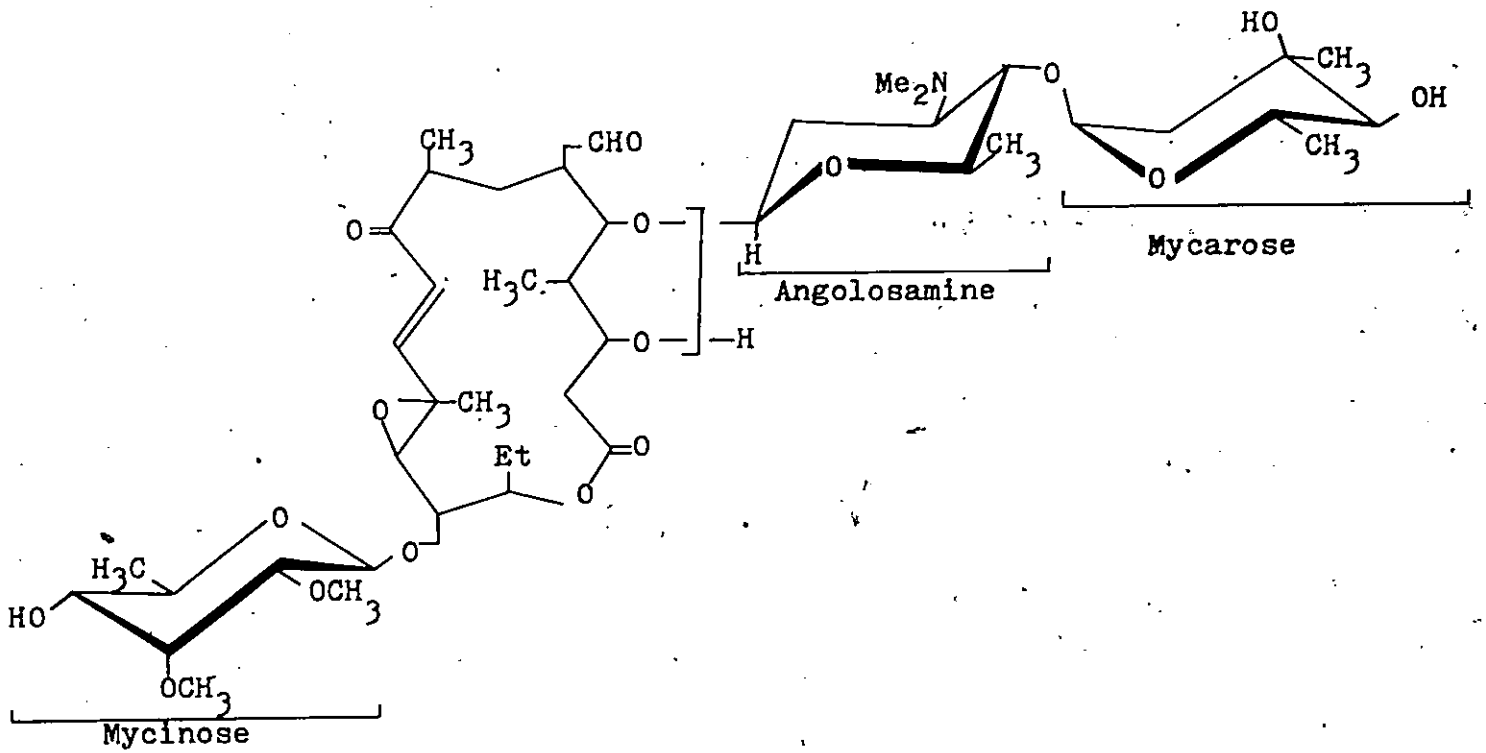
3 (Nystatin)



4 Spiramycin A, R = H
B, R = Ac
C, R = COEt

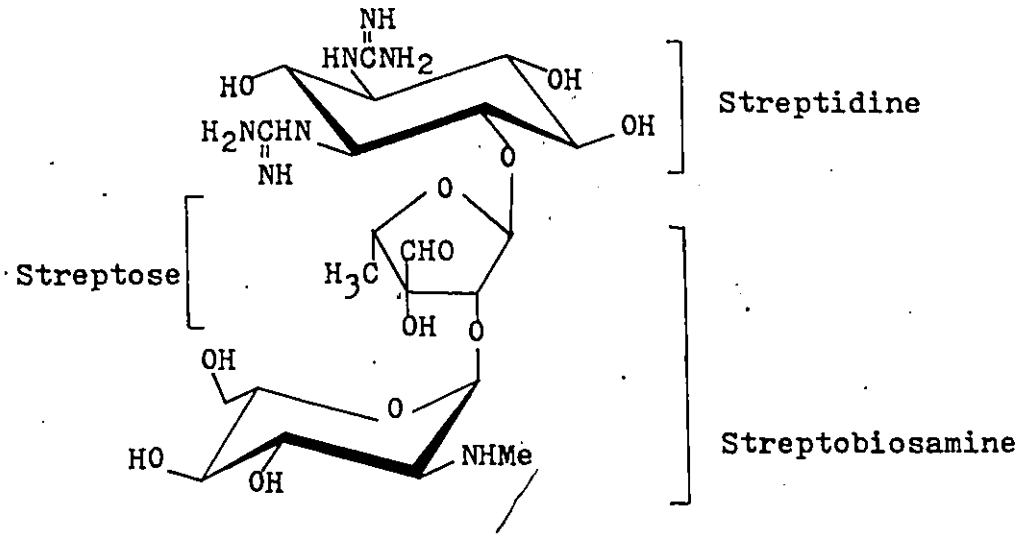


5 (Erythromycin)

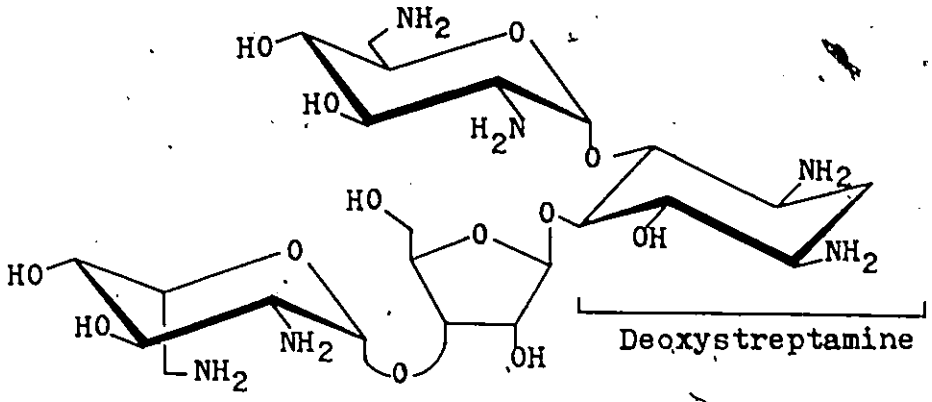


6 (Angolamycin)

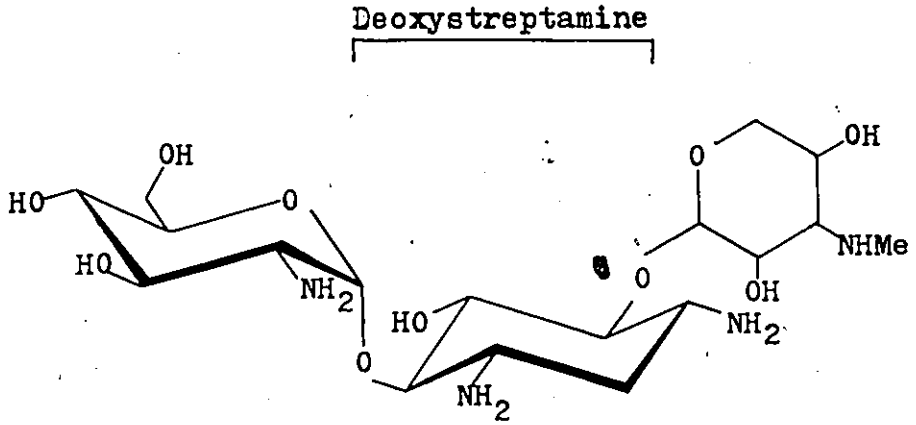
(ii) Cyclitol antibiotics, e.g. streptomycin (7), neomycin B (8) and gentamycin (9).



7 (Streptomycin)

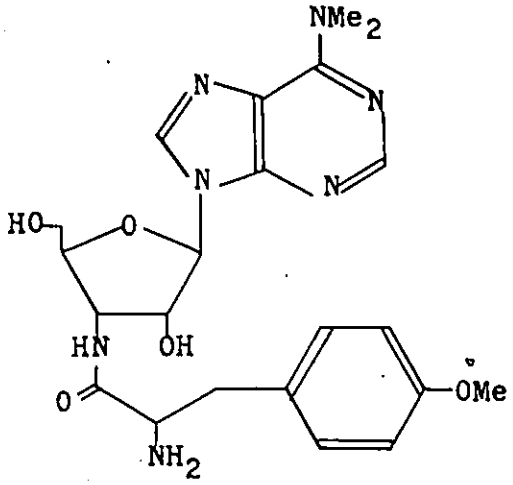


8 (Neomycin B)

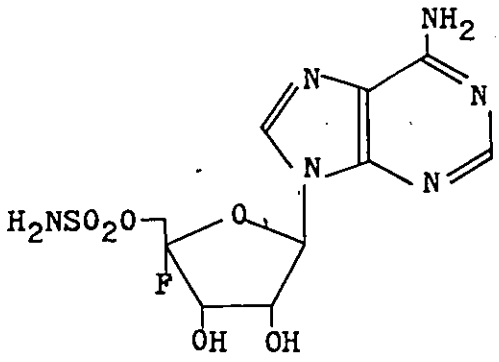


9 (Gentamycin)

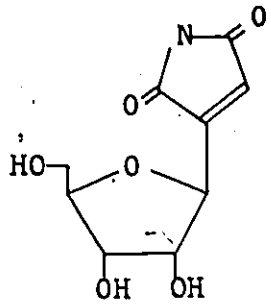
(iii) Nucleoside antibiotics, e.g. puromycin (10), nucleocidin (11) and showdomycin (12).



10 (Puromycin)

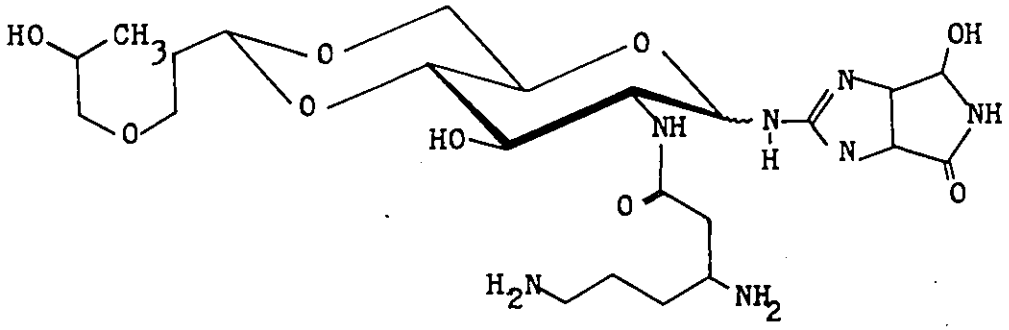


11 (Nucleocidin)



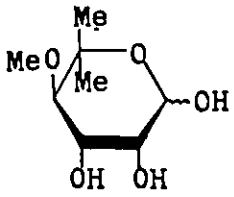
12 (Showdomycin)

(iv) Glycosylamine types, e.g. racemomycin O (13).

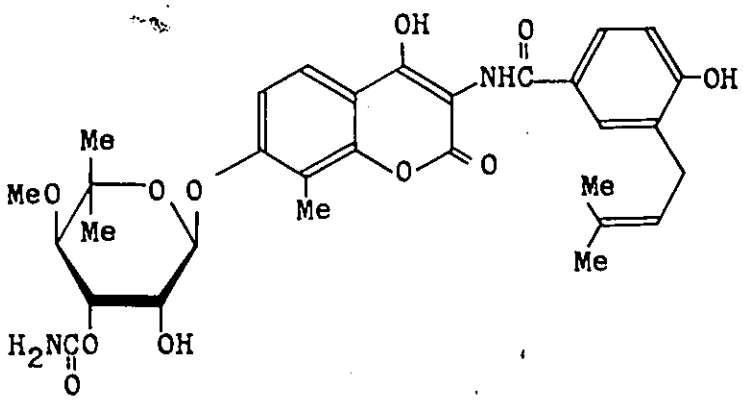


13 (Racemomycin O)

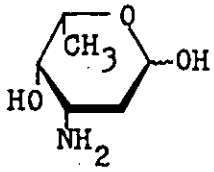
(v) Aromatic types, e.g. novobiocin (14) and daunorubicin (15).



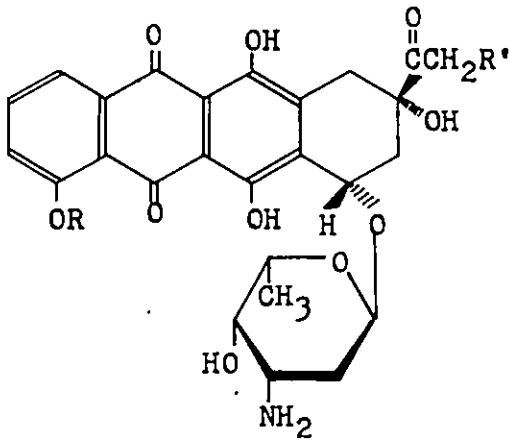
Noviose



14 (Novobiocin)



15a (Daunosamine)



15 (Daunorubicin, R=Me; R'=H)
16 (Adriamycin, R=Me; R'=OH)
17 (Carminomycin, R=R'=H)

The class of macrolides is divided into the polyene types and a group containing highly branched, polyfunctional macrocyclic lactone rings, from which the name "macrolide" is derived[8]. The latter group is further subdivided into those antibiotics that contain nitrogen and those that are nitrogen-free.

The macrolide antibiotics form one of the most interesting groups in which a carbohydrate component occurs in combination with a macrocyclic residue of different biosynthetic origin. It has been noticed[9] also that the glycosidic linkage between sugars with a C-5 methyl group and their macrolide aglycone is α- for L-sugars and β- for D-sugars.

Mode of Action of Antibiotics

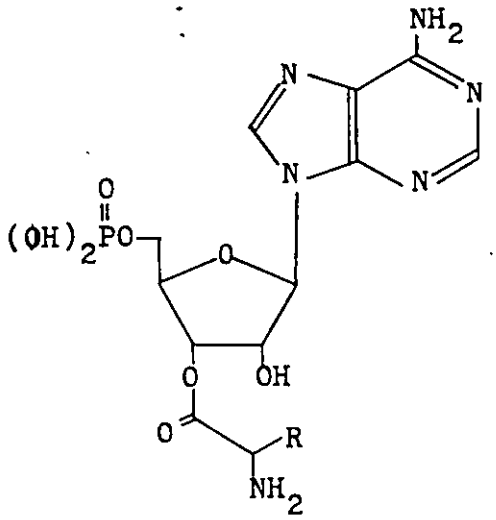
The last decade has wittnessed an extraordinary development in the understanding of the molecular events involved in nucleic acid and protein synthesis. New and powerful tools, which have demonstrated how genetic information may be replicated and translated into specific proteins, have helped to elucidate the mechanism of action of many clinically useful antibiotics.

Protein biosynthesis requires that each of the amino acids undergoes activation in the presence of ATP and a specific, amino acid-activating enzyme to form an aminoacyl-AMP (aa-AMP) intermediate. This activated, enzyme-

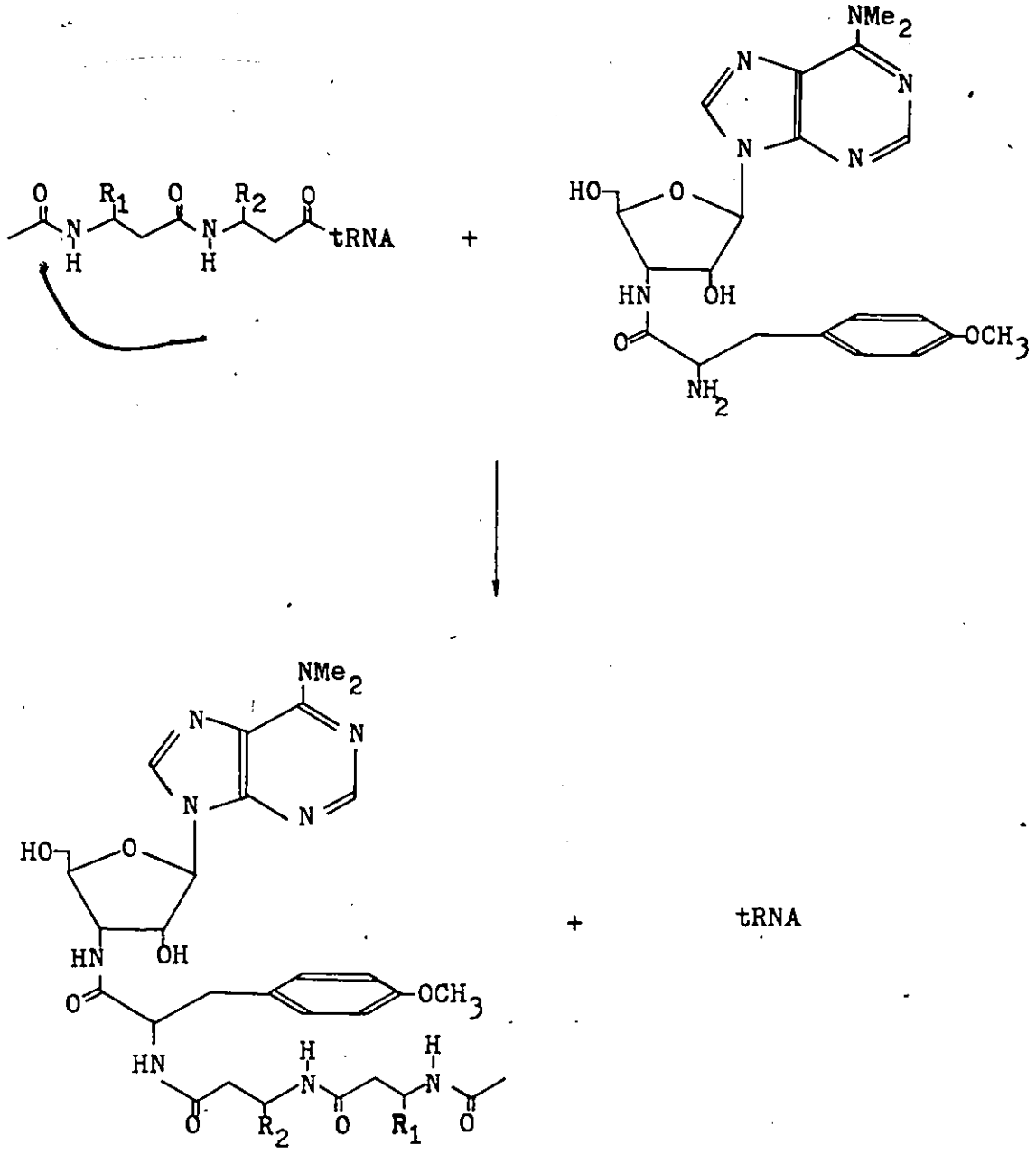
bound intermediate transfers the aminoacyl moiety to the free 3'-hydroxyl function of the ribose in the terminal adenosine of tRNA forming aminoacyl-tRNA (aa-tRNA). There are two binding sites (A and B) for aa-tRNA on the 50S ribosome subunit. In this scheme the particular aa-tRNA specified by the mRNA codon on the 30S subunit at this time binds at site A in a nonenzymic reaction. In the presence of an enzyme (Transferase I) and GTP, the aa-tRNA is translocated to site B on the ribosome. This step results in activation of the carboxyl of the aa-tRNA for peptide bond formation. A new incoming aa-tRNA then binds to site A and the activated aminoacyl group at site B is transferred enzymically (Transferase II) to the amino group of the aa-tRNA at site A, with release of the tRNA originally bound to the first amino acid. This results in the formation of a dipeptidyl-tRNA at site A which is then activated by translocation to site B for repeat of the peptide bond-forming reaction, with resultant chain elongation.

Puromycin (10) acts as an analogue of aminoacyl-tRNA on protein synthesis in *vitro*[10,11]. The structure of puromycin sufficiently resembles aminoacyl-adenosine (18) for it to participate in peptide chain elongation in a similar way to aminoacyl-tRNA. Puromycin binds weakly to site A of the ribosome, reacts with the activated ester carbonyl

of a peptide from site B to form "one amino acid longer peptide" (Scheme I), which immediately falls off the ribosome. The protein synthesis is thus terminated prematurely and an amino acid or a polypeptide is released with puromycin attatched by a peptide bond to its carboxyl end. Therefore puromycin is used in laboratories to stop protein synthesis at any required moment.



18 (Aminoacyl-adenosine)


NMe2
N
N
N
N
HO
O
HN
OH
OCH3
NH2
O
R1
O
R2
O
N
H
N
H
tRNA
+
NMe2
N
N
N
N
HO
O
HN
OH
OCH3
O
HN
H
N
O
R2
H
N
O
R1
O
+
tRNA

(Scheme I)

Daunorubicin* (15), the antibiotic isolated from cultures of Streptomyces peucetius, represents another group of antibiotics, generally known to interfere with the biosynthesis of nucleic acids. Members of this group are often considered to be of very limited clinical usefulness as antimicrobial agents since they lack requisite selective toxicity as compared to several members of the group represented by puromycin. Daunorubicin preferentially inhibits cellular RNA synthesis[12,13] and enzymic DNA-dependent RNA synthesis[14,15]. It is a glycosidic antibiotic with an aglycone chromophore (daunomycinone) linked to an amino sugar (daunosamine 15a)[16]. It complexes with DNA in vitro[12,15,17] and in vivo[12], increases the viscosity of DNA, decreases the sedimentation coefficient of DNA, increases the Tm** of DNA and precipitates DNA at high concentrations of the antibiotic[12b,15,17]. The antibiotic exerts pronounced antitumor activity[18].

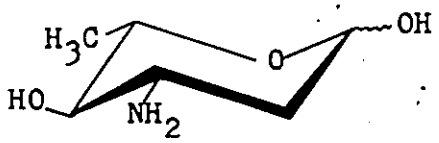
Adriamycin[19] (16) and carminomycin[20] (17) are two antibiotics very closely related to daunorubicin with similar antitumor activity. Recent studies[21], involving analysis of the behavior of daunorubicin and adriamycin on cultured heart cells, revealed that the beating rate

---

* Also known as daunomycin.

**The midpoint of the temperature denaturation curve.

decreased by about 50% with respect to the basal value after daunorubicin or adriamycin treatment. However, 4'-epi-adriamycin (in which the sugar moiety has been replaced synthetically by acosamine (19), the C-4 epimer of daunosamine), when subjected to a similar analysis in doses of up to 5μg/ml did not affect the beating rate of cultured heart cells, and yet the antitumor activity was retained at the same level. These reults clearly indicate the importance of exploring similar modifications in the sugar components of various antibiotics, which could lead to a variety of clinically useful drugs that might eventually become the ultimate weapon against cancer.

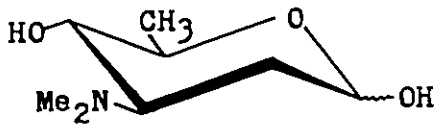


19 (Acosamine)

Specific Aims of This Study

Nitro sugars, in which a hydroxyl group of the carbohydrate has been replaced by a nitro group, have played an important role in the development of synthetic methods for several types of amino sugars. In view of the

preceding discussion, it was deemed useful to widen the scope of preparative nitro and hence amino sugar chemistry as follows. Members of the D- and the known[22] L- series of the methyl 3,6-dideoxy-3-nitrohexopyranosides should be likely candidates for points of departure in attempts to establish and utilize new methods for the synthesis of 3-amino polydeoxy sugars of the type of desosamine, daunosamine, or angolosamine (20, the sugar component of angolamycin) mentioned earlier.



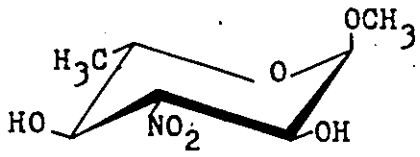
20 (Angolosamine)

The work contemplated would involve a search for new or improved ways of introducing a deoxy function in position 2 or 4 of the nitro sugars mentioned. A systematic study of the formation of unsaturated nitro intermediates and their hydrogenation would be a part of the project. Nitroolefinic carbohydrate derivatives are commonly made from acetylated precursors by elimination of acetic acid in a heterogeneous system (the Schmidt-Rutz reaction[23]),

which does not always give satisfactory results. Further, it was to be investigated whether entry into the 3,6-dideoxy-3-nitrohexose series can be gained starting from 4,6-O-benzylidenated 3-deoxy-3-nitrohexoses by the Hanessian reaction[24] with N-bromosuccinimide. Success in this direction would greatly enhance access to the D-series of 3,6-dideoxy-3-nitro sugars as it would lead to the use of D-glucose as the ultimate starting material. In contrast to the L-series, where 6-deoxy sugars (especially L-rhamnose) can serve as economical starting points, 6-deoxy-D-hexoses are not readily available either from commercial sources or by convenient laboratory procedures. It was also considered to use glycals (1,2-unsaturated sugar derivatives), which can be made quite easily, as starting compounds for the synthesis of 3-amino polydeoxy sugars. The ultimate aim of the thesis was to devise syntheses of some carbohyrate antibiotics components or structural or configurational analogs thereof.

A Short Review of Prior Work Pertinent to the Present Projects

The methyl 3,6-dideoxy-3-nitrohexopyranosides having the α-L-gluco (21), α-L-manno (22), α-L-galacto (23), and α-L-talo (24) configurations and their 2,4-diacetates have been thoroughly investigated [25] as starting materials for the preparation of 2,3- and 3,4- unsaturated derivatives.



