BRANCHED-CHAIN NUCLEOSIDES: SYNTHESIS OF STRUCTURAL ANALOGS OF PSICOFURANINE AND OF THE POLYOXIN COMPLEX

BY

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ABSTRACT

The synthesis of a number of C-carbamoyl, hydroxymethyl, and amino branched-chain sugars and the conversion of these compounds to their respective pyrimidine or purine nucleosides are reported.

The acetone initiated photochemical addition of formamide to 2,3,4,6-tetra-O-acetyl-1-deoxy-D-arabino-hex-1-enopyranose (22) afforded 3,4,5,7-tetra-O-acetyl-2,6-anhydro-D-glycero-D-ido-heptonamide (152), 3,4,5,7-tetra-O-acetyl-2,6-anhydro-D-glycero-D-talo-heptonamide (153), and 4,5,6,8-tetra-O-acetyl-3,7-anhydro-1-deoxy-2-methyl-D-glycero-D-talo-octitol (154) in 55, 7, and 23% yields respectively. Reduction of the heptonamide 152 with diborane followed by acetylation gave 1-acetamido-3,4,5,7-tetra-O-acetyl-2,6-anhydro-1-deoxy-D-glycero-D-ido-heptitol 155 in 70% yield. Treatment of compounds 152 and 153 with sodium methoxide in anhydrous methanol afforded 2,6-anhydro-D-glycero-D-ido-heptonamide (158) and 2,6-anhydro-D-glycero-D-talo-heptonamide (159), respectively.

The photoamidation of 1,2,4,6-tetra-O-acetyl-3-deoxy-α-D-erythro-hex-2-enopyranose (24) afforded 1,2,4,6-tetra-O-acetyl-
3-C-carbamoyl-3-deoxy-α-D-glucopyranose (161), 1,2,4,6-tetra-O-acetyl-3-C-carbamoyl-3-deoxy-α-D-allopyranose (162), 1,2,4,6-tetra-O-acetyl-3-C-carbamoyl-3-deoxy-α-D-altropyranose (163), and 1,2,4,6-tetra-O-acetyl-3-deoxy-3-C-(2-hydroxy-2-propyl)-α-D-mannopyranose (164) in 46, 13, 1, and 7% yields, respectively. Condensation of the halogenose of the gluco-amide 161 with bis(trimethylsilyl)thymine followed by deacetylation gave the nucleoside 1-(3'-C-carbamoyl-3'-deoxy-β-D-glucopyranosyl)thymine (166) in 40% yield. A similar condensation with bis(trimethylsilyl)N4-acetylcytosine and subsequent deacetylation afforded 1-(3'-C-carbamoyl-3'-deoxy-β-D-glucopyranosyl)cytosine (168).

The photoamidation of 3-acetoxy-1,2:5,6-di-O-isopropylidene-α-D-erythro-hex-3-enofuranose (171) afforded 3-O-acetyl-4-C-carbamoyl-1,2:5,6-di-O-isopropylidene-α-D-gulofuranose (172) and 3-O-acetyl-3-C-carbamoyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (173) in 65 and 26% yields. Hydrolysis of the 5,6-O-isopropylidene group of 172 resulted in cyclization to afford 3-O-acetyl-6-deoxy-1,2:5,6-di-O-isopropylidene-α-D-gulofuranose-4,6-carbolactone (176) in 73% yield. Deacetylation and removal of the 1,2-O-isopropylidene group of 176 afforded the completely unblocked 6-deoxy-α-(and β)-D-gulofuranose-4,6-carbolactone (179). Reduction of compound 176 with sodium borohydride followed by a sodium metaperiodate cleavage and sodium borohydride reduction afforded 4-C-hydroxymethyl-1,2-O-
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The photoamidation of (E,Z)-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-α-D-ribo-hexofuranose (11) and (12) gave 3-C-[[(R) and (S)-carbamoyl(methoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (200) and (201) in a combined yield of 45% and a minor photohydroxylation
product 203. Compound 201 was converted to 1,5,6-tri-O-acetyl-2,3-dideoxy-3-C-[(S)-(carbamoyl)methyl]-α(and β)-D-allofuranose-3',2-carbolactone (205) and 1,5,6-tri-O-acetyl-2,3-dideoxy-3-C-[(R)-(methoxycarbonyl)methyl]-α-D-allofuranose-3',2-carbolactone (204).

The addition of hydrazoic acid and sodium azide to (Z)-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-α-D-ribo-hexofuranose (12) was found to yield 3-azido-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methyl-α-D-glucofuranose (206, 80%) and 3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-[3'-diazo(methoxycarbonyl)methyl]-α-D-glucofuranose (207, 7%). A similar reaction in the absence of hydrazoic acid afforded a 46% yield of 207. Reduction of compound 206 afforded a near quantitative yield the 3-amino-3-deoxy compound 208. Removal of the methyl ester of 208 gave the free β-amino acid 209. Treatment of compound 210, the 3-acetamido derivative of 208, with 66% acetic acid, cleavage of the resulting diol with periodate followed by reduction, afforded the 3-acetamido-3-deoxy-α-D-xylofuranose 212. Benzoylation of 212 followed by acid treatment and subsequent acetylation afforded 3-acetamido-1-O-acetyl-5-O-benzoyl-2,3-dideoxy-3-C-methyl-α (and β)-D-xylofuranos-3',2-carbolactone (215) and (216). Condensation of the halogenose derived from 215 or 216 with $N^6$-benzoyl-$N^6,9$-bis(trimethylsilyl)adenine afforded the α and
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Treatment of the α-Diazo-ester 207 with copper sulfate in refluxing cyclohexane afforded a quantitative yield of 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-spiro-2'-[(R) and (S)-(methoxycarbonyl)methyl aziridine] (221) and (222). Selective trifluoroacetylation of (222) afforded separation of 221 and the trifluoroacetamido derivative of 222. Reduction of 207 with hydrogen and palladium on carbon afforded 208 (43%) and the 3'-hydrazone 224 in 28% yield. Hydrogenolysis of 224 gave a quantitative yield of the α,β-diamino-ester sugars 225 and 226. Separation of 225 and 226 as their di-trifluoroacetamido-derivatives 227 and 228 followed by a sodium hydroxide treatment afforded the synthesis of 2-D and 2-L-(3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl)glycine (229) and (230).
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I. OBJECTIVE

Since the early 1950's the interest in synthesizing deoxy- and branched-chain nucleosides has increased markedly owing to the finding that such modifications of naturally occurring nucleosides has resulted in interesting changes in their biological activity. The synthesis of analogs of branched-chain nucleosides of known biological activity, as measured by their ability to inhibit the growth of KB cells in culture, has led to many compounds of modified activity which might be used as inhibitors or biochemical tools.

The primary objective of this work was to apply the known photochemical addition of formamide to olefins, to a number of unsaturated sugars. Such photoamidations lend themselves to the synthesis of a number of C-carbamoyl sugars which may be converted to aminomethyl, or hydroxymethyl branched-chain sugars. The stereochemical aspect of photoamidation was studied in order to determine if any generalities of such additions could be formulated.

In particular the branching obtained at C-3 and C-4 was viewed as desirable; the former as it has often been found that
branching at that position is observed in many naturally occurring carbohydrates with biological activity and the latter because, particularly in the furanose system, there are few methods available for the functionalization of the C-4 position.

In the second part of this work a similar end was pursued. The synthesis of 3-amino sugars and nucleosides of these, which contained the elements of a β-amino acid at the C-3 position was undertaken. The possibility of synthesizing diamino sugars related to the polyoxin sugar moiety in which the amino acid residue was attached to C-3 of the furanose ring was doubly attractive because of the biological activity of the polyoxins, and that the introduction of branching at C-3 on the sugar moiety of naturally occurring nucleosides has resulted in interesting biological consequences.

In order to provide some background to subsequent discussions a brief summary will be made of the synthesis of branched-chain sugars, photochemical additions to sugars, photoamidation, and nucleoside and glycosyl amino acid synthesis.
II. Introduction

The first reported branched-chain sugar, apiose (1), was isolated from parsley by Vangerichten. Almost thirty years elapsed before O. Th. Schmidt showed the structure of apiose to be 3-C-hydroxymethyl-D-glyceroaldotetrose. In 1919 E. Fischer and Freudenberg isolated hamametose from a tannin in Hamamelis virginiana. Its structure was later shown to be 2-C-hydroxymethyl-D-ribose (2). Little interest in these discoveries was shown until the last two decades during which several branched-chain sugars have been isolated from micro-organisms, higher plants and as glycosidic components. Apiose has since been found to occur in cell wall polysaccharides. Increased interest in the synthesis of branched-chain sugars is in part due to the finding that nucleosides with branched-chain sugars can exhibit cytostatic or virostatic activity of possible therapeutic value.

Branched-chain sugars have been divided into two groups. Branching which occurs by substitution of a hydrogen atom by a group R leads to Type A while substitution by R of a hydroxyl group affords Type B. Compounds classed in Type B are referred to as "deoxy". D-Apiose and D-hamametose are
representative of Type A. L-evenitrose\textsuperscript{17} (3) exemplifies a Type B sugar.

\begin{center}
\begin{tabular}{ccc}
\textbf{1} & \textbf{2} & \textbf{3} \\
\end{tabular}
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1.2 \textbf{Synthesis of Branched-Chain Sugars}

A brief survey of reactions utilized in the introduction of branching into sugars will be discussed below. There have been several recent reviews on the synthesis of branched-chain sugars\textsuperscript{5,6,18} and so only the most recent advances in this area will be discussed. A more detailed discussion will be made of photochemical addition reactions and the utilization of unsaturated sugars in obtaining branched-chain sugars.

1.2.1 \textbf{Synthesis of Sugars of Type A, RCOH}

The addition of diazomethane to keto sugars has been widely used to yield sugars of Type A\textsuperscript{19,20}. This addition leads to the formation of an epoxide 4 which may be then converted via
reduction to the C-methyl compound (4a), hydrolized to the C-hydroxymethyl compound (4b) or into the C-aminomethyl compound (4c), by reaction with ammonia.

Organolithium and organomagnesium reagents have been used to synthesize compounds with similar branching as in 4a. As an example, treatment of the 3-ulose 5 with methylmagnesium iodide or methyllithium afforded compound 6 having the D-ribo configuration\(^{21}\). Interestingly, the reaction of diazomethane with 5 afforded, after lithium aluminum hydride reduction, the compound 7 which is epimeric at C-3\(^{21}\).
C-methyl groups have also been introduced by the use of the sulfur ylid dimethylsulphoxonium methylide, via nucleophilic attack on the carbonyl group. The reaction of 5 with this sulfur ylid followed by reduction of the resulting epoxide gave 6, the same product obtained from the reaction of methylmagnesium iodide with 5.

Acetonitrile in liquid ammonia has been condensed with ketoses to yield branched-chain cyanomethyl carbohydrates which were then reduced to afford the branched-chain aminoethyl carbohydrates. The base catalyzed condensation of nitromethane to keto sugars has been widely utilized to synthesize sugars of Type A. The nitromethyl group may be reduced to afford the aminomethyl sugars of Type A or transformed via elimination to α-nitro olefins which allows the accessibility of "deoxy" nitromethyl branched-chain sugars of Type B via subsequent catalytic reduction. Recently, the potassium permanganate oxidation of 8 was carried out to yield, after reduction of the resulting aldehyde, the branched-chain hydroxymethyl sugar 9.
Similar branched-chain sugars have been synthesized by the reaction of 2-lithio-1,3-dithiane with keto sugars to produce the blocked aldehyde which can be unblocked and reduced to afford hydroxymethyl branched-chain sugars\textsuperscript{28,29}.

1.2.2 \textit{Synthesis of Sugars of Type B, RCH}

The synthetic availability of sugars of this type has greatly increased in recent years by application of the Wittig reaction to keto sugars\textsuperscript{30-41}. The method was first applied by Rosenthal and Nguyen in 1967\textsuperscript{30}. The reaction of 10 with phosphonoacetic acid trimethyl ester and potassium tert-butoxide afforded good yields of the \textit{E} and \textit{Z} branched-chain sugars 11 and 12. Catalytic reduction of the double bond gave the saturated methoxycarbonylmethyl branched-chain sugar 13. The ester was readily reduced to yield the hydroxymethyl sugar 14. Aldehyde nucleosides have been condensed with a Wittig reagent to afford deoxy homologues of the nucleosides\textsuperscript{42}.
J. M. J. Tronchet has recently used the Wittig reaction to yield the unsaturated cyano derivative 15; oxidation of 15 by potassium permanganate followed by reduction with sodium borohydride gave the hydroxymethyl sugar 16 which is a C-3 epimer of apiose. The apiose precursor 17 was earlier synthesized by application of the Grignard reaction to the ulose 18. Similarly, treatment of the L-enantiomer of 18 with methylthiomethylenetriphenylphosphorane gave the methylthiomethylene analogs 19. Desulfurization of this compound yielded the 3-C-methyl-3-deoxy branched-chain sugars 20 and 21.
The reaction of carbon nucleophiles with carbohydrate oxiranes is another general method of the synthesis of sugars of Type B and has been recently reviewed by Williams. Thusly oxiranes have been opened with organometallic reagents, cyanide, and diethyl malonate carbanion. The use of aziridines for the synthesis of amino sugars of Type B has been recognized and will be discussed later in Sec. 5-3.

2. Unsaturated Sugars

The increased activity in the field of unsaturated sugars is reflected in two reviews by Ferrier. Quite recently Kiss has reviewed the subject of β-elimination of carbohydrates containing uronic acid residues. Baer has reviewed the synthesis of unsaturated nitro sugars. In addition, the use of the Wittig reaction, as previously mentioned, has led to a plethora of functionalized exocyclic unsaturated sugars.

This discussion will be necessarily selective and brief. A discussion of addition reactions applied to unsaturated sugars will follow in Sec. 5-2.

2.1 Synthesis of Unsaturated Sugars

Improved methods for the synthesis of 1-deoxyald-1-enopyranoses and the conversion of these into 2,3-unsaturated glucopyranosyl derivatives have been reviewed. Improved yields
of 22 were obtained from the corresponding glycosyl bromide by effecting dehydrohalogenation with tetra-N-butylammonium bromide in the presence of diethylamine. 1,5-diazabicyclo-[5.4.0]-undec-5-ene (DBU) has been utilized to afford high yields of 23 from the glycosyl halide of galactose. Treatment of 22 with boron trifluoride etherate in anhydrous benzene effected isomerization of the double bond to afford excellent yields of 24.

Facile synthesis of the 4,5-unsaturated uronate 25 by treatment of the triacetate 26 with DBU has been reported. Subsequent reduction of the ester with sodium borohydride gave 27.
Interestingly, the hex-4-enopyranose moiety has been reported to occur in the antibiotic sisomycin\textsuperscript{60}. Another general method of obtaining 4,5-enes is the alkali elimination of 4-O-sulfonate uronates\textsuperscript{61}. Similarly, this method has been applied to 28 and 29 to provide the 3,4-ene 30 in the pentose series\textsuperscript{62}.

![Chemical structures](image)

\(28\) R=H; \(R'=\text{OMs}\)

\(29\) R=OMs; \(R'=\text{H}\)

\(30\)

\(31\)

This methodology has also been applied to 3'-0-methanesulfonfyl uronates to provide the 3'4'-ene nucleoside 31\textsuperscript{63}.

The discovery of unsaturated sugars as components of nucleoside antibiotics such as Angustmycin A\textsuperscript{64} and Blasticidin S\textsuperscript{65} has encouraged considerable development of synthetic routes to 2',3'-, 3',4'- and 4',5'-unsaturated nucleosides\textsuperscript{66,67}. Quite recently, Moffatt and co-workers\textsuperscript{68} have devised a method of synthesizing 2',3'- and 3',2'-trans halo acetates from several readily available ribo nucleosides by their reaction with 2-acetoxyisobutyryl halides. Hence, when adenosine was treated with 2-acetoxyisobutyryl bromide, 32 was obtained in good yield. Treatment of this halo acetate with chromous acetate and ethylenediamine afforded 9-(2',3'-dideoxy-β-D-glycero-pent-2-enofuranosyl) adenine (33) in 60% yield.
Other approaches to the synthesis of unsaturated sugars involve the dehydration of nitromethane adducts produced from the condensation of nitromethane with keto or aldehydo sugars. As mentioned earlier, the Wittig reaction has been used to afford many unsaturated sugars such as exocyclic methylenic, methoxycarbonyl methylenic and cyanomethylenic functionalities attached to hexoses and pentoses. Tronchet and co-workers have also synthesized a large number of exocyclic-unsaturated sugars. A variety of α,β-unsaturated carbonyl compounds has been synthesized recently via oxidation and subsequent elimination of partially G-acetylated sugars in the presence of sulfur trioxide and triethylamine. Fraser-Reid and Holder have treated 3,4-di-O-methanesulfonyl derivatives of glucose with sodium iodide and zinc-copper couple, followed by triethylamine, to afford 3,4-unsaturated sugars. Subsequent oxidation of the C-2 hydroxyl group led to a facile synthesis of 3,4-dideoxy-α-D-glycero-hex-3-enopyranosidulose. Finally, the use of
deoxyhalogeno sugars in the synthesis of unsaturated sugars has been very recently reviewed by Szarek.\textsuperscript{72}

3. Application of Photochemical Reactions to Carbohydrates

Until the last decade the photochemical process, with the exception of the photodegradation\textsuperscript{73} of common monosaccharides and disaccharides, has received little attention. Along with the development of methods for the synthesis of suitably functionalized sugars containing a chromophore or unsaturations, the use of photochemistry in carbohydrate synthesis has increased notably. The following discussion will be restricted to photoadditions to unsaturated sugars. No mention will be made of photoeliminations or photorearrangements in carbohydrates. Such reactions have involved studies on the photoelimination and rearrangements of 6-azido sugars\textsuperscript{74}, 3-azido sugars and glycosyl azides\textsuperscript{75,76} to give aldehydes, ketones, and the corresponding next lower sugars respectively via the intermediate nitrenes. Collins and Gupta\textsuperscript{77,78} have studied the known photochemical fragmentations of carbonyl compounds\textsuperscript{79,80} and applied these to the field of pyranosid-2,3- and 4-uloses. Further discussion of these topics is unnecessary and beyond the scope of this thesis. For a review of the photodegradation of simple sugars see Phillips' account\textsuperscript{73}. 
3.1 Photoadditions to Unsaturated Sugars

Horton and Turner\textsuperscript{81} were one of the first groups to apply the addition of photochemically generated excited species to unsaturated carbohydrates. Their study involved the photo-catalyzed addition of thioacetic acid\textsuperscript{82} to the unsaturated sugar \textsuperscript{34}, to afford the C-acetylthio-sugar \textsuperscript{35} formed in 54\% yield by anti-Markovnikoff addition. Subsequently, the photoaddition of phosphines\textsuperscript{83} and 1,3-dioxolane\textsuperscript{84} to the 5-ene \textsuperscript{34} were found to afford the 5-deoxy sugars \textsuperscript{36} and \textsuperscript{37} respectively.

Szarek and Jewell\textsuperscript{84} also reported the sensitized photo-addition of 1,3-dioxolane to 3-deoxy-1,2:5,6-di-O-isopropylidene-3-methylene-\alpha-D-ribo-hexofuranose. The allo-adduct, \textsuperscript{38}, was obtained in 55\% yield. Therefore, it can be seen that the addition of 1,3-dioxolane to unsaturated sugars can be an effective method of chain extension or chain branching.

K. Matsuura and co-workers\textsuperscript{85,86} have extended the photochemical addition of 1,3-dioxolane to 3,4,6-tri-O-acetyl-\alpha-D-glucal (\textsuperscript{39}), 2-acetoxy-3,4,6-tri-O-acetyl-\alpha-D-glucal (\textsuperscript{22}) and the 2,3-unsaturated glycoside \textsuperscript{40}.\[\text{Diagram or chemical structures here}\]
The photochemical addition of 1,3-dioxolane to 39 was found to take place regiospecifically at C-1 from both the α- and β-faces to give the 1:1 adducts 41 and 42 in good yield. The sensitized reaction of the 2-acetoxy enose 22 with dioxolane, gave selective addition exclusively at C-1 with the predominant product being the thermodynamically more stable isomer 43 and the less favourable minor product D-glycero-D-talo-heptose ethylene acetal (44). In the reaction of the 2-enose 40, no regioselectivity was observed with addition taking place at both C-2 and C-3. However, only the most thermodynamically favoured isomers, 45 and 46 were formed. These authors suggested that these reactions proceed, in part at least, by means of a cis-addition mechanism. The photochemical addition of dioxolane, thioacetic acid and benzyl mercaptan to the 4-enose 47 has been studied.
The photoaddition of secondary alcohols\(^{87}\) to \(^{40}\) has been carried out\(^{88}\) and found to yield the C-2 1:1 adduct with the tertiary alcohol group attached to the \(\alpha\)-face of the sugar. Rosenthal and Shudo\(^{89}\) reported the sensitized photoaddition of isopropyl alcohol to the 3-enose \(^{48}\) and found the products to be the C-3 adduct \(^{49}\) and the novel 1:2 adduct \(^{50}\) formed in 31 and 8% yields, respectively.

\[
\begin{align*}
\text{R} & = \text{OAc} & \text{R} & = -\text{C(CH}_3^\text{2})\text{OH} & \text{R} & = -\text{C(CH}_3^\text{2})\text{OH} \\
\end{align*}
\]

Ong and Whistler\(^{90}\) have applied the photoaddition of acetone to the glycal \(^{39}\) to afford the oxetane \(^{51}\) in 33% yield. Matsuura and co-workers\(^{91}\) have studied the solvent effects of the photoaddition of acetone to \(^{39}\) and found the oxetane \(^{51}\) to be the major product if the irradiation was carried out in a solution of
90% acetone-10% isopropyl alcohol. When the irradiated solution was composed of less than 50% acetone the major product was \(52\) resulting from the attack of the ketyl radical \((\cdot C(CH_3)_2OH)\) on the double bond.

The formation of the oxetane is an example of the Paterno-Buchi reaction\(^92\) in which the biradical \(53\), arising by the electrophilic addition of an excited electron deficient carbonyl oxygen atom to the alkene, results in ring closure. The greater electron density at C-2 as opposed to the electron poor C-1, was suggested to be the reason for preferential O-attachment to C-2 in the formation of \(51\). The thermodynamic stabilities of the radical intermediates was suggested to account for the resulting configurations of the two products with the thermodynamically more stable, all equatorial product \(52\) predominating. It should be noted that the photoaddition to \(39\) of the ketyl radical to afford \(52\) was previously found to occur as a side product in the acetone initiated photochemical addition of 1,3-dioxolane to \(39\)^85.
The photoaddition of lactonitrile 54 to the enoses 39, 22 and 40 has recently been studied. It was found that irradiation of 39 or 22 in a solution of 54 afforded the corresponding α and β anomers of the 1'-cyanoethyl-hex-2-enopyranosides 55, 56 and 57, 58. It was further discovered that the products arise from the photochemical liberation of hydrogen cyanide from 54, followed by an acid catalyzed double bond migration and trans-glycosidation. The acid catalyzed reaction of 39 and 22 with alcohols has been known for some time to afford the corresponding 2-enopyranosides.

Fraser-Reid and co-workers have carried out the benzophenone sensitized 1,4-addition of methanol to the enone 59 to give the hydroxymethyl derivatives 60 and 61 in 65% and 14% yields, respectively.
Very recently the same authors\textsuperscript{96} used this type of addition to attach ethylene glycol to the enone 62 to afford the unusual sugar 63 which was then oxidized to 64 and epimerized to the erythro isomer 65. The structure 65 (R= anthracycline residue), which was proposed as the constitution of the antitumor antibiotic Pillarmycin A\textsuperscript{97}, has been questioned because treatment of 64 (or 65, R=Me) with methanolic hydrogen chloride under conditions similar to those used in the structure elucidation of Pillaromycin A, did not afford a methyl pillaroside\textsuperscript{96}.
Other examples of photochemical additions to unsaturated sugar derivatives are the addition of 2,3-dimethylbut-2-ene to \( \alpha,\beta \)-unsaturated keto-sugars\(^{98}\), the addition of furane to keto and aldehydo sugars to give 6-glycosyl-2,7-dioxabicyclo[3.2.0]hept-3-enes\(^{99}\) and the addition of alcohols to the heterocyclic bases of various purine\(^{100}\) and pyrimidine\(^{101}\) nucleosides.

3.2 Photoamidation

The light induced addition of formamide to unsaturated substrates has been reported in a variety of cases, namely, (a) the addition to terminal olefins\(^ {102}\), (b) the addition to nonterminal and cyclic olefins\(^ {103}\), (c) the addition to \( \alpha,\beta \)-unsaturated esters\(^ {104}\), and (d) the addition to acetylenes\(^ {105}\). These photochemical reactions lead to high yields of 1:1 adducts and serve as a method of obtaining higher homologous amides, and their derivatives, from olefins. The addition reaction of formamide to olefins may take place when induced directly by light (wavelengths of 220-250 nm) or may be initiated by sensitizers such as acetone or benzophenone. However, the use of sensitizers gives greater yields of the higher homologous amides than those obtained by direct irradiation. With terminal olefins the 1:1 addition products were formed via an anti-Markovnikov addition. Formamide addition to nonterminal or cyclic olefins resulted in addition to either carbon of the double bond to afford 1:1 adducts. Interestingly, the addition to norbornene has been shown to be stereospecific, leading exclusively
to the \textit{exo} isomer\textsuperscript{103}. One might expect in the case of sterically hindered cyclic olefins to obtain preferential addition to the double bond from the least hindered face of the unsaturation. With \( \alpha,\beta \)-unsaturated esters the addition occurs primarily at the \( \beta \)-carbon except in the case of ethyl cinnamate. These reactions are exemplified below.

\[
\text{RCH}=\text{CH}_2 + \text{HCONH}_2 \xrightarrow{\text{sens} \ 	ext{hv}} \text{RCH}_2\text{CH}_2\text{CONH}_2
\]

\[
\text{hv} \quad \text{RCH}=\text{CH} \quad \text{CONH}_2
\]

\[
\text{RCH}=\text{CHCO}_2\text{R}^\prime + \text{HCONH}_2 \xrightarrow{\text{sens} \ 	ext{hv}} \text{RCH}_2\text{CH}_2\text{CONH}_2
\]

The free radical mechanism proposed for these additions involves the generation of the carbamoyl radical \( \cdot\text{CONH}_2 \) (a)-(b) which then adds to the unsaturated system (c)-(d) as illustrated below\textsuperscript{102}. Telomerization can occur as shown in (e)-(f) and such

\[
\text{H-CONH}_2 \xrightarrow{\text{hv}} \cdot\text{CONH}_2 \quad \text{(a)}
\]

\[
\text{H-CONH}_2 + \text{sens} \xrightarrow{\text{hv}} \cdot\text{CONH}_2 + \text{sens} \quad \text{(b)}
\]

\[
\text{RCH}=\text{CH}_2 + \cdot\text{CONH}_2 \xrightarrow{} \text{RCHCH}_2\text{CONH}_2 \quad \text{(c)}
\]

\[
\text{RCHCH}_2\text{CONH}_2 + \text{HCONH}_2 \xrightarrow{} \text{RCH}_2\text{CH}_2\text{CONH}_2 + \cdot\text{CONH}_2 \quad \text{(d)}
\]
products as 2:1 to 4:1 adducts have been observed. Chain termination can occur in many ways such as shown in (g). The role of the sensitizer, usually acetone or benzophenone, was in dispute as to whether its primary process was one of hydrogen atom abstraction from a formamide molecule, or of energy transfer from the photoactivated sensitizer molecule to formamide resulting in the generation of the carbamoyl radical\textsuperscript{106}. This problem was recently resolved\textsuperscript{107} when the triplet energy of formamide (4.2eV) was found to be 0.7 eV higher than that of the excited acetone triplet (3.5 eV). As a consequence, the only possible mechanism consists of abstraction of the formyl hydrogen from ground state formamide by the excited n-\pi* triplet of acetone. This is further substantiated by the production of isopropyl alcohol and the isolation of side products resulting from the addition of the ketyl radical, (\cdotC(CH\textsubscript{3})\textsubscript{2}OH) to olefins in acetone sensitized photoamidations.
3.3 Photoamidation of Unsaturated Carbohydrates

The application of the photochemical addition of formamide to unsaturated sugars has been undertaken by Rosenthal and co-workers in an effort to determine the stereochemical course of the reaction. Rosenthal and Shudo photoamidated the 3,4-enose 48 to afford the 3-C-carbamoyl branched-chain sugars 66 and 67 (total yield 31%) along with some previously mentioned photo-alkylation products (p. 16). These products resulted from the trans addition of the carbamoyl radical (·CONH₂) and a hydrogen atom to the unsaturation via anti-Markovnikov addition. In an earlier study the addition of formamide to 3,4,6-tri-acetyl-D-glucal (39) was reported to yield the three carbamoyl sugars 68, 69 and 70 in a combined yield of 75% in an approximate ratio.
of 2:2:3. As previously found by Elad\textsuperscript{103(b)}, the attack of the carbamoyl radical occurred at both ends of the cyclic olefin. Finally, Rosenthal and Baker\textsuperscript{109} reported the photoamidation of the exocyclic olefin 71 to give the 3-\text{-}C\text{-}methylene carbamoyl sugar 72 as an alternate synthesis to the ammonia treatment of the saturated ester 13. As Szarek et al. found in the photoaddition of 1,3-dioxolane to 71 (p. 14), the allo product was the only product formed. Compound 72 was utilized in the synthesis of a peptidyl branched-chain sugar related to puromycin.

4. Intramolecular Participation in Amide Hydrolysis

Intramolecular participation in amide hydrolysis has wide significance in peptide and protein chemistry\textsuperscript{110}. Because of this, numerous kinetic studies of these reactions are ongoing\textsuperscript{111-113}. For example, an imidazole group of a histidyl residue and a hydroxyl group of a seryl residue have been implicated in the catalytic activity of serine proteinases\textsuperscript{114}. An unusual feature
of these reactions is that in addition to requiring a favourable configuration of the interacting groups with the formation of a relatively unstable intermediate, the most powerful catalysis is obtained from neighbouring groups, such as hydroxyl which may act as a proton donor as well as a powerful nucleophile.

The intramolecular catalysis by aliphatic hydroxy groups has been widely recognized; the enhanced solvolysis rates for aldonamides, 4-hydroxybutramides, 5-hydroxyvaleramide and similar compounds have been attributed to this cause.

The hydrolysis of 4-hydroxybutramide (73) is catalysed by both hydroxide and hydronium ions at a rate of about 18 times greater than that for butyramide. Presumably, the mechanisms involved in such hydrolyses are those shown below.

\[
\begin{align*}
\text{Acid} & \quad \text{OH} \quad + \text{NH}_2\text{R} \quad \overset{+\text{H}_2\text{O}}{\underset{-\text{H}_2\text{O}}{\rightleftharpoons}} \quad \text{OH} \quad + \text{H}_2\text{O} \\
\text{Base} & \quad \text{OH} \quad \underset{-\text{H}^+}{\overset{+\text{H}^+}{\rightleftharpoons}} \quad \text{OH} \quad \overset{\text{OH}^-}{\rightleftharpoons} \quad \text{OH}^- \\
\end{align*}
\]
5. Addition Reactions to Unsaturated Compounds

5.1 1,4-Michael and 1,3-Dipolar Additions to Olefins

The numerous examples of 1,4-Michael type additions and 1,3-dipolar additions to conjugated olefins are too varied in substrate and adducts to be discussed at any length in this thesis. Only the addition of hydrazoic acid and azides to conjugated olefins will be mentioned.

Boyer\(^{119}\) established that olefins conjugated with electron withdrawing groups undergo addition reactions with hydrazoic acid. Although hydrazoic acid is a very weak acid and may be unable to protonate the heteroatom of the activating group, the mechanism of this addition is considered to be of the \(\text{Ad}^N\) type as illustrated below.

\[
\begin{align*}
\text{R-C=CH}_2 + \text{N}_3\text{H} & \rightarrow \text{R-C-C=H} \\
\text{R-C=CH}_2 + \text{N}_3\text{H} & \rightarrow \text{R-C=C=O} \\
\text{R-C=CH}_2 + \text{N}_3\text{H} & \rightarrow \text{R-C=C=OH} \\
\end{align*}
\]

This reaction has been applied to unsaturated carbonyl, carboxyl, alkoxy carbonyl, nitrile and nitro compounds to give the corresponding β-azido saturated compounds. The reaction is usually
carried out in aqueous acetic acid either at room temperature for long periods of time or at higher temperatures for shorter periods of time.

Huisgen et al.\textsuperscript{120} have extensively studied the addition of organic azides such as phenyl azide and 4-methoxyphenyl azide to similar systems. This involved the 1,3-dipolar addition of the aryl azide to the unsaturated substrate as shown below.

\[
\begin{align*}
+ & \quad \begin{array}{c}
R-N=N=N=N \rightarrow \nabla \\
+ & \quad \begin{array}{c}
\text{R-N} \\
\text{a=b}
\end{array}
\end{array}
\end{align*}
\]

The orientation of addition usually occurs such that the electron withdrawing group of the olefin is located at the 4-position of the resulting \(\Delta^2\)-triazoline. This is illustrated below in the addition of phenyl azide to methyl acrylate (74) to

\[
\begin{align*}
\begin{array}{c}
\text{Ph-N} \\
\text{Ph-N} \\
\text{CH}_2=\text{CHCOCH}_3
\end{array} & \quad \begin{array}{c}
\rightarrow \\
\text{CO}_2\text{CH}_3
\end{array}
\end{align*}
\]

give the \(\Delta^2\)-triazoline 75. The most thoroughly studied additions
of azides are those to angle-strained double bonds such as those of bicyclo[2.2.1] heptene derivatives, norbornene and norbornadiene which react with phenyl azide exothermically and quantitatively. The addition of phenyl azide to the bicyclo [2.2.1] heptene system takes place via exclusive exo attack and fails altogether if exo attack is sterically hindered by substituents at the methylene bridge as in 76.

Similar addition reactions have been carried out by Huisgen and co-workers on unstrained conjugated alkenes. These reactions require long reaction times (for example, 14 months in the case of methyl crotonate and phenyl azide) if a triazoline product is to be obtained as they must be done at low temperatures to prevent degradation of the resulting triazolines. The addition of phenyl azide to methyl acrylate afforded a 77% yield of the triazoline after 5 days at room temperature. The dimethyl ester of fumaric acid gave, in the presence of 4-methoxyphenyl azide, a 59% yield of the corresponding \( \Delta^2 \)-triazoline after 25 days at room temperature. All of these \( \Delta^2 \)-triazolines pyrolyze with the expulsion of nitrogen to give substituted aziridines such as 77. The base catalyzed decomposition of 75 gave methyl...
2-diazo-3-anilinopropionate (78) exclusively. The thermolysis of 78\textsuperscript{123} gave no aziridine products but resulted in the formation of methyl 3-anilino acrylate. Similar 1,3-dipolar addition reactions of aryl azides have been carried out on α,β-unsaturated nitriles and nitro compounds with analogous results\textsuperscript{120}.

5.2 Addition Reactions to Unsaturated Sugars

As previously mentioned (p. 9), the area of unsaturated sugars has recently been reviewed\textsuperscript{52,53} and therefore this discussion will deal primarily with examples of addition reactions related to those discussed in sec. 5.1.

The 1,4-Michael type addition of ammonia, sodium azide and hydrazoic acid to the α,β-unsaturated-ulose 79 has been studied\textsuperscript{124}. Treatment of 79 with ammonia gave the 4-amino-3,4-dideoxy-2-ulose 80 which upon reduction and benzoylation gave 81. The addition of hydrazoic acid to 74 in the presence of acetic
acid, gave, after reduction and benzoylation, the same compound 81.

However, treatment of 79 with sodium azide under mildly acidic conditions gave after reduction only the C-4 epimeric amine 82, presumably via thermodynamic control.

Michael-type additions to sugar nitroolefins have been increasingly explored in recent years. The addition of hydrazoic acid to 83 gave the 2-azido-2,3-dideoxy-3-nitro adduct 84.125

Paulsen and Greve126 have recently carried out the addition of HCN in the presence of catalytic amounts of triethylamine to 83 to give mainly the 2-cyano-3-nitro-gluco-derivative 85. Elimination
of nitrous acid gave the cyanoolefin 86. Similar treatment of terminal nitroolefins such as 87 afforded the cyanoolefin 88. Baer and Rank\textsuperscript{127} have studied the reaction of N-bromo-acetamide with the olefin 87 in the presence of a catalytic amount of sodium acetate. In this way, high yields of 5-acetamido-6,6-dibromo-6-nitro-sugars 89 and 90 were obtained. Treatment of 87 with ammonia

effected amination with concomitant O→N acetyl migration to give 91 and 92.
Funabachi and co-workers\textsuperscript{128} have recently done a study of the control parameters on the stereoselectivity of Michael type additions to sugar nitroolefins. Their study considered the addition of two nucleophiles (\(\text{CH}_3\text{O}^-\) and \(\text{PhCH}_2\text{S}^-\)) to terminal nitroolefins such as 87. They examined six parameters, namely (a) bulkiness of substituents at C-3, (b) reaction solvent, (c) reaction temperature, (d) reaction time, (e) bulkiness of the nucleophiles and (f) the ground state conformation of the starting materials. Their criterion for measuring the effect of these parameters on the course of the reaction was the product ratio of D-gluco 93 to L-ido 94 formed during the addition. They found that consideration must be given to the rate of isomerization of 93 to 94. This interconversion appears to be dependent upon parameters (b), (c) and (d).

Tronchet and co-workers\textsuperscript{129} have applied the 1,3-dipolar addition of diazomethane and aromatic nitrile-oxides to the exocyclic-3-C-methylenic sugar 71 to yield the \(\Delta_1\)-pyrazoline 95 and the spiro -\(\Delta_2\)-isoxazolines 96 and 97.
Although not mechanistically related to the preceding discussions, some mention should be made of some other addition reactions which have been applied to unsaturated sugars. For example, the hydration of exocyclic double bonds via hydroboration\textsuperscript{130,131} and the oxo-reaction\textsuperscript{132}, have been shown to afford the synthesis of branched-chain hydroxymethyl sugars. The oxymercuration\textsuperscript{133} reaction has been applied to exocyclic methylenic sugars to give branched-chain methyl sugars\textsuperscript{134}. The Simmons Smith reaction for the synthesis of cyclopropyl derivatives\textsuperscript{135} and the addition of nitrosyl chloride\textsuperscript{136,137} have also been applied to enoses.

5.3 Carbohydrate Aziridines

Carbohydrate aziridines have typically been synthesized via the trans-diaxial ring opening of anhydro-sugars with the azide ion to afford the azido-hydroxy sugar. Subsequent sulfonation of the hydroxyl group followed by ring closure effected by lithium
aluminium hydride afforded the aziridino-sugar$^{138,139}$. Such aziridines can then be ring opened themselves by the azide ion to give diamino sugars after reduction of the amino-azido sugar$^{139}$. Very recently the strategy of utilizing sugar aziridines to synthesize diamino sugars has been employed in the synthesis of streptolidine (rosenine)$^{140,141}$ which is a guanidino amino acid widely distributed as a component of many streptomyces antibiotics.

Recently, a number of spiro-aziridine sugars have been synthesized. Umazawa and co-workers$^{142}$ found that upon exposing 98 to acetolysis conditions, the spiro-aziridine 99 was produced.

Jean-Marc Bourgeois$^{143}$ has synthesized the analogous aziridino sugars 100 and 101 from the cyanohydrin-tosylate or mesylate 102 and 103 (obtained from 10 by standard procedures$^{144}$). Treatment of 102 (or 103) with lithium aluminium hydride afforded good yields of 100. Treatment of the cyano-sulfonates with Grignard reagents gave the dimethyl or diethyl aziridine 101. Hydrogenation
of 100 gave excellent yields of the 3-amino 3-C-methyl-3-deoxy sugar 104; treatment of 100 with HCl gave the expected amino sugar 105 having the -CH₂Cl branched-chain.

6. Nucleosides

6.1 Branched-Chain Nucleosides

The term branched-chain nucleoside has, through common usage, become the term used to refer to compounds in which a nitrogen heterocycle, usually a purine or pyrimidine is linked to the anomeric position, through nitrogen, of a carbohydrate which contains branching in its carbon skeleton.

The demonstration that the "aminonucleoside" 6-dimethylamino-9-(3'-amino-3'-deoxy-β-D-ribofuranosyl) purine (106), obtained by the hydrolysis of puromycin, had biological activity which differed (qualitively and quantitatively) from that of the antibiotic itself¹⁴⁵, stimulated the synthesis of many other...
nucleoside analogues modified at the 3'-position and other positions of the carbohydrate moiety\textsuperscript{146}. Excellent examples of branched-chain nucleosides possessing biological activity are the $2'\text{-C}_-\text{C'}$- and $3'\text{-C}_-\text{C'}$-methyl nucleosides [\textsuperscript{107-109}]\textsuperscript{147,148} which are effective antivaccinia agents in mice\textsuperscript{149}. Very recently the nitromethyl branched-chain sugar nucleosides [\textsuperscript{110-111}] have been synthesized and found to be active against KB tumor cells\textsuperscript{150}. 

\begin{align*}
\text{106} & \quad \text{NMMe}_2 \\
\text{107} & \quad \text{R}^1=\text{CH}_3; \text{R}^2=\text{H} \\
\text{108} & \quad \text{R}^1=\text{H}; \text{R}^2=\text{CH}_3
\end{align*}
6.2 Nucleoside Synthesis

The number of methods employed in nucleoside synthesis has greatly expanded in the last few years. There have been several reviews of these synthetic methods\textsuperscript{151,152}, and quite recently, there has been an excellent review\textsuperscript{153} of the mechanisms of these reactions. A discussion of these various methods would be unnecessary and beyond the scope of this thesis.

Only the procedures used in the synthesis of compounds discussed in the experimental section, and the background to these procedures, shall be dealt with here.

The fusion of blocked carbohydrates having either an acyl or halo substituent at the anomeric position has been used in the
synthesis of many nucleosides. The procedure usually involves heating at high temperatures, a mixture of the appropriately blocked sugar and the purine or pyrimidine heterocycle under high vacuum for 10 minutes to an hour. The use of an acidic catalyst (p-toluenesulfonic acid, SnCl₄, TiCl₄, etc.) was first reported as necessary but later studies, by Ishido et al., demonstrated that with certain purines, catalysis by Lewis acids was not required. It has been found that while acylated derivatives of adenine and guanine afforded nucleoside products, amino- or hydroxy-purines with very high melting points were unreactive. "Fusibility", i.e. achieving a melt of the reactants, is not the only criterion for the non-catalytic fusion reaction as pointed out by Ishido. The acidity of the purine was an important factor as 6-chloro, 6-iodo, 6-cyano, 2,6-dichloro, and 2,6,8-trichloro-purine gave nucleoside products where as the more weakly acidic purines, such as theophylline and 6-methoxypurine, did not. Quite recently, a mechanistic study by Hosono et al. on the fusion reaction has appeared. They concluded that the formation of 9-β-D-ribofuranosyl-2,6-dichloropurine (112) from the fusion of 2,6-dichloropurine (113) with β-D-ribofuranose tetraacetate (114) in the absence of a catalyst proceeded in "second order fashion involving considerable first order character, i.e., the reaction conceivably proceeds through a bimolecular mechanism involving considerable unimolecular character". Furthermore, they determined
that the acetic acid liberated in the reaction had no catalytic effect and that the rate-determining step is the elimination of acetic acid from the dissociable proton of the purine and the C-1 acetate of the sugar. The mechanism was shown as follows:

![Mechanism Diagram]

The same authors suggested that the mechanisms of catalyzed fusion reactions were similar to the above except that the activation of the purine occurs by interaction with the acidic catalyst. Watanabe, Hollenberg and Fox interpret this in the following fashion: a) formation of a molecular complex between the catalyst and base to give 115 in equilibrium with 116, and b) attack of the acylated sugar by the activated purine 116 to give 117 which goes to the nucleoside 118 with concomitant regeneration of the catalyst. The catalysis by toluenesulfonic acid (dichloroacetic acid, etc) can be explained in a similar manner in that the acid protonates the N-3 position of the purine
to give a purine cation analogous to 115\textsuperscript{153}, followed by abstraction of the N\textsubscript{9} proton by the conjugate base of the catalyst and conversion to the nucleoside with liberation of the protic acid catalyst.

The stereochemistry of the nucleoside products from fusion reactions is dependent upon the method used and of course, whether there is a participating group at C\textsubscript{2} of the sugar. Honsono et al. reported\textsuperscript{158} the fusion without a catalyst, afforded the β-N\textsuperscript{9}-nucleoside 112 exclusively. Fusion of the α-acetate (the anomer of 114) with 113 without a catalyst afforded an α,β-mixture of nucleosides in a 2:3 ratio. Similar fusion of the β-anomer with sulfonic acid as a catalyst initially gave only the β-nucleoside but on extending the fusion time an anomeric mixture of nucleosides was obtained. Finally, treatment of the pure β-nucleoside 112 with a catalytic amount of sulfonic acid for 10 minutes at ~150° led to the production of an anomeric mixture.
This set of data has been rationalized by the mechanism as shown below.