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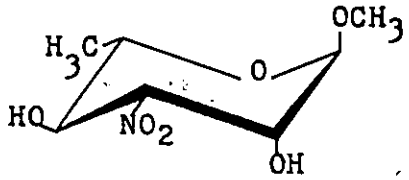

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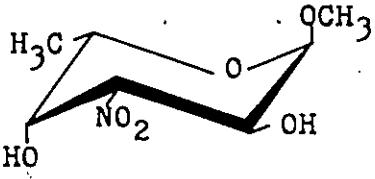

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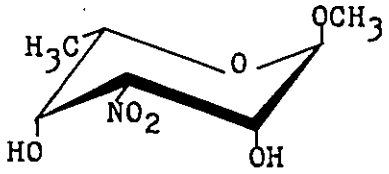
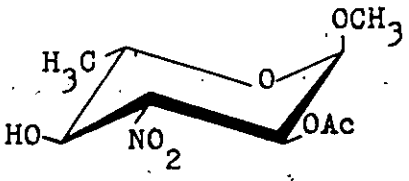


24

In accordance with the previously observed[26], greater reactivity of its 2-hydroxyl group, compound 21 upon treatment with 1 mole of acetyl chloride and triethylamine[27,28] gave predominantly the 2-acetate 25 (yield, 51% based on reacted 21). Conversely, the greater reactivity at



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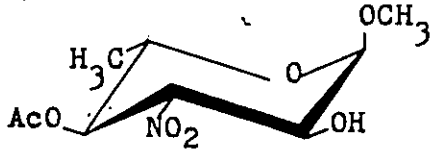

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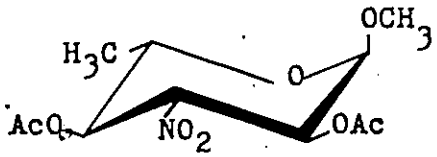
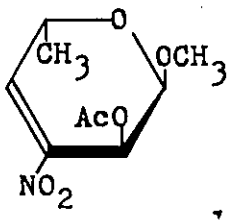


26

position 2 is also reflected in an enhanced lability of the

2-acetyl group in the diacetate 26 towards acid-catalyzed methanolysis. The 4-acetate 27 has thus been described[25]. On the other hand, positional reactivities appeared inverse in base-catalyzed dehydroacetoxylation. Thus, action of basic silica gel upon 26 and 27 effected elimination of acetic acid to give the 3,4-unsaturated monoacetate 28 and the nonacetylated derivative 29, respectively. The 2,3-unsaturated isomer 30 could not be obtained by this procedure.



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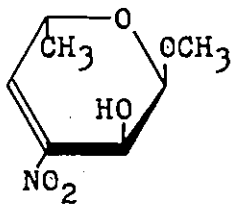

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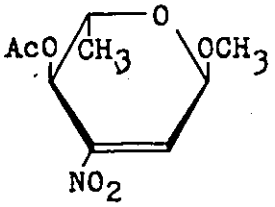
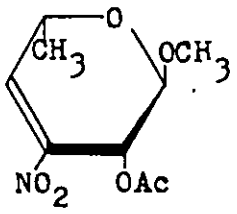


30

By contrast to the dehydroacetoxylation of 27, action of silica gel upon the isomeric monoacetate 25 was rather ineffective. Furthermore, application of the Schmidt-Rutz reaction[23] to 26 under the usual conditions of refluxing

in dry benzene in the presence of dry sodium bicarbonate gave 28 in only 4% yield, and 30 was not observed[25]. The major product (21%) proved to be the unexpected Δ^3-α-L-threo isomer 31. It thus appears from these observations that compound 30 is not producible by the above-mentioned



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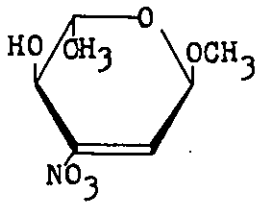
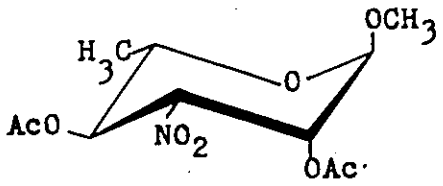


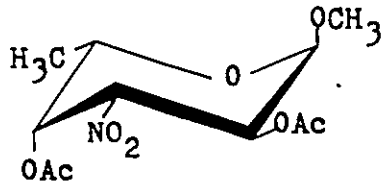
32

methods. Moreover, the nitroolefin 32 was only obtained when 22 was subjected to the conditions of partial acetylation with acetyl chloride-triethylamine, in which case more than half was recovered unchanged and a small proportion of diacetate 33 was formed. The main reaction product was 32 and it was isolated in 47% yield (based on consumed 22). This was subsequently acetylated to 30.



33

When methyl 2,4-di-O-acetyl-3,6-dideoxy-3-nitro-α-L-galactopyranoside (34) was subjected to dehydroacetoxylation by silica gel it gave a mixture of 28 and 35 in nearly equal proportions[25]. Partial acetylation or deacetylation was not studied in this case.



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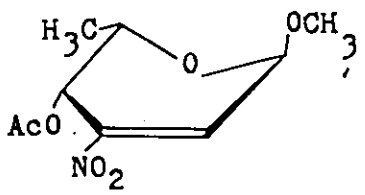
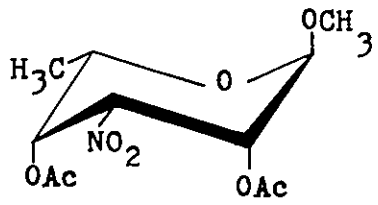


35

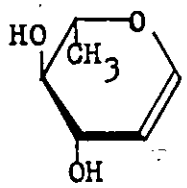
Compound 31 could also be obtained[25], but only in low yield and impure form, when the diacetylated talopyranoside 36 was treated in the same fashion with silica gel. However, compound 36 itself was difficult to obtain in pure form because of its observed tendency to eliminate acetic acid[25].



36

Various glycals have been used efficiently on several occasions in the synthesis of different 2-amino-2-deoxy sugars[29,30] having the D-gluco, D-manno, D-galacto and D-talo configurations. The synthesis involves the addition of a nitrogenous reagent (NOCl, N_2O_4) across the double bond of the glycal followed by subsequent reduction of the adduct to the corresponding amino derivative. In one instance the glycosyl halide of an N-carbamate derivative of a 2-amino-2-deoxy sugar was synthesized directly by the chromous chloride-catalyzed addition of N-chlorocarbamate (ROCONHCl) to glycal triacetates[31]. Subsequent reaction with alcohols under Koenigs-Knorr conditions afforded the β-glycosides. In the case of glucal triacetate, the addition was stereoselective, giving almost entirely glucopyranosides[31].

It seemed complementary to try to utilize glycals in new synthetic routes leading, this time, to 3-amino-2,3,6-trideoxy sugars, particularly in cases where nitro sugars may not be appropriate starting materials. Recently[32], the 6-deoxy glycal L-rhamnal (37) has been utilized in a similar approach.



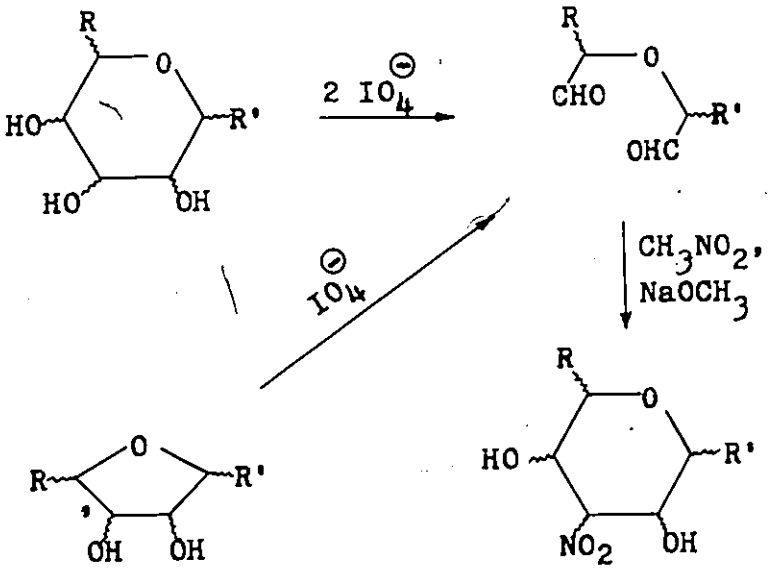
37

PART I

The Reaction of N-bromosuccinimide with Benzylidene Acetals of Nitro Sugars

RESULTS AND DISCUSSION

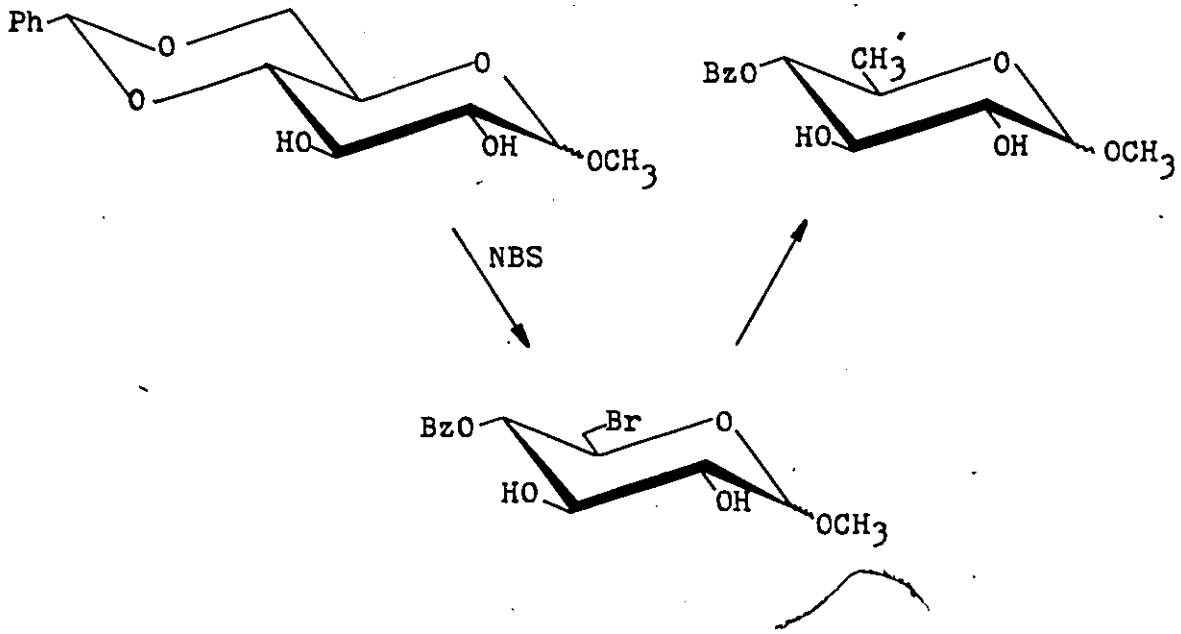
Nitro sugars are rarely prepared as free, reducing sugars[33] but are usually handled as glycosides which are utilized as precursors of a wide variety of amino sugars. They have been thoroughly reviewed by Baer[34] and the formation of nitro sugar derivatives by cyclization of dialdehydes with nitromethane[35] and other nitroalkanes[36] has been reviewed by Lichtenthaler. The cyclization of dialdehydes with nitromethane (Scheme II) continues to be an important method for the preparation of nitrogenous sugars and has been the subject of further study, mostly by the groups of Baer and Lichtenthaler. The method has



(Scheme II)

been extended to nucleosides and to the synthesis of branched-chain sugars[35,37]. Although chemical transformations of nitro sugars have been extensively studied with a view to the synthesis of rare amino sugars[69,37-43], it appeared at the outset of the present research work that this field is capable of further exploitation and expansion of its scope.

One unexplored area concerned the convenient and economical preparation of methyl 3,6-dideoxy-3-nitrohexopyranosides in the D-series, which might serve as starting compounds for syntheses of such amino sugars as D-angolosamine, D-desosamine, or D-daunosamine. Several nitro sugars of the structure mentioned are known in the L-series, and these are readily made by the nitromethane procedure starting from commercial L-rhamnose. One could, of course, prepare the D-enantiomers in the same fashion from a suitable 6-deoxy-D-hexose, but none was commercially available and most published procedures for making, for instance, 6-deoxy-D-glucose seemed rather laborious. Most attractive in this regard appeared the Hanessian-Hullar reaction in which a 4,6-O-benzylidenated hexopyranoside is converted by the action of N-bromosuccinimide (NBS) into a 6-bromo-6-deoxy derivative which can then be reductively debrominated to give the 6-deoxy compound[46-49], Scheme III. Two questions presented themselves in this



(Scheme III)

connection. First, can the NBS reaction be applied to nitro hexosides ? If so, the approach would have a certain advantage over the inverse sequence of using it merely as a source of 6-deoxyhexoside which would subsequently afford nitro sugars in the conventional way. The advantage would lie in the fact that a 4-O-benzoylated and therefore, partially blocked, nitro sugar derivative would arise which should be useful for further, selective functionalization. The second matter of interest was the question as to

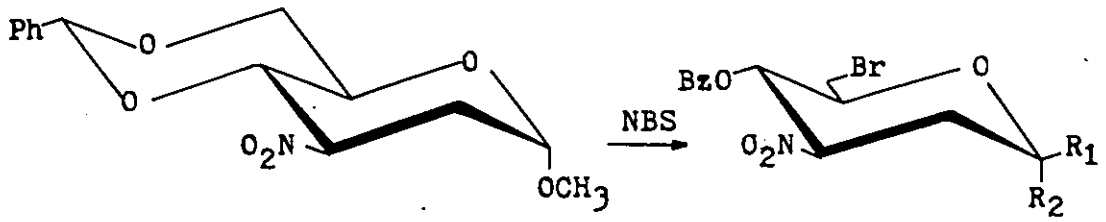
whether a 6-bromo-3-nitro derivative can be selectively reduced at C-6, without affecting the nitro group. Bifunctional reduction to the corresponding 3-amino-3,6-dideoxy sugar would negate any plans of subsequently performing structural modifications based on the activating effect of the nitro group.

The known compounds, methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-arabino-hexopyranosides (38)*, methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-glucopyranoside (42), and methyl 2-O-acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (44) were selected for the study. The question of compatibility of these compounds with the Hanessian-Hullar reaction was not a trivial one since many nitro sugar derivatives of this structural type (including, in fact, compound 44) had been found[50] to undergo facile bromination at the nitromethine carbon atom, to give geminal bromonitro compounds, by the action of N-bromoacetamide (and also by NBS in the one case examined). However, the reaction conditions for these geminal brominations (which proceed by an ionic mechanism) differ from those of the desired reaction, and the results proved that there was little reason for concern.

Compound 38 was treated with a slight excess (18 mol.%) of NBS in refluxing carbon tetrachloride in the presence of barium carbonate as an acid scavenger. The workup

*For a fast, convenient preparation of 38 see Experimental, Part II.

procedure was essentially as directed in the literature[47]. The crude syrupy product did not prove homogeneous and column chromatography was necessary. Pure crystalline methyl 4-O-benzoyl-6-bromo-2,3,6-trideoxy-3-nitro-α-D-arabino-hexopyranoside (39) was thus obtained in 64% yield. Subsequent fractions from the column were unexpectedly found to contain what proved to be 40, the β anomer of 39. It was isolated crystalline in 16% yield. (Structural and



38

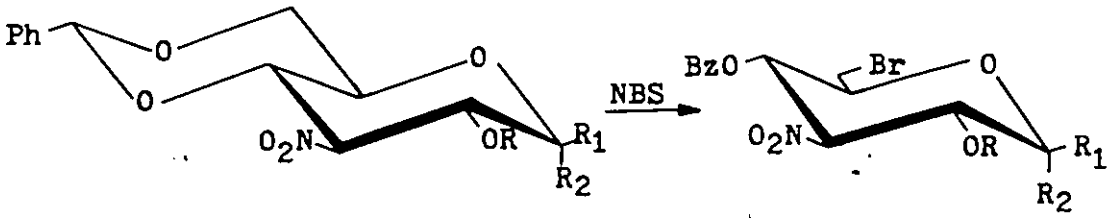
39 R_1=H, R_2=OCH_3

40 R_2=H, R_1=OCH_3

configurational proof of these and other new compounds will be discussed at the end of this part). It was considered that partial anomerization was caused by traces of hydrogen bromide formed in a side reaction during the bromination process. Apparently the barium carbonate, operating in the

heterogeneous phase, was unable to neutralize the acid rapidly enough. This conclusion appeared reasonable considering the high reactivity at the anomeric center generally observed in 2-deoxy glycosides[43, 51-54], and was supported by the fact that no anomerization was observed when the reaction was performed in the presence of a larger excess of barium carbonate. In this case the product 39 was obtained in 80% yield without chromatographic purification.

The NBS reaction with compounds 42 and 44 was successful also, furnishing the 6-bromo derivatives 43 and 45, respectively, in crystalline form in yields of 60 and 56%. In the case of 45, no chromatographic purification was necessary; the compound crystallized directly from the reaction mixture upon partial evaporation of the solvent.



42 $R=R_1=H$, $R_2=OCH_3$

43 $R=R_1=H$, $R_2=OCH_3$

44 $R=Ac$, $R_1=OCH_3$, $R_2=H$

45 $R=Ac$, $R_1=OCH_3$, $R_2=H$

It has thus been demonstrated that the Hanessian-Hullar reaction proceeds normally in nitro sugars. It has provided the first examples of 6-bromo-3-nitro hexose derivatives, and compounds of this type should prove useful for various synthetic purposes.

Unfortunately, our first endeavours to debrominate these compounds by selective reduction were fruitless. Catalytic hydrogenation using 10% palladium on charcoal was attempted. This catalyst should be effective[47] in replacing the bromine atom and on the other hand, was assumed to attack the nitro group only slowly. (It may, for example, be employed to selectively saturate nitroalkenes[34,55]). However, reaction with compound 39 in the presence of one molar equivalent of triethylamine (to neutralize the hydrobromic acid produced) led to a complex mixture of products that were ill separated in t.l.c., and nothing could be isolated or identified. Evidently there was no clean selective reduction, and changes in reaction conditions, such as the use of lower temperature or different solvent or base, were not helpful. Similar difficulties were encountered with compounds 43 and 45. In one small-scale hydrogenation of 43, a product was obtained which according to preliminary examination by n.m.r. appeared to be the desired 3,6-dideoxy-3-nitro derivative (Fig 1), but this result was not reproducible

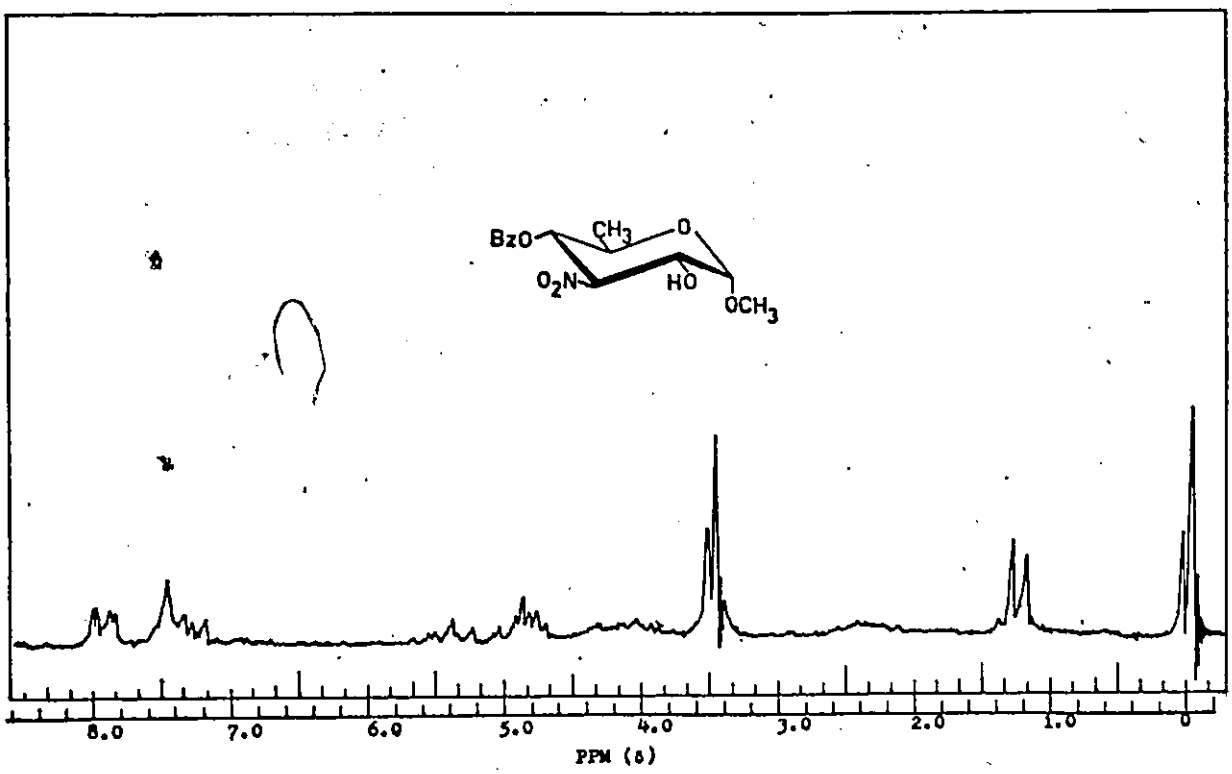


Fig. 1; crude product of hydrogenation of the glycoside 43

in subsequent experiments. The approach was abandoned for the time being. Yet it may still be worthwhile in future work to try other methods of reduction eventhough the choice is limited by the sensitivity of the compounds under both strongly acidic or alkaline conditions. One could also contemplate to attempt hydrogen bromide elimination by means of silver fluoride (which has been achieved in non-nitro analogs[56]), thereby generating a 5,6-double bond which perhaps could then be hydrogenated selectively although in this case one would have to deal with the problem of epimerism at C-5.

Configurational and Structural Proof of Bromides 39, 40, 43 and 45

Compounds 39, 40, 43, and 45 gave microanalytical data in agreement with their structures. They showed infrared bands in the regions 1715 - 1730 cm^{-1} and 1550 - 1565 cm^{-1} as expected for benzoate ester and nitroalkane functions, respectively. The conversion of the benzylidene acetals into benzoate esters was also readily recognizable n.m.r. spectroscopically by the disappearance of the characteristic singlet of the phenylmethine proton (δ 5.6 region) and the resolution of the narrow five-proton multiplet for the phenyl group (δ 7.4 region) into two distinct multiplets corresponding to two and three protons (see Figs. 2, 3, 4, and 5). Compound 45 (Fig. 2) gave, in order of increasing

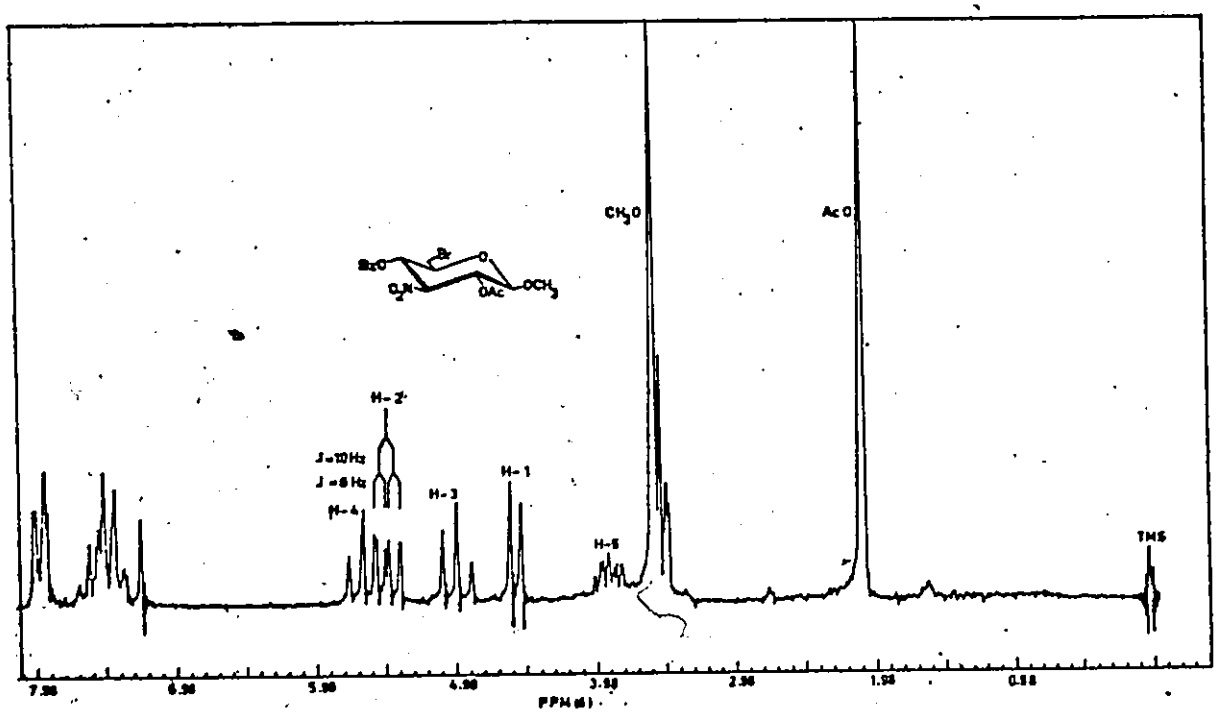


Fig. 2; n.m.r. spectrum of 45

field, a triplet for H-4, a quartet for H-2, a triplet for H-3, and a doublet for H-1 which all contained only large splittings that required all-axial proton orientation and thus confirmed the β-gluco configuration. Retention of the O-acetyl group was indicated by a 3-proton singlet at δ 2.10. In compound 43 (Fig. 3), the H-1 signal was shifted

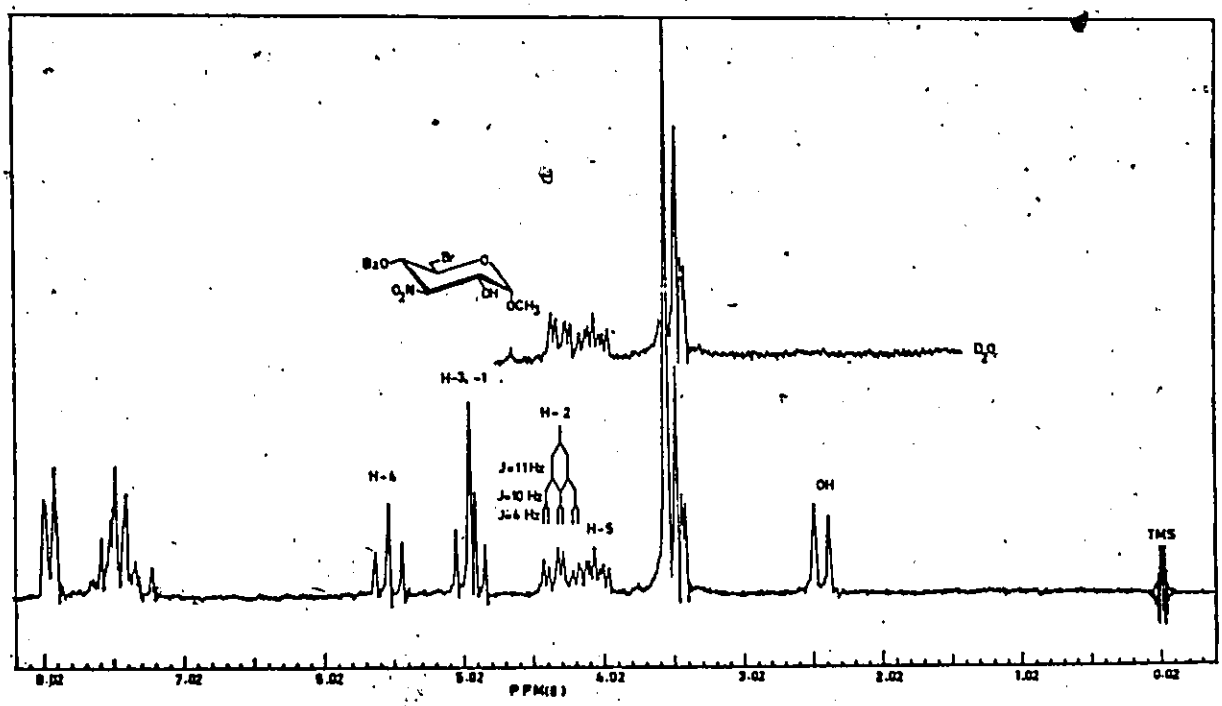


Fig. 3; n.m.r. spectrum of 43

slightly downfield, and the H-2 signal upfield, relative to 45; this was due, respectively, to equatorial orientation of H-1 and lack of an ester function at C-2. The splitting pattern indicated a small vicinal coupling between H-1 and

H-2 whereas the vicinal couplings between H-2, H-3, H-4 and H-5 were large, in agreement with the α-gluco configuration.