It is assumed that the autocatalyzed fusion of the \( \beta \)-ribofuranose tetraacetate 119 with the base would go with anchimeric assistance by the 2-acetoxy function to give the acetoxonium ion 120 which would be attacked by the purine anion to afford the \( \beta \)-nucleoside 121. With the \( \alpha \)-acetate 122, the assistance could come from the lone pair on the ring oxygen to afford the carboxonium ion 123 which would provide for the finding of anomeric mixtures of nucleosides from \( \alpha \)-acetates. The interconversion of the \( \alpha \) and \( \beta \)-nucleosides 124 and 121 is
understandable via the mechanism shown.

The use of silylated heterocycles\textsuperscript{159} in the fusion procedure has enhanced yields of nucleosides due to the fact that silylated heterocycles are better nucleophiles. Again, catalysts may be used but are not required. The mechanism of nucleoside formation with silylated pyrimidines is shown below\textsuperscript{153}.

Presumably, a similar mechanism to that previously discussed for the fusion of "active" purines exists for the fusion of silylated purines. In solution with acid catalysts, it is believed that the formation of nucleosides proceeds via a Hilbert-Johnson type mechanism involving N-3 glycosylation followed by transglycosylation to give N-9 nucleosides. However, as yet there is no evidence of N-3 glycosides occurring as
intermediates or products arising from fusion reactions\textsuperscript{153}. Hence Hosono's mechanism (p. 39) may explain fusion reactions with silylated purines as well.

6.3 Nucleoside Antibiotics

6.3.1 Psicofuranine and Decoyinine\textsuperscript{13}

Psicofuranine (angustmycin C) and decoyinine (angustmycin A) are two adenine-ketose nucleoside antibiotics elaborated by the Streptomyces. They are structural analogs of adenosine with modifications in the glycoside moiety. Both psicofuranine (125) and Decoyinine (126) are antibacterial and antitumor nucleoside antibiotics.

\begin{center}
\begin{tikzpicture}[scale=0.7]
  \draw (0,0) node[circle,draw] (A) {Ad};
  \draw (0,-1) node[circle,draw] (B) {Ad};
  \draw (-0.5,0) node[circle,draw] (C) {O};
  \draw (-0.5,-1) node[circle,draw] (D) {O};
  \draw (0.5,0) node[circle,draw] (E) {O};
  \draw (0.5,-1) node[circle,draw] (F) {O};
  \draw (C) edge[<->] (D);
  \draw (E) edge[<->] (F);
  \draw (C) edge[<->] (A);
  \draw (C) edge[<->] (B);
  \draw (D) edge[<->] (B);
  \draw (D) edge[<->] (E);
  \draw (F) edge[<->] (E);
  \draw (F) edge[<->] (A);
  \draw (A) edge[<->] (B);
  \draw (A) edge[<->] (C);
  \draw (B) edge[<->] (C);
  \draw (B) edge[<->] (D);
  \draw (B) edge[<->] (E);
  \draw (C) edge[<->] (E);
  \draw (C) edge[<->] (F);
  \draw (D) edge[<->] (F);
  \draw (D) edge[<->] (B);
  \draw (E) edge[<->] (A);
  \draw (E) edge[<->] (B);
  \draw (F) edge[<->] (A);
  \draw (F) edge[<->] (B);
\end{tikzpicture}
\end{center}

\texttt{125 Psicofuranine} \hspace{2cm} \texttt{126 Decoyinine}

Psicofuranine was isolated from \textit{Streptomyces hyrescopicus} var. \textit{decoyicus} in 1954; Decoyinine was isolated from the same \textit{Streptomyces} in 1956. The structure elucidation of 125 was reported by Yuntsen\textsuperscript{160} and the total syntheses\textsuperscript{161} of psicofuranine confirmed
the structure to be that shown above. Hoeksema et al. concluded the structure of decoyinine to be 6-amino-9-(6'-deoxy-β-D-erythro-hex-5'-enofuran-2'-ulosyl)purine (126) which was confirmed by Robins and co-workers in 1968 by total synthesis.

Both psicofuranine and decoyinine inhibit bacterial cells and Walker adenocarcenoma-256 in rats. Gram-positive organisms are more sensitive to decoyinine than gram-negative organisms and both nucleoside antibiotics inhibit B. subtilus and M. tuberculosis.

The site of action of both antibiotics in the cell is suggested to be the inhibition of xanthosine monophosphate aminase which is an aminase system controlling the conversion of xanthyllic acid to guanylic acid. It has been shown that this inhibition can be reversed by guanine containing compounds. Furthermore, psicofuranine has been found to be incorporated into the RNA of bacterial and mammalian tissues.

Psicofuranine was synthesized via the condensation of D-psicosyl chloride tetraacetate (127) and chloromercuri-6-acetamidopurine. Deacylation afforded the antibiotic 125.
Decoyinine was conveniently synthesized via the 6'-0-tosyl-1',3',4'-orthoformyl-psicofuranine (128) by elimination of the tosyl group followed by removal of the orthoformyl blocking group.

Very recently, Leland and Kotick\textsuperscript{168} reported the synthesis of 9-[4'-C-(hydroxymethyl)-α-L-threo-pentofuranosyl]-adenine (129), a structural analog of psicofuranine. The 4-C-hydroxymethyl sugar 130 was synthesized by the method of Schaffer\textsuperscript{169}, who first synthesized 130 by the basic condensation of formaldehyde with the aldehyde 131.
The same authors also applied this condensation to 1,2-O-isopropylidene-\(\alpha\)-D-allofuranose 132 in an effort to synthesize the \textit{erythro-}\(\alpha\)-D-pentofofuranose 133. However, the reaction gave only a 26\% yield of 133 with the major product being 131, arising presumably by epimerization at C-3 during the reaction.

6.3.2 The Polyoxins\textsuperscript{13}

The polyoxins represent a new group of peptidyl nucleoside antibiotics that are antifungal in their actions. To date, twelve polyoxins (A-L) have been isolated from \textit{Streptomyces cacaoi} var. \textit{asoensis} and characterized. All twelve polyoxins contain three common structural features: (i) an \(\alpha\)-L-amino acid, (ii) a \(-5\)-amino-furanuronoside and (iii) a pyrimidine chromophore.

The constitution of all twelve polyoxins, as elucidated by Isono and co-workers\textsuperscript{170} since 1966, are depicted in Table II. All twelve members of this series except C and I, exhibit extreme toxicity towards the phytopathogenic fungus, \textit{Pellicularia filamentosa} f. \textit{sasakii}, which causes sheathblight in rice plants. Interestingly, the polyoxins act specifically against phytopathogenic fungi and lack activity against bacteria. They also exhibit little or no toxicity towards mice, fish or plants.

The mode of action of the polyoxins is suggested to be the inhibition of glucosamine uptake\textsuperscript{171} and therefore\textsuperscript{172}
Table I: Polyoxins A-L.

<table>
<thead>
<tr>
<th>Polyoxin</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>$\text{CH}_2\text{OH}$</td>
<td>$\text{CO}_2\text{H}$</td>
<td>$\text{OH}$</td>
</tr>
<tr>
<td>B</td>
<td>$\text{CH}_2\text{OH}$</td>
<td>$\text{OH}$</td>
<td>$\text{OH}$</td>
</tr>
<tr>
<td>D</td>
<td>$\text{CO}_2\text{H}$</td>
<td>$\text{OH}$</td>
<td>$\text{OH}$</td>
</tr>
<tr>
<td>E</td>
<td>$\text{CO}_2\text{H}$</td>
<td>$\text{OH}$</td>
<td>$\text{H}$</td>
</tr>
<tr>
<td>F</td>
<td>$\text{CO}_2\text{H}$</td>
<td>$\text{OH}$</td>
<td>$\text{OH}$</td>
</tr>
<tr>
<td>G</td>
<td>$\text{CH}_2\text{OH}$</td>
<td>$\text{OH}$</td>
<td>$\text{OH}$</td>
</tr>
<tr>
<td>H</td>
<td>$\text{CH}_3$</td>
<td>$\text{OH}$</td>
<td>$\text{OH}$</td>
</tr>
<tr>
<td>J</td>
<td>$\text{CH}_3$</td>
<td>$\text{OH}$</td>
<td>$\text{OH}$</td>
</tr>
<tr>
<td>K</td>
<td>$\text{H}$</td>
<td>$\text{OH}$</td>
<td>$\text{OH}$</td>
</tr>
<tr>
<td>L</td>
<td>$\text{H}$</td>
<td>$\text{OH}$</td>
<td>$\text{OH}$</td>
</tr>
<tr>
<td>C</td>
<td>$\text{OH}$</td>
<td>$\text{COOH}$</td>
<td>$\text{R}$</td>
</tr>
<tr>
<td>I</td>
<td>$\text{OH}$</td>
<td>$\text{OH}$</td>
<td>$\text{OH}$</td>
</tr>
</tbody>
</table>
the site of action may be related to cell-wall chitin biosynthesis. Polyoxin A has been shown to be a more successful inhibitor of tobacco mosaic virus than blasticidin S.

Naka and co-workers reported the first chemical synthesis of a sugar component of the polyoxins, that being methyl (5-benzamido-3-O-benzoyl-5-deoxy-1,2-O-isopropylidene-α-D-allo-furan)uronate (134). More recently, Moffat and co-workers have described the synthesis of the basic polyoxin nucleoside skeleton as well as its L-talo isomer. As well, Emoto and co-workers have described the preparation of "thymine polyoxin C" (137).
Rosenthal and Shudo\textsuperscript{177}, in this laboratory, have synthesized stereospecifically an analog of the polyoxins' sugar moiety in which the $\alpha$-$L$-amino acid moiety was attached to C-3 of a hexofuranose to afford 2-$L$-(3-deoxy-1,2-0-isopropylidene-$\alpha$-$D$-allofuranos-3-yl)glycine (138). Rosenthal and Richards\textsuperscript{178} synthesized the corresponding $D$ isomer 139. More recently, Rosenthal, Richards and Shudo\textsuperscript{179} reported the synthesis of the 3-hydroxy analogs of 138 and 139 which are 140 and 141.

\begin{align*}
\text{138} & \quad \text{139} \\
\text{140} & \quad R=\text{NH}_2; \quad R_1=\text{H} \\
\text{141} & \quad R=\text{H}; \quad R_1=\text{NH}_2
\end{align*}
7. Synthesis of Glycosyl* Amino Acids

Of the small number of glycosyl amino acids synthesized and reported to date, the most popular procedure has been displacement of either the secondary methanesulfonyloxy$^{174,175}$ or the toluenesulfonyloxy$^{177}$ group with sodium azide followed by reduction of the azide to an amine. Moffat's$^{175}$ procedure utilizes the reaction of the 5'-aldehydo nucleoside 142 with sodium cyanide in aqueous methanolic potassium carbonate and hydrogen peroxide to form the epimeric hydroxyamides 143 and 144. Sulfonation of the 5'-hydroxy group of 143 followed by azide displacement, acid hydrolysis and hydrogenation afforded the basic polyoxin skeleton 135. The D-isomer 136 was synthesized from 144 in the same manner. Similarly, the methods of Naka$^{174}$ and Emoto$^{176}$ utilized the azide displacement of the 5-sulfonyloxy

![Chemical structures](image)

142
143 R=H; R$_1$=OH
144 R=OH; R$_1$=H

* Used in the extended sense, through the indicated, non-anomeric carbon atom.
group of a suitably blocked hexofuranose, followed by oxidation of the 6-hydroxyl and subsequent reduction of the azide to afford the 5-amino-5-deoxy allofuranuronic acid. The configuration of the so formed amino acid was assumed to be that arising from simple $S_N^2$ displacement of the sulfonate by the azide group.

Rosenthal and co-workers utilized the $E$ and $Z$-unsaturated esters 11 and 12 to afford the 3-deoxy- and 3-hydroxy-$D$ and $L$-glycosyl amino acids 138, 139, 140 and 141. Their methodology consisted of stereospecifically dihydroxylating the exocyclic unsaturation of the $Z$-isomer 12 with potassium permanganate or osmium tetroxide via exclusive exo attack of the oxidizing reagent on the double bond to give the $\alpha$-hydroxy ester 145. Subsequent monoacetylation of the $\alpha$-hydroxyl group, stereoselective dehydration with thionyl chloride and pyridine, followed by stereoselective hydrogenation and deacetylation gave the 3-deoxy $\alpha$-hydroxy ester 146. Application to 146 of the sulfonation,
displacement and reduction sequence discussed above afforded the $\alpha$-$L$-amino acid 138 after removal of the 5,6-$\alpha$-isopropylidene blocking group. Similar treatment of the $E$-isomer 11 afforded the $\alpha$-$D$-amino acid 139. The 3-hydroxy analogs 177, 140, and 141 were produced in a similar manner simply by not carrying out the elimination step in the above sequence, by achieving selective monotosylation of the dihydroxy compounds 145 and its $D$-isomer and displacing the sulfonyl group with azide ion which was then reduced.

Rosenthal and Dooley have applied the azlactone synthesis to the 3-ulose 10 to afford the blocked benzamido derivatives of 138 and 139 in two steps, i.e., methanolysis and reduction of the unsaturated azlactones 147 and 148.

147

148

Brink and Jordan have applied the addition of ethyl isocyanoacetate to 10 to afford the N-formyl ethylate derivatives of 138 and 139.
Umezawa and co-workers\textsuperscript{142}, in synthesizing the novel \(-3\text{-amino-}3\text{-C-carboxy-}3\text{-deoxy derivative 149, used the Buchener hydantoin synthesis\textsuperscript{184} to prepare the hydantoin 150. Hydrolysis with barium hydroxide then gave the partially blocked compound 149.}
III. RESULTS AND DISCUSSION

The work to be described in the following sections will be divided into two basic units; (1) Studies on the photochemical addition of formamide to unsaturated sugars and the utilization of the resulting C-carbamoyl sugars in the synthesis of chain extended sugars, hydroxymethyl branched-chain sugars, and nucleosides having branching in the sugar moiety of either the carbamoyl unit or groups derived from this; (2) The addition of sodium azide and hydrazoic acid to α,β-unsaturated esters to afford structural analogs of the sugar moiety of the polyoxins and nucleosides of these. The order that these topics shall be discussed is summarized under the following headings:

1. Photochemical Addition of Formamide to Unsaturated Sugars

1.1 Photoamidation of 2,3,4,6-Tetra-O-acetyl-1-deoxy-D-arabino-hex-1-enopyranose (22)

1.2 Photoamidation of 1,2,4,6-Tetra-O-acetyl-3-deoxy-α-D-erythro-hex-2-enopyranose (24) and Synthesis of 1-(3'-C-Carbamoyl-3'-deoxy-β-D-glucopyranosyl)thymine and Cytosine (166) and (168)
1.3 Photoamidation of 3-O-Acetyl-1,2:5,6-di-O-isopropylidene-α-D-erythro-hex-3-enofuranose (171); Synthesis of a Structural Analog of Psicofuranine

1.4 Photoamidation of (E, Z)-3-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-α-D-ribo-hexofuranose (11) and (12)

2. Addition of Sodium Azide and Hydrazoic Acid to (Z)-3-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-α-D-ribo-hexofuranose (12)

2.1 Synthesis of 3'-Amino Nucleosides

2.2 Synthesis of Analogs of the Sugar Moiety of the Polyoxins

1.1 Photoamidation of 2,3,4,6-Tetra-O-acetyl-l-deoxy-D-arabino-hex-1-enopyranose (22)

Previously it has been mentioned that the photochemical addition of 1,3-dioxolane\textsuperscript{86} and acetone\textsuperscript{91} to 22 has been studied and the stereochemical course of these anti-Markovnikov photoadditions has been inferred to proceed through a cis mechanism\textsuperscript{86}. As well, the stereochemistry of the major products is that of the thermodynamically more stable isomers. The addition of formamide to the 3,4-unsaturated sugar 48\textsuperscript{89} took place exclusively via trans addition of the addends. The photoamidation
of tri-\(_O\)-acetyl-D-glycal (39)\(^{108}\) proceeded with no stereoselectivity and gave products arising from both cis and trans addition.

With these facts in mind, the extension of the photoamidation reaction to 2,3,4,6-tetra-\(_O\)-acetyl-1-deoxy-D-arabino-hex-1-enopyranose (22) was undertaken to determine whether any stereochemical generalities could be made about the photoaddition of formamide.

1.1.1 2,3,4,6-Tetra-\(_O\)-acetyl-1-deoxy-D-arabino-hex-1-enopyranose (22)

Compound 22 was synthesized by known procedures\(^{185,50}\) from the well known 2,3,4,6-tetra-\(_O\)-acetyl-\(\alpha\)-D-glucopyranosyl bromide\(^{186}\) (151). The first procedure\(^{185}\) used was the treatment of the glycosyl bromide 151 with diethylamine in a solution of dry benzene for 32 hours at room temperature to afford the crystalline product 22 in 50% yield. An improved method\(^{56}\) consisted of the treatment of the same bromide with tetra-\(\text{N}\)-butylammonium bromide in anhydrous acetonitrile in the presence of diethylamine for 20 minutes at room temperature. The obvious advantage of the reduced reaction time as well as the increased yield of 22 (80%), is due to the use of the quarternary ammonium salt, and the polar solvent acetonitrile instead of benzene.
Lemieux and Lineback\textsuperscript{187} considered the mechanism of the above dehydrobromination to be an "E2 leaning towards E1" in which the amine solvates the intermediate glycosyloxocarbonium bromide and eventually scavenges the C-2 proton.

1.1.2 Irradiation of 2,3,4,6-Tetra-O-acetyl-1-deoxy-D-arabino-hex-1-enopyranose (22)

When a solution of 22 in formamide containing acetone and tert-butanol was irradiated through a pyrex filter according to Elad's procedure\textsuperscript{103}, a mixture of three products 152, 153, and 154 was formed in 55, 7 and 23\% yields, respectively. The major product 152 was readily obtained pure by fractional crystallization of the product mixture from ethanol-petroleum ether (b.p. 30-60°). Column chromatography of the mother liquors on silica gel afforded the two minor products 153 and 154 as well as an additional quantity of the major product 152.

The structures of the photoaddition products were determined primarily from their infrared (i.r.) and proton magnetic
resonance (p.m.r.) spectra. The i.r. spectra of 152 and 153 showed amide peaks at 3575, 3450 and 1700 cm⁻¹ whereas 154 exhibited an hydroxyl peak at 3600 cm⁻¹ and no amide peaks.

The p.m.r. spectra of 152, 153 and 154 (see Table II) clearly showed doublets which were attributed to a single methine hydrogen, thus establishing the carbamoyl and ketyl radical [(CH₃)₂COH] had added exclusively to C-1 of 22. Irradiation of the methine doublets in the p.m.r. spectra of the heptonamides 152 and 153 led to a collapse of the H-3 quartets to doublets having J₃,4 = 7.5 and 4.4 Hz, respectively. Therefore, H-3 of 152 must be in the axial orientation and H-3 of 153 must be in the equatorial orientation. The J₂,₃ of compound 153 (2 Hz) suggested an H-2e-H-3e relationship. Lemieux and Fraser-Reid found that α-glucopyranose derivatives have J₁,₂ values in the range 3-3.6 Hz. The J₁,₂ value of compound 152 (5.2 Hz) is well outside of this range. In an attempt to corroborate the assigned configuration of C-2 of 152, the diborane reduction according to the method of Brown, of the heptomide, was carried out. Acetylation of the reduction product afforded the acetamido derivative 155 which was different from the known 1-acetamido-3,4,5,7-tetra-O-acetyl-2,6-anhydro-1-deoxy-D-glycero-D-gluco-heptitol (C-2 epimer of 155) previously reported by Fletcher. A first order analysis of the p.m.r. spectrum of compound 155 showed it to be 1-acetamido-3,4,5,7-tetra-O-acetyl-
Table II. NMR SPECTRAL DATA OF 152, 153, 154, and 155.

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<td>5.19 (t)</td>
<td></td>
<td>5.02 (q)</td>
<td>5.0 (t)</td>
</tr>
<tr>
<td>H-5</td>
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<td>6.01 (m)</td>
<td>4.75 (t)</td>
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</tr>
<tr>
<td>H-6</td>
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<td>5.6-5.91 (m)</td>
<td>6.37 (m)</td>
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<td>H-7,7(^1)</td>
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<td>7.89, 7.90, 7.96, 8.04</td>
<td>7.9, 7.92, 7.96, 8.0</td>
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<tr>
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<td>4.15 (s)</td>
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<td>CH(_3)</td>
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<td>OCOCH(_3)</td>
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<td>7.88, 7.94, 8.0, 8.04</td>
<td>7.89, 7.90, 7.96, 8.04</td>
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s, singlet; d, doublet; t, triplet; m, multiplet; o, octet.

Coupling constants in Hz

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<tr>
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</table>

These data were obtained in CDCl\(_3\) and in [(CD\(_3\))\(_2\)CO]\(^*\) by the use of tetramethylsilane as the internal standard.

\(^\dagger\) Obtained in CDCl\(_3\) + \(10\mu\) of concentrated Eu(fod)\(_2\)-d\(_{4}\).
Figure I: Partial 100 MHz NMR Spectrum of 3,4,5,7-Tetra-O-acetyl-2,6-anhydro-D-glycero-D-ido-heptonamide (152) in \((\mathrm{CD}_3)_2\mathrm{CO}\).

Irradiation of (a) H-2 and H-6; H-4
Figure II: Partial 60 MHz NMR Spectrum of 3,4,5,7-Tetra-O-acetyl-2,6-anhydro-D-glycero-D-talo-heptonamide (153). (a) in CDCl₃; (b) in CDCl₃ + 10 μl of concentrated Eu(fod)₃-d₂₆.
Figure III: Partial 100 MHz NMR Spectrum of 3,4,5,7-Tetra-O-acetyl-2,6-anhydro-D-glycero-D-talo heptonamide (153) in CDCl$_3$. Irradiation of (a) H-3; (b) H-2; (c) H-4 and H-5.
Figure IV: Partial 100 MHz NMR Spectrum of 4,5,6,8-Tetra-O-acetyl-3,7-anhydro-1-deoxy-2-methyl-D-glycero-D-talo-octitol (154) in CDCl₃. Irradiation of (a) H-4; (b) H-7.
2,6-anhydro-1-deoxy-\(D\)-glycero-\(D\)-ido-heptitol. As the C-2 configuration of 155 and the heptonamide 152 must be the same, compound 152 must be 3,4,5,7-tetra-O-acetyl-2,6-anhydro-\(D\)-glycero-\(D\)-ido heptonamide. Compound 153 is the C-3 epimer of 152 and so must be 3,4,5,7-tetra-O-acetyl-2,6-anhydro-\(D\)-glycero-\(D\)-talo-heptonamide. Proof that compounds 152, 153 and 154 all exist in the \(4C_1(D)\) conformation is provided by the magnitude of the \(J_{4,5}\) values of 7.5, 8.5, 8 Hz.

A first order analysis of the p.m.r. spectrum of the hydroxyalkylation photoproduct 154 readily showed that it had \(J_{3,4} = 0.8\) Hz, indicative of an H-3e-H-4e relationship, and \(J_{4,5} = 3\) Hz which suggested an H-4e-H-5a configuration. Thus the configurations of C-3 and C-4 of 154 must be the same as the configuration of C-2 and C-3 of 158 and compound 154 must be 4,5,6,8-tetra-O-acetyl-3,7-anhydro-1-deoxy-2-methyl-\(D\)-glycero-\(D\)-talo-octitol.

It is interesting to note that while the 1,3-dioxolan-2-yl radical \(^{86}\) was found to add from both the \(\alpha\) - and \(\beta\) - face of the ring, the carbamoyl and ketyl radicals have added to C-1 in anti-Markovnikov fashion of the 2-acetoxy-1-enopyranosyl ring from the \(\alpha\) -face exclusively. This selective \(\alpha\)-addition can be rationalized by an explanation put forth by Huyser and Jeffrey \(^{192}\) concerning the free radical addition of methanethiol to 4-t-butyl-cyclohexene. If 22 exists in the \(4C_5(D)\) conformation as suggested,
attack of the carbamoyl (or ketal) radical on the \( \alpha \)-face yields an adduct radical 156 having a chair conformation. On the other hand, attack of the radicals on the \( \beta \)-face would lead to the adduct radical 157 having the twist boat conformation. Most likely, the more stable adduct radical 156, which is in the chair conformation, would be formed faster than 157 and hence the products would be those arising from attack on the \( \alpha \)-face.

It should be noted that molecular models of the 1-enose show no steric preference for attack on either the the \( \alpha \)- or \( \beta \)-faces.

The crystalline unblocked heptonamides 158 and 159 were obtained by treatment of 152 and 153 with sodium methoxide in anhydrous methanol followed by deionization with Amberlite IR-120(H+) resin, filtration, and removal of the solvent. Further evidence that the C-1 configuration of 152 and 153 was the same
was that 158 and 159 exhibited positive Cotton effects in their circular dichroism spectra.

1.2 Photoamidation of 1,2,4,6-Tetra-O-acetyl-3-deoxy-\(\alpha\)-D-erythro-hex-2-enopyranose (24) and Synthesis of 1-(3'-C-Carbamoyl-3'-deoxy-\(\beta\)-D-glucopyranosyl)thymine and Cytosine (166) and (168)

In view of the results discussed in sec 1.1, it was thought that application of the photochemical addition of formamide to 24 might further elucidate the stereochemistry of this addition. Furthermore, the possibility of synthesizing branched-chain carbamoyl sugars, and nucleosides of these, appeared attractive in view of the biological activity of gougerotin\(^\text{13}\) in which the sugar moiety contains a \(\text{C}\)-amide residue, specifically that of glucopyranuronamide.

1.2.1 1,2,4,6-Tetra-O-acetyl-3-deoxy-\(\alpha\)-D-erythro-hex-2-enopyranose (24)

The 2-enopyranose 24 was first synthesized\(^\text{193}\) from 22 via an acid catalysed isomerization with zinc chloride in acetic anhydride. Catalytic amounts of sulfuric acid or p-toluenesulfonic acid in acetic anhydride were found to effect the same isomerization of the 1,2 double bond to the 2,3 position. The mechanism appears to involve the acid generated allylic oxocarbonium ion \(\text{160}\), which
then combines with acetic acid to afford 24 in 60% yield, as well as a small amount of the \( \beta \)-anomer of 24.

An experimentally simpler method of obtaining 24 from 22 is to effect the isomerization with a catalytic amount of boron trifluoride etherate in anhydrous benzene\(^{56} \). This latter method was the one of choice for the synthesis of 24 as the reagents were easier to purify and handle and the yield of 24 is slightly higher.

1.2.2 Irradiation of 1,2,4,6-Tetra-\( \alpha \)-acetyl-3-deoxy-\( \alpha \)-D-erythro-hex-2-enopyranose (24)

Irradiation of 24 in a solution of formamide, acetone and tert-butanol by the same procedure used for the irradiation of 22, gave a mixture of four products 161, 162, 163 and 164 in 46, 13, 1, and 7% yields, respectively. The principal product 161 was readily obtained pure by fractional crystallization of the product mixture from benzene-petroleum ether (b.p. 30-60\(^\circ\)). Column chromatography of the mother liquors, after removal of 161 by
filtration, readily afforded the remaining components in pure form.

The structures of these photoproducts were readily deduced by analysis of their i.r. and p.m.r. spectra. Compounds 161, 162 and 163 showed amide peaks at 3475 and 1690 cm⁻¹, whereas 164 exhibited an hydroxyl peak at 3600 cm⁻¹ and no amide peaks. The p.m.r. spectra of 161, 162, 163 and 164 (see Table III) clearly indicated a single methine hydrogen, thus establishing that the carbamoyl and ketyl radicals had added exclusively to C-3 of 24. In the p.m.r. spectrum of compound 161, the lone high field triplet at 7.02 clearly displayed two very
large coupling constants of 12 Hz, which were assigned to $J_{3,4}$ and to $J_{2,3}$. Confirmation of the $J_{2,3}$ coupling constant was provided by a first-order analysis of the H-2 signal, which was observed at $\tau 4.75$ as a quartet and showed $J_{2,3} = 12$ Hz. The large magnitude of the coupling constants of H-3 showed that the carbamoyl and C-2 acetoxy group must be in the equatorial orientation. Further confirmation of the assignment of configuration of C-2 was provided by the fact that the H-1 signal had a coupling constant of 3.4 Hz, which corroborated the cis-arrangement of the C-1 and C-2 acetoxy groups. The trans-diaxial arrangement of H-2, H-3 and H-4 was confirmed by double-irradiation experiments. Therefore, compound 161 must be 1,2,4,6-tetra-O-acetyl-3-C-carbamoyl-3-deoxy-\(\alpha\)-D-glucopyranose.

A similar first-order analysis of the p.m.r. spectrum of the amide 162 indicated that 162 was epimeric with 161 differing only in its configuration at C-3. The magnitude of $J_{1e,2}(3.9$ Hz) of compound 162 was similar to that of 161, thus indicating the cis-arrangement of the C-1 and C-2 acetoxy groups. The H-2 signal of compound 162 was a quartet at $\tau 4.77$ that showed a much smaller $J_{2,3}$ value (6 Hz) than did compound 161 (12 Hz), thus suggesting that H-3 is equatorially oriented. Confirmation of this assignment was provided by the fact that H-3 quartet at $\tau 6.62$ consisted of two doublets of spacing 6 and 5 Hz. Irradiation of the H-3 quartet changed the H-2 quartet to a doublet having
J_{1,2} 3.9 Hz and collapsed the H-4 quartet at \( \tau 5.02 \) to a doublet having \( J_{4,5} 9.5 \) Hz. The magnitude of \( J_{3,4} \) (5 Hz) confirmed that H-3 must be equatorially oriented. The H-6 signal was observed as a multiplet at \( \tau 5.84 \). Irradiation at the latter frequency collapsed the H-5 octet to a doublet having \( J_{5} 9.5 \) Hz, thus confirming the assignment of H-4 and that \( \text{compound 162} \) exists in the \( 4C_1(D) \) conformation which is essential for the assignment of the C-3 configuration. Thus compound \( \text{162} \) must be 1,2,4,6-tetra-O-acetyl-3-C-carbamoyl-3-deoxy-\( \alpha \)-D-allopyranose.

Compound \( \text{163} \), which was isolated in only 1\% yield, was tentatively assigned the \textit{altro} configuration (the C-2 epimer of compound \( \text{162} \)) on the basis of the following spectral evidence. The H-1 signal (\( \tau 4.0 \)) was a much narrower doublet with \( J_{1,2} 2.5 \) Hz, thus indicating H-1 and H-2 were diequatorial. Because the H-2 quartet at \( \tau 4.64 \) exhibited this doublet in addition to a doublet of \( J_{2,3} 5 \) Hz, it was considered that H-3 must be in an equatorial orientation. This was confirmed from a first-order analysis of the H-3 quartet at \( \tau 6.83 \), which showed two doublets of 5 and 5.4 Hz. Furthermore, irradiation at \( \tau 6.83 \) collapsed the H-2 signal to a doublet having \( J_{1,2} 2.5 \) Hz, and also collapsed the quartet at \( \tau 4.7 \), H-4, to a doublet having \( J_{4,5} 7.0 \) Hz. Irradiation at \( \tau 4.66 \) (H-4 and H-2 signals) collapsed the H-3 signal to a singlet. This assignment of structure of compound \( \text{163} \) is based on the premise that \( \text{163} \) exists in the \( 4C_1(D) \) conformation (evidenced by \( J_{4,5} 7 \) Hz),
Table III. NMR SPECTRAL DATA OF 161, 162, 163, and 164.

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s, singlet; d, doublet; t, triplet; m, multiplet; o, octet.

Coupling constants in Hz

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These data were obtained in CDCl₃ by use of tetramethylsilane as the internal standard.
Figure V: Partial 100 MHz NMR Spectrum of 1,2,4,6-Tetra-O-acetyl-3-C-carbamoyl-3-deoxy-\(\alpha\)-D-gluco-
pyranose (161) in CDC\(_3\). Irradiation of (a) H-1; (b) H-2.
Figure VI: Partial 100 MHz NMR Spectrum of 1,2,4,6-Tetra-O-acetyl-3-C-carbamoyl-3-deoxy-α-D-allopyranose (162) in CDCl$_3$. Irradiation of (a) H-3.
Figure VII: Partial 100 MHz NMR Spectrum of 1,2,4,6-Tetra-0-acetyl-3-C-carbamoyl-3-deoxy-\(\alpha\)-\(D\)-altropyranose (163) in CDCl\(_3\). Irradiation of (a) H-3.
Figure VIII: Partial 100 MHz NMR Spectrum of 1,2,4,6-Tetra-O-acetyl-3-deoxy-3-C-(2-hydroxy-2-propyl)-α-D-mannopyranose (164) in CDCl₃. Irradiation of (a) H-3, (b) H-1.
a premise that is certainly tenuous, as α-D-altropyranoses have been shown\(^{194}\) to exist in both \(4C_1(D)\) and \(1C_4(D)\) conformations. Possibly the acetoxymethyl group, which is larger, and equatorial (in the \(4C_1(D)\) conformation), has a greater influence than the carbamoyl group in determining conformation.

The complete structure of the branched-chain hydroxyisopropyl sugar derivative \(164\) was similarly deduced from its p.m.r. spectrum. The very small \((J_{1,2} 1.9 \text{ Hz})\) coupling constant of H-1 clearly indicated that H-2 must be in the equatorial orientation. Irradiation of the H-1 signal at \(\tau 4.02\) collapsed the H-2 triplet to a doublet at \(\tau 4.80\) that showed \(J_{2,3} 2.5 \text{ Hz}\). The H-3 quartet at \(\tau 7.60\) showed \(J_{2,3} 2.5 \text{ Hz}\) and \(J_{3,4} 10 \text{ Hz}\). Irradiation at \(\tau 4.80\) collapsed the latter quartet to a doublet having \(J 10 \text{ Hz}\), and also collapsed the H-1 doublet to a singlet. Irradiation at \(\tau 7.60\) collapsed the H-4 signal at \(\tau 4.75\) to a doublet showing \(J_{4,5} 12 \text{ Hz}\), and the H-2 signal collapsed to a doublet having \(J 1.9 \text{ Hz}\). Thus \(164\) must be 1,2,4,6-tetra-O-acetyl-3-deoxy-3-C-(2-hydroxy-2-propyl)-α-D-mannopyranose. Compound \(164\) was formed by the addition of the ketyl radical (from acetone) and hydrogen to \(24\) similarly as the acetone initiated photoamidation of \(22\) gave \(154\).

The rationalization of the product distribution from the irradiation of the 1-enopyranose \(22\), when applied to that of the irradiation of \(24\), would predict \(162\) or \(163\) to be the predominate product. However, as it was noted (p. 66) previously, there is no
steric preference for α- or β-face attack on 22. By inspection of molecular models, it may be seen that the least-hindered approach of the carbamoyl or ketyl group to C-3 of the double bond of 24 is from above the double bond, because of the steric hindrance of the C-4 and C-1 acetoxyl groups. Hence, products of the C-3-gluco configuration, 161 and 164, predominate. As with 22, an anti-Markovnikov addition has taken place. The addition of the carbamoyl or ketyl free radical to C-3 is followed by addition of hydrogen to C-2 of compound 24. In this last step there appears to be no product stability control.

1.2.3 Synthesis of 1-(3'-C-Carbamoyl-3'-deoxy-α-D-glucopyranosyl) thymine (166) and Cytosine (168)

Initial attempts in the synthesis of nucleosides of the 3-C-carbamoyl sugar 161 via the titanium tetrachloride complex of the sugar acetate and 6-benzamidochloromercuripurine195 were unsuccessful. Attempts to condense 2,4,6-tri-O-acetyl-3-C-carbamoyl-3-deoxy-α-D-glucopyranosyl bromide with 6-benzamidochloromercuripurine in the presence of cadmium carbonate, in boiling xylene were also unsuccessful. In both instances a complex mixture of products, accompanied by extensive decomposition, was obtained. No nucleoside like products were observed by thin layer chromatography (t.l.c.). In order to determine if the free amide functionality of 161 was interfering in these condensations, an attempt to block the amide group with 4,4'-dimethoxybenzhydrol196 was made. However, compound 161 appeared to be largely unstable.
to the blocking conditions employed (4,4'-dimethoxybenzhydrol in acetic acid and sulfuric acid).

Synthesis of the glycosyl halide of 161 was achieved by treatment of the acetate 161 with hydrogen bromide saturated glacial acetic acid at room temperature for one hour. After the thorough removal of all acetic acid and hydrogen bromide, immediate fusion of the glycosyl bromide with 2,4-bis(trimethylsilyl)thymine\textsuperscript{197} at 130-140° at 15 torr for thirty minutes afforded, after column chromatography, the crystalline protected nucleoside 165 in 40% yield. Assignment of the structure of 165 was achieved as follows. The ultraviolet (u.v.) absorption spectrum of 165 had maxima at 207 and 260 nm which was consistent with N-1 glycosylation\textsuperscript{198}. Baker's \textit{trans} rule\textsuperscript{199} would predict the formation of a \(\beta\)-nucleoside which was confirmed by p.m.r. evidence. The p.m.r. spectrum showed H-1' as a doublet at 4.2 with \(J_{1',2'} = 9\) Hz clearly indicating that 165 had the \(\beta\)-anomeric configuration,
The p.m.r. spectrum of 165 also contained a broad exchangeable singlet at \( \tau = 1.0 \) corresponding to the N-3 proton. Two other broad exchangeable singlets at \( \tau = 2.4 \) and 2.9 provided evidence of the presence of the 3'-\( \zeta \)-carbamoyl moiety. A one proton triplet at \( \tau = 7.0 \) with \( J = 10 \text{ Hz} \) was assigned to H-3' and provided evidence that the \textit{gluco}-configuration of the sugar was unchanged.

Treatment of compound 165 with sodium methoxide in anhydrous methanol afforded the free crystalline nucleoside 166 after removal of the sodium ions with an exchange resin and evaporation of the solvent. Recrystallization of the unblocked nucleoside from ethanol-methanol afforded pure 1-(3'-\( \zeta \)-carbamoyl-3-deoxy-\( \beta \)-D-glucopyranosyl)thymine (166). The \( \beta \)-anomeric configuration was further substantiated by the circular dichroism (c.d.)\(^{199} \) spectrum of 166 which had values of +3777 and -2260 at 274 and 243 nm, respectively.

A similar fusion of the glycosyl bromide of 161 with 2,4-bis(trimethylsilyl)-\( N^4 \)-acytelycytosine\(^{197} \) for twenty minutes at 100° and 15 torr afforded 1-(2',4',6'-tri-\( O \)-acetyl-3'-\( \zeta \)-carbamoyl-3'-deoxy-\( \beta \)-D-glucopyranosyl)\( N^4 \)-acytelycytosine (167) in 55% yield. As with 166 the use of Baker's trans rule would predict a \( \beta \)-nucleoside. This was borne out by the p.m.r. spectrum of 167 which showed H-1' at \( \tau = 3.99 \) with \( J_{1',2'} = 10 \text{ Hz} \). The presence of the branched-chain carbamoyl group was evidenced by two broad singlets at \( \tau = 2.36 \) and 2.88 which disappeared upon the addition of
deuterium oxide. A large triplet at \( \tau 6.94 \) with \( J \) 10.4 Hz confirmed the gluco-configuration of the sugar moiety. The u.v. spectrum of \( 167 \) had maxima at 208, 250 and 298 nm which was consistent with \( N^-1 \) glycosylation of \( N^4 \)-acetyl-cytosine. Deacetylation of \( 167 \) was accomplished by the same method as that used in unblocking \( 165 \). However, t.l.c. on silica gel showed the presence of a minor impurity. The nucleoside \( 1-(3' \text{-} C^-\text{carbamoyl}\text{-}3'\text{-deoxy}\text{-}\beta\text{-}D\text{-glucopyranosyl})\text{cytosine (168), was obtained in 65% yield after column chromatography on silica gel. The minor impurity was not isolated or identified. Analytically pure compound was obtained by passage of \( 168 \) through a column of Bio-Rad 1 x 2(OH) resin according to the procedure of Dekker^\text{200}. Collection of the charring, u.v. absorbing fractions eluted from the resin column and removal of the solvent gave pure \( 168 \) which was recrystallized from ethanol-methanol. The u.v. spectrum of \( 168 \) in neutral solution had maxima at 209, 237 and 267 nm. A bathochromic shift of the maxima, \( \lambda_{\text{max}} \) 210 and 274 nm, was observed in acidic solution which verified the site of glycosylation as \( N^-1 \)^\text{201}. The c.d. spectrum of \( 168 \) with a positive Cotton effect at 274 nm and the \( H^-1'-H^-2' \) coupling constant of 9.5 Hz was consistent with the \( \beta \)-anomeric configuration.
1.3 Photoamidation of 3-O-Acetyl-1,2:5,6-di-O-isopropylidene-\(\alpha\)-\(D\)-erythro-hex-3-enopyranose (171). Synthesis of a Structural Analog of Psicofuranine

As mentioned previously (p. 23), the photochemical addition of formamide to 48, the 3-deoxy analog of 171, was carried out to afford the C-3 amides 66 and 67. It was thought that owing to the presence of the 3-O-acetate of 171 that carbamoylation (addition of \(\cdot\)CONH\(_2\) and hydrogen) would take place so as to lead to the functionalization of the C-4 position.

1.3.1 3-O-Acetyl-1,2:5,6-di-O-isopropylidene-\(\alpha\)-\(D\)-erythro-hex-3-enopyranose (171)

Compound (171) was synthesized by the method of Meyer zu Reckendorf\(^{202}\) with a few minor changes. The hydrate (170) of 1,2:5,6-di-O-isopropylidene-\(\alpha\)-\(D\)-ribo-hexofuranos-3-ulose (10) was prepared by the oxidation of 1,2:5,6-di-O-isopropylidene-\(\alpha\)-\(D\)-glucofuranose\(^{203}\) (169) via the "catalytic" ruthenium tetroxide\(^{204a}\) method.
Treatment of 170 with acetic anhydride and pyridine under anhydrous conditions at 70° for five hours (instead of sixteen hours) afforded a higher yield of 171 (90% instead of 77%). After five hours the reaction appeared complete as evidenced by t.l.c..

1.3.2 Irradiation of 3-0-Acetyl-1,2:5,6-di-0-acetyl-isoprolyliden-α-D-erythro-hex-3-enofuranose (171)

The 3,4-unsaturated sugar was irradiated in the same way as 22 and 24 in a solution of formamide, acetone and tert-butanol. After 48 hours, t.l.c. showed that most of the starting material had disappeared and subsequent workup of the reaction mixture gave a syrup which was comprised of primarily two products 172 and 173 and a small amount of 171. It was noted that some decomposition had occurred. It was thought that as 171 has acid labile protecting groups, that trace amounts of formic acid present in formamide might be responsible for such decomposition. Weissberger has noted the difficulty of removing formic acid present in formamide. This
problem did not arise in the previously described irradiations as the fully acetylated sugars 22 and 24 are quite acid stable. Column chromatography of the product mixture on silica gel afforded pure 172 and 173 in 65 and 26% yields, respectively, based on starting material consumed.