In the spectra of 39 (Fig. 4) and 40 (Fig. 5), the ring proton signal at lowest field (near δ 5.6) attributable to H-4 was a triplet with large splitting, indicative of

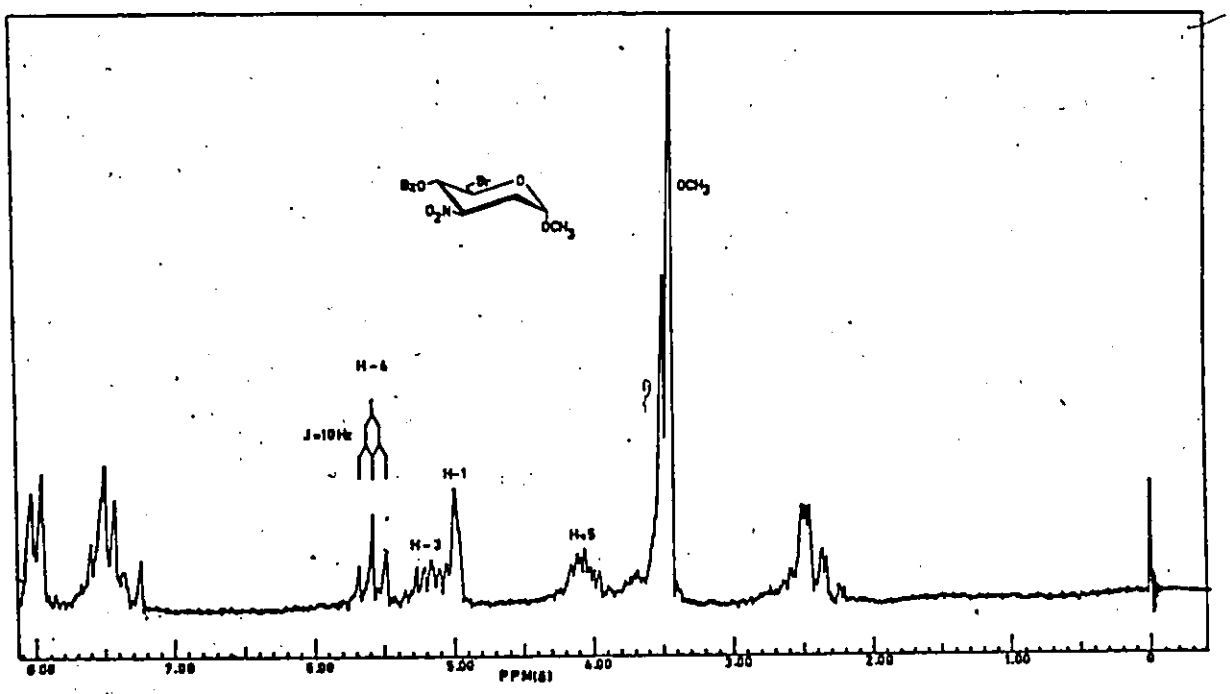


Fig. 4; n.m.r. spectrum of 39

triaxial proton arrangement at C-3, C-4, and C-5 in both compounds. This left only C-1 as the site of configurational difference for these isomers. The H-1 signal of 39 was a narrow multiplet at δ 5.00, presumably containing two small vicinal couplings with the C-2 methylene protons whereas

the H-1 signal of 40 occurred at δ 4.60 and was a quartet showing one small and one large coupling. These features required an equatorial anomeric proton in 39 and an axial one in 40, and led to the α- and β-glycoside designations as indicated. This was also in accord with the higher (+ 71.5°) and lower (+ 26.5°) specific rotation of 39 and 40, respectively.

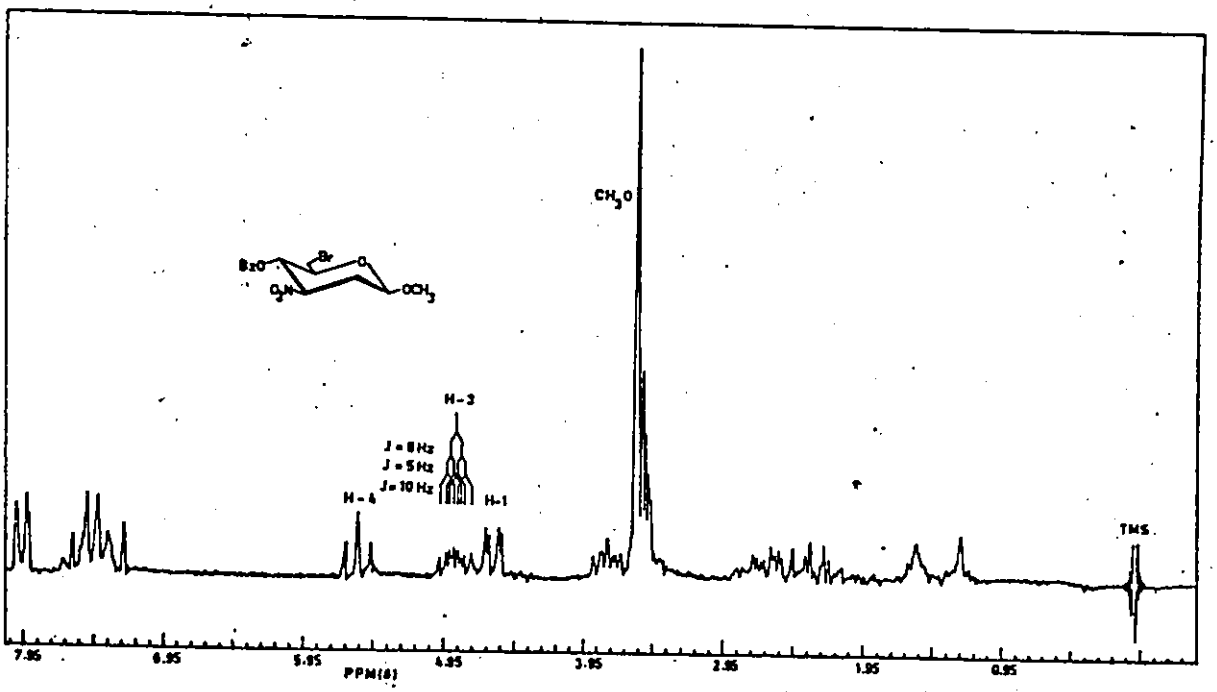


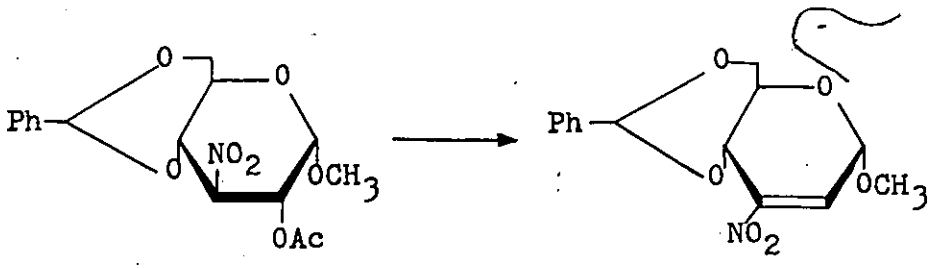
Fig. 5; n.m.r. spectrum of 40

PART II

Synthesis of Nitroolefins
Via
Methanesulfonates

RESULTS AND DISCUSSION

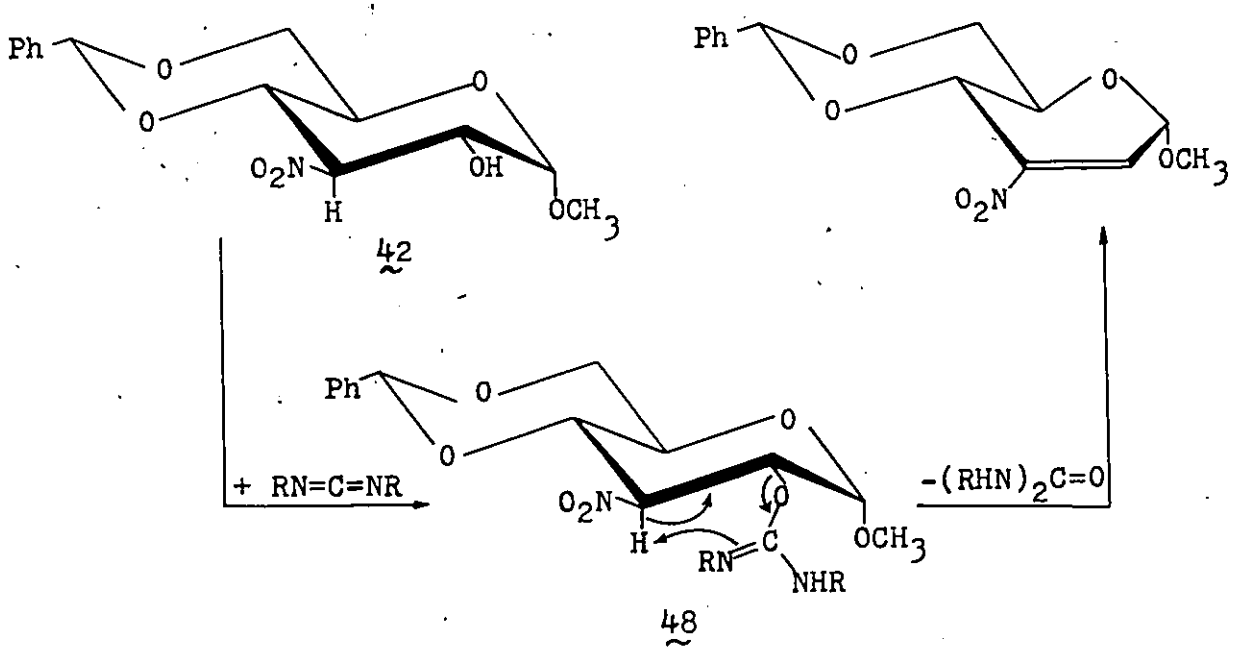
Sugars that contain a nitroalkene grouping are key intermediates for many syntheses in the field of nitrogenous carbohydrates. They may serve for the introduction of a deoxy function by slective hydrogenation, or of various other functionalities by nucleophilic additions, at the carbon atom in the β-position of the nitro group. Carbohydrate nitroolefins have customarily been made by dehydroacetoxylation of O-acetyl derivatives with sodium bicarbonate in refluxing benzene (the Schmidt-Rutz reaction[34]). Although this procedure normally works reasonably well, it sometimes fails to go to completion or requires inconveniently long reaction times as for instance in the case 46 ⟶ 47[44].



46 47

More recently, dehydroacetoxylations were studied in partially acetylated methyl 3,6-dideoxy-3-nitro-α-L-hexopyranosides and found to occur at room temperature by the action of silica gel[25]. This work has furnished several useful nitroolefinic derivatives but yields were not high. Improved access to such compounds remained a desirable goal of research.

A first attempt in this direction involved treatment of a nitro alcohol, namely compound 42, with the mild dehydrating agent dicyclohexylcarbodiimide (DCC). The reaction is based on conversion of the alcoholic oxygen into a better leaving group (Scheme IV). The intermediate 48

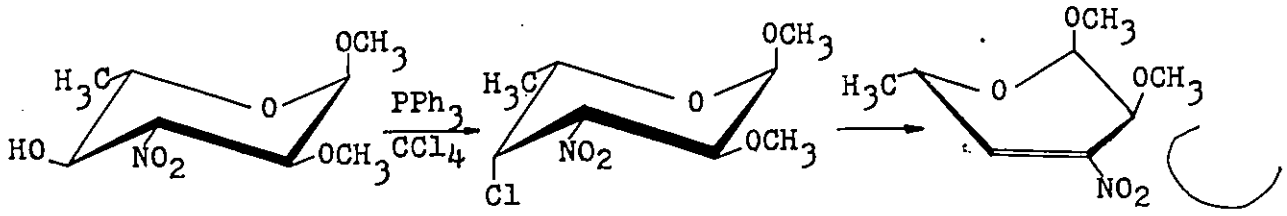


(Scheme IV)

should react as shown, via a six-membered transition state in which the nitromethine hydrogen, being in a favorable position cis to the oxygen function, should be readily abstracted.

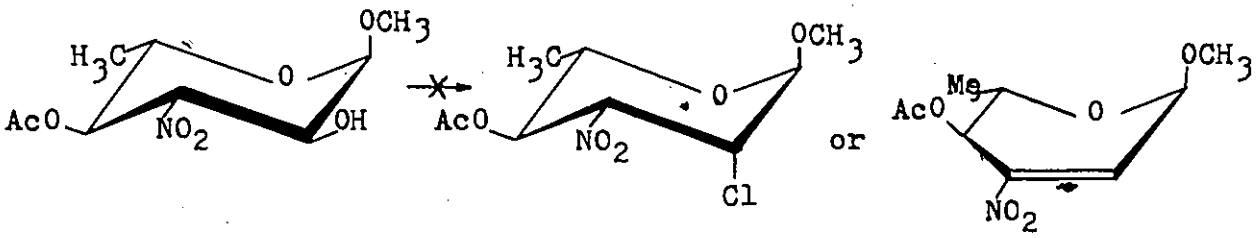
The reaction was carried out with excess reagent in dry ether at 25°. However, t.l.c. examination after several days revealed no appreciable change in the reaction mixture. The starting material seemed to remain unchanged. It is not known whether steric hindrance or other factors contributed to the failure of the reaction. The approach was abandoned.

Another possibility of olefination consists of substitution of the alcoholic hydroxyl group by a chlorine atom by means of triphenylphosphine in carbontetrachloride[57], followed by dehydrohalogenation. This procedure had afforded[26] a chloro derivative (50) from a nitro sugar (49), and facile dehydrohalogenation occurred to give an olefin (51). It was therefore examined whether the similar nitro sugar 52, which was prepared according to the literature[25],



49 50 51

could be olefinated in similar fashion. Unfortunately, the attempt was unsuccessful in that no reaction seemed to occur. Only starting material was isolated.

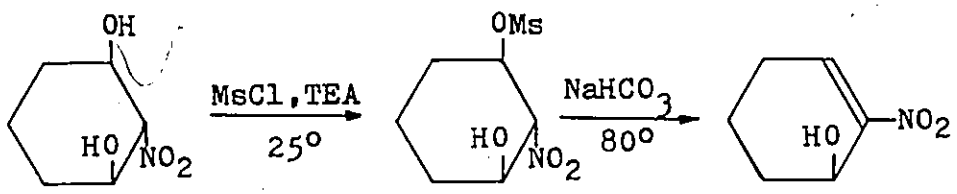


52

More fruitful proved subsequent investigations involving nitro sugar methanesulfonates. In contrast to carboxylic esters, which tend to undergo acyl-oxygen fission, esters of sulfonic acid are generally cleaved at the alkyl-oxygen bond. The methanesulfonate anion is an excellent leaving group and these esters are therefore useful intermediates in many synthetic schemes. However, sulfonates of nitro alcohols do not seem to have been described in the literature thus far. There are certainly no examples in nitro sugars, and none could be found in other areas of aliphatic chemistry. In an isolated instance, Hassner[59] has tried to dehydrate

a steroidal nitro alcohol by treatment with p-tolylsulfonyl chloride in pyridine but failed. However, while the present project on the synthesis and chemical behavior of nitro sugar methanesulfonates was well underway a brief note[60] appeared according to which simple aliphatic nitro alcohols can be dehydrated by the action of methylsulfonyl chloride in the presence of triethylamine; no mention was made of the isolation of any intermediary mesyl esters.

Our first experiments were performed on trans,trans-2-nitro-1,3-cyclohexanediol (53) which served as a model for nitro sugars. When reacted at room temperature with 1 molar equivalent of mesyl chloride in dichloromethane solution in the presence of triethylamine, it gave a crystalline monomesylate (54) in 60% yield. In addition, there

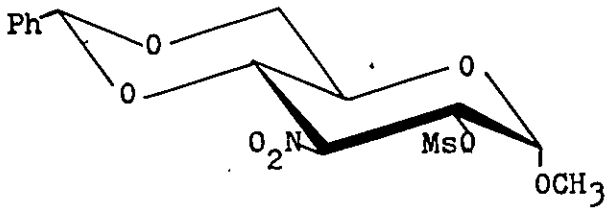


53 54 55

seemed to arise some dimesylate (faster moving on t.l.c.) and a small amount of olefin (55). Treatment of 54 with

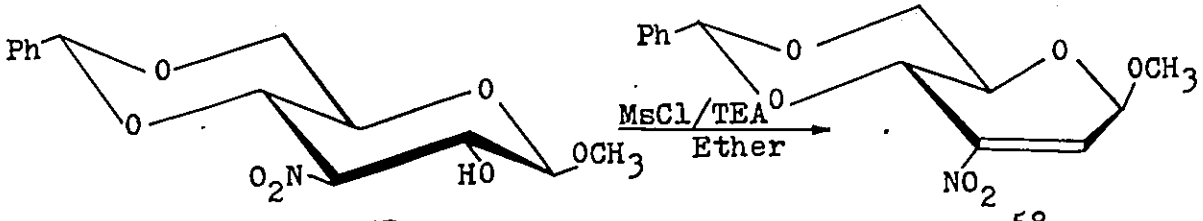
sodium bicarbonate in refluxing benzene for 3h gave 2-nitrocyclohex-2-ene-1-ol (55) which was readily isolated in 97% yield in this way whereas it had previously been obtained[61] by alkaline dehydration of 53 in lesser yield and only after column chromatographic purification.

When methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-glucopyranoside (42) was treated with mesyl chloride and triethylamine in dry ether at 25°, the isolated product (90%) proved to be the 2,3-unsaturated derivative 47 and not the mesylate (56) that might have been expected on the basis of the experience in the mesylation of 53. The



56

β-anomer (57) was similarly converted by mesyl chloride and triethylamine in ether into the olefin 58 in a yield of 78%.



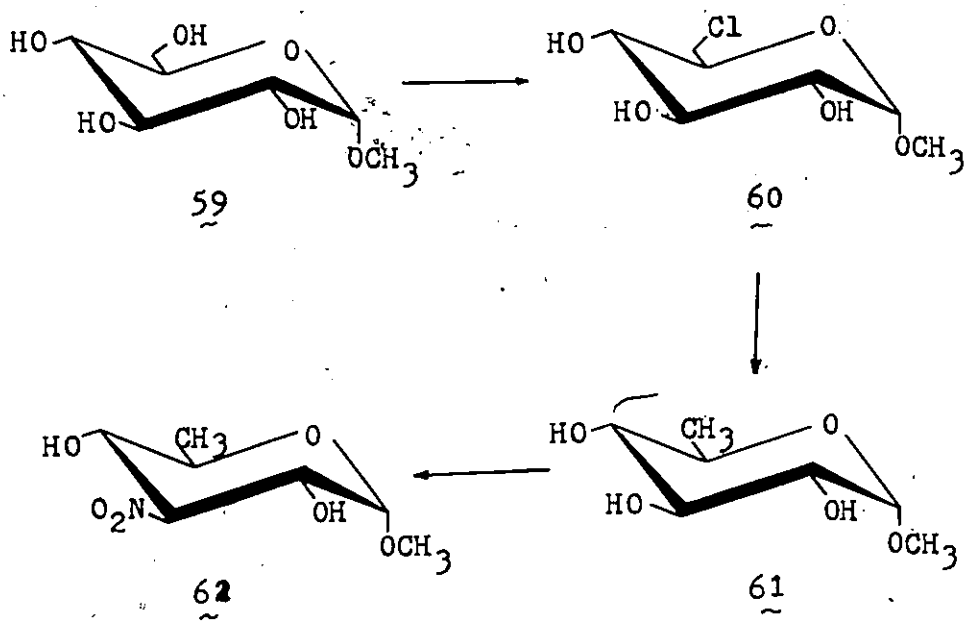
57 58

Obviously these olefins must arise from intermediary mesylate esters which apparently are unstable and a molecule of methanesulfonic acid is eliminated under the reaction conditions. This was indicated by the fact that when the reaction of 42 was carried out in dichloromethane, the 2-mesylate 56 was isolated in 20% yield although nitroolefin 47 was the major product in this case too, according to examination by t.l.c. Preparation of these particular nitroolefins from the alcohols by acetylation followed by dehydroacetoxylation can be done routinely as mentioned in the introduction, but the present procedure was found to offer advantages of greater simplicity and much shorter reaction times.

The facile dehydromesyloxylations just mentioned encouraged an extension of the study to the synthesis of unsaturated derivatives of 3,6-dideoxy-3-nitro-α-D-hexopyranosides. Such compounds, with either 2,3- or 3,4-unsaturation, would be useful precursors for the synthesis of saturated trideoxy nitro sugars and the corresponding amines, the latter being of interest as components of antibiotics. Considerable work has been published[25] on nitroolefins of this kind in the enantiomeric L-series, but the procedures employed for generating the double bond — dehydroacetoxylation by bicarbonate or silica gel — were not always satisfactory from the viewpoint of yields and were

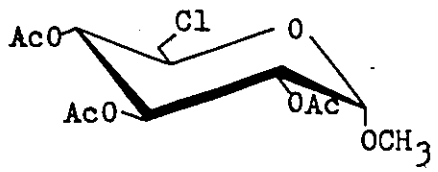
tolerable only because of the relatively easy accessibility of the starting sugars in that series.

For the present studies in the D-series, methyl 3,6-dideoxy-3-nitro-α-D-glucopyranoside (62) was required. This compound should be obtainable by the nitromethane cyclization method from methyl 6-deoxy-α-D-glucopyranoside (61), which in turn can be made according to the literature[62] from methyl α-D-glucopyranoside (59) via the 6-chloro derivative 60.



For the purpose of this work the preparation of 61 was simplified by use of a procedure which avoids the need of tedious chromatographic purification of its precursor 60.

The latter was prepared essentially as described[63], but the crude product was converted, without prior chromatographic isolation, into its 2,3,4-triacetate 63. Lithium aluminum hydride reduction of 63 was effected in the same way as described for 60[62] and the 6-deoxy glycoside 61 was obtained in 45% yield. Compound 61 was then oxidized with sodium metaperiodate, and the product was cyclized with nitromethane in the presence of sodium methoxide,

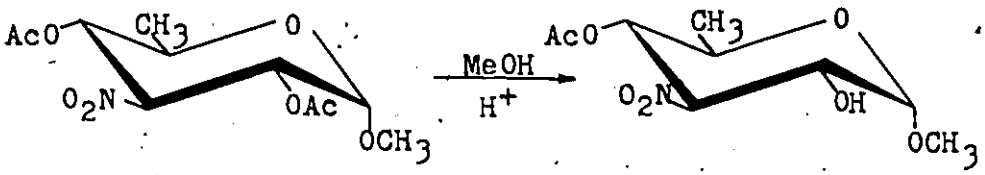


63

exactly as detailed[22] for the preparation of the L-enantiomer of 62 except that a reaction time of 3h (instead of 40 min) was allowed for the cyclization. The extended time was chosen in consideration of studies[64] indicating that this will favor formation of 62 over its manno isomer. Compound 62 was thus obtained in 35% yield by direct crystallization from the mixture of products, and processing of the mother liquor by column chromatography[22c] was dispensed with.

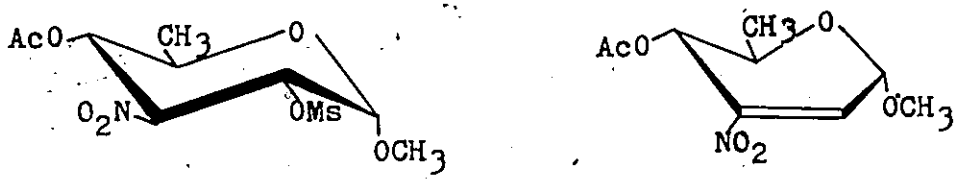
The nitro glycoside 62 was converted into its diacetyl derivative 64 as described[25] for the L-enantiomer, followed by partial acid-catalyzed methanolysis which was slightly

modified, for convenience, by addition of acetylchloride as a source for hydrogen chloride in methanol. The 4-acetate 65 was thus obtained in 50% yield.



64 65

When compound 65 was treated with mesyl chloride and triethylamine in ether, it gave in 80% yield the crystalline 2-mesylate 66, instead of the expected nitroolefin 67, in contrast to the behavior of 42 and 57 towards mesylation. As for the reason of the apparent high stability

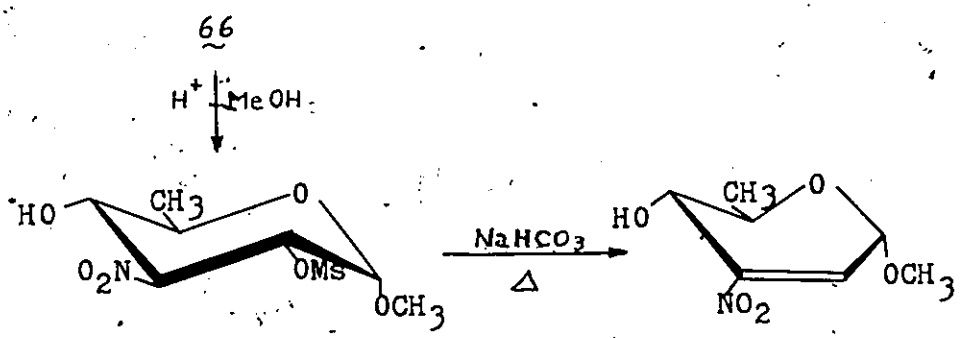


66 67

of this mesylate, one could perhaps speculate that in the benzylidene compounds 42 and 57, because of the presence of the rigid, trans-fused acetal ring the pyranoside ring is

already somewhat distorted in the direction of the half-chair, which would lower the energy barrier of its going over completely into the half-chair conformation of the olefin. This favorable factor would be absent in 66.