Both 172 and 173 were determined to be photoamidation products as their i.r. spectra had peaks at 3500, 3400 and 1695 cm⁻¹ and 3450 and 1690 cm⁻¹ respectively. Interestingly, no products arising from the addition of the ketyl radical [HOC(CH₃)₂] to 171 were isolated. Whether or not the increased steric hindrance about the unsaturation in 171 due to the 3-0-acetate was responsible for the lack of these products is difficult to say.

\[
\begin{align*}
\text{171} & \xrightarrow{hv} \text{HCONH₂} \\
\end{align*}
\]

\[
\begin{align*}
\text{172} & \quad + \quad \text{173}
\end{align*}
\]
Firstly, the structure proof of the major product 172 will be discussed. The p.m.r. spectrum of 172 had a low field doublet at $\tau$3.45 with $J$ 3.5 Hz which was assigned to H-1. The C-2 proton signal at $\tau$5.18 was a quartet with $J_{1,2}$ 3.5 Hz and $J_{2,3}$ 5.5 Hz which indicated the cis relationship of H-2 and H-3. Hence, the C-3 acetate must be "down" and the carbamoyl radical must have added to C-4 of 171. Confirmation of the above assignments was provided by irradiation at $\tau$3.45 which collapsed the H-2 quartet to a doublet having $J$ 5.5 Hz. Deacetylation of 172 with sodium methoxide afforded 4-C-carbamoyl-1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-gulofuranose (174). Slessor has found that 171 rearranged on contact with platinum and palladium in the presence of hydrogen to give the exocyclic 4-ene sugar. It was not inconceivable that such a rearrangement might have taken place photochemically. If such a rearrangement had occurred, the presence of 5-C-carbamoyl products might be expected. This might be verified by 3,5-\(\gamma\)-lactone formation if the 3-hydroxyl and C-5 chain were cis. Hydrolysis of the 5,6-O-isopropylidene group of 172 with 5% aqueous hydrochloric acid in methanol afforded the 4,6-spiro-\(\gamma\)-lactone 176 in 73% yield. Evidence for the lactone structure was obtained from the i.r. spectrum of 176 which contained a strong absorption at 1795 cm\(^{-1}\) which is typical of \(\gamma\)-lactones. There was no amide absorption usually present at 1680 - 1695 cm\(^{-1}\). The absorption of the 3-O-acetate at 1750 cm\(^{-1}\) of 176 did not interfere with the visibility of the lactone band.
The p.m.r. spectrum of 176 did not contain any amide signals between 2 and 4T. A one proton, broad, D$_2$O exchangeable singlet at $\tau$7.25 was assigned to the C-5 hydroxyl group which was evidenced in the i.r. of 176 by a peak at 3550 cm$^{-1}$. Presumably, compound 176 was formed via intramolecular participation of the C-6 hydroxyl group of the intermediate diol 175, during the acid catalyzed hydrolysis of the amide. It is widely held$^{117,209,210}$ that such hydrolyses involve the rate determining attack of the participating group on the carbonyl carbon of the amide which has been protonated in a pre-equilibrium step. Further,

![Chemical Structures]

176 $\text{R}=\text{OAc}; \text{R}'=\text{H}$

177 $\text{R}=\text{H}; \text{R}'=\text{H}$

178 $\text{R}=\text{OAc}; \text{R}'=\text{Ts}$
there is compelling evidence\textsuperscript{211} that amides are protonated predominately on the carbonyl oxygen atom.

The problem of determining the absolute configuration of C-4 of \textit{176} was approached by measuring the circular dichroism spectrum of \textit{177} (deacetylated \textit{176}). The deacetylation of \textit{176} was accomplished with sodium methoxide in methanol to afford a 90% yield of \textit{177}. The i.r. of \textit{177} displayed a strong $\gamma$-lactone absorption at 1775 cm$^{-1}$ and no ester absorptions. Presumably, the lactone \textit{176} might be opened with methoxide to give the methyl ester of the corresponding 4-uronate but recyclization of the $\gamma$-hydroxy ester would be expected upon neutralization to give \textit{177}. No such ester was isolated. It was necessary to remove the 3-0-acetate previous to obtaining the c.d. spectrum as the lactone absorption occurs at $\sim$220 - 230 nm which might be masked by the acetate absorption. A study\textsuperscript{212} of seven sugar $\gamma$-lactones resulted in the generalization that $\gamma$-lactones having the (S) or the (R) configuration at the 2-carbon (the carbon adjacent to the carbonyl function in a lactone ring) will have a positive and negative Cotton effect, respectively. The c.d. spectrum of \textit{177} showed a strong negative Cotton effect at 225 nm. This led to the prediction that \textit{177}, and hence \textit{176} and \textit{172}, had the (R) configuration at C-4 (which is C-2 of the lactone). Tosylation of the 5-hydroxyl group of \textit{176} with tosyl chloride in pyridine afforded 3-0-acetyl-6-deoxy-1,2-0-isopropylidene-5-0-tosyl-$\alpha$-O-gulofuranose-4,6-carbolactone (\textit{178}). Compound \textit{178} was highly crystalline and suitable for X-ray analysis. X-ray analysis of \textit{178} by the direct
method established the absolute configuration of C-4 as being (S)*. It would appear that the application of the previously mentioned c.d. rule to spiro-lactones should be done with caution. The sector rule devised by Jennings, Klyne and Scopes\textsuperscript{213}, when applied to compound 177, resulted in ambiguous predictions of the sign of the Cotton effect.

The completely unblocked compound 6-deoxy-\(\alpha\)-(and \(\beta\))-D-gulofuranose-4,6-carbolactone (179) was obtained by treating 177 with 80% aqueous trifluoroacetic acid. An \(\alpha,\beta\)-mixture of the spiro-lactone was isolated in 75% yield. Proof of the presence of the lactone was obtained from the i.r. spectrum of 179. The anomeric mixture exhibited two low field signals in its p.m.r. spectrum at \(\tau 4.7\) and \(\tau 4.85\) with \(J 4\) Hz and 1.5 Hz which were assigned to the \(\alpha\)- and \(\beta\)-anomeric protons of 179, respectively. No evidence of the presence of an aldehyde was found in the i.r. or p.m.r. spectra of 179. Elemental analysis was consistent with the assigned structure.

\begin{center}
\includegraphics[width=0.5\textwidth]{179.png}
\end{center}

* X-ray analysis of 178 was performed by Dr. J. Trotter and Dr. S. Phillips, Department of Chemistry, University of British Columbia.
Isomerization to the pyranose structure is possible but unlikely as it would produce a trans-fused 5-6 ring system having two axial hydroxyl groups on the pyranose ring.

The structure of the minor amide 172 was determined primarily by intramolecular cyclizations involving the amide group in a variety of ways. As previously mentioned, the i.r. spectrum of 173 indicated the presence of the amide group and this was corroborated by the presence of a broad two proton singlet at $\tau 3.57$ in the p.m.r. of 173, which disappeared upon the addition of deuterium oxide. A doublet at $\tau 4.12$ with $J 4$ Hz was assigned to H-1. The H-2 signal was observed at $\tau 4.67$ as a doublet with the same coupling constant. This indicated either an H-2-H-3 trans-relationship and hence a small or no $J_{2,3}$ value, or that the carbamoyl radical had added to C-3 of 171. Inherent in the first possibility was that the point of carbamoyl attachment must be at C-4. Double bond migration in 171 prior to addition, as previously discussed, might have led to C-5 carbamoylation. Deacetylation of 173 gave crystalline 3-C-carbamoyl-1,2:5,6-di-Q-isopropylidene-\(\alpha\)-D-allofuranose (180). The i.r. spectrum of 180 showed the presence of the hydroxyl and the amide groups. It was evident that no lactonization had occurred and so C-5 carbamoylation with the C-3 acetate and C-4 chain cis was tentatively ruled out. C-4 attachment of the carbamoyl group in 173 was ruled out in the following manner. Removal of the 5,6-Q-isopropylidene blocking group of 173 with 66% acetic acid
or 5% aqueous hydrochloric acid gave the diol amide 181 in 90% yield.

\[ \text{R=0Ac} \quad 181 \]

\[ \text{R=H} \quad 180 \]

The p.m.r. spectrum of 181 showed the presence of the hydroxyl groups as it contained a two proton exchangeable signal between \( \tau 6.5 \) and 7.5. The amide protons occurred at \( \tau 3.52 \) as a broad singlet. Confirmation of the presence of the amide group was provided by the i.r. spectrum of 181 which had absorptions at 3200 and 1695 cm\(^{-1}\). It was expected that if 181 was a C-4 carbamoyl compound differing in configuration at C-3 and/or C-4 from 172, lactonization with the C-6 hydroxyl group would occur in analogy with compound 175. Further, if 181 contained a C-3 amide cis to the diol chain one might expect lactonization to occur involving the C-5 hydroxyl group and the amide. Unfortunately treatment of 181 with base catalysts which are known to promote such intramolecular cyclizations such as carbonate or imidazole\(^{111}\), did not effect lactonization.
In an attempt to obtain additional structural data on compounds 173 and 181, cleavage of the diol structure was undertaken. Treatment of compound 173 with sodium metaperiodate afforded mainly two compounds. Chromatographic separation of the two components was achieved on silica gel. The crystalline compound 182 was determined to be 3-O-acetyl-1,2-O-isopropylidene-\(\alpha\)-D-allo-pentodialdofuranose-3,5-carbolactam (182).

\[
\begin{align*}
\text{181} & \quad \text{182 \( R = H \)} \\
\text{183} & \quad \text{182 \( R = \text{Ac} \)}
\end{align*}
\]

This assignment was based on structure analysis of the corresponding tri-acetate 183 obtained by the treatment of 182 with acetic anhydride and pyridine. The i.r. of 183 had absorptions at 1770 and 1720 cm\(^{-1}\) which corresponded to the imide structure\(^{208}\) (-CO-N-CO-). The acetate absorption occurred at 1750 cm\(^{-1}\). The p.m.r. spectrum of 183 displayed three acetate singlets at \(\tau\) 7.48, 7.82, and 7.89 which were assigned to the N-acetate, and the two O-acetate groups, respectively. The spectrum contained no exchangeable protons. A low field singlet at \(\tau\) 3.38 was assigned to H-5. The H-4 proton occurred at \(\tau\) 5.44 as a singlet. The unobservable H-4-H-5 coupling constant suggested a trans relationship.
between these protons on the cis fused system. Cyclization would not be expected to occur if the amide and intermediate aldehyde were trans on the five membered ring. The H-1 and H-2 signals were observed at \( \tau 4.14 \) and 4.8 as doublets with \( J_{1,2} 4 \) Hz.

As the generation of the C-5 aldehyde destroys the known asymmetry at that center, in the diol 181, the trans relationship of H-4 and H-5 could not be used to assign the absolute configuration of C-4 (and hence C-3).

In other words, the C-4 chain and the amide group were either cis "up" or cis "down" in relation to the furanose ring.

Before discussing the structure of the second product obtained from the periodate cleavage of 181, the synthesis of the 3,5 lactone derived from 181 will be mentioned.

As the synthesis of the aminal 182 proved the cis relationship of the C-4 chain and the amide group, it was viewed that it must be possible to lactonize 181. Such a lactone would retain the known C-5 configuration of compound 181. The p.m.r. spectrum of this lactone would offer proof of the C-4 configuration by the magnitude of the H-4-H-5 coupling constant. A cis 3,5-\( \gamma \)-lactone such as 184 would have a very small \( J_{4,5} \) value. If the

![Chemical Structure](image)
configurations of C-3 and C-4 were the opposite of that shown in 181, the corresponding cis 3,5-\(\gamma\)-lactone would have a large J\(_{4,5}\) value. As previously mentioned, acidic or basic treatment of compound 181 did not afford cyclization. However, pyrolyses of the amide diol 181 at 150° and 0.5 torr in a short path bulb to bulb apparatus afforded two analytically pure compounds. The lower boiling product proved to be acetamide which was identical with commercially available material. The second product proved to be the desired lactone, namely, 5-deoxy-1,2-\(\alpha\)-isopropylidene-\(\alpha\)-D-allofuranose-3,5-carbolactone (185). The i.r. spectrum of compound 185 had a strong absorption at 1790 cm\(^{-1}\) verifying the presence of a \(\gamma\)-lactone structure. Application of the previously mentioned c.d. rule (p. 87) for determining the absolute configuration at the 2-carbon of the lactone (C-3) to 185, which had a positive Cotton effect, predicted the configuration of C-3 to be (S).

As the p.m.r. spectrum of 185 was not sufficiently resolved to allow the individual observation of the C-4 and C-5 signals, 185 was acetylated to give 3,6-di-O-acetyl-5-deoxy-1,2-\(\alpha\)-isopropylidene-\(\alpha\)-D-allofuranose-3,5-carbolactone (186). The p.m.r. spectrum of 186 showed H-1 and H-2 as doublets at \(\tau\)4.05 and 4.87, respectively. A one proton singlet at \(\tau\)5.21 was assigned to H-4. H5 was observed as an unresolved quartet at \(\tau\)5.38 with J\(_{5,6}\) 6 Hz and J\(_{5,6}\), 1.5 Hz. Hence the lactone ring must be above the furanose ring as shown below, and C-3 must have the R-configuration. The mechanism shown
Figure IX: 60 MHz NMR Spectrum of 3,6-Di-O-acetyl-5-deoxy-1,2-O-isopropylidene-α-D-allofuranose-3,5-carbolactone (186) in CDCl₃.
below could account for the loss of acetamide during the cyclization

\[
\text{HOC}_2\text{H}_2\text{N}\text{CH}_3\quad \xrightarrow{\Delta} \quad \text{HOC}_2\text{H}_2\text{N}\text{CH}_3
\]

\[\text{ROCH}_2\quad \xrightarrow{\text{H}+} \quad \text{HOC}_2\text{H}_2\text{N}\text{CH}_3\]

181

\[\quad -\text{CH}_3\text{CONH}_2\]

185 \(R=H\)

186 \(R=\text{Ac}\)

of the amide diol. No lactone was isolated which was blocked at
the 3 position. It is very difficult to explain why no
lactonization of 181 occurred in acidic or basic solutions.

Returning to the products of the periodate cleavage of
the diol, it was shown that an aminal 182 resulted from the
cyclization of the amide group and the aldehyde produced during the
cleavage of the diol. The p.m.r. of the second product 187 contained a total of eight protons excluding the methyls of an acetate and isopropylidene group. A cleavage product should have at the most seven protons other than those of the blocking groups. There were two exchangeable protons at 6.1 and 6.4. The former appeared as a broad doublet with J 12 Hz and the latter as a very broad singlet. A one proton unresolved quartet at 4.43 with J 12 Hz collapsed to a sharp doublet of J 4.5 Hz upon the addition of deuterium oxide. The large coupling constant of 12 Hz was attributed to an NH-H coupling. Irradiation of the H-1 doublet at 4.12 with J 3.6 Hz collapsed the doublet at 5.19 to a singlet which was assigned to H-2. Irradiation of the doublet (after exchange) at 4.43 collapsed the doublet at 5.38 to a singlet. A doublet at 5.05 with a very large coupling constant of 11 Hz, and a second doublet (partially overlapping the doublet at 5.38) at 5.3 with the same coupling constant were assigned to the C-6 protons. The two remaining doublets at 4.43 and 5.38 were assigned to H-5 and H-4, respectively. The i.r. spectrum of 187 contained an hydroxyl absorption at 3500 cm\(^{-1}\) and carbonyl absorptions at 1750 and 1720 cm\(^{-1}\) which were assigned to the acetate and lactam groups, respectively. The elemental analysis of 187 was consistent with the molecular formula \(C_{12}H_{17}NO_7\cdot\frac{1}{2}H_2O\). The high resolution mass spectrum of 187 gave a parent ion \((M^+ - 286.9960)\) calculated to be \(C_{12}H_{17}NO_7\) \((M^+ - 287.1004)\). The fragmentation pattern showed the
Figure X: Partial NMR 100 MHz Spectrum of 3-O-Acetyl-5-deoxy-1,2-O-isopropylidene-\(\beta\)-L-talofuranose-3,5-carbolactam (187) in CDC\(_3\). (a) with D\(_2\)O; Irradiation of (b) H-1; (c) H-5.
loss of water leaving m/e-C_{12}H_{15}NO_6 and the loss of acetic acid resulting in m/e-C_{10}H_{13}NO_5 suggesting a primary alcohol and the cis relationship of the C-3 acetate and H-4. As the absolute configuration of C-3 and C-4 had been determined from the structure analysis of the lactone 186 and as 187 has a lactam group with the nitrogen atom attached to C-5, it must be 3-O-acetyl-5-deoxy-1,2-O-isopropylidene-β-L-talofuranose-3,5-carbolactam. At first glance the formation of 187 from the diol 181 was most disturbing as it appears to be the result of the amide nitrogen atom displacing an hydroxyl group, which is widely held to be a very poor leaving group. However, it is not inconceivable that the cyclic intermediate formed during the cleavage reaction of the diol, is susceptible to

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{OH} & \quad \text{OH} \\
\text{CONH}_2 & \quad \text{HO}_4^- \\
\text{AcO} & \quad \text{AcO} \\
\text{181} & \quad \text{187}
\end{align*}
\]

attack by the nitrogen of the 3-C-amide group. It should be noted that such a displacement would involve inversion at C-5. The H-4-H-5 coupling constant of 4.5 Hz confirmed that H-4 and H-5 were cis on the fused ring system and therefore the configuration of C-5 must have inverted to give 187. Clearly compound 187 had the
opposite C-5 configuration to that of C-5 of the lactone 186 which had no observable $J_{4,5}$ value.

Near the end of this work a literature search revealed that the 5,3-hemiacetal of 3-C-hydroxymethyl-1,2-O-isopropylidene-\(\alpha\)-D-ribo-pentodialdose (190) had been reported by Paulsen \(^{29}\). It was evident that the 3,5-\(\gamma\)-lactone 185 could be converted into 190, via reduction to the 3-C-hydroxymethyl branched-chain sugar 188, followed by subsequent cleavage and cyclization. By comparison of the hemiacetal derived from 185 to that synthesized by Paulsen, a

\[
\begin{align*}
185 & \quad & 188 \quad R=H \\
189 & \quad & 190 \quad R=OAc
\end{align*}
\]

corroborating structure proof of the amide 173 and the compounds derived from it would be obtained. Hence, the lactone 185 was treated with sodium borohydride in methanol which afforded 3-C-hydroxymethyl-1,2-O-isopropylidene-\(\alpha\)-D-allofuranose (188) in 70% yield. Paulsen had obtained 188 by the addition of 2-lithio-1,3-dithiane to the keto sugar 10, deblocking, reduction of the resulting 3-C-aldehyde, and removal of the 5,6-O-isopropylidene group. No p.m.r. data was reported but an optical rotation value of $+30^\circ$ was reported. The product obtained from the reduction of 185 had a rotation of $+28.4^\circ$. Compound 188 was
completely characterized as its tri-acetate 189. Cleavage of the diol structure of 188 with sodium metaperiodate under the conditions reported by Paulsen29 afforded the 5,3-hemiacetal 190 in 30% yield. The p.m.r. of 190 was identical with that reported in the literature and the optical rotation of 190 was in good agreement with the reported value. As the cyclization of the hydroxy-aldehyde to give the hemiacetal 190 is reversible, the 5-exo alcohol predominated because of greater thermodynamic stability. The C-5 configuration was proven by the p.m.r. spectrum which contains a one proton singlet at δ4.6 which was assigned to H-5. Hence, firm chemical proof of the C-3 and C-4 configurations of 185 and the precursor amide 173 was obtained.

1.3.3 Synthesis of a Structural Analog of Psicofuranine

The ready synthesis of the 4-C-amide 172 and conversion of it into the 4,6-γ-lactone 176 promoted interest in the synthesis of nucleosides which would be branched at carbon four. As mentioned in the introduction Psicofuranine which has antibiotic properties13 may be viewed as a branched-chain hydroxymethyl sugar nucleoside. Only one 4' substituted nucleoside other than those related to Nucleocidin has been reported168. With this in mind the conversion of 172 into a branched-chain 4'-C-hydroxymethyl nucleoside was undertaken.
1.3.4 Reduction of 3-O-Acetyl-6-deoxy-1,2-O-isopropylidene-α-D-
gulofuranose-4,6-carbolactone (176)

The reduction of lactones to hydroxyl compounds has been accomplished in the past with lithium aluminium hydride\textsuperscript{215a} in tetrahydrofuran. Reduction of 176 with vitride [bis(2-methoxyethoxy)aluminum hydride] in tetrahydrofuran gave good yields of 4-C-hydroxymethyl-1,2-O-isopropylidene-α-D-gulofuranose (191) when the reaction was carried out on a small scale (less than 0.10 g of 176). However, when larger scale reactions were carried out the tetra-alcohol product was very difficult to separate from the resulting inorganic salts. Wolfrom et. al.\textsuperscript{215b} has reported the reduction of sugar lactones with sodium borohydride under very acidic conditions. It was found that treatment of 176 with sodium borohydride in methanol-water resulted in a 79% yield of 191. Isolation of the product was accomplished by the removal of the sodium ions with an exchange resin and azeotropic distillation with methanol. The p.m.r. spectrum of 191 in acetone-\textit{d}_6 contained a doublet at \textit{r}4.17 with J 4 Hz which was assigned to H-1. A quartet at \textit{r}5.28 with J 4 Hz and 5.8 Hz was assigned to H-2. The magnitude of J\textsubscript{2,3} 5.8 Hz confirmed that no epimerization at C-3 had occurred during the reduction. The H-3 signal occurred at \textit{r}5.58 as a doublet. The tetra-alcohol was fully characterized at its tetra-acetate 192.
1.3.5 Periodate Cleavage of 4-\(\text{C}\)-hydroxymethyl-1,2-\(\text{O}\)-isopropylidene-\(\alpha\)-\(\text{D}\)-gulofuranose (191)

To synthesize the 4-\(\text{C}\)-hydroxymethyl branched-chain sugar for nucleoside synthesis it was necessary to cleave the 5,6-diol structure and reduce the resulting aldehyde. Treatment of 191 with sodium metaperiodate resulted in the desired cleavage and subsequent reduction of the aldehyde with sodium borohydride gave 4-\(\text{C}\)-hydroxymethyl-1,2-\(\text{O}\)-isopropylidene-\(\alpha\)-\(\text{D}\)-erythro-pentofuranose (193) in 88% yield. Compound 193 was reported just as this work was being completed. This synthesis was discussed in the Introduction. Acetylation of the triol was achieved with pyridine and acetic anhydride to afford 4-\(\text{C}\)-acetoxymethyl-3,5-di-\(\text{O}\)-acetyl-1,2-\(\text{O}\)-isopropylidene-\(\alpha\)-\(\text{D}\)-erythro-pentofuranose (194) in 90% yield.
1.3.6 Synthesis of 4-C-Acetoxyethyl-1,2,3,5-tetra-O-acetyl-α and β-D-erythro-pentofuranose (195)

In preparation for the synthesis of a nucleoside of the branched-chain hydroxymethyl sugar the 1,2-O-isopropylidene group had to be removed and a suitable leaving group attached to the anomeric carbon. Towards this end, the triacetate 194 was treated with 80% aqueous trifluoroacetic acid to afford the triacetylated sugar which was free at the 1 and 2 positions. Acetylation of the product of the hydrolysis reaction with acetic anhydride and pyridine gave a mixture of the α- and β-anomers of 4-C-acetoxyethyl-1,2,3,5-tetra-O-acetyl-D-erythro-pentofuranose (195) in a combined yield of 80%. The β-anomer predominated as the anomeric region in the p.m.r. spectrum of the mixture showed a doublet at τ3.6, J1,2 4 Hz and a singlet at τ3.8 for H-1α and H-1β, respectively, in a ratio of 1:4.

1.3.7 Synthesis of 9-(4'-C-Hydroxymethyl-α-D-erythro-pentofuranosyl) adenine (198) and 9-(4'-C-Hydroxymethyl-β-D-erythro-pentofuranosyl)adenine (199)

To carry out the condensation of the heterocycle with the branched-chain sugar 195, the α,β-peracetylated sugar was first converted to the more reactive glycosyl bromide. This was accomplished by treating a solution of 195 in dichloromethane with
hydrogen bromide-saturated glacial acetic acid for 1 hour at room temperature. Careful removal of the acids under diminished pressure afforded a brown syrup which was immediately mixed with \( N^6 \)-benzoyl-\( N^6 \), 9-bis(trimethylsilyl)adenine\(^1\). The resulting mixture was fused at 130-135° and 15 torr for 30 minutes. T.l.c. of the product on silica gel showed the presence of two major components which charred and absorbed ultraviolet light. A third nucleoside-like minor component was also evidenced. Column chromatography afforded separation of these components to give \( N^6 \)-benzoyl-9-(4'-\( C \)-acetoxyethyl-2',3',5'-tri-\( D \)-acetyl-\( \alpha \)-\( D \)-erythro-pentofuranosyl)adenine (196) and the \( \beta \)-anomer 197 each in 20% yield. The third component, obtained in about 5% yield, was not identified. The p.m.r. spectra of 196 and 197 displayed doublets at \( \tau 3.36 \) and 3.73 with \( J_{1',2'} \) values of 4 Hz and 5.8 Hz. As the coupling constants are both large they could not be used as proof of the anomeric configurations of 196 and 197. However, it has been observed in the past that the anomeric signal of the \( \alpha \)-\( D \)-anomer usually appears at lower field than that of the \( \beta \)-\( D \)-anomer\(^2\). On this basis compound 196 was tentatively assigned the \( \alpha \)-\( D \)-configuration and 197 the \( \beta \)-\( D \)-configuration. The \( \alpha \)-\( D \)-anomer 196 had a triplet at \( \tau 5.23 \) with \( J \) 4 Hz and a doublet at \( \tau 4.42 \) which were assigned to H-2' and H-3'. This was confirmed by irradiation experiments. Similarly, the \( \beta \)-\( D \)-anomer 197 displayed an unresolved quartet at 3.83 \( J_{2',3'} \) 5.5 Hz and a doublet at \( \tau 4.1 \)
Figure XI: 100 MHz Spectrum of $N^6$-Benzoyl-9-(4'-C-acetoxyethyl-2',3',5'-tri-O-acetyl-$\alpha$-D-erythro-pentofuranosyl)adenine (196) in CDC$_3$. 
Figure XII: 100 MHz Spectrum of $N^6$-Benzyol-9-(4'-O-acetoxymethyl-2',3',5'-tri-O-acetyl-$\beta$-D-erythropentofuranosyl)adenine (197) in CDCl$_3$. 
for H-2' and H-3', respectively. As neither could be induced to crystallize both compounds were unblocked with sodium methoxide in anhydrous methanol to afford 9-(4'-\(\text{C}_2\)-hydroxymethyl-\(\alpha\)-D-erythro-pentofuranosyl)adenine (198) and the \(\beta\)-D-anomer (199). The site of glycosylation was established as \(N^9\) as the u.v. spectra of both 198 and 199 had maxima at 258 nm. The assignment of the anomeric configurations as above was confirmed by the c.d. spectra of 198 and 199. Compound 198 displayed a positive Cotton effect, \(\left[\alpha\right]_{255}^{30} +1480^\circ\), at 255 nm while compound 199 displayed a very small negative Cotton effect. It is well known that \(\alpha\) and \(\beta\)-D-anomers of adenine nucleosides have positive and negative Cotton effects, respectively\(^{218}\). The p.m.r. spectrum of 198 contained a doublet at \(\tau 3.31\) with \(J 6.5\) Hz whereas the p.m.r. of 199 contained a doublet at \(\tau 3.59\) with \(J 2.5\) Hz. These signals were assigned to anomeric protons of the \(\alpha\) and \(\beta\)-anomeric nucleosides, respectively.

\[
\begin{align*}
195 & \\
\text{AcO} & \quad \text{O} \\
\text{AcO} & \quad \text{OAc} \\
\text{Ac} & \quad \text{OAc} \\
\text{NHR'} & \\
\text{RO} & \quad \text{OR} \\
197 & \quad \text{R=Ac; R'=Bz} \\
199 & \quad \text{R=R'=H} \\
196 & \quad \text{R=Ac; R'=Bz} \\
198 & \quad \text{R=R'=H}
\end{align*}
\]
1.4 Photoamidation of (E), (Z)-3-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-α-D-ribo-hexofuranose (11) and (12)

In view of the great interest in the synthesis of analogs of the sugar moiety of the polyoxins, we were interested in synthesizing sugars which had branching at the three carbon containing an amino acid residue. Such syntheses have been reported by Rosenthal, Richards and Shudo\textsuperscript{177-179} from this laboratory. However, the method employed involved a ten step sequence from (11) or (12).

It was viewed that the photoamidation reaction applied to 11 and 12 might offer a two step sequence to the same glycosyl amino acids. This would involve the attachment of the carbamoyl

* Used in the extended sense.
radical to the branching carbon (α to the methyl ester of 11 and 12), followed by a Hofmann rearrangement of the α-carbamoyl ester to the α-amino ester. As mentioned in the Introduction, Elad\textsuperscript{104} reported the photoaddition of formamide to simple α,β-unsaturated esters afforded the corresponding β-carbamoyl esters. However, photoamidation of ethyl cinnamate gave the corresponding α-carbamoyl ester. Therefore, it was interesting to determine if formamide would add to 11 and 12 at the α or β-carbon.

1.4.1 Synthesis of (E), (Z)-3-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-\textalpha-\textD-ribo-hexofuranose (11) and (12)

Using the procedure of Rosenthal and Nguyen\textsuperscript{30} the ketose 10 was condensed with the carbanion formed from carbomethoxy-methyl dimethylphosphonate and potassium tert-butoxide in dimethyl formamide. After work up two spots were visible on t.l.c. Isolation of the higher \( R_f \) spot by column chromatography afforded a mixture of the pure (E) and (Z)-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-\textalpha-\textD-ribo-hexofuranose (11) and (12). Fractional crystallization of the mixture from hexanes allowed the isolation of the pure Z-isomer 12. The structures of the E- and Z-isomers were determined by C.M. Richards\textsuperscript{219} by inspection of the p.m.r. spectra of 11 and 12. In the E-isomer,
H-4 is under the deshielding influence of the ester function and thus the H-4 signal at $\tau 4.2$ is at lower field than the H-4 signal of the $Z$-isomer which is at $\tau 5.32$. Furthermore, in the $Z$-isomer, H-2 and the ester function are cis with respect to each other with a consequent lowering of the $\tau$ value of H-2 to $\tau 4.23$ in contrast to the much higher $\tau$ value of H-2 in the $E$-isomer at $\tau 5.32$.

1.4.2 Irradiation of (E), (Z)-3-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-$\alpha$-D-ribo-hexofuranose (11) and (12)

Irradiation of a mixture of 11 and 12 (or 12 alone) in formamide containing acetone and tert-butanol by the same procedure as previously described afforded, after the usual work up, three products. Very careful column chromatography of the mixture on silica gel allowed the isolation of the three pure components 200, 201 and 202. It should be noted that it was not possible to obtain
large quantities of 200 and 201 separate from each other. The compounds 200 and 201 were shown to be amide products by their i.r. spectra which had absorptions at 3520, 3420 and 1700 cm$^{-1}$. The methyl ester absorption was observed at 1750 cm$^{-1}$. The product resulting from the addition of the ketyl radical [(CH$_3$)$_2$COH] displayed a hydroxyl absorption at 3500 cm$^{-1}$ and no amide peaks in its i.r. spectrum. The two amides were obtained in equal quantities in a combined yield of 45%. The acetone addition product was isolated in 21% yield. It should be noted that the isomeric (at C-1') acetone addition product of 202 was most likely present in the mixture but could not be obtained pure. The p.m.r. spectra of 200, 201 and 202 showed the H-2 signals as triplets at $\tau$5.08, 5.16, and 5.13 with $J_{2,3}$ of 3.7, 4.0 and 3.7 Hz respectively, thus establishing that the carbamoyl and ketyl radicals had added to 11 and 12 at the $\alpha$-carbon exclusively, and that C-3 had the allo configuration.

The assignments of H-1 and H-2 were confirmed by irradiation experiments. If attachment of the carbamoyl or ketyl radical had taken place at C-3, the H-2 signal of such products would have been a doublet. Presumably, the C-3 radical resulting from $\alpha$-carbamoylation is more stable than the alternative radical formed by carbamoyl attack at C-3. The acetone addition product was only characterized by p.m.r. and i.r. and the configuration at the $\alpha$-carbon was not determined.
Before attempting to prove the configuration at the branching carbon it was interesting to attempt the Hofmann rearrangement of the α-carbamoyl esters 200 and 201. Unfortunately, the application of two variations of the Hofmann rearrangement reaction to either 200, 201 or a mixture of both resulted in either no reaction or extensive decomposition. The methods employed were treatment of the amides with (A) a sodium hypochlorite solution in dimethoxyethane, (B) sodium methoxide and bromine in anhydrous methanol and, (C) lead tetraacetate in dimethylformamide. Possibly, the reason for the failure of these attempts lies in a low migratory aptitude of the R group of 200 or 201 (R = R-CH-CO₂Me).

\[
\begin{align*}
R-NH₂ & \xrightarrow{\text{hydrolysis}} R-N=C=O & \xrightarrow{\text{hydrolysis}} R-NH₂
\end{align*}
\]

It is held that electron withdrawing groups decrease migratory amplitudes.

A tentative proof of the configurations of the α-carbons of 200 and 201 was obtained as follows. Treatment of 201 with 66% aqueous acetic acid followed by acetylation with acetic anhydride in pyridine gave a compound tentatively assigned the structure 203. Treatment of compound 203 with 80% aqueous trifluoroacetic acid followed by acetylation gave primarily two compounds as observed by t.l.c. of the reaction mixture. Chromatography of this mixture afforded the isolation of compounds 204 and 205.
The i.r. spectrum of 204 contained a strong absorption at 1795 cm\(^{-1}\) which verified that lactonization had occurred. There were no amide absorptions in the i.r. spectrum of 204 and the p.m.r. spectrum clearly showed the presence of the methyl ester as a three proton singlet at \(\delta 6.27\). Therefore, the C-2 hydroxyl group must have lactonized during the acid hydrolysis of the amide to afford the C-3' methoxycarbonyl 3',2-lactone 204. A quartet at \(\delta 6.4\) with \(J_{2,3} 6\) Hz and \(J_{3,3'} 2\) Hz was assigned to H-3. The magnitude of the H-3-H-3' coupling constant suggested a trans relationship between those protons. Therefore, the C-3' configuration of 204 must be \(R\) and the C-3' configuration of 201 must then be \(S\). Compound 200 which only differed from 201 in the configuration
of C-3' must have the R configuration at that center.

The i.r. spectrum of compound 205 clearly showed the presence of the lactone and amide groups. As 205 was a mixture of α and β-anomers a first order analysis of the p.m.r. spectra was very difficult. A quartet at τ6.44 with $J_{2,3}$ 7 Hz and $J_{3,3'}$ 4 Hz was tentatively assigned to H-3 of the β-anomer of 205. The larger $J_{3,3'}$ value of 4 Hz suggests that the chirality of C-3' of 205 is S.

2. Addition of Sodium Azide and Hydrazoic Acid to (Z)-3-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-α-D-ribo-hexofuranose (12)

In this work our prime objective was to synthesize 3-amino sugars, and nucleosides of these, which contained the elements of a β-amino acid at C-3 of a sugar. The possibility of synthesizing diamino sugars related to the polyoxin sugar moiety and β-hydroxy-α-amino acids in which the amino acid residue was attached to C-3 of the furanose ring was doubly attractive because of the biological activity of the polyoxins, and that the introduction of branching at C-3 on the sugar moiety of naturally occurring nucleosides has been found to result in interesting changes in the biological activity of nucleosides.
2.1 Synthesis of 3'-Amino Nucleosides

2.1.1 The Addition of Hydrazoic Acid in the Presence of Sodium Azide in Dimethylformamide to (Z)-3-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-\(\alpha\)-D-ribo-hexofuranose (12)

When a solution of (12) was treated with excess sodium azide and hydrazoic acid in dimethylformamide at 55° for 5 days in a sealed flask, two products were isolated in 80 and 7% yield. The products were shown to be 3-azido-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methyl-\(\alpha\)-D-glucofuranose (206) and 3-amino-3-deoxy-3-C-[3'-diazo(methoxycarbonyl)methyl]-1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-glucofuranose (207).

The structures of 206 and 207 were readily deduced by analysis of their i.r., p.m.r. u.v. and mass spectra. The i.r. spectrum of 206 exhibited a strong azide absorption at 2137 cm\(^{-1}\).

\[
\begin{align*}
\text{H} & \hspace{1cm} \text{CO}_2\text{Me} \\
\text{HN}_3 & \rightarrow \\
\text{NaN}_3 & \hspace{1cm} \text{Me}_2\text{OC}
\end{align*}
\]

\(\text{12} \hspace{1cm} 206 \hspace{1cm} 207\)
The p.m.r. spectrum of 206 contained an AB quartet at $\tau$6.96, $J$ 18 Hz, which was assigned to the C-3' methylene protons. The i.r. spectrum of 207 had two absorptions at 3410 and 3350 cm$^{-1}$ which indicated the presence of a primary amine and a strong absorption at 2101 cm$^{-1}$ corresponding to a conjugated diazo group. The absorption of the $\alpha$-diazo-carbonyl ester group of 207 occurred at 1685 cm$^{-1}$ in good agreement with that reported$^{120}$ for such a group. The u.v. spectrum of 207 had a maximum at 269 nm ($\varepsilon$7630) which is typical of diazo-esters$^{120}$. The p.m.r. spectrum of 207 contained a two proton broad singlet at $\tau$7.95 which disappeared upon the addition of deuterium oxide. This confirmed the presence of the primary amine. The high resolution mass spectra of 206 and 207 did not show the parent ions (M$^+ - 357.37$, $C_{15}H_{23}N_3O_7$). However, the fragmentation of the two compounds was strongly suggestive of their structures. The major fragments in the mass spectra of 206 and 207 were m/e 342.1303 ($C_{14}H_{20}N_3O_7$) and m/e 314.1239 ($C_{14}H_{20}NO_7$), respectively. These correspond to the loss of a methyl from 206 and the combined loss of a methyl and nitrogen from 207. The loss of 15 (methyl) from such sugars is well documented$^{224}$. The loss of nitrogen from 207 was suggestive of the diazo structure. The configuration of C-3 of 206 and 207 was shown to be identical by the hydrogenation of 206 with 5% palladium on charcoal and 207 over the same catalyst with trace amounts of copper sulphate present, to give the same $\beta$-amino ester 208. It is
well known that hydrogenolysis of a diazo group can be achieved in this way\textsuperscript{225}. The absolute configuration at C-3 of both compounds was inferred to be \textit{gluco} for mechanistic reasons\textsuperscript{226}. It is known that hydrogenation of the unsaturated ester \textsuperscript{12} proceeds from "topside" attack on the double bond to afford the \textit{allo}-sugar \textsuperscript{13\textsuperscript{30}}. Dihydroxylation of \textsuperscript{12}\textsuperscript{177} occurs from the same face i.e. the least hindered face of the molecule. In an attempt to confirm that \textsuperscript{206} and \textsuperscript{207} did have the \textit{gluco}-configuration, it was thought that the azide octant rule\textsuperscript{227} might be utilized. There has been extensive application of this rule to pyranose azides\textsuperscript{228,229} but to our knowledge there has been no report of similar applications to furanose azides. The c.d. spectrum of \textsuperscript{206} was obtained and the Cotton effect associated with the weak transition in the vicinity of 280-295 nm was found to be negative. This was in agreement with the octant rule. To confirm that C-3-azido-hexofuranoses of opposite configuration at that center, have opposite Cotton effects in accord with the azide octant rule, the c.d. spectra of 3-azido-3-deoxy-1,2:5,6-di-O-isopropylidene-\textit{\alpha}-D-glucofuranose (\textsuperscript{209})\textsuperscript{230} and 3-azido-3-deoxy-1,2:5,6-di-O-isopropylidene-\textit{\alpha}-D-allofuranose (\textsuperscript{210})\textsuperscript{231} were obtained. Compounds \textsuperscript{209} and \textsuperscript{210} were found to exhibit a negative and positive Cotton effect respectively in the vicinity of 280-290 nm. The octant rule was applied in the same manner as by previous authors\textsuperscript{228,229}. The azide is assumed to point away from the ring and the division between the front and rear octants
Figure XIV. Circular Dichroism Spectra of 3-Azido-3-C-(methoxy-carbonyl)methyl glucofuranose 206, 3-Azido glucofuranose 209, and 3-Azido allofuranose 210.
passes through N-1 as does the horizontal axis. In applying the rule to compound 206, the 3-C-(methoxycarbonyl)methyl group was assumed to make no net contribution to the Cotton effect. Hence, as 206 had a negative Cotton effect further evidence of the C-3 gluco configuration was obtained. A subsequent chemical proof of this assignment will be discussed below. As mentioned previously, 206 and 207 have the same configuration at C-3, so 207 must have the gluco configuration.

Compound 206 was thought to be produced via a 1,4-Michael-type addition of hydrazoic acid to 12. It was found that no reaction occurred if 12 was treated with hydrazoic acid in dimethylformamide in the absence of sodium azide. Most likely the azide ion is the attacking species and hydrazoic acid served as a proton source. The use of hydrazoic acid has the advantage over other acids generally used such as acetic acid, in that it is not strong enough to hydrolyze the acid labile blocking groups of 12.

2.1.2 The Addition of Sodium Azide in Dimethylformamide to 12 in the Absence of Hydrazoic Acid

Because of the possible synthetic utility of the α-diazoester 207, an attempt to increase the yield of 207 from 12 was carried out. It was found that if the reaction was carried out with sodium azide in the absence of hydrazoic acid under otherwise similar conditions, the major addition product was 207 (46%). Only
trace amounts of 206 were isolated from these non-protic reactions. It should be noted that no triazoline products were isolated. $\Delta^2$-Triazolines are the major products obtained from the 1,3-dipolar addition of organic azides to conjugated esters$^{120}$. As well, no aziridine products were isolated which Huisgen et al. have shown to result from the thermal degradation of triazolines$^{120,123}$. Rather, 207 is thought to arise from the base catalyzed decomposition of a charged triazoline which resulted from the 1,4-Michael addition of the azide anion to 12. Huisgen has demonstrated that such decompositions, catalyzed by triethylamine, of aryl substituted $\Delta^2$-Triazolines leads to $\beta$-anilino-$\alpha$-diazo esters$^{120}$. The base in this case would be the charged triazoline itself. This is in accord with Huisgen's suggestion that some substituted triazolines
are sufficiently basic to promote auto-catalysis to afford the β-anilino-α-diazo ester products which have been isolated in some 1,3-dipolar additions\textsuperscript{120}.

It was found that sodium azide, with or without hydrazoic acid, would not react with the $E$-isomer\textsuperscript{11}. Also, methyl-4,6-O-benzylidene-2,3-dideoxy-3-C-[(E)-(methoxycarbonyl)methylene]-α-D-hexopyranoside was recovered quantitatively after being exposed to the same reaction condition for 10 days. Presumably, increased angle-strain in $\underline{12}$ enhances its reactivity. It is well known that such strain increases the reactivity of olefins towards undergoing addition reactions\textsuperscript{122,123}. This increased strain may be produced in $\underline{12}$ by steric interactions of the methoxycarbonyl group and the C-2 oxygen of the adjacent isopropylidene group. In the $E$-isomer\textsuperscript{11} this interaction is not present.

2.1.3 Hydrogenation of the 3-Azido Sugar $\underline{206}$ to Afford 3-Amino-3-dideoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)-methyl-α-D-glucofuranose ($\underline{208}$)

Hydrogenation of compound $\underline{206}$ with 5% palladium on charcoal afforded the β-amino ester $\underline{208}$ in 96% yield. The i.r. spectrum of $\underline{208}$ confirmed the presence of the primary amine with absorptions at 3400 to 3100 cm\textsuperscript{-1}. Two doublets at $\tau 4.15$ and 5.47 were assigned to H-1 and H-2. An AB system was observed at $\tau 7.2$ with $J_{AB}$ 18 Hz which was assigned to the C-3' methylene protons.
2.1.4 Hydrolysis of 208 to Give 3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(hydroxycarbonyl)methyl-α-D-gluco-furanose (209)

Treatment of the β-amino ester 208 with sodium hydroxide in methanol under reflux for 30 minutes resulted in the hydrolysis of the methyl ester. Removal of the sodium ions was achieved by passage of the solution through a short column of Rexyn RG-51(H⁺) resin. Collection of the charring fractions and removal of the solvent gave the free β-amino acid 209 in 85% as a crystalline mass. Compound 209 was readily purified by sublimation. The i.r. spectrum of 209 contained a broad absorption at 3200 to 2600 cm⁻¹ which is typical of a free acid. Elemental analysis confirmed the composition.
2.1.5 Synthesis of Nucleosides from Compound 208

In order to synthesize a pentofuranosyl nucleoside from 208 the following steps were followed: (1) blocking of the 3-amino group, (2) removal of the 5,6-O-isopropylidene group, (3) cleavage of the 5,6-diol structure and reduction of the resulting aldehyde, (4) blocking of the 5-hydroxyl group, (5) removal of the 1,2-O-isopropylidene group, (6) blocking of the anomeric hydroxyl, and (7) fusion of the glycosyl halide of the resulting sugar with an appropriate heterocycle.

2.1.6 Acetylation of 208, Removal of the 5,6-O-Isopropylidene Group, Cleavage, Reduction and Benzoylation to Afford 3-Acetamido-5-O-benzyl-3-deoxy-1,2-O-isopropylidene-3-C-(methoxycarbonyl)methyl-α-D-xylofuranose (213)

Treatment of compound 208 with acetic anhydride in pyridine afforded after work up 3-acetamido-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methyl-α-D-glucofuranose (210) in 98% yield. The presence of the N-acetate was apparent from the i.r. spectrum of 210 with absorptions at 3500, 3400, and 1695 cm\(^{-1}\) and the p.m.r. spectrum which had a broad exchangeable one proton singlet at \(\tau 3.8\).