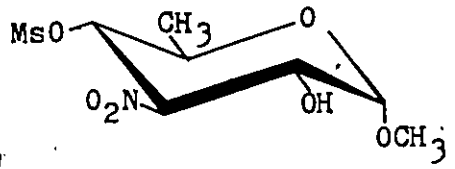
Acid catalyzed methanolysis of the 2-mesylate 66 led almost quantitatively to methyl 3,6-dideoxy-2-O-methylsulfonyl-3-nitro-α-D-glucopyranoside (68) which was then converted in 92% yield into the olefin, methyl 2,3,6-trideoxy-3-nitro-α-D-erythro-hex-2-enopyranoside (69), by means of sodium bicarbonate in refluxing benzene (3h).



68 69

In contrast to partial acetylation by acetyl chloride and triethylamine in ether of the L-enantiomer of glycoside 62[25], which had led to the 2-acetate 25, partial mesylation by mesyl chloride and triethylamine in dichloromethane occurred exclusively in position 4, giving the stable

4-mesylate 70. When excess mesyl chloride and triethylamine was used, the 2,4-dimesylate 71 was obtained in 75%



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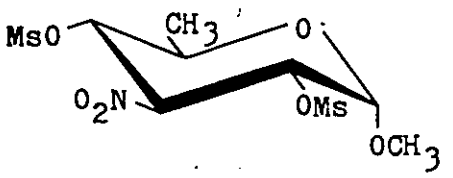
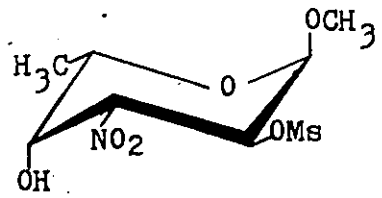


71

yield. No significant elimination was observed here either.

Because of the high stability of the mesyl esters 66, 68, 70 and 71, it was interesting to study the behavior of stereoisomeric 3,6-dideoxy glycosides of the galacto and manno series.

Methyl 3,6-dideoxy-3-nitro-α-L-galactopyranoside (23)[65] was mesylated by use of excess reagent. The reaction was relatively sluggish and the expected 2,4-dimesylate was not observed, but the 2-mesylate 72 was obtained crystalline in 48% yield. The remainder of the product was a syrupy



72

mixture of what appeared to be mainly two compounds that failed to separate in column chromatography. The n.m.r. spectrum (Fig. 6) of the mixture revealed that it contained non-mesylated nitroolefins, showing signals in the olefinic proton region (δ 7.0-7.3) but not in the mesyl group region (δ 3.0); OCH_3 and $C\text{-}CH_3$ signals occurred in their proper places. Evidently the galactoside 23, unlike the glucoside 62, underwent dehydration* to a considerable extent during

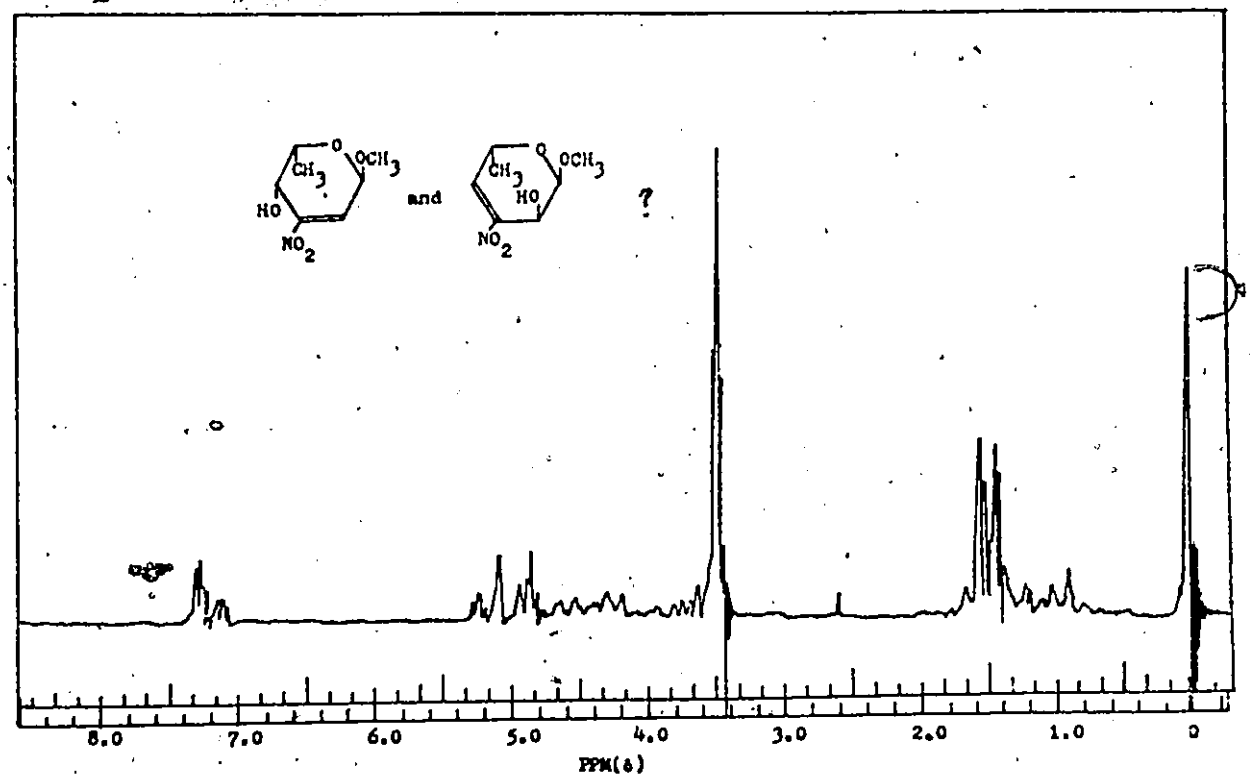
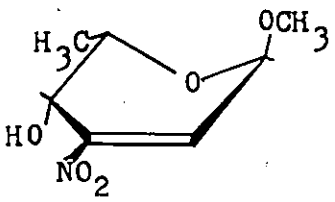


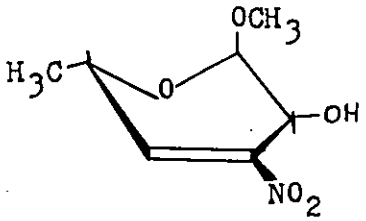
Fig. 6

* An enhanced tendency for dehydration in the 3-deoxy-3-nitro galactopyranose system, to give 2,3-unsaturation, has been noted and commented upon previously[45].

the process of mesylation, which might suggest a lesser stability of its sulfonic esters. It was therefore very surprising to note that the isolated monomesylate 72 was quite resistant to elimination as it remained unchanged for 6 h in refluxing benzene or toluene in the presence of sodium bicarbonate. One is thus led to conclude that 72 was not an intermediate in the formation of the olefins. Although the structures of the latter have not been established, formulae 73 and 74 suggest themselves at first glance and if they are correct it may be assumed that



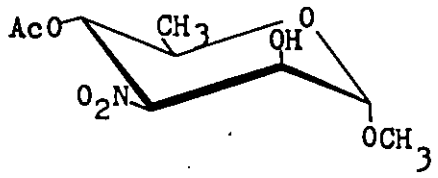
73



74

74 arose by an elimination facilitated by the axiality of the C-4 substituent, and that perhaps the isomer 73 owes its origin to an allylic rearrangement of 74 which may have occurred during chromatographic processing. Structure 73 is considered[25] to be less strained than 74 because of an unfavorable $A^{(1,2)}$ effect in the latter (see the discussion on p. 54), and this might provide the driving force for rearrangement of part of the material.

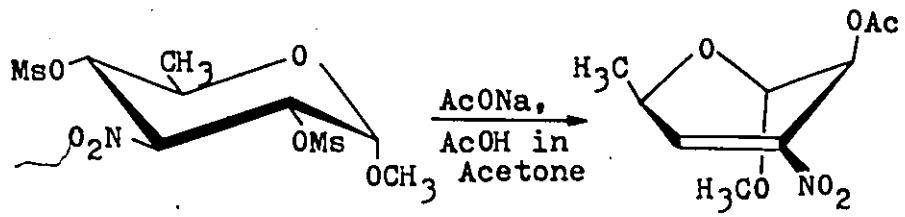
Support for the idea of preferential axial elimination came from the behavior of methyl 4-O-acetyl-3,6-dideoxy-3-nitro-α-D-mannopyranoside 75 in mesylation.



75

In strong contrast to its α-D-gluco isomer (65), the mannoside 75 (whose free hydroxyl group is axial) was smoothly converted into the nitroolefin 67 in a yield of 65% and no intermediary mesylate could be isolated.

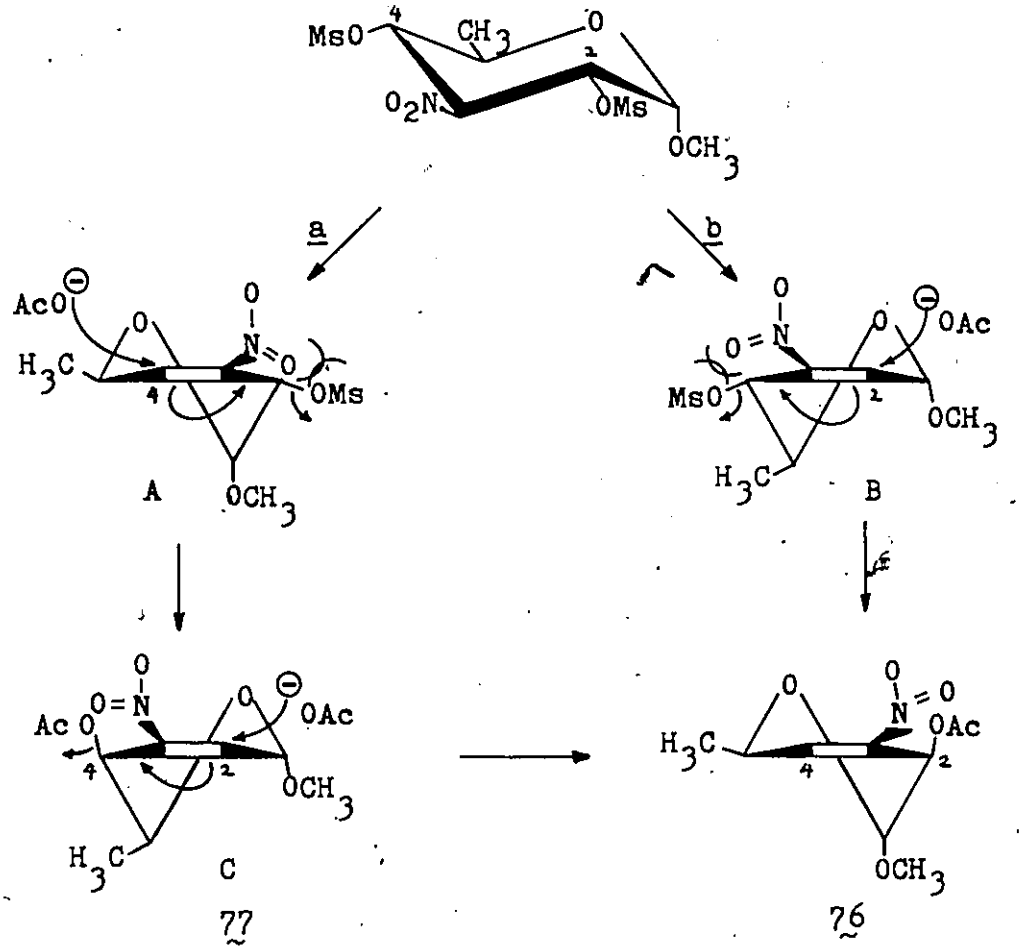
Let us now return to the gluco series. Although the aforementioned experiments in that series furnished isolable mono- and dimesyl esters and no olefination occurred during mesylation, elimination of the mesyl functions from the products is, nevertheless, possible. One example, the reaction 68 → 69, has already been described (p.48). Further, it was found that the dimesylate 71 loses both sulfonic ester functions very readily when it is treated for 10 min with acetic acid / sodium acetate in refluxing acetone. The product isolated in 75% yield proved to be methyl 2-O-acetyl-3,4,6-trideoxy-3-nitro-α-D-threo-hex-3-enopyranoside (76).



71 76

That is to say, the 4-mesyloxy group was eliminated, and the 2-mesyloxy group was replaced by an acetoxy group with inversion of configuration. A nucleophilic displacement would be most unlikely to account for the latter phenomenon. Secondary sulfonic ester groups on sugar rings are difficult to displace by S_N2 type reactions, and especially so at C-2[66]. Displacement normally requires an aprotic solvent of high dielectric constant (e.g. DMF, HMPT) and long reaction times at high temperatures. The facile conversion 71 → 76 is thought to have occurred, rather, by a sequence of eliminations and additions as shown in Scheme V. An analogous mechanism has been proposed[67] for a less facile and relatively low-yielding reaction of the corresponding L-gluco 2,4-diacetate with

sodium bicarbonate, which had given[25] the L-enantiomer of 76. Two paths could lead to 76, involving a primary elimination of the 4-mesyloxy group (a) or of the 2-mesyloxy

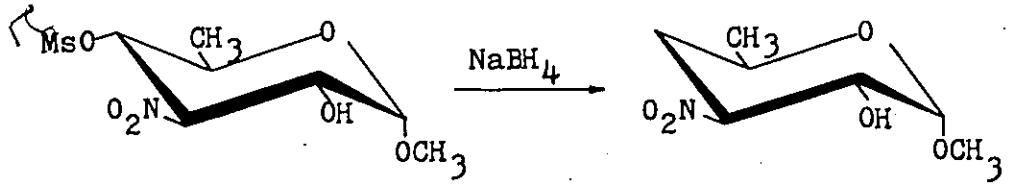


(Scheme V)

group (b). Both primary products A and B would suffer from $A^{(1,2)}$ strain and be prone to react further. Nucleophilic addition of acetate ion with concomitant elimination

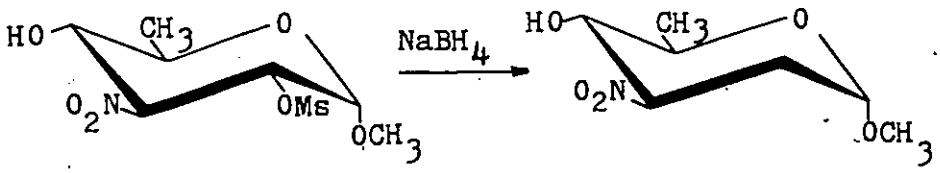
of the second mesylate group would lead, from B, directly to the observed product 76 whereas, from A, it would give an intermediate C which is also free from $A^{(1,2)}$ strain. However, C may be expected to rearrange to 76 since the electron-withdrawing effect of the anomeric center would tend to make the nitroolefinic C-2 more susceptible to nucleophilic attack (relative to C-4 in 76). The rearrangement could proceed by an intermolecular addition-elimination as depicted, or alternatively, perhaps by an intramolecular acetoxyl migration through a six-membered cyclic transition state.

The finding that nitro sugar mesylates can undergo facile elimination by the action of base to furnish nitroolefins, together with the known possibility of selectively reducing the olefinic double bond of the latter with sodium borohydride[68], made it conceivable that this reaction sequence from a mesyloxy to a deoxy function can be carried out in one operation. Indeed, treatment of the 4-mesylate 70 with sodium borohydride in ethanol at room temperature led directly to the corresponding 4-deoxy derivative 78,



70 78

methyl 3,4,6-trideoxy-α-D-xylo-hexopyranoside, isolated crystalline in 60% yield. The L-enantiomer of this glycoside has been previously described[25] and used in a stereospecific synthesis of L-desosamine[69], the enantiomer of an amino sugar constituent of several antibiotics. The present procedure therefore provides a convenient entry for a new synthetic route to natural D-desosamine*. In similar fashion, 2-mesylate 68 upon treatment with sodium borohydride gave in 75% yield a product of reductive elimination. Although the product was not crystalline and some doubt existed as to its homogeneity (see the next section), it must have consisted largely of the 2-deoxy glycoside 79. This could



68 79

be concluded on the basis of its conversion, in good yield, into a known compound as outlined in part III.

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* A low-yield stereospecific synthesis of the natural product was achieved by Richardson[70] starting from methyl 3-amino-3-deoxy-D-glucopyranoside.

In addition to its utility in the synthesis of unsaturated and deoxy sugars as demonstrated in this part, the mesylation of nitro sugars may conceivably become useful in the future for further preparative purposes. For example, it might be worthwhile to investigate whether conditions can be developed to reduce nitro sugar mesylates to the amine stage without disturbing the ester function, a proposition which would seem to offer some challenge since sulfonic esters may be cleaved by certain reductants. Should selective reduction prove feasible, then a new avenue could be opened to epimines, by subsequent intramolecular displacement of a suitably disposed mesyloxy group by the amino group engendered. Carbohydrate epimines are valuable intermediates for numerous synthetic purposes[71-73].

Proof of Structures and Configurations

All reactions involved in the synthesis of 54, 56, 66, 68, 70, 71 and 72, namely O-mesylations, can safely be assumed to cause no configurational changes, and hence the original configuration of the respective starting materials should apply to these products.

Compound 54 was shown to be the product of monomesylation by the presence of absorption bands at 3200-3600 (OH) and 1165 cm^{-1} (OMs). The n.m.r. spectrum (Fig. 7) exhibited a sharp 3-proton singlet at δ 2.98 (OMs). It also

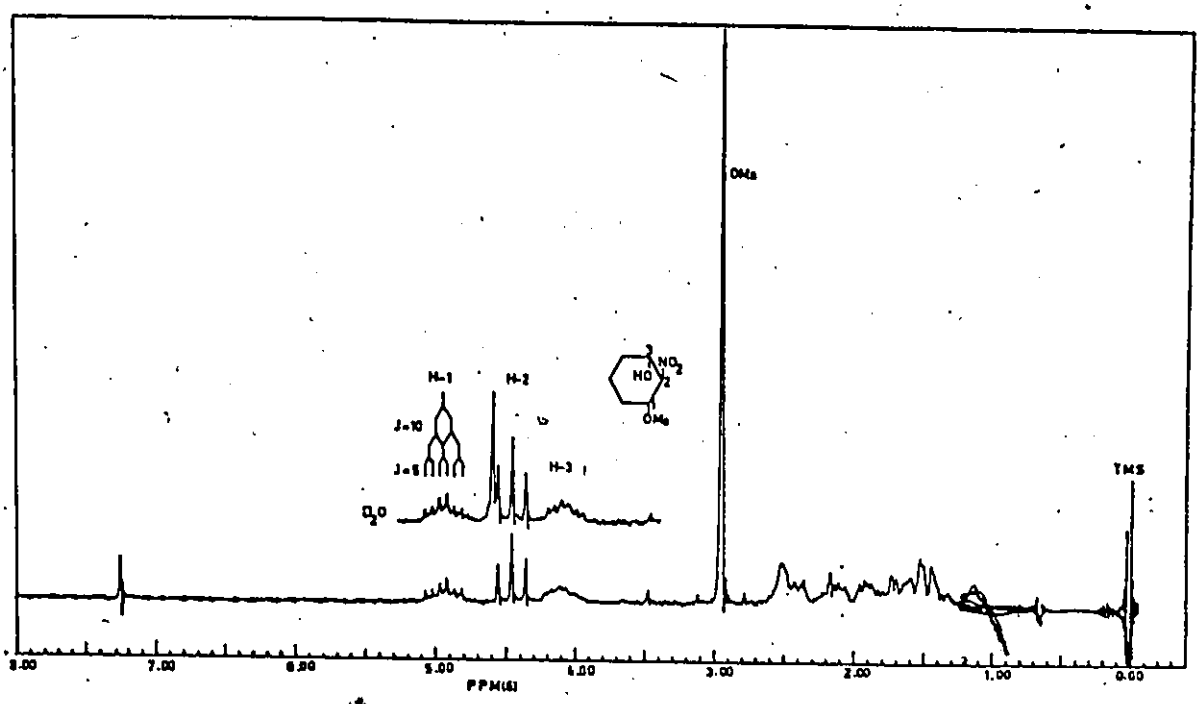


Fig. 7; n.m.r. spectrum of 54

included a resolved sextet (δ 4.95) corresponding to H-1, a triplet (δ 4.47) for H-2, and a multiplet (δ 4.10) due to H-3. That all three substituent groups (OH, NO_2, OMs) were equatorially oriented was suggested by the large coupling constant (J 10 Hz) of the H-2 signal.

The glycoside 56 was confirmed to be the mesylation product of 42 by the disappearance of the hydroxyl absorption in the i.r. spectrum and the development of a sharp singlet at δ 3.03 (OMs) in its n.m.r. spectrum (Fig. 8). Similarly, in addition to an acetoxy methyl signal at δ 2.10, a sharp singlet at δ 3.01 (OMs) was observed in the n.m.r. spectrum of compound 66 (Fig. 9) whose i.r. spectrum was

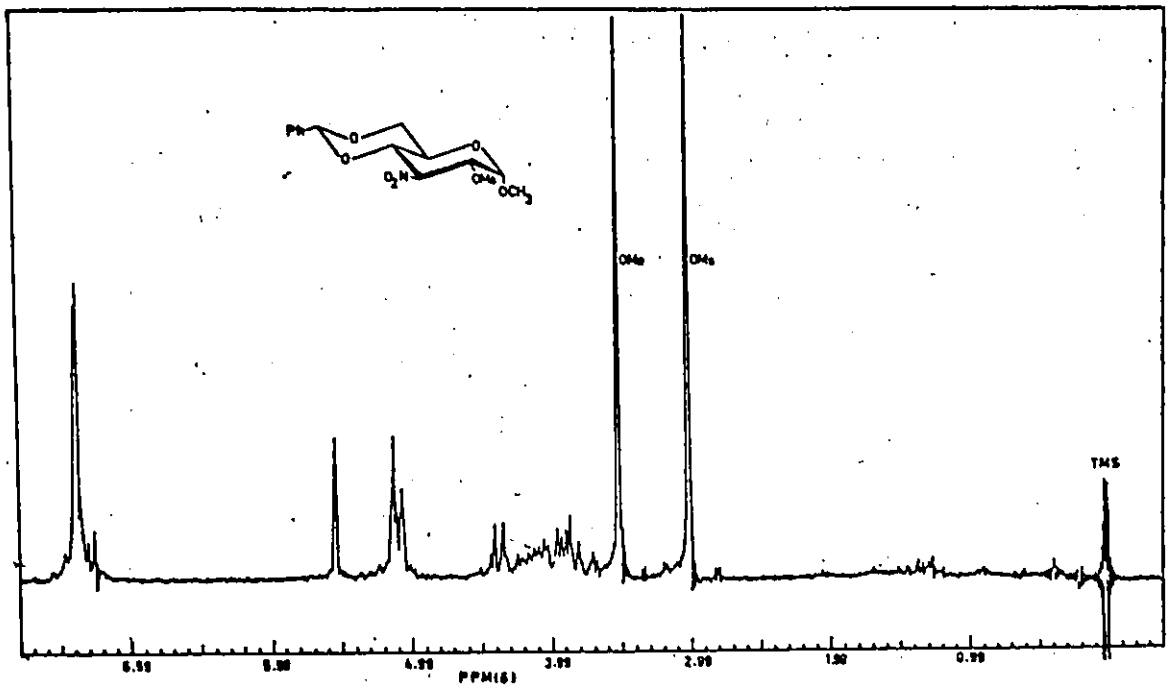


Fig. 8; n.m.r. spectrum of 56

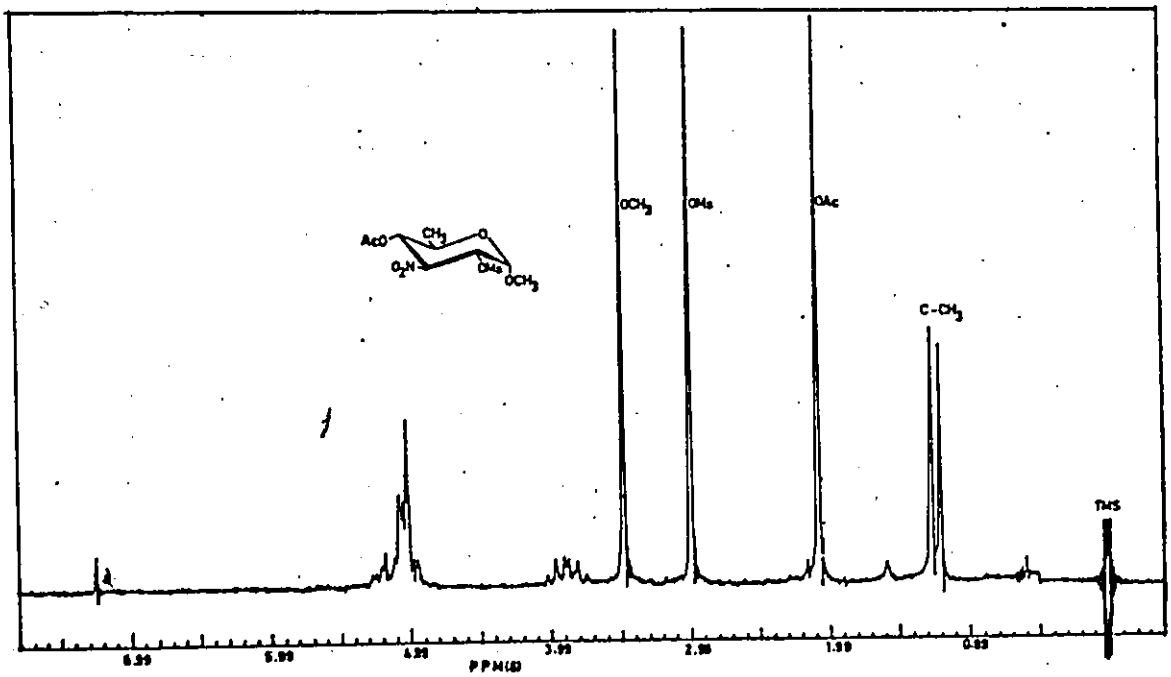


Fig. 9; n.m.r. spectrum of 66

free of any hydroxyl absorption. The i.r. spectrum also showed bands attributable to an acetate ester and a mesyl group at 1740 and 1175 cm^{-1}, respectively. Derived from this is compound 68 whose i.r. spectrum contained absorption bands at 3500 and 1170 cm^{-1}, clearly indicating the presence of a hydroxyl and a mesyl group, and no ester carbonyl band was seen. The n.m.r. spectrum (Fig. 10) was also in support of this by showing a signal at δ 3.03 due

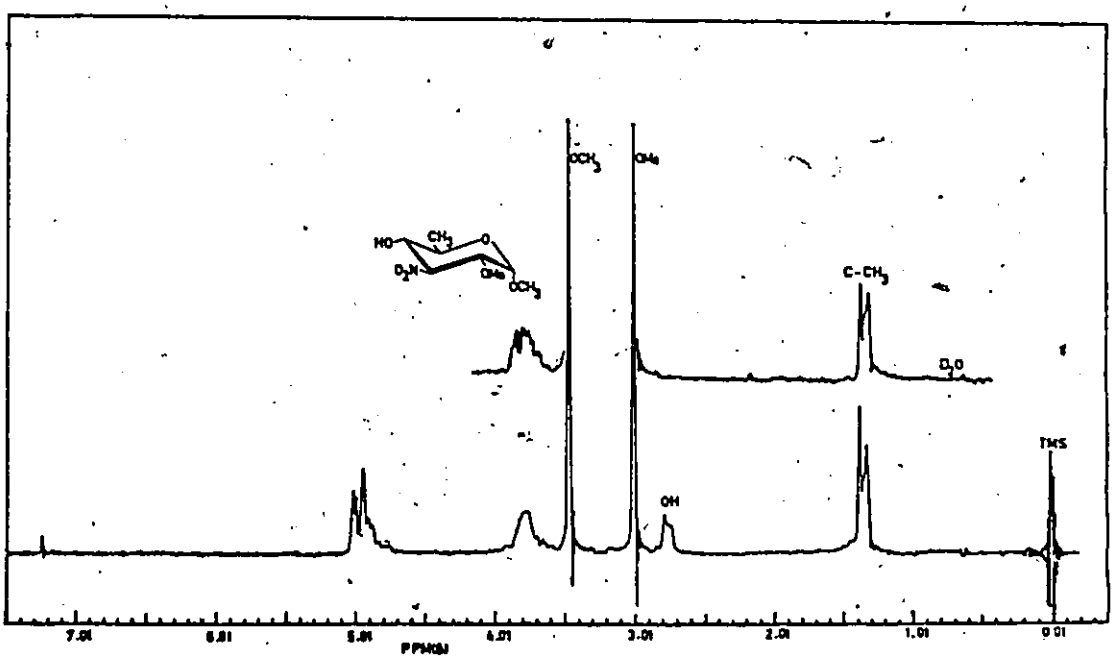


Fig. 10; the n.m.r. of compound 68

to a mesyl group while lacking an acetoxy methyl signal.

The 4-mesylate 70 exhibited an n.m.r. splitting pattern (see Fig. 11) similar to that of its positional

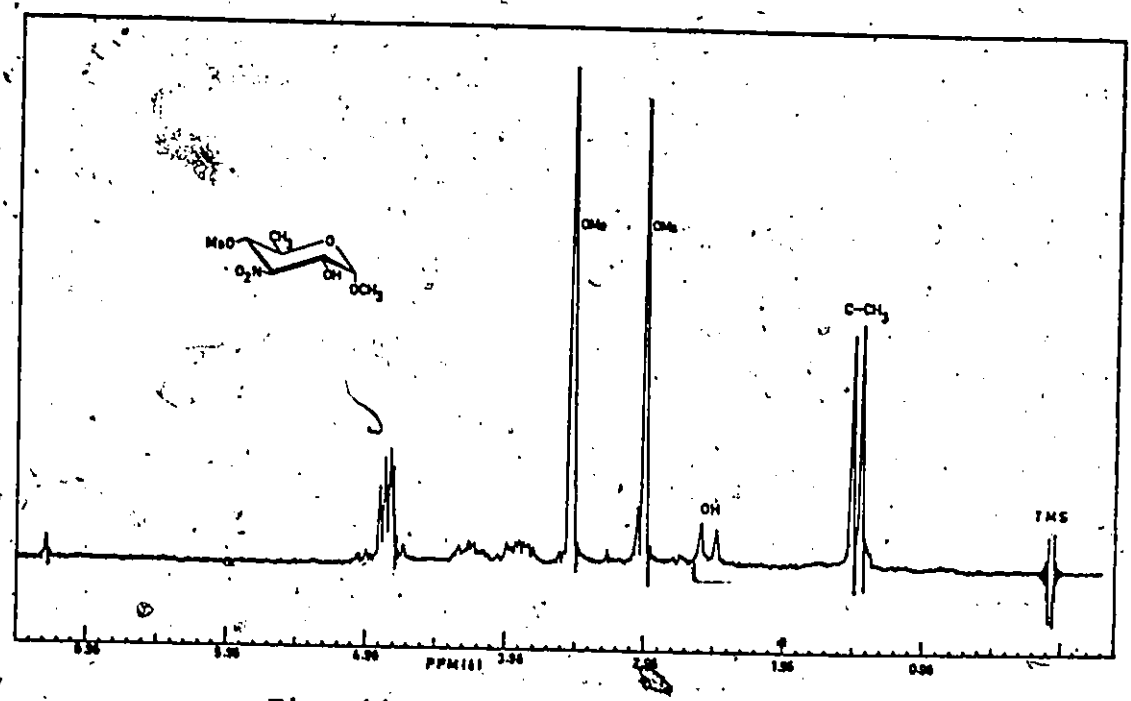


Fig. 11; n.m.r. spectrum of 70

isomer 68 and was distinguished from it by the appearance of a multiplet with large (11 Hz) and small (~6 Hz) splittings at δ 4.2 corresponding to one proton (H-2). This assignment was further supported by the splitting pattern (doublet) and the coupling constant (11 Hz) of the C-2 hydroxyl group at δ 2.48. Its i.r. spectrum showed bands at 3295 (OH) and 1170 cm^{-1} (OMs).

The dimesylate 71 showed an i.r. band positioned at 1170 cm^{-1} due to the OMs groups, and there was no hydroxyl absorption. The n.m.r. spectrum (Fig. 12) exhibited two sharp 3-proton singlets at δ 3.01 and 3.03, confirming the

presence of two mesyl groups.

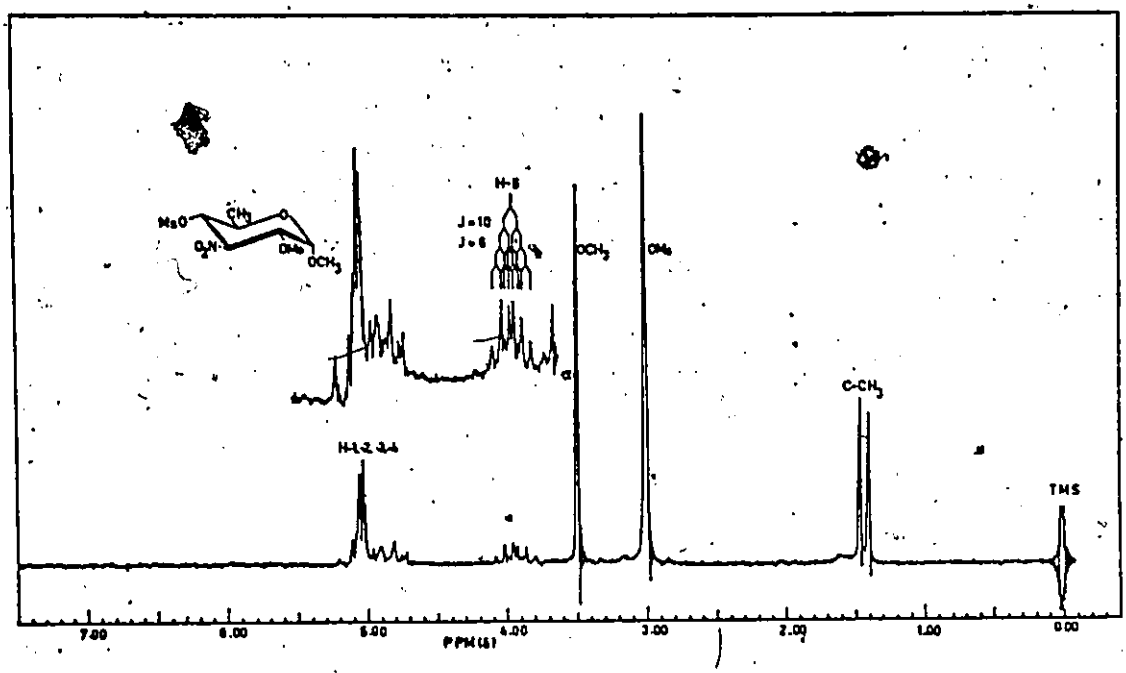


Fig. 12; n.m.r. spectrum of 71

In the n.m.r. spectrum of 72 (Fig. 13), the appearance of a one-proton quartet with a coupling constant of 3 Hz. ($J_{3,4}$) at δ 4.92 attributable to H-3 indicated equatorial orientation of H-4 (i.e. axial OH at C-4). Another quartet was seen at lower field (δ 5.30) and was assigned to H-2; it had coupling constants $J_{1,2}$ = 3.7 and $J_{2,3}$ = 11 Hz. The spectrum also showed a mesyl signal located at δ 3.14. The i.r. spectrum of this substance indicated the appearance of a hydroxyl group which absorbed at 3570 cm^{-1}. The mesyl

group stretch frequency appeared at 1160-1170 cm^{-1}.

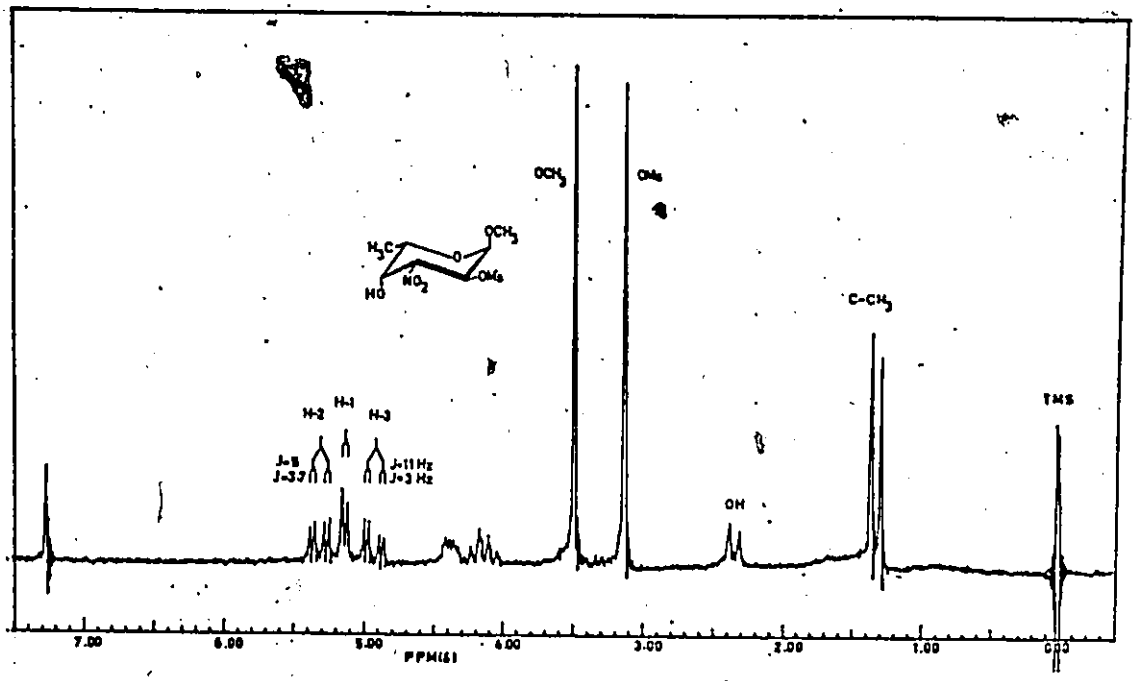


Fig. 13; n.m.r. spectrum of 72

Compound 79, which was obtained by sodium borohydride reduction of either 68 or 69 was a non-crystallizable syrup despite chromatographic purification. Unfortunately it did not give wholly correct microanalytical data, and it displayed some features in its n.m.r. spectrum (see Fig 14) which may cast doubt on its homogeniety. The spectrum, run either in chloroform-d or pyridine, showed the substituent resonances expected of 79, namely, a 3-proton doublet at δ 1.14 for $C-CH_3$ and a 3-proton singlet at δ 3.41 for $O-CH_3$,

with a 2-proton multiplet assignable to the C-2 methylene group at δ 2.33. The remaining ring protons, however, gave partially overlapping signals that could not be analyzed satisfactorily. It is possible that the spectra were affected by remnants of boric acid, or that other foreign matter was present, or that the compound displays a conformational behavior not yet understood. In the latter connection it is interesting to note that the specific rotation was positive ($+23^{\circ}$) in water but negative (-34.5°) in chloroform solution. The i.r. spectrum of this material showed a broad OH absorption band at 3200 cm^{-1}.

All the foregoing i.r. spectra contained absorption bands in the range 1550-1560 cm^{-1} corresponding to nitro groups.

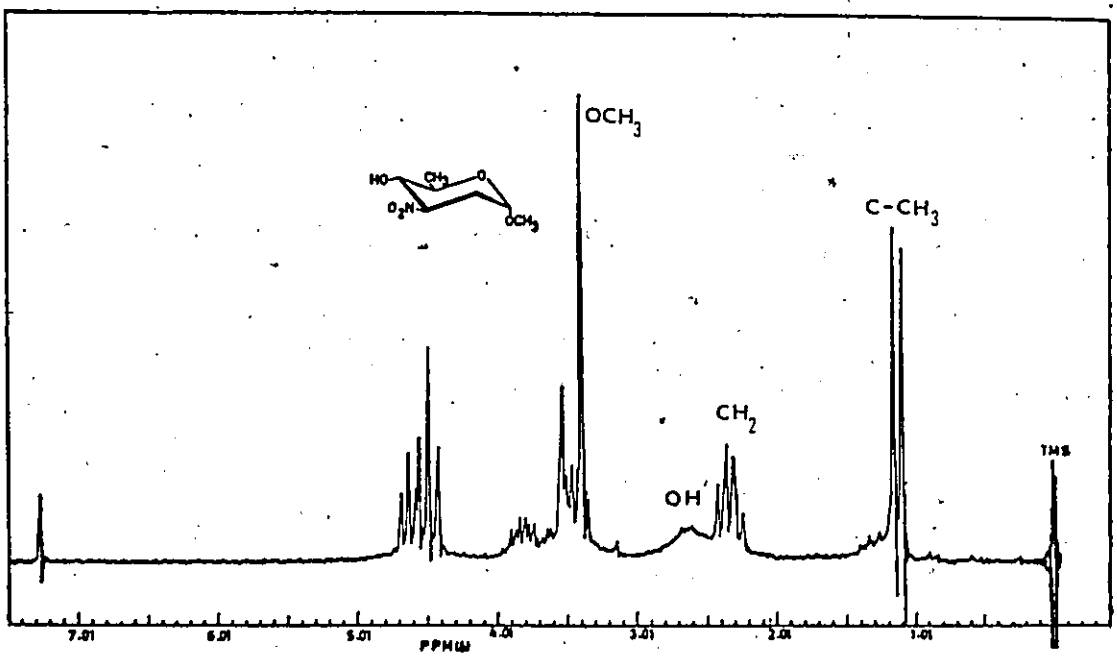
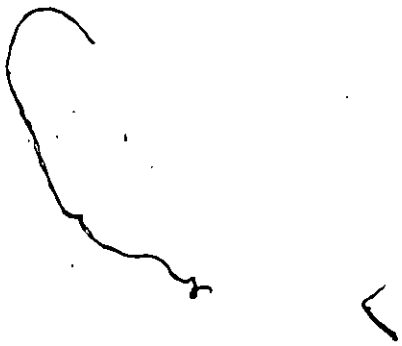


Fig. 14; n.m.r. spectrum of 79

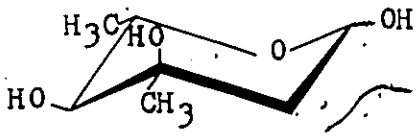
PART III

The Synthesis of D-Angolosamine



RESULTS AND DISCUSSION

The macrolide antibiotic angolamycin, isolated by Swiss workers[6], was shown[74] to contain two neutral sugar moieties (L-mycarose 80 and D-mycinose 81) together with



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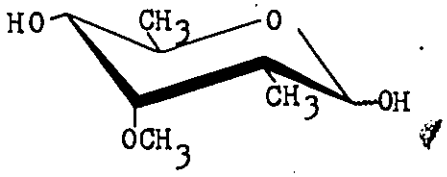


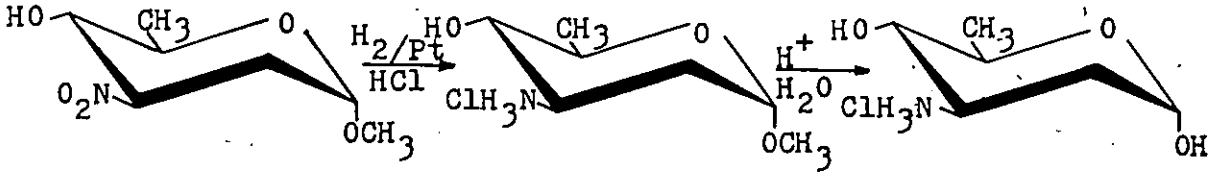
81

a previously unknown amino sugar component (angolosamine) which proved to be 2,3,6-trideoxy-3-dimethylamino-D-arabino-hexose (20). A structure for the complete antibiotic was proposed[7] in 1972, at which time it was also found that angolamycin and a similar product, shincomycin A[5], appear in fact identical according to mass spectral analysis.

A synthesis of the amino sugar angolosamine has not yet been reported, and such a synthesis has now been performed and will be discussed in the following paragraphs.

In part II of this discussion, the synthesis of several new deoxy nitro sugar derivatives has been described. The present part embodies a further exploration of the utility of such nitro sugars as potential intermediates for the synthesis of amino sugars that may command interest in the chemistry of antibiotics.

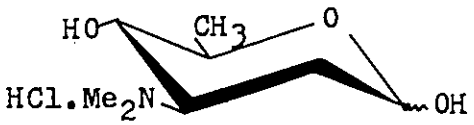
The nitro sugar 79, methyl 2,3,6-trideoxy-3-nitro-α-D-arabino-hexopyranoside, which is now readily available (although in impure form), served as the starting material. The next preparative operation performed with the product confirmed that 79 must have been its chief component. Hydrogenation with Adams catalyst in methanol in the presence of 1 equivalent of hydrogen chloride gave a 68% yield of crystalline methyl 3-amino-2,3,6-trideoxy-α-D-arabino-hexopyranoside hydrochloride (82) which agreed well in its melting point and $[\alpha]_D$-value (with opposite sign) with the known[75] synthetic L-enantiomer. Acid hydrolysis of 82 afforded crystalline, downward mutarotating 3-amino-2,3,6-trideoxy-α-D-arabino-hexopyranose hydrochloride (83). This compound



79 82 83

had previously been synthesized by a different approach and characterized also as its N-acetyl derivative[43]; some glycosidic derivatives had been prepared as well[43,76]. More recently, the L-enantiomer of 83 was discovered[77] to occur in nature as a constituent of an antibiotic, actinoidin. It has been named acosamine and synthesized[78] along with several glycosidic derivatives[75,78]. Synthetically modified analogs of daunorubicin and adriamycin containing L-acosamine in place of daunosamine (the L-lyxo isomer 15a) were reported[21] to show interesting biological properties (see introduction, p.15).

N,N-Dimethylation of 82 by the Eschweiler-Clarke procedure[79] and hydrolysis of the product gave 2,3,6-trideoxy-3-dimethylamino-D-arabino-hexose that was isolated as a crystalline hydrochloride (84). It proved identical with D-angolosamine hydrochloride from angolamycin according



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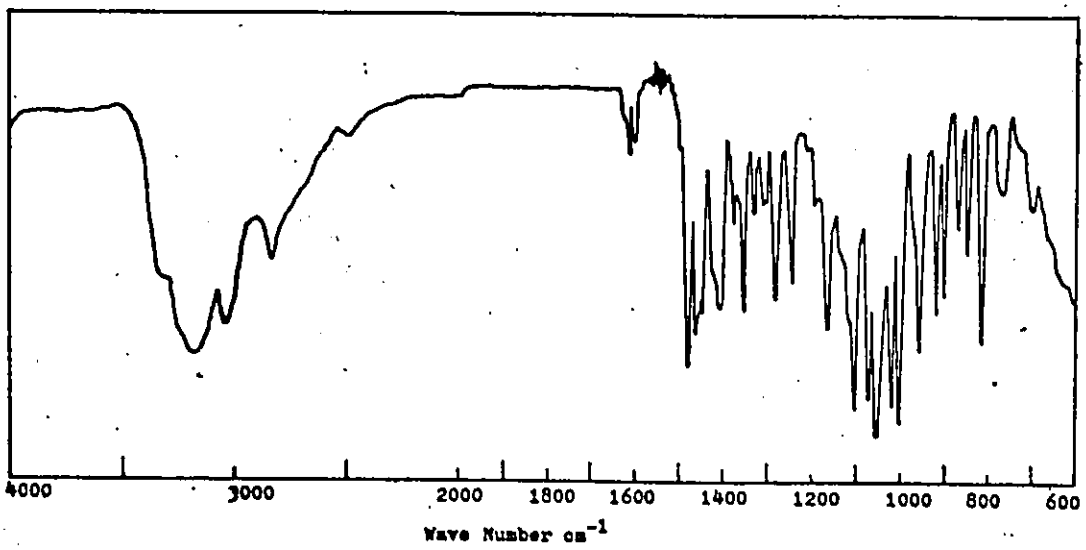
to melting point, optical rotation, and infrared spectrum (Fig. 15)



(Infrared Spectrum of Synthetic D-Angolosamine)

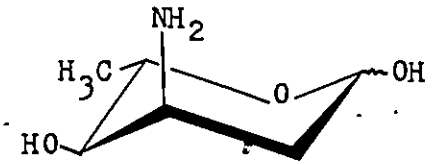
Fig. 15

PART IV

A Stereospecific Synthesis of D-Ristosamine

RESULTS AND DISCUSSION

Ristosamine (85), a stereoisomer of daunosamine (15a) has been found to exist as a constituent of the antibiotic ristomycin, elaborated by Proactinomyces fructiferi var. ristomycin[80], which exhibits a wide antibacterial spectrum[81] and can be classified among the vancomycin-type antibiotics[82]. Assignment of structure as 3-amino-2,3,6-trideoxy-L-ribo-hexopyranose (85) was based on chemical degradation, n.m.r.



85

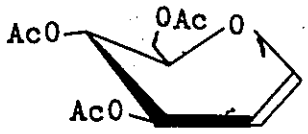
and mass spectral studies[83], and synthesis[32,84].

A stereospecific synthesis of the previously unknown D-enantiomer* of ristosamine has now been completed as follows.

Methyl 3,4,6-tri-O-acetyl-2-deoxy-β-D-arabino-hexopyranoside (88) was prepared from commercial 3,4,6-tri-O-acetyl-D-glucal (86) via the 2-chloromercuri glycoside 87

* During the preparation of this Thesis, an independent synthesis using a different approach was published (92).

essentially as described in the literature[85], with a minor modification in the work-up procedure for convenience (see Experimental).



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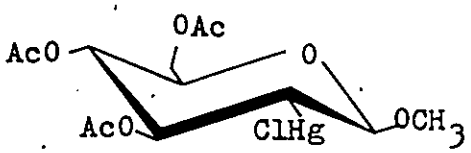

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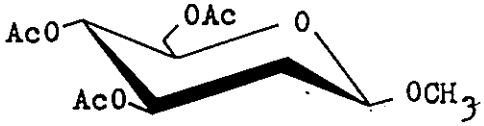
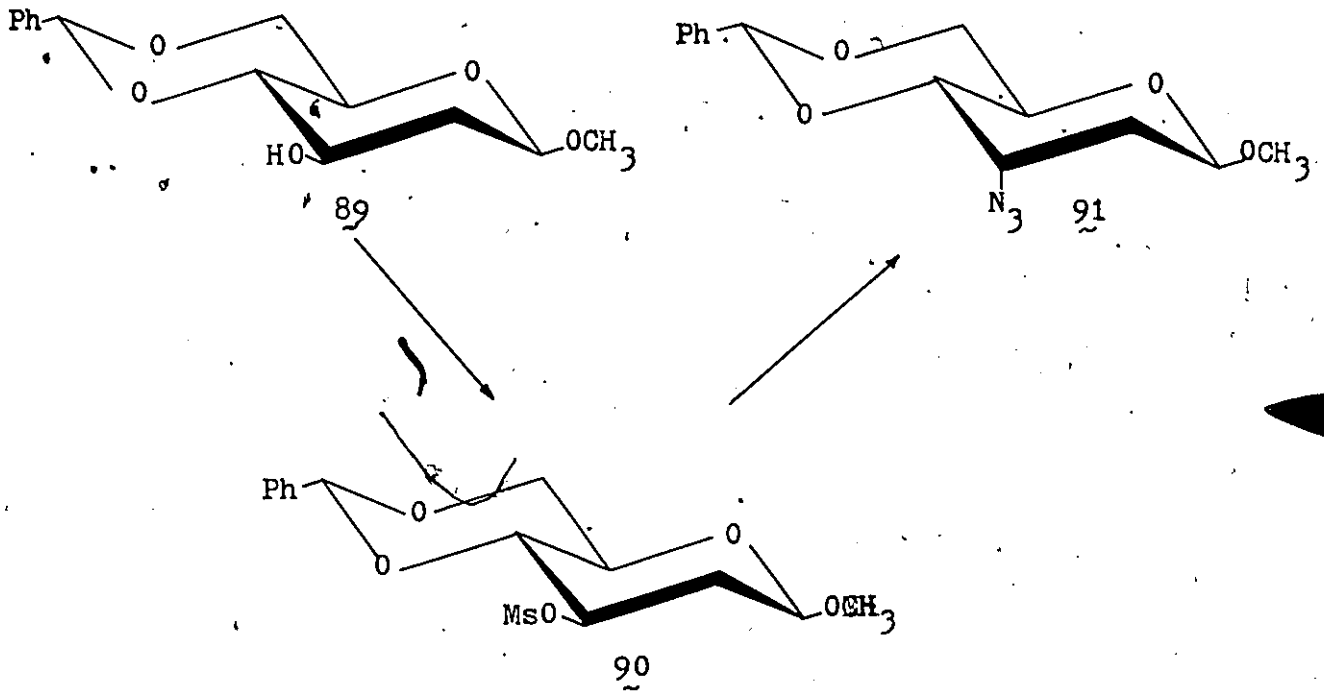