Subsequent removal of the 5,6-O-isopropylidene group from 210 was achieved with 66% acetic acid to give a near quantitative yield of 3-acetamido-3-deoxy-1,2-O-isopropylidene-3-C-(methoxy-
carbonyl)methyl-α-D-glucofuranose (211). Application of the sodium metaperiodate reaction to the diol 211 followed by reduction of the
resulting aldehyde with sodium borohydride afforded the pentose 3-acetamido-3-deoxy-1,2-0-isopropylidene-3-C-(methoxycarbonyl)methyl-\(\alpha\)-D-xylofuranose (212) in good yield. This same sequence was carried out on the trifluoroacetamide analog of 210. This was obtained by acetylation 208 with trifluoroacetic anhydride in pyridine. Unfortunately, the reduction step with sodium borohydride (211 → 212) after periodate cleavage, gave two compounds. These proved to be the 5-hydroxy sugar with and without the trifluoroacetate attached to the 3-amino group. In fact sodium borohydride has been used to remove trifluoroacetates from amino functions\(^{232}\). It would have been desirable to use the trifluoroacetate as it is more readily removed than N-acetates. The alternative sequence would have been hydrolysis, cleavage and reduction of the 5,6-tail of the free amino compound 208 and then trifluoroacetylation. However, subsequent benzoylation of the 5-hydroxyl group may have presented problems.

Benzoylation of the 5-hydroxy-acetamido compound 212 was achieved with benzoyl chloride in pyridine. Work up of the reaction and purification of benzoate 213 by column chromatography afforded pure 3-acetamido-5-0-benzoyl-3-deoxy-1,2-0-isopropylidene-3-C-(methoxycarbonyl)methyl-\(\alpha\)-D-xylofuranose (213) in an overall 50% yield from 210. The i.r. spectrum of 213 showed the presence of the acetamido group (3500 - 3300 cm\(^{-1}\)). The p.m.r. spectrum of 210 verified the presence of the benzoate with multiplets at \(\tau\)1.8 - 2.1 and \(\tau\)2.4 - 2.6.
2.1.7 Hydrolysis of the 1,2-0-Isopropylidene Group of 213:

Synthesis of 3-Acetamido-1-0-acetyl-5-0-benzoyl-2,3-
dideoxy-3-C-methyl-α( and β)-D-xylofuranose-3',2-carbolactone (215) and (216)

Only two steps remained to be completed before the nucleoside condensation could be carried out; (5) removal of the 1,2-0-isopropylidene group of 213 and (6) suitably blocking the anomeric hydroxyl group.

Hydrolysis of the 1,2-0-isopropylidene group was achieved as previously described with 80% aqueous trifluoroacetic acid. As expected, lactonization occurred involving intramolecular participation of the C-2 cis-hydroxyl group during the acid catalized hydrolysis of the ester. Very recently, a similar
lactonization was reported\textsuperscript{233} during the acid hydrolysis of 5,6-
di-0-acetyl-3-deoxy-3-C-(R)-ethoxycarbonyl(formylamino)methyl-
1,2-0-isopropylidene-\alpha-D-allofuranose. The lactonization which
resulted in the isolation of the \( \alpha,\beta \) mixture of alcohols 214 in
90\% yield, gave firm chemical proof of the previous assignment of
the C-3 configuration of 206 and 207. Acetylation of the mixture
with acetic anhydride and pyridine gave the \( \alpha \)- and \( \beta \)-anomers 215
and 216. Chromatography of the mixture of acetates on silica gel
afforded pure 3-acetamido-1-0-acetyl-5-0-benzoyl-2,3-dideoxy-3-
C-methyl-\alpha-D-xylofuranose-3',2-carbolactone (215) and the \( \beta \)-anomer
216 in a 1:3 ratio. The i.r. spectra of 215 and 216 contained
absorptions at 1800 cm\(^{-1}\) which confirmed the \( \gamma \)-lactone structure.
Absorptions at 1680 and 1690 cm\(^{-1}\) confirmed the presence of the
amide group. The p.m.r. spectrum of 215 had a doublet at \( \tau 3.41 \)
with \( J 5 \) Hz while the p.m.r. spectrum of 216 contained a doublet
at \( \tau 3.82 \) with \( J 1 \) Hz. These signals were assigned to H-1 of the
\( \alpha \) and \( \beta \)-anomers, respectively.

\textbf{2.1.8} Fusion of the Glycosyl Bromides of 215 and 216 with \( N^6 \)-Benzoyl-
\( N^6 \),9-bis(trimethylsilyl)adenine: Synthesis of 9-(3'-Aceta-
mido-2',3'-dideoxy-3'-C-methyl-\( \alpha \)(and \( \beta \))-D-xylofuranos-3'',2'-
carbolactone-yl)adenine (219) and (220)

In preparation for the fusion reaction to obtain nucleosides
of the \( \beta \)-acetamido lactone sugar, the more reactive glycosyl bromides
of 215 or 216 were synthesized. This was done as previously
discussed by treatment of the acetate with hydrogen bromide
saturated glacial acetic acid. Fusion of the glycosyl halide so
obtained with \( N^6 \)-benzoyl-\( N^6 \),9-bis(trimethylsilyl)adenine\(^{197} \) at
150\(^\circ\) and 15 torr for 25 minutes afforded after work up and column
chromatography pure \( N \)-benzoyl-9-(3'-acetamido-5'-O-benzoyl-2',3'-
dideoxy-3'-\( \alpha \)-methyl-\( \alpha \)-D-xylofuranos-3",2'-carbolactone-yl)adenine
(217) and the \( \beta \)-anomer 218 in 14 and 36\% yields, respectively.
Unfortunately, the gentler method\(^{234} \) of nucleoside formation of
heating a solution of the silylated base, stannic chloride, and the
sugar acetate in dichloroethane did not give nucleoside products
from 215 or 216 as evidenced by t.l.c..

The anomeric configurations of 217 and 218 were readily
assigned from the relative magnitudes of \( J_{1',2'} \) which were 4 and
0.8 Hz, respectively. Proof that the \( \gamma \)-lactone structure was
intact in both nucleosides was obtained from their i.r. spectra
which had strong absorptions at 1800 cm\(^{-1}\). The site of glycosylation
was confirmed as being \( N^9 \) as both 217 and 218 had maxima at 278 nm
in their u.v. spectra. This is in accord with that previously
observed for \( N^9\)-\( N^6 \)-benzamidopurine nucleosides\(^{217} \). The benzoate
groups of 217 and 218 were readily removed with sodium methoxide
in methanol to afford 9-(3'-acetamido-2',3'-dideoxy-3'-\( \alpha \)-methyl-
\( \alpha \)-D-xylofuranos-3",2'-carbolactone-yl)adenine (219) and 9-(3'-acetamido-2',3'-dideoxy-3'-\( \alpha \)-methyl-\( \beta \)-D-xylofuranos-3",2'-carbolactone-
yl)adenine (220) in good yield. The u.v. spectra of 219 and 220,
Figure XV: 100 MHz NMR Spectrum of N$^6$-Benzyol-9-(3'-acetamido-5'-O-benzyol-2',3'-dideoxy-3'-C-methyl-$\beta$-D-xylofuranos-3'',2'-'carbolactone-yl)adenine (218) in CDC$_3$. 
Figure XVI: 100 MHz NMR Spectrum of $N^6$-Benzoyl-9-(3'-acetamido-5'-O-benzoyl-2',3'-dideoxy-3'-C-methyl-$\alpha$-D-xylofuranos-3',2'-carbolactone-yl)adenine (217) in CDC$_3$. 
\( \lambda_{\text{max}} \) 258 and 205 nm, confirmed that the site of glycosylation was N9217. The p.m.r. spectra of 219 and 220 confirmed the \( \alpha \) and \( \beta \)-anomeric configuration assignments. The coupling constant observed for H-1'-H-2' for the \( \alpha \)-nucleoside 219 was 4 Hz. The \( \beta \)-nucleoside 220 had a smaller H-1'-H-2' coupling constant of 2 Hz. The c.d. spectra of 219 and 220 confirmed this assignment218 as 219 had a positive Cotton effect and 220 exhibited a negative Cotton effect. The i.r. of 219 had an absorption at 1795 cm\(^{-1}\) (\( \gamma \)-lactone) and had no ester or acid absorption. Interestingly, it was found that the lactone system of the \( \alpha \)-nucleoside could be opened by heating in water. The p.m.r. of 219 in deuterium oxide showed a doublet at \( \tau \)3.45 which, upon heating the sample to 60-70\(^\circ\) for 2 or 3 minutes, disappeared and a different doublet at \( \tau \)3.3 appeared. These doublets were assigned to the anomeric protons of the \( \gamma \)-lactone and free acid form of the \( \alpha \)-nucleoside, respectively. The infrared spectrum of the n.m.r. sample after heating, cooling, and subsequent removal of solvent at low temperature contained a broad absorption between 2800 - 2400 cm\(^{-1}\) typical of a free acid. Presumably, the heterocyclic base of the \( \alpha \)-nucleoside may assist in this ring opening as the \( \beta \)-nucleoside did not exhibit the same equilibrium. Fusion of the mixture of lactone and acid forms of 219 at \( \sim \)160\(^\circ\) and 0.2 torr resulted in the loss of water with lactonization as evidenced by i.r. as above.
2.2 Synthesis of Analogs of the Sugar Moiety of the Polyoxins

2.2.1 Synthesis of 3-Spiro-2'-Aziridines

It will be recalled that the addition of sodium azide to the unsaturated ester 12 was found to afford the β-amino-α-diazo ester 207. Compound 207 was viewed as an excellent precursor for the possible synthesis of 3-spiro-2'-(methoxycarbonyl) methyl aziridines. Diazocompounds are well known to react with copper catalysts to generate metal-carbene complexes. If compound 207 could be induced to give a spiro aziridine, the possibility of opening such an aziridine to give β-amino-α-amino esters was very attractive.
2.2.2 Treatment of 3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-[1'-diazo(methoxycarbonyl)methyl]-α-D-glucofuranose (207) with Copper Sulfate

When a solution of 207 and anhydrous copper sulfate in cyclohexane was vigorously refluxed until t.l.c. showed all the starting material had disappeared, two products were obtained. Removal of the catalyst and evaporation of the solvent afforded a mixture of the 3-spiro-2'-aziridine sugars 221 and 222 in quantitative yield. The diastereomeric aziridines could not be chromatographically separated. Hydrogenation of the mixture of 221 and 222 gave the 3-amino sugar 208 quantitatively which proved that 221 and 222 differ only in the configuration at C-2'. The molecular constitution of the mixture was confirmed by elemental analysis. The i.r. spectrum of the mixture had an amine absorption at 3600 - 3200 cm\(^{-1}\) and an absorption at 1730 cm\(^{-1}\) corresponding to the methyl ester.

The mechanism of the reaction of copper sulfate with 207 is thought to involve the generation of a metal-carbene complex\(^{235}\), followed by intramolecular attack of the 3-amino group on this complex. Diazoacetate was reported to add to piperidine in the presence of copper cyanide and copper chloride. It is preferable to view these reactions as proceeding by attack of the nitrogen on the complex rather than carbene insertion into the N-H bond as
metal generated carbene reactions are usually free of insertion products.

Treatment of the Mixture of $\text{221}$ and $\text{222}$ with Trifluoroacetic Anhydride

In an effort to separate the diastereomeric aziridines it was thought that the $N$-acyl derivatives of $\text{221}$ and $\text{222}$ would be chromatographically separable. Treatment of the mixture of aziridines with trifluoroacetic anhydride in pyridine gave two products. T.L.C. on silica showed a higher $R_f$ spot and one of the same $R_f$ as the starting material. Surprisingly, complete acetylation of the mixture could not be achieved. Addition of excess anhydride, pyridine, or heating of the mixture did not change the reaction mixture composition as observed by t.L.C. Work up of the reaction followed by column chromatography afforded

\begin{align*}
\text{221} & \quad R'=\text{CO}_2\text{Me}; \quad R=\text{H}; \quad R''=\text{H} \\
\text{222} & \quad R'=\text{H}; \quad R=\text{CO}_2\text{Me}; \quad R''=\text{H} \\
\text{223} & \quad R'=\text{H}; \quad R=\text{CO}_2\text{Me}; \quad R''=\text{CO}_\text{CF}_3
\end{align*}
the isolation of pure 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-spiro-2'\-[(S)-(methoxycarbonyl)methyl-N-trifluoroacetyl aziridine] (223) and 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-spiro-2'\-[(R)-(methoxycarbonyl)methyl aziridine] (221). The structure of crystalline 221 was readily determined from its i.r. and p.m.r. spectra. The i.r. spectrum of 221 had an amine peak at 3300 cm\(^{-1}\). The p.m.r. of 221 had doublets at \(\tau 4.05\) and 5.25 with \(J 4.4\) Hz which were assigned to H-1 and H-2 respectively. A broad one proton singlet at \(\tau 6.95\) which sharpened upon the addition of deuterium oxide was assigned to H-2'. The H-1' signal occurred at \(\tau 7.9\) as a broad exchangeable singlet. The stereochemistry of C-2' was determined by the stereoselective deamination of 221 with iso-amyl nitrate which afforded the exclusive formation of (E)-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl) methylene-α-D-ribo-hexofuranose (11). The (E)-isomer (11) is clearly distinguishable from the (Z)-isomer (12) by their p.m.r. spectra as previously discussed (p.109). The deamination of aziridines via the elimination of nitrous oxide, from the intermediate N-nitrosoaziridine, is known\(^{237}\) to proceed stereospecifically with retention of configuration. Therefore 221 must have the R-configuration at C-2'. It was previously shown that 221 and 222 differed only in the configuration at C-2' and therefore 222 must have the C-2'-S-configuration.
The i.r. spectrum of 223 had no amine peaks but showed two ester peaks at 1728 and 1714 cm\(^{-1}\). The fluorine n.m.r. of 223 had a singlet corroborating the presence of the trifluoroacetate. The p.m.r. spectrum of 223 had doublets at \(\tau 4.1\) and \(\tau 4.8\) with \(J 3.6\) Hz which were assigned to H-1 and H-2, respectively. This was confirmed by irradiation experiments. A sharp one proton singlet at \(\tau 5.88\) was assigned to H-2'. The reason for the selective acetylation of 222 in the presence of 221 is obscure.

Benzoylation of the mixture of aziridines was carried out with benzoyl chloride and pyridine in dichloromethane. Both aziridines were benzoylated and were separated by column chromatography. Their structures were confirmed by p.m.r. and i.r. As there was little interest in continuing with these compounds, which would result in the necessity of removing benzamide groups, they were not further characterized.

Several attempts were made to ring open the aziridines 221 and 223 with sodium azide but none of these were successful. Possibly, this was due to the fact that \(S_N^2\) attack upon the aziridine
structure would have to take place from the endo face of the [3.3.0]bicyclo system formed by the furanose ring and the 1,2-O-isopropylidene ring. The competitive intermolecular reaction of 207 with trifluoroacetamide in the presence of copper sulfate failed. The only product isolated from the fusion of 207, trifluoroacetamide and copper sulfate was a mixture of 221 and 222 which resulted from an intramolecular reaction. It was found that trifluoroacetamide itself catalyzed the intramolecular cyclization of 207 at room temperature. Interestingly, the product thus obtained was almost exclusively 222 with a small amount of 221, as evidenced by n.m.r.

2.2.4 Synthesis of β-Amino-α-amino Acids from 207. Analogs of the Sugar Moiety of the Polyoxins

The alternative route to β-amino glycosyl α-amino acids* from compound 207 was to reduce the diazo group to an amino function. Hydrogenation of 207 with 5% palladium on charcoal afforded compound 208 and a 30% yield of 3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-methoxalyl-α-D-glucofuranose hydrazone (224). The structure of 224 was readily deduced from its u.v., i.r. and p.m.r. spectra. The u.v. spectrum of 224 with an absorption at 270 nm was typical of a conjugated hydrazone238. The p.m.r. spectrum of 224 had a broad two proton exchangeable singlet at τ1.75 which was assigned to the -NH₂ of the hydrazone group. The

* Use in the extended sense.
3-amino protons occurred as a broad singlet at \( \tau 8.4 \) which disappeared upon the addition of deuterium oxide. Subsequent reductive cleavage of the hydrazone 224 with activated Raney-nickel and hydrogen at 50 p.s.i. led to a facile synthesis of methyl-2-D- and 2-L-(3-amino-3-deoxy-1,2:5,6-di-0-isopropylidene-\( \alpha \)-D-glucofuranos-3-yl)glycinate (225) and (226) in 91%. Unfortunately, the diastereoisomers 225 and 226 could not be separated. However, trifluoroacetylation of the mixture afforded the di-trifluoroacetamide derivatives 227 and 228 which were readily separated by chromatography. The p.m.r. spectra of 227 and 228 had amide peaks at \( \tau 1.53 \) and \( \tau 2.38 \) with \( J_{\text{NH, H'}} \) of 10 and 8 Hz, respectively. The H-1' protons of 227 and 228 occurred as doublets at \( \tau 4.6 \) and \( \tau 4.58 \) with the above respective coupling constants. The 3-amide protons occurred at \( \tau 3.1 \) and \( \tau 2.8 \) in the p.m.r. spectra of 227 and 228, respectively. The fluorine n.m.r. of 227 and 228 confirmed the presence of the trifluoroacetates. Reduction of 207 directly with Raney-nickel and hydrogen gave 208 and a mixture of 225 and 226, with 208 predominating. Because of this, stepwise reduction of 208 was preferable. Removal of the trifluoroacetate and methyl groups from 227 and 228 with sodium hydroxide gave the pure \( \beta \)-amino-glycosyl-\( \alpha \)-amino acids. The c.d. spectra of 229 and 230 were obtained and found to have negative and positive Cotton effects respectively. Hence 229 must be D-2-(3-amino-3-deoxy-1,2:5,6-di-0-isopropylidene-\( \alpha \)-D-glucofuranos-3-yl)glycine and 230 must be
Figure XVII: 60 MHz NMR Spectrum of Methyl-2-D-(3-trifluoroacetamido-3-deoxy-1,2:5,6-di-O-isopropylidene-\(\alpha-D\)-glucofuranos-3-yl)N-trifluoroacetylglucinate (227) in C\(\text{DCl}_3\). (b) 200 Hz offset.
Figure XVIII: 60 MHz NMR Spectrum of Methyl-2-L-(3-trifluoroacetamide-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl)N-trifluoroacetylglycinate (228) in CDCl₃.
L-2-(3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl)glycine.

\[
\text{H}_2/\text{Pd},
\]

\[
\text{NH}, \quad \text{TO \ Me}^+ 208 \text{H}_2\text{NN}/^*\text{C}0\text{Me}^0.\]

\[
\text{R}^=\text{H}; \text{R}^'=\text{NH}_2 \quad 229
\]

\[
\text{R}=\text{NH}_2; \text{R}^'=\text{H} \quad 230
\]

\[
\text{R}^=\text{H}; \text{R}^'=\text{NH}_2; \text{R}''=\text{H} \quad 225
\]

\[
\text{R}=\text{NH}_2; \text{R}^'=\text{H}; \text{R}''=\text{H} \quad 226
\]

\[
\text{R}^=\text{H}; \text{R}^'=\text{NHCOCF}_3; \text{R}''=\text{COCF}_3 \quad 227
\]

\[
\text{R}=\text{NHCOCF}_3; \text{R}^'=\text{H}; \text{R}''=\text{COCF}_3 \quad 228
\]
The assignment of the configuration of the glycosyl α-amino acids was based on the fact that many D-α-amino acids exhibit negative Cotton effects. This method has been used successfully for other glycosyl α-amino acids prepared in this laboratory such as 138, 139, 140 and 141. Compound 139 was converted by Rosenthal and Richards to a derivative which had been prepared by Jordaan and co-workers and which the structure of, had been proven by X-ray analysis. Hence, as the D-configuration of 139, as predicted by a negative Cotton effect in the c.d., was confirmed by X-ray analysis, the method of assignment by c.d. seems reliable.

Figure XIX. Circular Dichroism Spectra of D and L-α,β-Diamino Acids 229 and 230.
IV. EXPERIMENTAL

1. General Methods

Nuclear magnetic resonance spectra were determined on a Varian T-60, HA-100 or XL-100 spectrometer. Absorptions are given in \( \tau \) units with tetramethylsilane (unless otherwise stated) as internal standard (set at \( \tau 10 \)). The following abbreviations are used in describing n.m.r. spectra: (d) = doublet, (s) = singlet, (t) = triplet, (q) = quartet, (m) = multiplet. Mass spectra were recorded on an A.E.I. MS9 spectrometer. Optical rotations were measured with a Perkin Elmer model 141 automatic polarimeter. Infrared spectra were recorded on a Perkin Elmer model 137 spectrometer and circular dichroism (cd) measurements were performed on a JASCO ORD/UV-5 spectropolarimeter or a JASCO J-20 Automatic Recording Spectropolarimeter. Ultraviolet spectra (uv) were recorded on a Unicam SP 800 spectrometer or a Carey 15 spectrometer. Melting points were determined on Leitz Microscope heating stage model 350, and are corrected. Elemental Analyses were performed by Mr. P. Borda, Department of Chemistry, University of British Columbia.
2. Chromatography

2.1 Column

Silica gel column chromatography was performed using 60-200 mesh (Davidson Chemical commercial grade H) or silica gel for t.l.c. (D-0, Mondray Ltd.) indicated as "t.l.c. grade silica gel". For t.l.c. grade silica gel column chromatography the ratio of material to absorbent, if not stated, was approximately 1 to 100. Columns were pressurized above the solvent reservoir to a pressure of 5-15 psi.

2.2 Thin Layer Chromatography

All thin layer chromatography was performed using silica gel for t.l.c. (D-0, Mondray Ltd.), containing 1% electronic phosphor. Compounds were detected by ultraviolet absorption, by spraying with 50% sulfuric acid followed by heating on a hot plate, or by spraying with 0.3% solution of ninhydrin in n-butanol followed by warming at 110° in an oven.

2.3 Paper Chromatography

Paper chromatograms were developed on Whatman No. 1 paper. Nucleosides were detected with ultraviolet light.
3. **Photochemical Reactions**

The light source in these reactions was a Hanova 450 W type L lamp. Large scale photochemical reactions were carried out by placing the lamp, and pyrex filter inside a water cooled quartz immersion-well apparatus which was placed inside a 3-necked pyrex vessel (capacity with lamp ~300 ml). The whole apparatus was wrapped in aluminum foil. All photolysis solvents were reagent grade, distilled and dried before use. All photochemical reaction mixtures were deoxygenated with Matheson prepurified nitrogen or argon prior to and during irradiations.