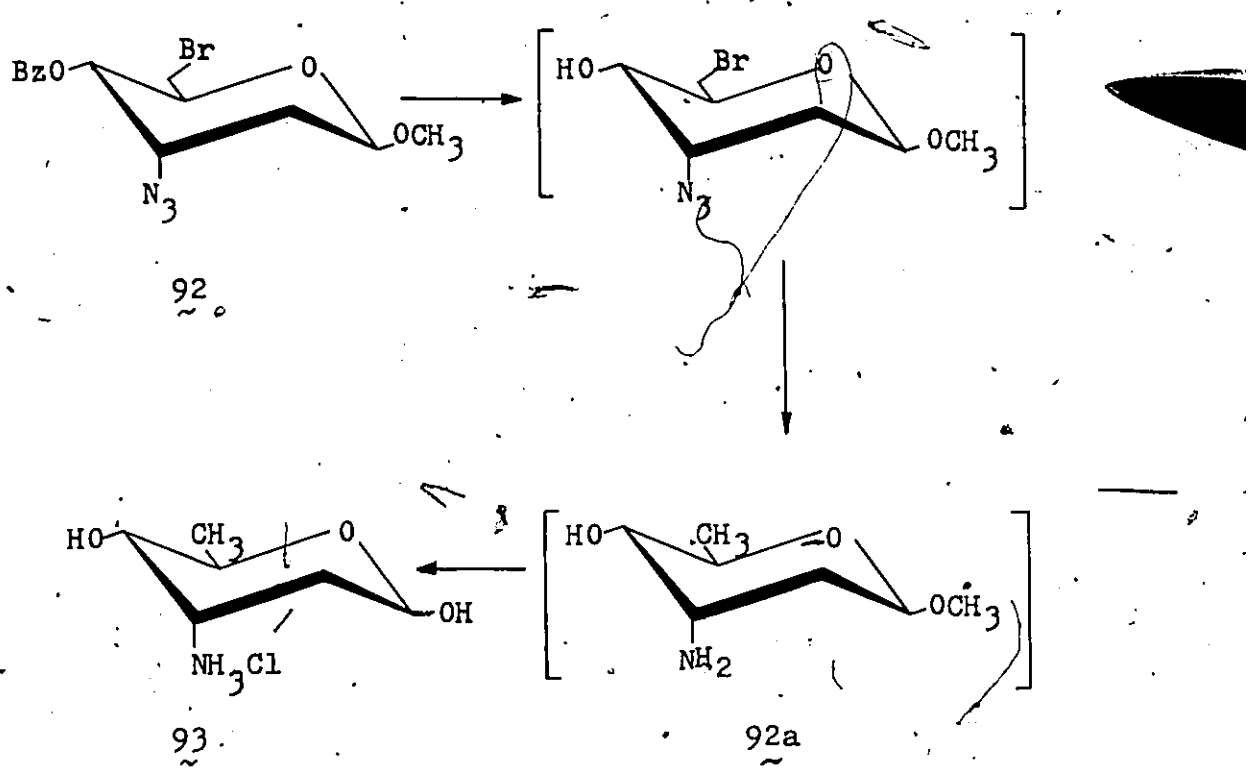
88

Compound 88 was then deacetylated with methanolic sodium methoxide and the product was immediately converted into its known[86] benzylidene acetal 89 (yield, 80%). Mesylation of this glycoside in pyridine furnished the mesylate 90 in 92% yield. The latter was subjected to a displacement reaction with excess sodium azide in DMF at



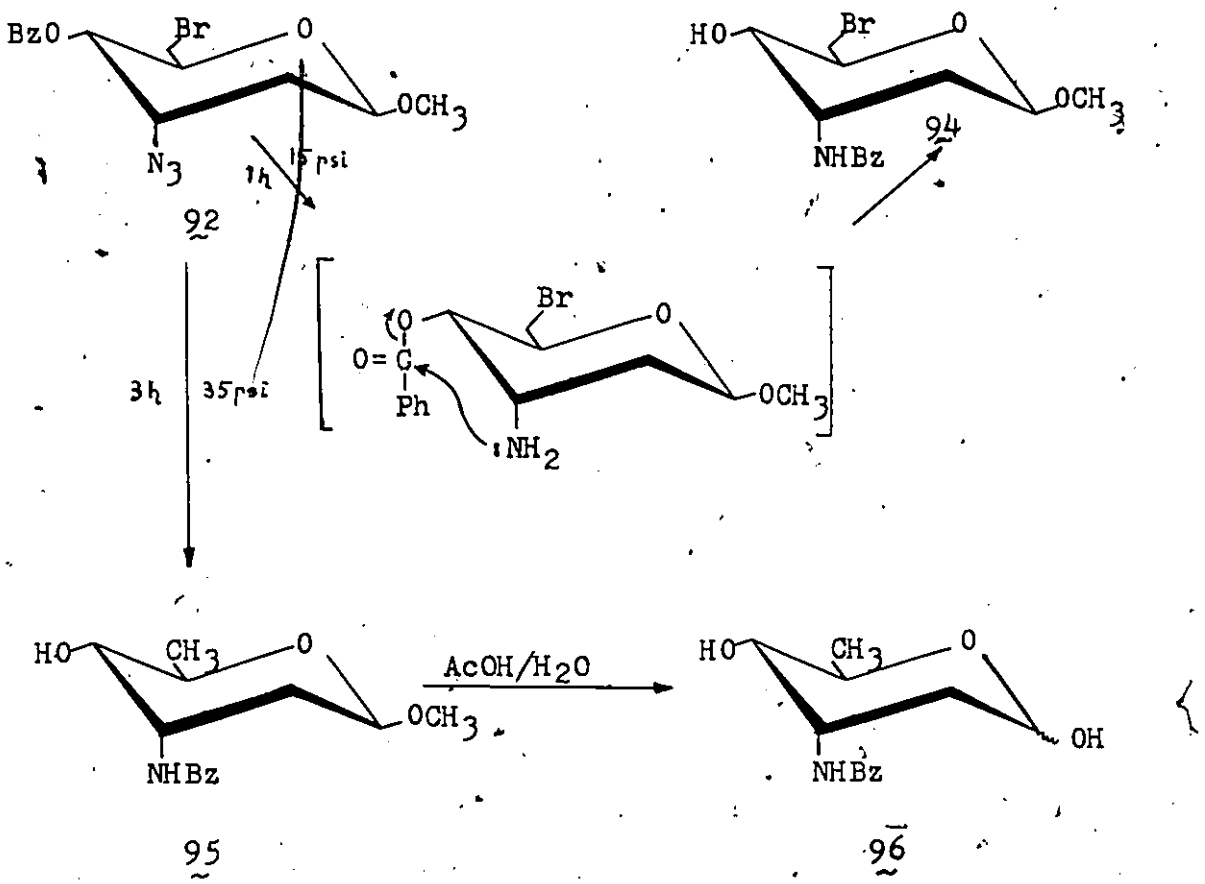
120° (17 h), which proceeded with inversion at C-3 to give methyl 3-azido-4,6-O-benzylidene-2,3-dideoxy-β-D-ribo-hexopyranoside (91) in a yield of 80%. The benzylidene acetal

ring of 91 was then opened by N-bromosuccinimide (cf. Part I) to produce methyl 3-azido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-β-D-ribo-hexopyranoside (92) in 69% yield as an analytically pure syrup. Part of this bromide was debenzoylated with sodium methoxide and hydrogenated catalytically in the presence of palladium on carbon (10%). Acid hydrolysis of the hydrogenation product gave the hydrochloride of D-ristosamine 93 which agreed well with its naturally occuring enantiomer, but with opposite sign of rotation (Scheme VI).



(Scheme VI)

Other parts of the bromide 92 were catalytically hydrogenated without prior debenzoylation (Scheme VII).



(Scheme VII)

Hydrogenation at 15 p.s.i. for 1 h caused reduction of the azido function to the amine stage but most of the bromine

remained. The product, though crystalline, could not be obtained in entirely pure form; its microanalytical carbon value was somewhat too high, which suggested that a minor proportion of 6-debrominated material was present. However, the main reaction product doubtless was the 6-bromo-3-benzamido compound 94 which originated from benzoyl migration from O-4 to the newly generated amino group. It is interesting to note that here like in the attempted hydrogenations of 6-bromo-3-nitro derivatives described in Part I, the nitrogenous function is evidently attaked by the hydrogenating agent more rapidly than the bromo function.

When the hydrogenation of 92 (with the same catalyst) was conducted at somewhat higher pressure (35 p.s.i.) and for an extended period of time (3 h), the 6-deoxy-3-benzamido derivative 95 was obtained in 75% yield. Hydrolysis of syrupy 95 with aqueous acetic acid afforded crystalline N-benzoyl-D-ristosamine in 81% yield. Its melting point and optical rotation including mutarotation compared satisfactorily with literature data recorded[32,83] for the L-enantiomer.

Proof of Structures and Configurations

The appearance of a sharp singlet at high field (δ 2.98) in the n.m.r. spectrum (Fig. 16) of 90 is indicative of a mesyl group. This was also indicated by an absorption band at 1170 cm^{-1} in its i.r. spectrum. No configurational

change should be expected in the course of the preparation of 90 from 89.

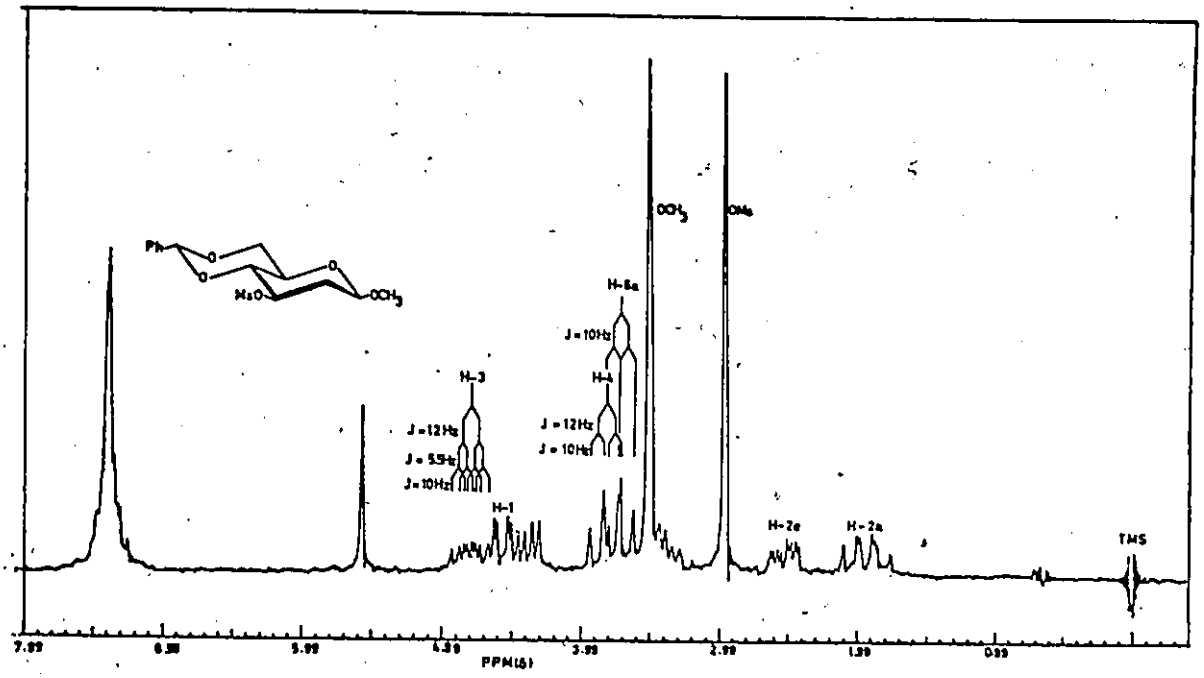


Fig. 16; n.m.r. spectrum of 90

The appearance in the n.m.r. spectrum of azide 91 (see Fig. 18), of a quartet at δ 4.35 which was most likely assignable to H-4 ($J_{4,5}$ = 9Hz and $J_{3,4}$ = 3.5 Hz) was in accord with an equatorial proton and hence axial azido group at C-3, as expected as a result of displacement of the equatorial mesylate. (Another quartet occurred at δ 4.70; it was attributable to H-1 and showed $J_{1,2a}$ = 9 and $J_{1,2e}$ = 2.5 Hz). The presence of the azido group was shown by an absorption band at 2090 cm^{-1} (Fig. 17).

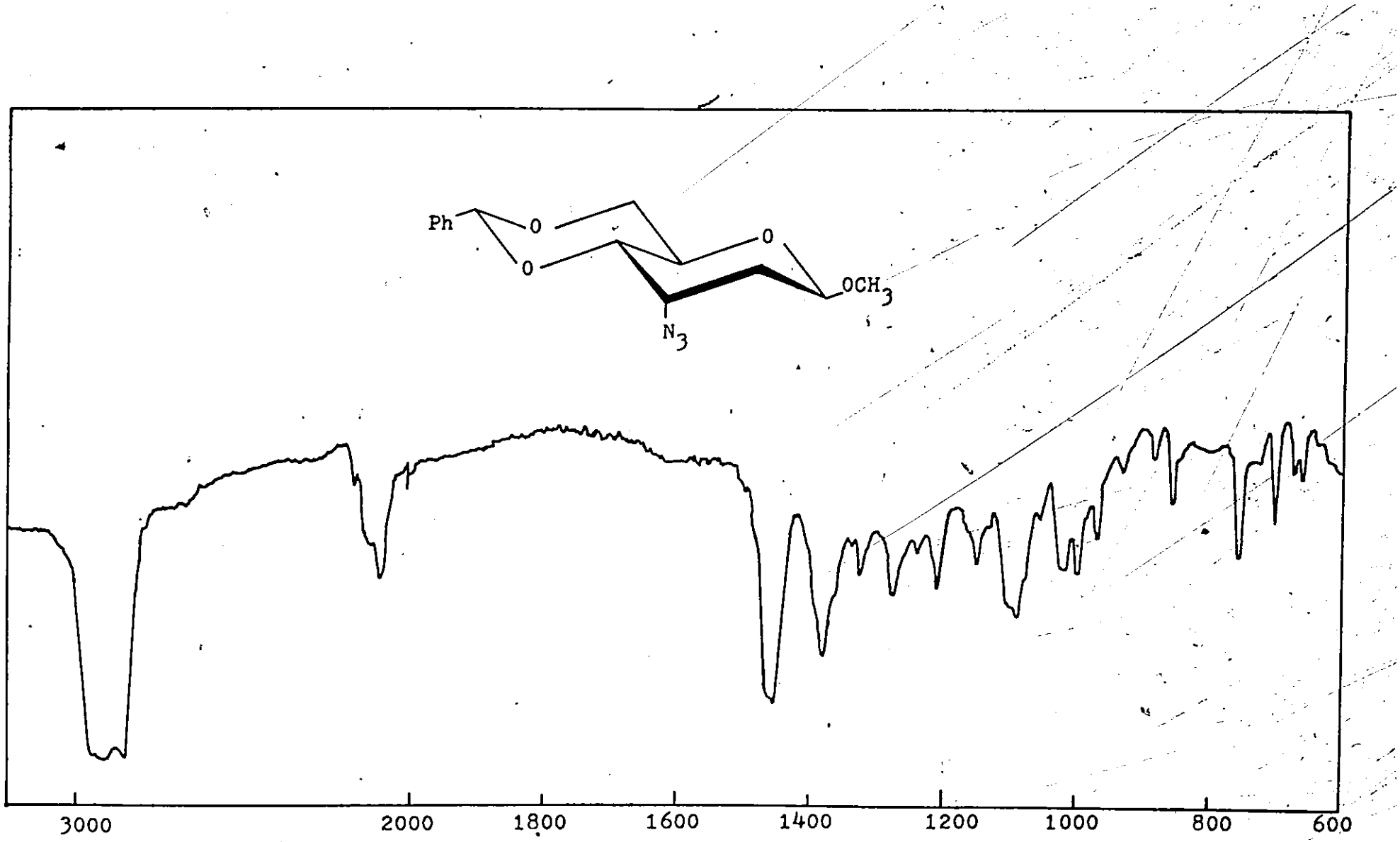


Fig. 17: infrared spectrum of the azide 91

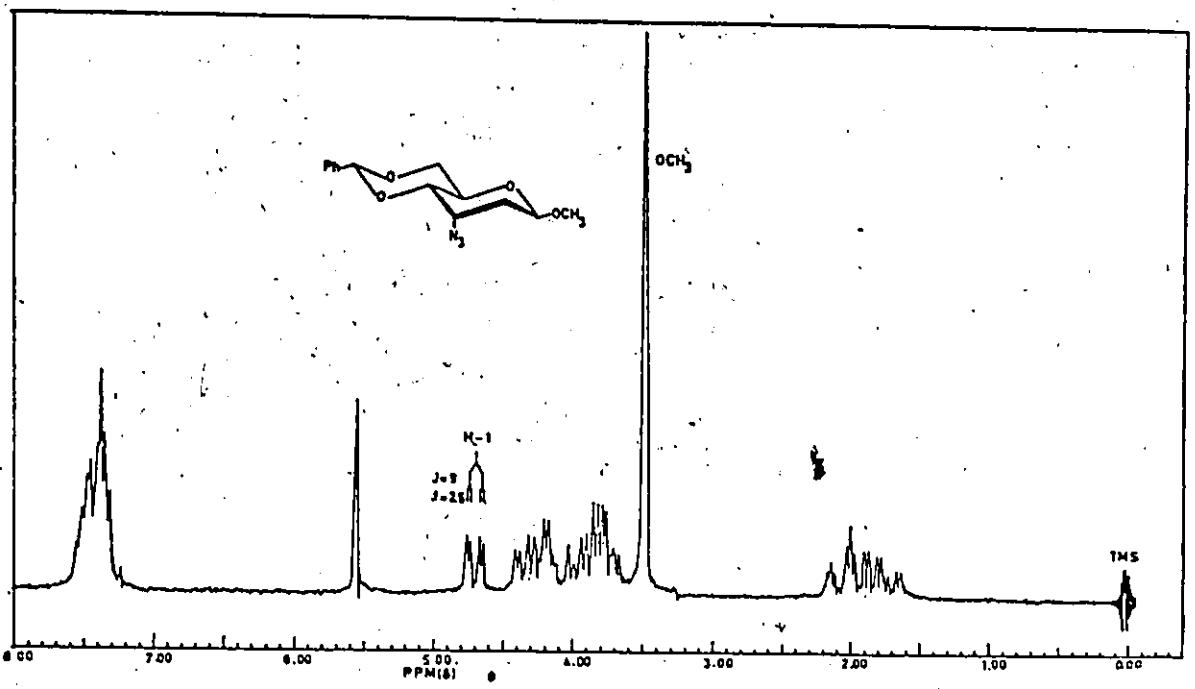


Fig. 18; n.m.r. spectrum of 91

The opening of the benzylidene acetal ring of 91 by NBS was indicated, in the n.m.r. spectrum of 92 (Fig. 19), by the absence of the benzylidene proton and the appearance, in the aromatic region, of the characteristic signals of a benzoate ester (multiplets with intesities of two and three protons centered at δ 8.07 and 7.50, respectively). This was also confirmed by an absorption band at 1715 cm^{-1} in its i.r. spectrum. The n.m.r. signal belonging to H-4 (q, $J_{4,5}$ = 8 Hz and $J_{4,3}$ = 2.5 Hz) proved the axial configuration at C-3.

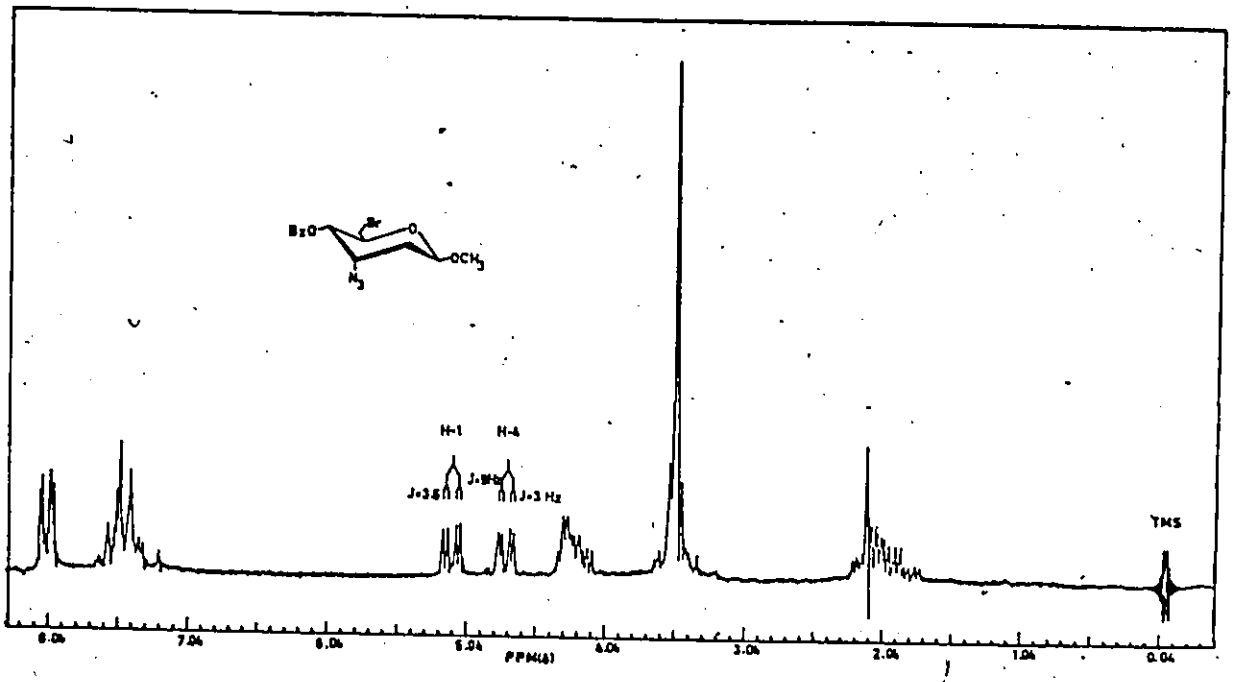


Fig. 19: n.m.r. spectrum of 92

The i.r. spectrum of 94 in chloroform solution indicated clearly the presence of a benzamido group by amide I and II bands at 1650 and 1510 cm^{-1}. The spectrum also contained broad absorption around 3400 cm^{-1} due to OH and NH vibrations. The benzoyl group was also reflected in the n.m.r. spectrum (Fig. 20) by two multiplets (2- and 3-proton intensity) at δ 7.7 and 7.5. Although the substance appeared chromatographically homogeneous it evidently contained an impurity as the microanalytical carbon value found was more than 1% higher than calculated.

Possibly some debrominated material (95) was present; minor peaks in the n.m.r. spectrum near δ 1.3-1.4 probably were due to the C-CH_3 group of this byproduct.

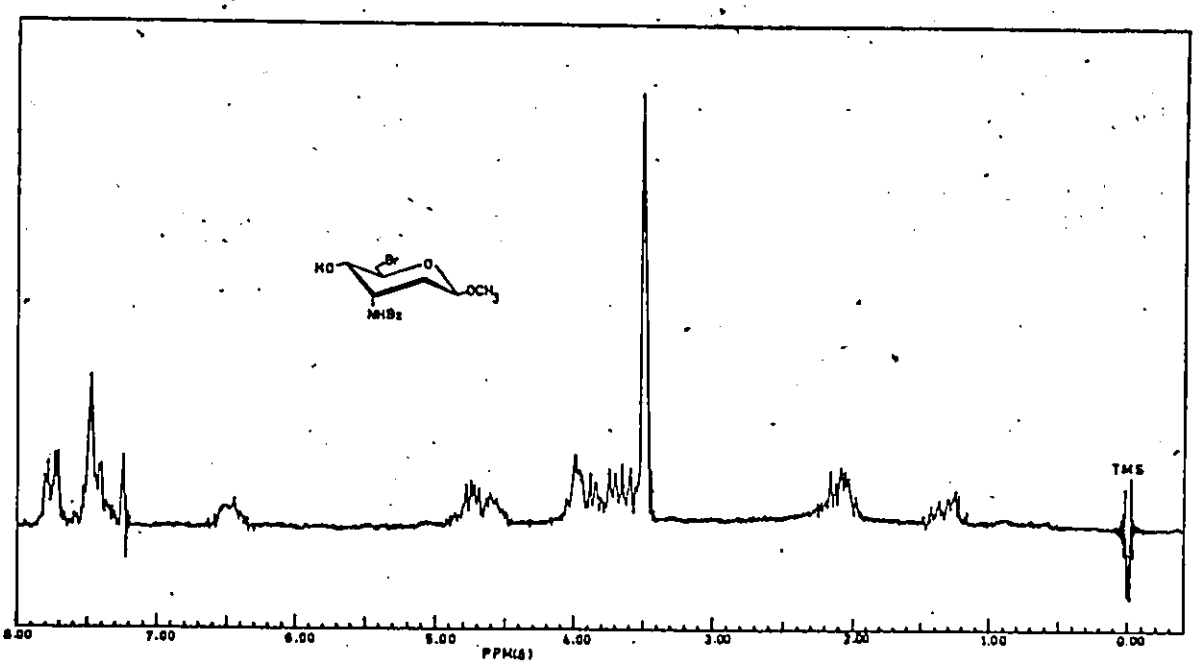


Fig. 20; n.m.r. spectrum of 94

As for the glycoside 95, the slightly impure sample showed vividly the C-CH_3 signal (d, J = 6 Hz) at δ 1.40 in its n.m.r. spectrum (Fig. 21) in addition to the O-CH_3 singlet at δ 3.46 and the characteristic benzoyl group multiplet in the aromatic region. The i.r. spectrum was similar to that of 94, showing broad OH and NH absorption in the 3400 cm^{-1} region and amide I and II bands at 1645 and 1510 cm^{-1}.

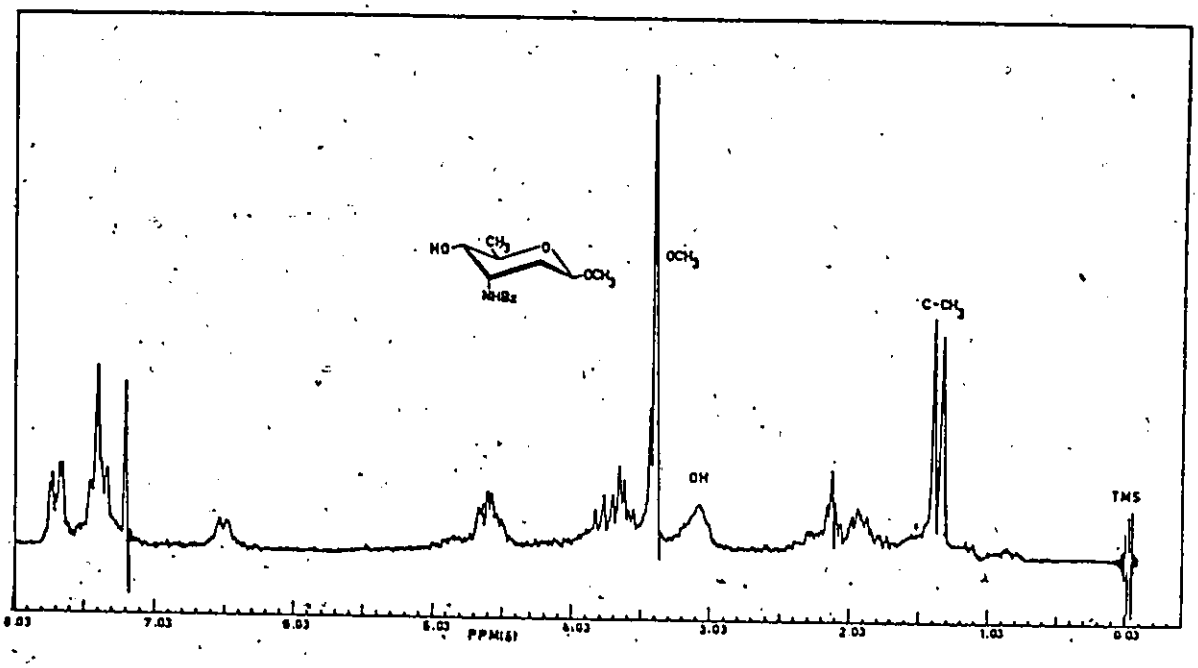


Fig. 21; n.m.r. spectrum of 95

EXPERIMENTAL

General Remarks

Melting points were measured in capillaries using a Gallenkamp Melting Point Apparatus equipped with a calibrated thermometer. The values are reported in degrees centigrade and are uncorrected.

Unless otherwise specified, infrared spectra were obtained from Nujol mulls on a Beckman IR-20 spectrophotometer.

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

Optical rotations were determined using a Perkin-Elmer automatic polarimeter, Model 141, equipped with sodium and mercury light sources. Measurements were recorded at room temperature.

All reactions were monitored by thin layer chromatography (t.l.c.) on silica gel G (E. Merck AG, Darmstadt, Germany), using 7.5-cm plates (microscope slides). The spots

were made visible by spraying the plates with a solution of 1% ceric sulfate in 10% sulfuric acid and heating on a hot plate. Preparative t.l.c. separations were carried out on 20 x 20 cm glass plates evenly coated to a depth of 0.4 mm with silica gel (same type used for t.l.c.). Development of the plates took place in a glass tank by vertical ascent of the solvent. The components were located by means of an ultraviolet lamp. The fractions were retrieved by washing them from the silica gel with ethyl acetate. Column chromatography was performed on silica gel 7734 (0.05-0.20 mm, 70-325 mesh ASTM).

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

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

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

PART I

THE REACTION OF N-BROMOSUCCINIMIDE WITH BENZYLIDENE ACETALS OF NITRO SUGARS

Methyl 2-O-Acetyl-4-O-benzoyl-6-bromo-3,6-dideoxy-3-nitro-β-D-glucopyranoside (45)

A suspension of benzylidene acetal 44[44,89] (1.00 g) and barium carbonate (0.50 g) in carbon tetrachloride (25 ml) containing N-bromosuccinimide (0.70 g) was refluxed with magnetic stirring for 2 h. The hot reaction mixture was filtered and the solid residue washed with hot carbon tetrachloride (2 x 15 ml). The combined filtrate was evaporated to dryness and the solution of the resultant syrup in ether (25 ml) was washed with water (15 ml) and dried ($CaCl_2$). Partial evaporation of the solution furnished several crops of crystalline 45. Complete evaporation of the mother liquor and treatment of the residue with ether (1 ml) and some pentane gave a yellowish oil which was decanted and triturated with additional pentane; this produced another crop of crystals. The total yield was 0.67 g (56%). Recrystallized from chloroform-petroleum ether, the product showed m.p. 181-182°, $[\alpha]_D$ -45.7° (c 0.4, chloroform), ν_{max} 1715 (CO)

and 1565 cm^{-1} (NO_2). The n.m.r. data: δ 7.95 and 7.47 (m, 2 + 3H, PhCO); 5.65 (t, 1H, $J_{3,4} = J_{4,5} = 10$ Hz, H-4); 5.48 (q, 1H, $J_{1,2} = 8$, $J_{2,3} = 10$ Hz, H-2); 4.98 (t, 1H, $J = 10$ Hz, H-3); 4.56 (d, 1H, $J_{1,2} = 8$ Hz, H-1); 3.90 (m, 1H, H-5); 3.59 (s, 3H, OMe); 3.54-3.46 (m, 2H, H-6,6'); 2.10 (s, 3H, OAc).

Anal. Calcd. for $C_{16}H_{18}BrNO_8$ (432.2): C, 44.46; H, 4.19; Br, 18.49. Found: C, 44.28; H, 4.07; Br, 18.38.

Methyl 4-O-Benzoyl-6-bromo-3,6-dideoxy-3-nitro-α-D-gluco-pyranoside (43)

The benzylidene acetal 42[87,88] (2.00 g), N-bromo-succinimide (1.50 g), and barium carbonate (1.0 g) were refluxed with magnetic stirring in carbon tetrachloride (100 ml) for 3 h. The hot solution was filtered, the inorganic residue washed with carbon tetrachloride (2 x 20 ml), and the filtrate evaporated. The syrupy product was purified by passage through a column of silica gel (50 g) with 20% ethylacetate in carbon tetrachloride and was then obtained crystalline (prisms, 1.50 g, 60%) from carbon tetrachloride at 0°; m.p. 126°, $[\alpha]_D$ +84° (c 1, chloroform); ν_{max} 3470 (OH), 1720 (CO), and 1560 cm^{-1} (NO_2). N.m.r. data: δ 7.95 and 7.45 (m, 2+3 H, PhCO); 5.56 (t, 1H, $J_{3,4} = J_{4,5} = 10$ Hz, H-4); 4.97 (t, 1H, $J_{2,3} = J_{3,4} = 10$ Hz, H-3); 4.95 (d, 1H, $J_{1,2} = 4$ Hz, H-1); 4.30 (sextet*, H-2, $J_{1,2} = 4$, $J_{2,3} = 10$, $J_{2,OH} = 11$ Hz; collapsing to q on D_2O exchange); 4.10 (septet, H-5); 3.60 (s, 3H, OMe); 3.51-1.44 (m, 2H, H-6,6'); 2.46 (d, 1H, J = 11 Hz, O-H; removed on D_2O exchange).

* Actually an octet that seemed poorly resolved because of the similarity of its two large splittings.

Anal. Calcd. for $C_{14}H_{16}BrNO_7$ (390.2): C, 43.09; H, 4.13; Br, 20.48. Found: C, 43.05; H, 4.04; Br, 20.72.

Methyl 4-O-Benzoyl-6-bromo-2,3,6-trideoxy-3-nitro-α-D-arabino-hexopyranoside (39)

The benzylidene acetal 38 (1.55 g), N-bromosuccinimide (1.60 g), and barium carbonate (2.00 g) were magnetically stirred in boiling carbon tetrachloride (100 ml) for 3 h. The hot solution was filtered, the filter residue washed with chloroform (10 ml), and the combined filtrate was evaporated to give a yellowish syrup. This was dissolved in ether (20 ml) which was then washed with water (2 x 5ml), dried (Na_2SO_4), and evaporated again. The pale yellow residue was dissolved in methanol (5 ml) from which 39 crystallized as needles after storage at 0° for several hours. The product (1.57 g, 80%) was collected, washed with cold methanol, and dried in the air at room temperature; m.p. 93-93.5°, $[\alpha]_D$ +70.5° (c 1, chloroform).

In an earlier experiment, 2.00 g of 38 and 1.50 g of NBS but only 1.00 g of barium carbonate were used, with conditions otherwise being the same as above. T.l.c. (20% ethylacetate in carbon tetrachloride) revealed the presence of a more slowly moving by-product (40) beside 39. The syrup obtained upon evaporation of the reaction solution was therefore chromatographed on a column of silica gel (50 g) using the above t.l.c. solvent. The fractions containing

the main product (faster moving) furnished 39, which crystallized from methanol as just described, in a yield of 1.63 g (60%); m.p. 93°, $[\alpha]_D$ +71.5° (chloroform); ν_{max} 1732 (CO) and 1550 cm^{-1} (NO_2). The n.m.r. data: δ 8.0 and 7.5 (m, 2 + 3 H, PhCO); 5.58 (t, 1H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4); 5.2 (m, 1H, $J_{3,4}$ =10, $J_{2a,3}$ =6, $J_{2e,3}$ = 4 Hz, H-3); 5.00 (narrow m, H-1), 4.1 (m, 1H, $J_{4,5}$ = 10 Hz, H-5); 3.5 region (overlapping signals, 5H, H-6, -6' and, at δ 3.44, OMe); 2.6-2.2 (ill resolved, 2H, H-2, -2').

Anal. Calcd. for $C_{14}H_{16}BrNO_6$ (374.2): C, 44.93; H, 4.31; Br, 21.36. Found: C, 45.06; H, 4.19; Br, 21.61.

Methyl 4-O-Benzoyl-6-bromo-2,3,6-trideoxy-3-nitro-β-D-arabino-hexopyranoside (40)

Continued elution of the chromatographic column mentioned in the second experiment of the preceding section yielded the β-anomer 40 which crystallized upon solvent evaporation and was recrystallized from ethylacetate-petroleum ether; yield, 400 mg (16%), m.p. 182-183°, $[\alpha]_D$ +26.5° (c 0.4, chloroform); ν_{max} 1715 (CO) and 1560 cm^{-1} (NO_2). The n.m.r. data: δ 8.00 and 7.55 (m, 2+3 H, PhCO); 5.57 (t, 1H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4); 4.87 (octet, 1H, $J_{3,4}$ = 10, $J_{2a,3}$ = 8, $J_{2e,3}$ = 5 Hz, H-3); 4.60 (q, 1H, $J_{1,2a}$ = 10, $J_{1,2e}$ = 2 Hz, H-1); 3.79 (m, 1H, $J_{4,5}$ = 10 Hz, H-5); 3.59 (s, 3H, OMe); 3.53 (m, 2H, overlapping the OMe signal, H-6, -6'); 2.5 region (broad m, 2H, H-2, -2').

Anal. Calcd. for $C_{14}H_{16}BrNO_6$ (374.2): C, 44.93; H, 4.31; N, 3.74. Found: C, 44.59; H, 4.43; N, 3.82.

Hydrogenation of methyl 4-O-benzoyl-6-bromo-3,6-dideoxy-3-nitro-α-D-glucopyranoside (43)

A solution of 43 (500 mg, 1.2 mmole) in methanol (10 ml) containing 1.4 mmole of triethylamine was shaken for 2 h with hydrogen in the presence of 10% palladium charcoal (70 mg) at 8-15°. The filtered solution was partially evaporated to a volume of approximately 2 ml, dry ether (5 ml) was added, and the triethylammonium salt was removed by filtration. On evaporation the filtrate gave a brownish residue (80 mg) which was seen by t.l.c. (20% ethylacetate in carbon tetrachloride) to consist of one major spot and two minor ones. The n.m.r. spectrum of the crude mixture is shown in Fig. 1. Attempted purification of the mixture by passage through a column of silica gel (10 g) with the above t.l.c. solvent was unsuccessful. All collected fractions proved to be blank. Subsequent elution with methanol was likewise fruitless.

Attempts to reproduce this result on the same scale, and in one instance on a larger scale, were not successful.

The reaction was also attempted with compounds 39 and 45 under various conditions, such as the use of different solvent (ethylacetate) or base (barium carbonate or sodium bicarbonate) but without success. Complex mixture of products that were

ill separated in t.l.c. (20% ethylacetate in carbon tetrachloride or 1 : 2 ethylactate-petroleum ether) ensued in each attempt, and nothing could be isolated or identified.

PART II

SYNTHESIS OF NITROOLEFINS VIA METHANESULFONATES

Attempted reaction of methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-glucopyranoside (42) with dicyclohexylcarbodiimide (DCC)

The glycoside 42[87,88] (50 mg) in anhydrous ether (6 ml) was magnetically stirred with 66 mg of DCC. After a reaction time of approximately 90 h at 25° there was no change visible in t.l.c. (1 : 2 ethylacetate- petroleum ether). The solvent was evaporated and the residue was passed through a 15-g silica gel column with chloroform for recovery of starting material.

Attempted reaction of methyl 4-O-acetyl-3,6-dideoxy-3-nitro-α-L-glucopyranoside (52) with triphenylphosphine

Compound 52[25] (22 mg) in carbon tetrachloride (4 ml) was treated with triphenylphosphine as directed[26]. After 50 h of reaction time, t.l.c. with 20% ethylacetate in carbon tetrachloride showed no change in the reaction mixture. The experiment was therefore discontinued without recovery of starting material.

Methyl 2,3,4-Tri-O-acetyl-6-chloro-6-deoxy-α-D-gluco-pyranoside (63)

Methyl α-D-glucopyranoside was chlorinated to give methyl 6-chloro-6-deoxy-α-D-glucopyranoside essentially as described in the literature[63], but the crude product was converted without prior chromatographic isolation into its 2,3,4-triacetate, as follows. Methanesulfonyl chloride (37.5 ml, 0.5 mole) was added to a stirred solution of the glucoside (19.4 g, 0.1 mole) in N,N-dimethylformamide (200 ml) under external cooling (18°). The cooling bath was removed and the temperature allowed to rise to 70 ± 5°, at which the reaction mixture was kept for 16 h. Then n-propyl alcohol (80 ml) and water (20 ml) was added, and stirring was continued for another 3 h at the same temperature. The reaction mixture was evaporated to near-dryness (50° bath, water aspirator), and added 1-propanol (50 ml) was evaporated from the residue. The dry, solid material was acetylated by stirring it overnight with acetic anhydride (50 ml) in dry pyridine (100 ml), at 25°. Excess anhydride was thereafter destroyed by the addition of methanol (50 ml) followed, after 1 h, by 1-propanol (50 ml). Coevaporation of the mixture with several additional portions of propanol gave a residue which was then dissolved in chloroform (50 ml). The solution was washed with water (3 x 20 ml), dried over Na_2SO_4, and evaporated to give the crystalline 63 (28 g, 83%),

m.p. 96-97° after recrystallization from methanol, $[\alpha]_D$ + 178°.

The above triacetate (7 g) was reduced (and simultaneously deacetylated) to furnish methyl 6-deoxy-α-D-glucopyranoside as reported [63] for the non-acetylated chloro compound except that 5 + 2 g (instead of 3 + 2 g) of lithium aluminum hydride was employed.

Methyl 3,6-Dideoxy-3-nitro-α-D-glucopyranoside (62)

Methyl 6-deoxy-α-D-glucopyranoside was oxidized on a 20-g scale with sodium metaperiodate, and the product was cyclized with nitromethane in the presence of sodium methoxide, exactly as detailed for the preparation[22] of the L-enantiomer of 62 from methyl α-L-rhamnopyranoside except that a reaction time of 3 h (instead of 40 min) was allowed for the cyclization. The nitro glycoside 62 was obtained in 35% yield by direct crystallization from the mixture of products, m.p. 140-142°, $[\alpha]_D$ + 163.2° (c 1, water). Lit.[22c] for L-62, m.p. 141-143°, $[\alpha]_D$ - 164.3° (water). The i.r. spectra of the enantiomers were superimposable.

Methyl 2,4-Di-O-acetyl-3,6-dideoxy-3-nitro-α-D-glucopyranoside (64)

Compound 64 was obtained in 94-99% yield by boron trifluoride-catalyzed acetylation of 62 with acetic anhydride as described[25] for the L-enantiomer; m.p. 110-112°, $[\alpha]_D$ + 156° (c 1, $CHCl_3$). Reported [25] for L-64: m.p. 113-113.5°,

$[\alpha]_D$ - 155.3° ($CHCl_3$) and[89] m.p. 109-110°, $[\alpha]_D$ - 154° ($CHCl_3$).

Methyl 4-O-Acetyl-3,6-dideoxy-3-nitro-α-D-glucopyranoside (65)

The procedure of partial methanolysis reported[25] for the L-series was slightly modified. The diacetate 64 (2.0 g) was dissolved in methanol (20 ml, dried over and distilled from magnesium) and acetone (2 ml, dried over molecular sieves type 4-A). Acetyl chloride (1 ml) was added, and the solution was agitated at 40° under exclusion of moisture. Progress of the reaction was monitored by t.l.c. (5% methanol in chloroform) which indicated complete disappearance of 64 after 3 h and appearance of two slower spots of similar strength (65 and 62). The reaction mixture was then evaporated to give a syrup which was chromatographed (with the above t.l.c. solvent) on a column of silica gel (50 g). The faster moving component (65) was obtained from the column in pure form (0.85 g, 50%) and crystallized on standing overnight after solvent evaporation; m.p. 110-111°, $[\alpha]_D$ + 176.5° (c 1, $CHCl_3$). Lit.[25] for L-65: m.p. 112-113°, $[\alpha]_D$ - 178.5° ($CHCl_3$). The i.r. and n.m.r. data of the two enantiomers were identical.

2t-Nitrocyclohexane-1r,3c-diol Monomethanesulfonate (54)

The diol[61,90] 53 (500 mg) was dissolved in dichloromethane (7 ml), and methanesulfonyl chloride (MsCl, 0.25 ml) was added with stirring at room temperature. After 5 min, triethyamine (0.5 ml) was added under cooling of the reaction vessel with cold water. After 30 min, some remnant 53 and a strong, slightly faster moving spot due to 54 were seen by t.l.c. with ethylacetate-carbon tetrachloride (1:1). There were two additional, faint, fast-moving spots that were not identified. Anhydrous ether (10 ml) was added, an insoluble precipitate was removed, and the clear filtrate was evaporated with addition of several portions of n-propyl alcohol. The resulting syrup was chromatographed on a column of silica gel (10 g) by means of the above t.l.c. eluent. The fractions containing fast-moving by-products were discarded. Subsequent fractions that contained 54 only yielded a syrup from which two portions of added propanol were evaporated. The material then crystallized on standing overnight at 25°; yield, 445 mg (60 %) of crystalline 54, m.p. 81-83°, ν_{max} (neat syrup) 3200-3600 (OH), 1550 (NO_2), and 1165 cm^{-1} (OMs). N.m.r. data: δ 4.95 (sextet, 1H, J = 10 and 5 Hz, H-1); 4.47 (t, 1H, J = 10 Hz, H-2); 4.1 (m, sextet after D_2O exchange, 1H, H-3).

Anal. Calcd. for $C_7H_{13}NO_6S$ (239.2): C, 35.14; H, 5.47; S, 13.40. Found: C, 35.19; H, 5.41; S, 13.18.

2-Nitrocyclohex-2-ene-1-ol (55)

A solution of 54 (300 mg) in dry benzene (3 ml) was heated for 3 h at reflux in the presence of dry sodium hydrogen carbonate (0.5 g). T.l.c. with ethylacetate-petroleum ether (1:2) revealed total conversion of 54 into one faster migrating product. The cooled reaction mixture was filtered and the filtrate evaporated to give 55 as a colorless oil (175 mg, 97%). Its n.m.r. spectrum ($CDCl_3$) agreed in every respect with that of 55 obtained previously by a different method[61].

An attempt was made to prepare 55 directly from 53, without the isolation of 54, by carrying out the mesylation in ether solution (partial suspension) using double the amount of mesyl chloride and triethylamine. Although 53 reacted completely according to t.l.c., the olefin 55 produced was accompanied by a product of very similar mobility (its mesyl derivative?), and 55 could only in part be separated by chromatography (yield, 40%).

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-α-D-erythro-hex-2-enopyranoside (47)

Nitro glycoside[87,88] 42 (100 mg) in anhydrous ether (5 ml) was treated with methylsulfonyl chloride (0.05 ml) for 15 min at 20°, then triethylamine (0.06 ml) was added under cooling with water, and the mixture was stirred at room temperature for 45 min. At this time t.l.c. (1 : 2

ethylacetate-petroleum ether) indicated conversion of most of 42, and the reaction was allowed to proceed for another 30 min. The supernatant solution was then decanted from a sticky, brown precipitate, washed with saturated, aqueous sodium bicarbonate solution followed by water, and dried over Na_2SO_4. Evaporation gave crystalline 47 (84 mg, 90%), m.p. 183-184°, undepressed upon admixture of authentic[55,91] 47. The n.m.r. spectrum was superposable on that of authentic 47.

Methyl 4,6-O-Benzylidene-3-deoxy-2-O-methylsulfonyl-3-nitro-α-D-glucopyranoside (56)

To nitro glycoside 42 (200 mg) in dichloromethane (3 ml) was added MsCl (0.06 ml) and, after 5 min, triethylamine (0.08 ml) was added with stirring and external cooling by cold water. After 5 min, t.l.c. (1:2 ethylacetate-petroleum ether) showed a spot of 56 together with a stronger spot of faster-moving 47. Anhydrous ether (10 ml) was added to the reaction mixture which was stirred at 0° for 15 min; the pecipitate was then removed by filtration and the filtrate evaporated to give a partially crystalline residue from which 2 portions of 1-propanol were evaporated. The mixture was chromatographed on silica gel (7 g) with the above t.l.c. solvent. This gave first 47 (123 mg, 65%), m.p. 183°, and secondly, 56 (50 mg, 20%), m.p. 215-216°; $[\alpha]_D$ + 73.1° (c 0.6 in chloroform). N.m.r. data: δ 7.40 (5H, Ph); 5.55 (s, 1H, PhCH); 5.1 region (unresolved, 3H,

H-1, -2, -3); 4.37 (q, 1H, $J_{5,6}$ =3 Hz, $J_{6,6'}$ = 9 Hz); 4.15 (m, 1H, H-5); 3.7-4.0 (2H, H-4 and -6'); 3.54 (s, 3H, OCH_3); 3.03 (s, 3H, OMs).

Anal. Calcd. for $C_{15}H_{19}NO_9S$ (389.4): C, 46.26; H, 4.91; S, 8.23. Found: C, 46.10; H, 4.77; S, 8.15.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-β-D-erythro-hex-2-enopyranoside (58)

From the nitroglycoside[44,58,88] 57 (200 mg), the olefin 58 (74 mg, 78.5%) was obtained by exactly the same procedure as described above for 56; the product was identified with an authentic sample[44,58] by an undepressed mixture melting point, 142-144°.

Methyl 4-O-Acetyl-3,6-dideoxy-2-O-methylsulfonyl-3-nitro-α-D-glucopyranoside (66)

To a stirred solution of the 4-acetate 65 (1.0 g) in anhydrous ether (15 ml) was added MsCl (0.5 ml) and, after 5 min, triethylamine (1.0 ml). The mixture was stirred for 10 min, after which 65 proved completely converted into 66 (t.l.c. with 1 : 2 ethylacetate-petroleum ether). The solution was decanted from a sticky precipitate and evaporated to dryness with several additions of 1-propanol. The remaining syrup crystallized upon trituration with hexane. Recrystallized from ethylacetate-petroleum ether, compound 66 (1.05 g, 80%) showed m.p. 161°, $[\alpha]_D$ + 154° (c 1, $CDCl_3$), ν_{max} 1740 (OAc), 1560 (NO_2), and 1175 cm^{-1} (OMs). N.m.r.

data: δ 5 region (unresolved, 4H, ring protons); 3.88 (m, 1H, H-5); 3.50 (s, 3H, OCH_3); 3.01 (s, 3H, OMs); 2.10 (s, 3H, OAc); 1.24 (d, 3H, J = 6.5 Hz, C-CH_3).

Anal. Calcd. for $C_{10}H_{17}NO_9S$ (327.3): C, 36.69; H, 5.23; S, 9.79. Found: C, 36.82; H, 5.25; S, 9.81.

Methyl 3,6-Dideoxy-2-O-methylsulfonyl-3-nitro-α-D-gluco-pyranoside (68)

A solution of the 4-acetate 66 (900 mg) in acetone (1 ml) and 3% methanolic hydrogen chloride (9 ml of a solution that had been made by adding 1 ml of acetyl chloride to 20 ml of dry methanol) was kept at 40-50° for a few hours until t.l.c. (5% methanol in chloroform) showed absence of starting material and sole presence of one new spot. The reaction mixture was then evaporated to give a brownish syrup which was passed through a 10-g silica gel column with ether to remove colored impurities. Evaporation of the effluent gave 772 mg of 68 which was recrystallized from ethylacetate-petroleum ether to give pure 68 (768 mg, 98%), m.p. 106-107°, $[\alpha]_D$ +148° (c 1, chloroform), ν_{max} 3500 (OH), 1560 (NO_2), and 1170 cm^{-1} (OMs). N.m.r. data: δ 3.49 (s, 3H, OMe); 3.03 (s, 3H, OMs); 1.36 (d, 3H, J = 6 Hz, C-Me).

Anal. Calcd. for $C_8H_{15}NO_8S$ (285.3): C,33.68; H, 5.30; S, 11.24. Found: C, 33.80; H, 5.30; S, 11.39.

Methyl 2,3,6-Trideoxy-3-nitro-α-D-erythro-hex-2-enopyranoside (69)

A solution of 68 (700 mg) in benzene (5 ml, dried over

CaH_2) and dry sodium bicarbonate (2.5 g) were heated overnight at reflux. The mixture was allowed to cool, then filtered, and the filter residue was washed twice with chloroform. The combined filtrate was evaporated to give a brown syrup that was decolorized by passage through a 15-g silica gel column with ether. Evaporation of the effluent gave crude crystalline 69 which was recrystallized from chloroform-petroleum ether. The yield of pure 69 was 427 mg (92%); m.p. 124-125°. Reported[25] for the L-enantiomer, 124-125°. The n.m.r. data of 69 were identical with those described[25] for its L-enantiomer.

Methyl 3,6-Dideoxy-2,4-di-O-methylsulfonyl-3-nitro-α-D-glucopyranoside (71)

The glucoside 62 (200 mg) in dichloromethane (10 ml) was treated with MsCl (0.08 ml, 1 molar equiv) and triethylamine (0.14 ml) as described for previous experiments. After a reaction time of 5 min there was no change visible in t.l.c. (1:2 ethylacetate-petroleum ether). Therefore, five additional 0.08-ml portions of MsCl and equivalent amounts of triethylamine were added in 5-min intervals, without cooling. Eventually progress of reaction resulting in complete consumption of 62 was noted. Ether was then added to the raection mixture to precipitate salt which was removed. On evaporation the filtrate gave a brownish residue which was repeatedly evaporated with 1-propanol until the smell of MsCl was no longer noticeable. The residue then crystallized

copiously upon trituration with ice water. The material was washed with cold water, dissolved in ethylacetate, dried with Na_2SO_4, and recrystallized by addition of petroleum ether. The yield was 260 mg (74%); m.p. 132-132.5°, $[\alpha]_D$ +110.5° (c 0.4, chloroform); ν_{max} 1555 (NO_2), 1170 (OMs). N.m.r. data: δ 4.7-5.1 (4H, ill resolved, H-1, -2, -3, -4); 3.93 (octet, 1H, H-5, $J_{4,5}$ = 10 Hz, $J_{5,6}$ = 6 Hz); 3.51 (s, 3H, OMe); 3.01 and 3.03 (2s, 6H, 2 OMs); 1.44 (d, 3H, J = 6 Hz, C-Me).

Anal. Calcd. for $C_9H_{17}NO_{10}S_2$ (363.4): C, 29.74; H, 4.71; S, 17.64. Found: C, 29.73; H, 4.79; S, 17.66.

Methyl 3,6-Dideoxy-2-O-methylsulfonyl-3-nitro-α-L-galacto-pyranoside (72)

The galactoside 23 (300 mg) in dichloromethane (7 ml) was treated with MsCl (0.1 ml) and TEA (0.2 ml in 1 ml of dichloromethane). The mixture was stirred for 90 min at 25°, after which period t.l.c. (1:2 ethylacetate-petroleum ether) indicated reaction to be incomplete. When the t.l.c. pattern remained unchanged after 4 h, a second and a third set of MsCl and TEA were added with a 30 min interval. This caused the reaction to become nearly complete, with only a trace of 23 remaining. Final addition of a fourth set of reagent portions resulted in complete disappearance of 23. There was one major product spot (72) and a quite strong spot that migrated faster (and was seen, by application of another

solvent, to be inhomogeneous). The reaction mixture was partially evaporated to a volume of 5 ml, ether (10 ml) was added, and the mixture kept in a refrigerator for 2 h and then filtered. The filtrate was evaporated with several additions of 1-propanol, and the resulting syrup was chromatographed on silica gel (10 g) using chloroform as eluent. Fractions containing fastmoving material yielded a thick oil (135 mg) which was seen by t.l.c. (with chloroform) to consist of two components moving close together. The n.m.r. spectrum of the oil suggested the presence of two non-mesylated, unsaturated glycosides, one of which appeared to preponderate. There were signals (total intesity, 1H) in the δ 7.0-7.3 region (nitroolefinic protons), unresolved signals (4H) at δ 3.6-5.3, two 3H signals close together near δ 3.5 (OCH_3), and two overlapping 3H doublets centered at δ 1.5 ($\underline{C}$-CH_3). Further elution of the column gave syrupy 72 which crystallized on standing for a few hours; large plates (200 mg, 48%), m.p. 175-176°, $[\alpha]_D$ -206.6° (c 0.2, chloroform); ν_{max} 3570 (OH), 1555 (NO_2), 1160-1170 cm^{-1} (OMs). N.m.r. data: δ 5.30 (q, 1H, $J_{1,2}$ =3.7 Hz, $J_{2,3}$ = 11 Hz, H-2); 5.13 (d, 1H, H-1); 4.92 (q, 1H, $J_{3,4}$ = 3 Hz, H-3); 4.4 (m, 1H, H-4); 4.13 (q, 1H, H-5); 3.50 (s, 3H, OCH_3); 3.14 (s, 3H, OMs); 1.32 (d, 3H, J = 7 Hz, $\underline{C}$-CH_3).

Anal. Calcd. for $C_8H_{15}NO_8S$ (285.3) : C, 33.68; H, 5.30; S, 11.24. Found: C, 33.54; H, 5.19; S, 11.12.

Attempted elimination of the mesyloxy group by refluxing 72 in the presence of sodium bicarbonate in benzene or toluene for 6 h was unsuccessful. The compound remained unchanged.

Methyl 4-O-Acetyl-2,3,6-trideoxy-3-nitro-α-D-erythro-hex-2-enopyranoside (67)

The 4-acetate 75[25] (100 mg) in anhydrous ether (5 ml) and MsCl (0.02 ml) were stirred for 15 min after which triethylamine (0.5 ml) was added with water-cooling. Stirring was continued for 45 min at room temperature. Processing of the mixture as previously described furnished crude 67 as a yellowish syrup which after purification by passage through silica gel (5 g) gave crystalline 67 (60 mg, 65%), m.p. 81-82°. (Reported[25] for L-enantiomer, 81-81.5°).

Methyl 3,6-Dideoxy-4-O-methylsulfonyl-3-nitro-α-D-gluco-pyranoside (70)

The glycoside 62 (2.0 g) and methylsulfonyl chloride (0.75 ml, 1 mol. equiv) were stirred together in dichloro-methane (60 ml), with external cooling to 10-15°, and triethylamine (1.3 ml) was added after 5 min. As no sign of reaction was detected by t.l.c. (5% methanol in chloro-form) after another 5 min, cooling was discontinued and three additional 0.7-ml portions of mesyl chloride along with equivalent amounts of triethylamine were introduced in 15-min intervals. Gradually during this operation

a faster spot representing 70 appeared in t.l.c., and the intensity of the spot of 62 diminished. Eventually a faint spot (still faster) corresponding to the dimesylate 71 made its appearance. At this stage the reaction was quenched by the addition of methanol (5 ml), and after 1 h the mixture was evaporated. Several portions of 1-propanol were successively added to and evaporated from the syrupy residue which was finally dissolved in chloroform (3 ml) and chromatographed on silica gel (85 g) by means of chloroform as eluent. Fractions containing the fast-moving, minor proportion of 71 formed were discarded. Subsequent fractions that contained only 70 were combined and evaporated to give a syrup which crystallized upon trituration with hexane (10 ml) and standing overnight under this solvent. The crystalline material (1.00 g, 36%) was recrystallized from ethylacetate-petroleum ether. The sharp needles showed m.p. 93-94.5°; $[\alpha]_D$ +96.6° (c 0.5, chloroform); ν_{max} 3300 (OH), 1550 (NO_2), and 1170 cm^{-1} (OMs). N.m.r. data: δ 4.75-5.00 (m, 3H, ill resolved, H-1, -3, -4); 4.2 (broad m, H-2); 3.85 (broad m, 1H, H-5); 3.49 (s, 3H, OMe); 2.96 (s, 3H, OMs); 2.48 (d, 1H, J = 11 Hz, removable with D_2O, OH); 1.43 (d, 3H, J = 6 Hz, C-CH_3).

Anal. Calcd. for $C_8H_{15}NO_8S$ (285.2): C, 33.68; H, 5.30; S, 11.24. Found: C, 33.74; H, 5.30; S, 11.15.

Further elution of the column with ether furnished 1.20 g (60%) of unchanged 62.

Methyl 3,4,6-Trideoxy-3-nitro-α-D-xylo-hexopyranoside (78)

To a magnetically stirred, ice cooled solution of the mesylate 70 (800 mg) in ethanol (20 ml) was added sodium borohydride (0.14 g) in small portions. The reaction was then allowed to continue for 30 min at 25°. Examination by t.l.c. (1:2 ethylacetate-petroleum ether) revealed total consumption of 70 and formation of a fast-moving product (78) accompanied by traces of faster and slower impurities. The solution was deionized with 5 ml of Amberlite IR-120(H^+) whereby it became acidic. It was neutralized carefully with triethylamine and evaporated. Several porions of methanol were then evaporated from the residue for removal of boric acid, and the material was chromatographed on a column of silica gel (17 g) by use of chloroform as eluent. The fractions containing the high-mobility contaminants were discarded, and the fractions containing the main product were evaporated to give 320 mg (60%) of a colorless syrup of 78 which crystallized from ether-petroleum ether as large needles, m.p. 55-56°, $[\alpha]_D$ +197.2° (c 0.5, chloroform). Reported[69] for L-78, m.p. 56-57°, $[\alpha]_D$ -198° (chloroform). Spectral data accorded with those of the enantiomer.

Methyl 2,3,4-Trideoxy-3-nitro-α-D-arabino-hexopyranoside (79)

See Experimental, Part III.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-α-D-arabino-hexopyranoside (38)

A solution of 42 (1.80 g) in anhydrous ether (50 ml) containing triethylamine (2.7 ml) was cooled to 10-15°, and methylsulfonyl chloride (1.3 ml) was added dropwise with stirring during a period of 30 min. T.l.c. (1:2 ethyl-acetate-petroleum ether) indicated complete conversion of 42 into the faster-moving product of dehydration. The reaction mixture was filtered and the filtrate was evaporated to give a yellowish oil which was dissolved in dichloromethane (10 ml). Careful addition of triethylamine (2 ml) at 10-15°, followed by anhydrous ether (25 ml) gave a precipitate of salts. This was separated by filtration and washed with water, whereby it partially dissolved. The aqueous washing filtrate was discarded whereas the water-insoluble filter residue was dissolved in ether (3 ml) and, after drying with $CaCl_2$, was combined with the main solution containing the product. Evaporation of the solvents gave a solid which was immediately dissolved in absolute ethanol (50 ml) and treated with sodium borohydride (1.0 g) in small portions at 15°. After stirring for 2 h the reaction mixture was filtered, the filter residue washed with ethanol (2x10 ml), and the combined filtrate evaporated completely. The syrupy material containing some solid was extracted twice with 15 ml of ethylacetate from which upon evaporation the

glycoside 38 was obtained in crystalline form (1.55g, 91%); m.p. 107-109°, $[\alpha]_D$ +68.5°(chloroform). Reported[68]: m.p. 108-111°, $[\alpha]_D$ +67.0° (chloroform).

Methyl 2-O-Acetyl-3,4,6-trideoxy-3-nitro-α-D-threo-hex-3-enopyranoside (76)

A mixture of 2,4-di-O-mesyl glycoside 71 (200 mg), sodium acetate (50 mg), and acetic acid (9 drops) in acetone (5 ml) was heated at reflux for 10 min. T.l.c. with chloroform indicated complete conversion of 71 into a new product. The reaction mixture was evaporated and the residue extracted with ether. The filtered extract was coevaporated with several portions of ethanol to give a syrup which was taken up in ethanol (0.5 ml) and kept overnight at 0°. Compound 76 (95 mg, 75%) was deposited in crystalline form and recrystallized from ethylacetate-petroleum ether; m.p. 81-82°, $[\alpha]_D$ +163° (c 1.3, chloroform). Reported [25] for L-76: m.p. 81-81.5°, $[\alpha]_D$ -165° (chloroform).

PART III

THE SYNTHESIS OF D-ANGOLOSAMINE

Methyl 2,3,4-Trideoxy-3-nitro-α-D-arabino-hexopyranoside (79)

(a) From the nitroolefin 69

Sodium borohydride (0.33 g) was added to a solution of 69 (500 mg) in 99% ethanol (13 ml), which was stirred at room temperature. Examination by t.l.c. (1 : 2 ethylacetate-petroleum ether) revealed that the reaction was complete after 10 min. Methanol (3 ml) was added, stirring was continued for another 15 min, the solvent was then evaporated to near dryness of the residue, and the latter was taken up in chloroform (10 ml). The suspension was filtered through a layer of Celite and the filtrate evaporated. The resulting syrup was dissolved in a small amount (1.5 ml) of fresh chloroform, and a voluminous precipitate which formed upon addition of acetone (8 ml) was removed and discarded. The filtrate was evaporated, and several portions of methanol were successively evaporated from the remaining residue which was finally passed through a column of silica gel (8 g) by means of chloroform. A fast-moving impurity that had been seen in t.l.c. was thus removed. The chromatographically homogeneous fractions containing the main product

yielded a syrup (377 mg, 75%) believed to consist chiefly of 79. Attempts at crystallization were unsuccessful. The material showed $[\alpha]_D$ +23° (c 0.6, water), -34.5° (c 0.6, $CHCl_3$); ν_{max} (neat) 3200 (broad, OH) and 1550 cm^{-1} (NO_2). The n.m.r. data: δ4.50 (2H, unresolved multiplet), 3.83 (1H, m, H-5), 3.5 region (unresolved multiplet), 3.41 (3H, s, O-CH_3), 2.33 (2H, q, H-2,2'), 1.14 (3H, d, J = 6.5 Hz, C-CH_3).

Anal. Calcd. for $C_7H_{13}NO_5$ (191.2): C, 43.97; H, 6.85; N, 7.32. Found: C, 43.11; H, 7.65; N, 6.68.

(b) From the 2-mesylate 68

Sodium borohydride (0.66 g) was added in small portions to a stirred solution of 68 (1.65 g) in 99% ethanol (25 ml), with cooling in a cold water bath. The further course of operations was as described under (a). There was obtained 829 mg (75%) of a syrup which was identical with the previous preparation according to ir and n.m.r. spectra.

Methyl 3-Amino-2,3,6-trideoxy-α-D-arabino-hexopyranoside Hydrochloride (82)

The syrupy nitro glycoside 79 (150 mg, approximately 0.8 mmol) was dissolved in absolute methanol (15 ml) to which exactly 0.055 ml (0.78 mmol) of acetyl chloride had been previously added. The solution was introduced in a high-pressure hydrogenation flask containing platinum catalyst (150 mg of PtO_2 prereduced in a few ml of methanol) and

shaken for 3 h under hydrogen at 40 p.s.i. and room temperature. The filtered solution gave upon evaporation a dry residue which was dissolved in 99% ethanol (1.5 ml). Dropwise addition of ether at 0° caused crystallization of 82 which was isolated after 3 h. The yield was 105 mg (68%); m.p. 193-195° decomp., $[\alpha]_D$ +112.7° (c 0.5, methanol). Lit.[75] for L-82: m.p. 196-198° decomp., $[\alpha]_D$ -115.5° (methanol).

3-Amino-2,3,6-Trideoxy-D-arabino-hexose Hydrochloride (83) (D-Acosamine Hydrochloride)

The amino glycoside 82 (50 mg) was hydrolyzed in 0.1 M hydrochloric acid (3 ml) for 1 h at 90°. The hydrolyzate was evaporated to a brownish syrup with the addition of several portions of 40% aqueous ethanol. The product was finally dissolved in ethanol, decolorized with activated charcoal, and recovered by evaporation to near dryness. Trituration of the residue with a few drops of ethylacetate gave crystalline 83, $[\alpha]_D$ +31° (initial) → +22° (final, 3 h; c 0.7, water). Lit.[78] for L-83: $[\alpha]_D$ -18.3° at equilibrium (c 0.43, water). This compound had been obtained previously[43] in a crystalline form (presumably the α-anomer) showing $[\alpha]_D$ +81.7° (in water) without mutarotaion. We have now hydrolyzed (1 h at 100° in 0.5 M hydrochloric acid) a sample of the N-acetyl derivative of 83 that was still available from the previous work[43] and found $[\alpha]_D$ +18° for the product in the hydrolysis solution. The reason for the apparent lack of mutarotation of the

earlier sample of 83 is not clear.

2,3,6-Trideoxy-3-dimethylamino-D-arabino-hexose Hydrochloride (84) (D-Angolosamine Hydrochloride)

A solution of the amino glycoside hydrochloride 82 (55 mg) in 37% aqueous formaldehyde (1.5 ml) was slightly basified with a few drops of 0.1 N sodium hydroxide solution, and 90% formic acid (3.5 ml) was then added. The mixture was heated to reflux for 5 h and then evaporated and co-evaporated with added portions of ethanol. The resultant material was taken up in cold ethanol (1 ml) and kept at 0° for 30 min, after which time an undissolved residue was filtered off and the filtrate evaporated to dryness. The product was hydrolyzed in 0.1 M hydrochloric acid (2 ml) for 1 h at 90°. Removal of the acid by coevaporation with 40% aqueous ethanol gave a semicrystalline, brownish mass which was decolorized in ethanolic solution with activated charcoal. Concentration of the filtrate, ice cooling, and dropwise addition of absolute ether readily gave crystalline 84 (19 mg, 32%) which was washed repeatedly with cold ether; m.p. 170-173.5°, $[\alpha]_D$ +5.5° (equilibrium; c 1, water). Lit.[74]: m.p. 172-174°, $[\alpha]_D$ +4.6° (water). The infrared spectrum of 84 is shown in Fig. 15; it agreed very well with the spectrum of the natural product reproduced in ref. 74.

PART IV

THE SYNTHESIS OF 3-AMINO-2,3,6-TRIDEOXY-D-RIBO-HEXOSE (D-RISTOSAMINE)

Methyl 4,6-O-Benzylidene-2-deoxy-β-D-arabino-hexopyranoside (89)

Methyl 3,4,6-tri-O-acetyl-2-deoxy-β-D-arabino-hexopyranoside (88), m.p. 97-98°, $[\alpha]_D$ -27° (c 1, chloroform), was prepared[85] from commercial 3,4,6-tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose via methyl 3,4,6-tri-O-acetyl-2-chloromercuri-2-deoxy-β-D-glucopyranoside, m.p. 173-175°, $[\alpha]_D$ +10.3° (c 1, chloroform). Solid sodium methoxide (200 mg) was added with stirring to a solution of 88 (1.7 g) in spectral grade methanol (10 ml). After 2 h, t.l.c. indicated complete conversion of 88 into a more slowly migrating product (1 : 2 ethylacetate-petroleum ether), and the solution was deionized by Amberlite IR-120(H^+) cation exchange resin, filtered, and evaporated. The colorless syrup obtained was stirred with benzaldehyde (10 ml) and anhydrous zinc chloride (1 g) for 14 h. Upon addition of water (10 ml) the reaction mixture was extracted with chloroform (20 ml).

The extract was washed with water (10 ml) and evaporated. Added portions of 1-propanol were repeatedly evaporated at 55° from the residue until the smell of benzaldehyde had waned. Recrystallized from ethylacetate - petroleum ether, the product (89) weighed 1.20 g (80%); m.p. 156-157°, $[\alpha]_D$ -66.2° (c 1, chloroform). Lit.[86] :m.p. 155-156°, $[\alpha]_D$ -67°.

Methyl 4,6-O-Benzylidene-2-deoxy-3-O-methylsulfonyl-β-D-arabino-hexopyranoside (90).

Methanesulfonyl chloride (0.9 ml, 3 mol. equiv.) was added with external cooling (15°) to a solution of 89 (1.0 g) in dry pyridine (10 ml). After 30 min the reaction mixture was evaporated under addition of 1-propanol (20 ml). The dry residue was washed with cold water, then extracted into ether. Evaporation of the dried ($CaCl_2$) solution gave 90 (1.20 g, 92%) which was recrystallized from ethylacetate-petroleum ether; m.p. 149° (dec.), $[\alpha]_D$ -61.8° (c 0.5, chloroform), ν_{max} 1170 cm^{-1} (OMs). N.m.r. data: δ7.38 (5H, Ph), 5.56 (s, 1H, Ph-CH), 4.77 (octet, H-3, $J_{2a,3}$ = 12, $J_{2e,3}$ = 5.5, $J_{3,4}$ = 10 Hz), 4.55 (q, H-1, $J_{1,2a}$ = 10, $J_{1,2e}$ = 2.5 Hz), 4.37 (q, H-6e, $J_{5,6e}$ = 4.5, $J_{6a,6e}$ = 10 Hz), 3.82 (q, H-4, $J_{3,4}$ =10, $J_{4,5}$ = 12 Hz), 3.73 (t, H-6a, $J_{5,6a}$ = 10 Hz), 3.54 (s, 3H, OMe), 3.4-region (m, broad, H-5), 2.98 (s, 3H, OMs), 2.53 (octet, H-2e, $J_{2a,2e}$ = 13 Hz), 1.94 (octet, H-2a).

Anal. Calcd. for $C_{15}H_{20}O_7S$ (344.4): C, 52.31; H, 5.85.

Found: C, 52.49; H, 5.92.

Methyl 3-Azido-4,6-O-benzylidene-2,3-dideoxy-β-D-ribo-hexopyranoside (91)

A solution of the 3-mesylate 90 (1.40 g) in N,N-dimethylformamide (30 ml, dried over molecular sieves type 4-A) containing sodium azide (0.80 g, 3 mol. equiv.) was stirred at 120° for 17 h. The cooled reaction mixture was evaporated with the addition of 1-propanol (50 ml). The crystalline residue was extracted with ether which, upon evaporation and recrystallization of the solute from ethyl-acetate-petroleum ether gave pure 91 (1.00 g, 84%); m.p. 93-94°, $[\alpha]_D$ -93.7° (c 0.4, chloroform), ν_{max} 2100 cm^{-1} (N_3). N.m.r. data: δ7.4-region (m, 5H, Ph), 5.56 (s, 1H, Ph-CH), 4.70 (q, H-1, $J_{1,2a}$ = 9, $J_{1,2e}$ = 2.5 Hz), 4.35 (q, probably H-4, J =3.5 and 9 Hz), 4.25-3.65 (m, 4H), 3.51 (s, 3H, OMe), 2.10 (octet, $J_{2a,2e}$ = 13 Hz, H-2e), 1.86 (octet, H-2a).

Anal. Calcd. for $C_{14}H_{17}N_3O_4$ (291.3): C, 57.72; H, 5.88; N, 14.42. Found: C, 57.53; H, 5.87; N, 14.17.

Methyl 3-Azido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-β-D-ribo-hexopyranoside (92)

A mixture of the benzylidene acetal 91 (0.80 g), N-bromsuccinimide (1.5 g, 3 mol. equiv.) and barium carbonate (2 g) in dry carbon tetrachloride (25 ml) was stirred at reflux temperature for 2 h. The color of the solution

gradually became yellow and red, and then fainted again to a pale yellow. The mixture was filtered while hot and the inorganic residue was washed with chloroform (10 ml). Evaporation of the filtrate gave a syrup whose ethereal solution was washed with water (10 ml), dried (Na_2SO_4), and evaporated. T.l.c. with 1 : 2 ethylacetate – petroleum ether showed a faint, slow-moving spot in addition to the main product. Column chromatography on silica gel (20 g) using the same t.l.c. developer yielded 92 as a thick oil (0.70g, 69%) that still contained a trace of the unidentified by-product. An analytical sample was further purified by preparative t.l.c. and then showed $[\alpha]_D$ -81.2° (c 0.7, chloroform); ν_{max} (neat oil) 2100 (N_3) and 1715 cm^{-1} (ester CO). N.m.r. data: δ8.07 and 7.5 (m, 2+3H, Ph-CO), 5.17 (q, H-1, $J_{1,2a}$ = 9, $J_{1,2e}$ = 3.5 Hz), 4.78 (q, H-4, $J_{3,4}$ = 3, $J_{4,5}$ = 9 Hz), 4.4-4.1 (m, 2H), 3.49 (s, 3H, OMe, superposed on m, 2H), δ2-region (m, 2H, H-2a, -2e).

Anal. Calcd. for $C_{14}H_{16}BrN_3O_4$ (370.2): C, 45.42; H, 4.35; Br, 21.58. Found: C, 45.57; H, 4.49; Br, 21.80.

3-Amino-2,3,6-Trideoxy-D-ribo-hexose hydrochloride (D-ristosamine hydrochloride) (93)

A solution of compound 92 (550 mg) in methanol (17 ml) containing sodium methoxide (50 mg) was kept at room temperature for 3 h after which time t.l.c. (1 : 2 ethylacetate - petroleum ether) indicated complete conversion of 92 into a

single, new product (presumably the de-O-benzoylated bromo derivative). The solution was deionized with Amberlite IR-120 (H^+) cation exchange resin and then hydrogenated for 4 h at ambient temperature and pressure in the presence of palladium on carbon (600 mg) and barium carbonate (400 mg). Evaporation of the filtered solution gave a pale yellow syrup which was extracted into ethylacetate. The product (92a), which could not be obtained crystalline, was recovered from the solvent and hydrolyzed by heating in 0.1 M hydrochloric acid for 1 h at 90°. Evaporation of the hydrolyzate with addition of several portions of aqueous, 40% ethanol gave a brownish, semicrystalline mass. The material was treated with activated charcoal in ethanol, recovered by solvent evaporation to dryness, washed repeatedly by trituration with ethylacetate, and finally crystallized from absolute ethanol by careful addition of dry ether and cooling. Compound 93 was obtained in the form of extremely hygroscopic crystals (155 mg, 57%); $[\alpha]_D$ +28.2° (initial) → +36.5° (24 h, constant; c 0.5, water). Lit.[32] for L-93, (-) 34.3°*.

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*The value recorded[32] for the L-93 is 34.3° (in water); the negative sign was omitted, presumably by an oversight. Lee and coworkers[84] have indeed found negative values for different samples of synthetic L-93.

Methyl 3-Benzamido-6-bromo-2,3,6-trideoxy-β-D-ribo-hexopyranoside (94)

Compound 92 (50 mg) in 99% ethanol (15 ml) was hydrogenated for 1 h at room temperature under pressure (15 p.s.i.) in the presence of 10% palladium on carbon (50 mg) and barium carbonate (30 mg). Evaporation of the filtrate gave a colorless syrup whic was dissolved in a small amount of ethylacetate. T.l.c. using 5% methanol in chloroform indicated total conversion of 92 into a main product (94) that was accompanied by a small proportion of a more slowly migrating product (presumably 95). Isolation of the main component by preparative t.l.c. (same t.l.c. solvent) gave 94 (23 mg, 50%) as colorless crystals, m.p. 146-147°, $[\alpha]_D$ -52.4° (c 0.3, chloroform); ν_{max} (chloroform) 3400 (broad; OH, NH), 1650 (amide I), and 1510 cm^{-1} (amide II). N.m.r. data: δ7.7 and 7.5 (m, 2+3H, Ph-CO), 4.74 (q, H-1, $J_{1,2a}$=6 and $J_{1,2e}$ = 3.5Hz), 3.51 (s, 3H, OMe), 2.1-region (broad m, 2H, H-2a, -2e). Ring protons resonating in the δ4.6-3.5-region (intensity 5H) gave ill resolved signals. There were minor peaks near δ1.3-1.4 due to a contamination (C-Me of 95?).

Anal. Calcd. for $C_{14}H_{18}BrNO_4$ (344.2): C, 48.85; H, 5.27. Found: C, 50.35; H, 5.37.

Methyl 3-Benzamido-2,3,6-trideoxy-β-D-ribo-hexopyranoside (95)

Compound 92 (50 mg) was hydrogenated as described for the preparation of 94 except that the hydrogen pressure was

35 p.s.i. and the reaction time, 3 h. Processing as for 94 furnished syrupy 95 (27 mg, 75%); $[\alpha]_D$ -31° (c 0.6, chloroform), ν_{max} (chloroform) 3400 (broad; OH, NH), 1645 (amid I) and 1510 cm^{-1} (amide II). N.m.r. data: δ7.7 and 7.4 (m, 2+3H, Ph-CO), 3.46 (s, 3H, OMe), 3.1 (1H, broad, removable by D_2O exchange), δ2.0-region (broad m, 2H, H-2a, -2e), 1.40 (d, 3H, J = 6 Hz, C-Me). Overlapping signals of ring protons in the δ3.5-4.7 region were difficult to assign.

3-Benzamido-2,3,6-trideoxy-D-ribo-hexose (N-benzoyl-D-ristosamine) (96)

A sample of 95 (17 mg) was refluxed for 3 h in 50% aqueous acetic acid (2 ml). The residue obtained on evaporation was crystallized from ethylacetate - ether to give 96 (13 mg, 81%); m.p. 135-137°, $[\alpha]_D$ +15.6° (initial) → +9.8° (15 min, constant; c 0.5, ethanol). Lit.[83] for L-96 : m.p. 131-133°, $[\alpha]_D$ -14° → -11° and[32] m.p. 126-128°, $[\alpha]_D$ -10° (ethanol). Reported[92] for 96: m.p. 128-129°, $[\alpha]_D$ +13.5° (equil., ethanol).

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