2,3,4,6-Tetra-O-acetyl-1-deoxy-D-arabino-hex-1-enopyranose (22)\textsuperscript{56}

To a solution of tetra-O-acetyl-\(\alpha\)-D-glucopyranosyl bromide\textsuperscript{186} (154, 25 g) and tetra-N-butylammonium bromide (19.6 g) in anhydrous acetonitrile (13 ml) was added diethylamine (13.5 g). The resulting yellow solution was stirred for 20 min. after which chloroform (175 ml) was added and the organic solution was washed successively with water (100 ml), 1% hydrochloric acid (100 ml), and 1% aqueous sodium hydrogen carbonate (100 ml). The chloroform solution was dried with anhydrous sodium sulfate, filtered, and evaporated under diminished pressure to a syrup (19 g, 95%) which was crystallized from ethanol to give pure (22); m.p. 61-63° (lit.\textsuperscript{185} 65-66°). Recrystallization did not improve the melting point. The method contined in ref. 185 gave 22 in 50% yield.
Irradiation of 2,3,4,6-Tetra-O-acetyl-1-deoxy-D-arabino-hex-1-enopyranose (22)

A mixture of compound 22 (2 g), formamide (30 ml), tert-butyl alcohol (15 ml) and acetone (15 ml) was added dropwise to a mixture of formamide (200 ml), tert-butyl alcohol (10 ml), and acetone contained in the photolysis cell. Irradiation was continued during the addition and prolonged for 24 h (or until all of the starting material had disappeared, as evidenced by t.l.c. developed with 10:5:1 benzene-ethyl ether-ethanol). After the solution had been concentrated to remove tert-butyl alcohol and acetone by evaporation (30 torr at 50°), the resulting mixture was diluted with saturated aqueous sodium chloride (200 ml). The resulting solution was then extracted with dichloromethane (4 x 200 ml). The combined dichloromethane extract was concentrated to 100 ml and the resulting solution was washed with saturated aqueous sodium chloride (50 ml), dried over anhydrous sodium sulfate, filtered, and evaporated under diminished pressure to a syrup (2.1 g). The main product 152 (0.4 g, 18%) was obtained by fractional crystallization from ethanol-petroleum ether (b.p. 30-60°). A second recrystallization of 152 from the same solvent mixture afforded analytically pure 3,4,5,7-tetra-O-acetyl-2,6-anhydro-D-glycero-D-ido-heptonamide; m.p. 158-159°, \([\alpha]_D^{26} +16.5° \text{ (c 0.38, chloroform); i.r. (nujol)} 3570, 3450 \text{ and } 1700 \text{ cm}^{-1} \text{ (CONH}_2\text{); n.m.r. data ((CD}_3)_2\text{CO): } \tau 3.3 \text{ (broad d, 2, NH}_2\text{,} \)
exchanges with $D_2O$), 4.38 (t, 1, $J_{4,5}$ 7.5 Hz, H-4), 4.93 (q, 1, $J_{3,4}$ 7.5 Hz, H-3), 5.19 (t, 1, $J_{5,6}$ 7.5 Hz, H-5), 5.48 (d, 1, $J_{2,3}$ 5.2 Hz, H-2), 5.32-5.6 (m, H-6), 5.67-5.95 (o, 2, H-7, H-7');

n.m.r. data (CDCl$_3$): $\tau$ 7.94, 7.95 (2s, 12, OAc). Irradiation at $\tau$5.48 produced a doublet at $\tau$4.93. Irradiation at $\tau$4.38 produced a doublet at $\tau$4.93 and $\tau$5.19. Irradiation at $\tau$4.93 produced a singlet at $\tau$5.48 and a doublet at $\tau$4.38.

Anal. Calc. for $C_{15}H_{21}NO_{10}$: C, 48.00; H, 5.67; N, 3.73. Found: C, 47.80; H, 5.53; N, 3.53.

After product 152 was removed from the crystallization solvents, the mother liquor was evaporated to a syrup (1.6 g). This syrup was chromatographed on t.l.c. silica gel (24.5 x 6.5 cm), with 10:5:1 benzene-ethyl ether-ethanol as a developer to afford the amide 152 (0.8 g, 36%), the amide 153 (0.16 g, 7%), and the alcohol 154 (0.54 g, 23%).

Compound 153 was recrystallized from ethyl ether-ethanol to yield pure 3,4,5,7-tetra-$O$-acetyl-2,6-anhydro-D-glycero-D-talo heptonamide; m.p. 150.5-152°, $[\alpha]^D_26+3.0^\circ$ (c 0.37, chloroform); i.r. (nujol) 3595, 3460 and 1700 cm$^{-1}$ (CONH$_2$); n.m.r. data (CDCl$_3$): $\tau$3.14, 3.46 (2 broad s, 2, NH$_2$, exchanges with $D_2O$), 4.18 (q, 1, $J_{3,4}$ 4.4 Hz, H-3), 4.64-4.8 (m, 2, H-4, H-5), 5.51 (d, 1, $J_{2,3}$ 2Hz, H-2), 5.6-5.91 (m, 2, H-7, H-7'), 6.01 (m, 1, H-6), 7.88, 7.94, 8.0, 8.04 (4s, 12, OAc). Irradiation at $\tau$4.18 produced a singlet at $\tau$5.51 and altered the multiplet at $\tau$4.64-4.8. Irradiation at
5.51 produced a doublet at 4.18. Irradiation at 6.01 simplified
the multiplet at 4.64-4.8. N.m.r. data (CHCl$_3$ and 10 μl of
concentrated Eu(fod)$_3$d$_{27}$ soln.): τ 3.18 (m, 1, H-3), 4.29 (q, 1,
J$_{3,4}$ 2.6 Hz, H-4), 4.45 (t, 1, J$_{4,5}$ 8.5 Hz, H-5).

Anal. Calc. for C$_{15}$H$_{21}$NO$_3$: C, 48.00; H, 5.64; N, 3.73.
Found: C, 47.88; H, 5.70; N, 3.50.

Compound 154 was recrystallized from ethanol-petroleum
ether (b.p. 30-60°) to yield pure 4,5,6,8-tetra-O-acetyl-3,7-
anhydro-1-deoxy-2-methyl-D-glycero-D-talo-octitol; m.p. 139-140°,
[a]$_D^{26}$-18.5° (c 0.2, chloroform); i.r. (nujol) 3600-3400 cm$^{-1}$ (OH);
n.m.r. data (CDCl$_3$): τ 4.4 (q, 1, J$_{4,5}$ 3Hz, H-4), 4.75 (t, 1, J$_{5,6}$
10 Hz, H-6), 5.02 (q, 1, J$_{5,6}$ 10 Hz, H-5), 5.8 (m, 2, H-8, H-8'),
6.37 (m, 1, H-7), 6.63 (d, 1, J$_{3,4}$ 0.8 Hz, H-3), 7.78 (broad s, 1,
OH, exchanges with D$_2$O), 7.89, 7.90, 7.96, 8.04 (4s, 12, OAc),
8.79 (s, 6, CH$_3$). Irradiation at 6.63 produced a doublet at
τ4.4. Irradiation at τ4.4 produced a doublet at τ5.02 and a
singlet at τ6.63. Irradiation at τ6.37 produced a doublet at τ4.75.

Anal. Calc. for C$_{17}$H$_{26}$O$_{10}$: C, 52.30; H, 6.71.
Found: C, 52.16; H, 6.76.

2,6-Anhydro-D-glycero-D-ido-heptonamide (158)

To a solution of 152 (0.04 g) in anhydrous methanol (2 ml)
was added a catalytic amount of sodium methoxide. After the
resulting solution was stirred for 10 min., the sodium ions were
removed with Amberlite IR-120 (H\(^+\)) resin. After filtering off the resin, removal of the solvent left a syrup (0.027 g). An analytical sample of \(158\) was crystallized from methanol-water; m.p. 219-221\(^\circ\), \([\alpha]_D^{26} +128^\circ\) (c 0.34, water); c.d. \(\Delta \varepsilon + 0.48 (\lambda_{\text{max}} 223 \text{ nm}, c 0.0031, \text{ water})\), \([\theta]_D^{223} +1585\); n.m.r. data (D\(_2\)O): \(\tau 5.33 (d, 1, J_{2,3} 1.5 \text{ Hz, H-2})\).

Anal. Calc. for \(C_7H_{13}NO_6\): C, 40.58; H, 6.32; N, 6.76.
Found: C, 40.86; H, 6.43; N, 6.45.

2,6-Anhydro-D-glycero-D-talo-heptonamide (159)

Compound \(153\) (0.021 g) was deacetylated as described above for the preparation of \(158\) to afford compound \(159\) (0.011 g) which was recrystallized from methanol-water; m.p. 212-214\(^\circ\), \([\alpha]_D^{26} +11.7^\circ\) (c 0.17, water); c.d. \(\Delta \varepsilon + 0.15 (\lambda_{\text{max}} 208 \text{ nm}, c 0.0028, \text{ water})\), \([\theta]_D^{208} +500\); n.m.r. data ((CD\(_3\))\(_2\)CO): \(\tau 5.86 (t, 1, J_{2,3} 1.5 \text{ Hz, H-3}), 6.02 (d, 1, J_{2,3} 1 \text{ Hz, H-2})\).

Anal. Calc. for \(C_7H_{13}NO_6\): C, 40.58; H, 6.32; N, 6.76.
Found: C, 40.71; H, 6.48; N, 6.50.

1-Acetamido-3,4,5,7-tetra-O-acetyl-2,6-anhydro-1-deoxy-D-glycero-D-ido-heptitol (155)

A solution of compound \(152\) (0.5 g) in anhydrous tetrahydofuran (15 ml) was added dropwise to a cooled solution (0\(^\circ\)) of diborane\(^{190}\) in tetrahydofuran (10 ml, 0.5 molar in BH\(_3\)) under dry
nitrogen. After the resulting solution was refluxed for 3 h, a 0.1 M HCl aqueous solution (10 ml) was added dropwise to the cooled solution (\(\sim 5^\circ\)) with stirring. After 30 min., the solution was heated to evaporate most of the remaining tetrahydrofuran and to complete hydrolysis. After the resulting aqueous solution was evaporated to near dryness, the residue was diluted with methanol (4 x 50 ml) and the solvent removed under diminished pressure. The resulting residue (0.175 g) was thoroughly dried under reduced pressure and dissolved in pyridine (5 ml) and acetic anhydride (2 ml) and stirred at ambient temperature for 24 h.

The solution was then evaporated to dryness and the residue taken up in water (10 ml) and extracted with dichloromethane (2 x 50 ml). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and the filtrate evaporated to dryness to yield a syrup (0.375 g, 70%) which was crystallized from ethyl ether; m.p. 124.5-125°, \([\alpha]_{D}^{26} +56.3^\circ\) (c 0.19, chloroform); i.r. (nujol) 3370, 3300 and 1690 cm\(^{-1}\) (-CONH-); n.m.r. data (CDCl\(_3\)):

\[\begin{align*}
 & \tau 4.15 \text{ (broad s, 1, NH, exchanges with D}_2\text{O)}, 4.70 \text{ (t, 1, J}_{4,5} 8 \text{ Hz, H-4)}, 4.90 \text{ (q, 1, J}_{3,4} 8 \text{ Hz, H-3)}, 5.0 \text{ (t, 1, J}_{5,6} 7.8 \text{ Hz, H-5)}, \\
 & 5.5-6.0 \text{ (overlapping peaks, 4, H-2, H-6, H-7, H-7')}, 6.36-6.65 \text{ (m, 2, simplified upon addition of D}_2\text{O, H-1, H-1')}, 7.9, 7.92, 7.96, 8.0 \text{ (4s, 15, Ac)}. \text{ Irradiation at } \tau 5.7 \text{ produced doublets at } \tau 4.90 \text{ and } \tau 5.0. \text{ Irradiation at } 6.5 \text{ simplified the multiplet at } 5.75.
\end{align*}\]

Anal. Calc. for C\(_{17}\)H\(_{25}\)N\(_1\)O\(_{10.5}\)H\(_2\)O: C, 49.51; H, 6.33; N, 3.39. Found: C, 49.56; H, 6.31; N, 3.32.
1,2,4,6-Tetra-O-acetyl-3-deoxy-α-D-erythro-hex-2-enopyranose (24)\textsuperscript{56}

To a solution of 2,3,4,6-tetra-O-acetyl-1-deoxy-D-arabino-hex-1-enopyranose\textsuperscript{56} (22, 5 g) in anhydrous benzene (100 ml), boron trifluoride etherate (0.1 ml in 5 ml of benzene) was added. After stirring for 2 h, the solution was treated with anhydrous sodium carbonate (20 g), activated carbon, and after stirring for 1 hr was filtered and taken to dryness under reduced pressure to afford 24 (3.0 g, 80%). Recrystallization from ethyl-ether gave pure 24; m.p. 65-66°, [lit\textsuperscript{193} 66-67°]. The method described in ref. 193 gave 24 in 60% yield.

Irradiation of 1,2,4,6-Tetra-O-acetyl-3-deoxy-α-D-erythro-hex-2-enopyranose (24)

Following the procedure used for the irradiation of 22 (p. 146), a mixture of compound 24 (8.7 g), formamide (30 ml), tert-butyl alcohol (15 ml), and acetone (15 ml) was added dropwise during 1 h to a mixture of formamide (200 ml), tert-butyl alcohol (10 ml), and acetone contained in the photolysis cell. Irradiation was continued during the addition and prolonged for 48 h after which time t.l.c., developed with 5:5:1 benzene-ethyl acetate-ethanol, showed all of the starting material had been consumed. After the solution had been concentrated by evaporation (30 torr at 50°) to remove any volatile solvents the resulting solution was diluted with saturated aqueous sodium chloride (200 ml). The
resulting solution was washed with dichloromethane (4 x 200 ml). The combined dichloromethane extracts were concentrated to 100 ml and the resulting solution was washed with saturated sodium chloride (50 ml), dried over anhydrous sodium sulfate, filtered and evaporated under diminished pressure to a syrup (9.0 g). The main product 161 (3.0 g, 35%) was obtained by fractional crystallization from benzene-petroleum ether (b.p. 30-60°). A second recrystallization from the same solvent mixture afforded analytically pure 161; m.p. 190-191°, [α]_{D}^{26} +108 (c 0.1, chloroform); i.r. (nujol) 3475 and 1690 cm^{-1} (CONH₂); n.m.r. data (CDCl₃); τ 3.9-4.3 (d, 2, NH₂, exchanges with D₂O), 3.63 (d, 1, J₁,₂ 3.4 Hz, H-1), 4.60 (t, 1, J₄,₅ 12 Hz, H-4), 4.75 (q, 1, J₂,₃ 12 Hz, H-2), 7.02 (t, 1, J₃,₄ 12 Hz, H-3), 7.8, 8.0, 8.1 (3s, 12, OAc). Irradiation at τ3.63 produced a doublet at τ4.75. Irradiation at τ7.02 produced a doublet at τ4.60 and τ4.75.

Anal. Calc. for C₁₅H₂₁NO₁₀: C, 48.00; H, 5.64; N, 3.73. Found: C, 48.05; H, 5.72; N, 4.00.

After product 161 had been removed from the crystallization solvents, the mother liquor was evaporated to a syrup. An aliquot (1.0 g) of this syrup was chromatographed on t.l.c.-grade silica gel (26.5 x 6 cm), with 10:5:1 benzene-ethyl ether-ethanol as developer to afford the gluco-amide 161 (0.2 g, 11.4%), the allo amide 162 (0.22 g, 12.7%), the altro amide 163 (0.018 g, 1.0%), and the manno alcohol 164 (0.12 g, 6.9%).
Compound 162 was recrystallized from ethyl acetate-petroleum ether (b.p. 30-60°); m.p. 41-42.5°, $\left[\alpha\right]_D^{26}+42.7°$ (c 1.0, chloroform); n.m.r. data (CDCl$_3$); $\tau$ 3.85 (d, 1, J$_{1,2}$ 3.9 Hz, H-1), 3.87-4.2 (broad d, 2, NH$_2$, exchanges with D$_2$O), 4.77 (q, 1, J$_{2,3}$ 6 Hz, H-2), 5.08 (t, 1, J$_{4,5}$ 9.5 Hz, H-4), 5.25 (o, 1, J$_{5,6}$ 8 Hz, H-5), 5.84 (m, 2, H-6, H-6'), 6.62 (q, 1, J$_{3,4}$ 5 Hz, H-3), 7.95, 7.96, 8.0 (3s, 12, OAc). Irradiation at $\tau$6.62 produced doublets at $\tau$4.77 and $\tau$5.08.

Anal. Calc. for C$_{15}$H$_{21}$NO$_{10}$: C, 48.00; H, 5.64; N, 3.73. Found: C, 48.29; H, 5.80; N, 3.46.

Compound 163 could not be obtained in a crystalline form; $\left[\alpha\right]_D^{26}+32.7°$ (c 0.5, chloroform); n.m.r. data (CDCl$_3$); $\tau$ 4.00 (d, 1, J$_{1,2}$ 2.5 Hz, H-1), 4.1-4.4 (broad s, 2, NH$_2$, exchanges with D$_2$O), 4.64 (q, 1, J$_{2,3}$ 5 Hz, H-2), 4.70 (q, 1, J$_{4,5}$ 7 Hz, H-4); 6.83 (q, 1, J$_{3,4}$ 5.4 Hz, H-3), 7.80, 7.90 (2s, 12, OAc).

Irradiation at $\tau$6.83 produced doublets at $\tau$4.64 and $\tau$4.70. Irradiation at $\tau$4.64 produced a singlet at $\tau$6.83.

Anal. Calc. for C$_{15}$H$_{21}$NO$_{10}$: C, 48.00; H, 5.64; N, 3.73. Found: C, 47.95; H, 6.00; N, 3.48.

Compound 164 was recrystallized from ethanol-petroleum ether (b.p. 30-60°); m.p. 94-95°, $\left[\alpha\right]_D^{26}+20.0°$ (c 0.3, chloroform); i.r. (nujol) 3600 cm$^{-1}$ (OH); n.m.r. data (CDCl$_3$); $\tau$4.02 (d, 1, J$_{1,2}$ 1.9 Hz, H-1), 4.57 (q, 1, J$_{4,5}$ 9.5 Hz, H-4), 4.80 (t, 1, J$_{2,3}$ 2.5 Hz, H-2), 7.60 (q, 1, J$_{3,4}$ 11 Hz, H-3), 7.95 (broad s, 1, OH, exchanges
with D$_2$O), 7.94, 7.95, 7.98 (3S, 12, OAc), 8.76, 8.82 (2S, 6, CH$_3$). Irradiation at $\tau$4.80 produced a singlet at $\tau$4.02 and a doublet at $\tau$7.60. Irradiation at $\tau$7.60 produced doublets at $\tau$4.57 and $\tau$4.80.

Anal. Calc. for C$_{17}$H$_{26}$O$_{10}$: C, 52.30; H, 6.71. Found: C, 52.49; H, 6.92.

1-(2',4',6'-Tri-O-acetyl-3-C-carbamoyl-3'-deoxy-β-D-glucopyranosyl) thymine (165)

1,2,4,6-Tetra-O-acetyl-3-C-carbamoyl-3-deoxy-α-D-glucopyranose (161, 0.2 g) was dissolved in anhydrous dichloromethane (1 ml), cooled to 0°, and treated with cold glacial acetic acid saturated with anhydrous hydrogen bromide (1 ml). After the mixture had been stirred for 1 h at room temperature, the solvent was removed under diminished pressure. Toluene (3 x 2 ml) was added to, and evaporated from, the product to remove all hydrogen bromide. The resulting halide (0.25 g) and 2,4-bis(trimethylsilyl)thymine (0.236 g) were intimately mixed, placed in a flask, evacuated to 15 torr and the flask sealed. The reaction mixture was slowly heated to 135-140° and maintained at that temperature for 30 min. After the reaction product had been tritutated with 4:1 methanol-saturated aqueous sodium hydrogen carbonate (5 ml), the volatile components were removed under diminished pressure. The residue was then extracted with hot
ethanol (5 x 5 ml) and the combined extracts were evaporated to yield a light brown syrup (0.232 g). This syrup was chromatographed on t.l.c. grade silica gel (10 x 2 cm), with 5:5:1 dichloromethane-ethyl acetate-ethanol as a developer, to give 165 (0.088 g, 40%) which was recrystallized from ethanol-methanol; m.p. 144-145°, 
\[\alpha\]_D^{24}-7.2° (c 0.2, methanol); \lambda_{\text{max}}^{\text{MeOH}} 207 nm (\varepsilon 7140), 260 nm (\varepsilon 7050); c.d. \Delta\varepsilon+ 0.95 (\lambda_{\text{max}} 270 nm, c 0.004 ethanol), [\theta]_{270}^{30}+3290, 
\Delta\varepsilon-0.199 (\lambda_{\text{max}} 245 nm), [\theta]_{245}^{30}-657; n.m.r. data ((CD_3)_2SO):

τ 1.0 (s, 1, NH, exchanges with D_2O), 2.32 (s, 1, H-6), 2.4, 2.9 (2 broad s, 2, NH_2, exchanges with D_2O), 4.2 (d, 1, J_1, 2, 9 Hz, H-1'), 4.80 (m, 2, H-2', H-4'), 7.00 (t, 1, J_2, 3, 10 Hz, H-3'), 8.0, 8.14, 8.2 (3s, 12, OAc and CH_3).

Anal. Calc. for C_{18}H_{23}O_{10}.CH_3OH: C, 48.20; H, 5.75; N, 8.87. Found: C, 48.30; H, 5.78; N, 8.61.

Attempted Synthesis of a Nucleoside from 6-Benzamidomercuripurine and 161

2,4,6-Tri-O-acetyl-3-C-carbamoyl-3-deoxy-\alpha-D-glucopyranosyl bromide (0.16 g), prepared as above for the synthesis of 165, was added to a suspension of 6-benzamidochloromercuripurine (0.28 g) and cadmium carbonate (0.11 g) in anhydrous xylene (15 ml). The resulting mixture was heated to 60° for 60 min. and refluxed for an additional 5 h. The reaction mixture was filtered and the solvent removed under diminished pressure to afford a residue which was taken up in dichloromethane (20 ml). The organic solution was
washed successively with aqueous potassium iodide (7 ml) and water. The resulting organic solution was dried with anhydrous sodium sulfate, filtered, and the solvent removed under diminished pressure to give a syrup (0.04 g). T.l.c. of the product developed with 5:5:1 benzene-ethyl acetate-ethanol indicated that no nucleoside-like products were present in the product mixture.

Further, the attempted condensation of 161 with 6-benzamidochloromercapurine by the titanium tetrachloride method yielded only anomerized and epimerized starting material.

1-(3'-C'-Carbamoyl-3'-deoxy-β-D-glucopyranosyl)thymine (166)

Compound 165 (0.04 g) was dissolved in anhydrous methanol (1 ml) containing sodium methoxide (0.001 g) and the solution was kept for 4 h at room temperature. The sodium ions were removed by stirring with Amberlite IR -120 (H+) resin, followed by filtration. The filtrate was evaporated to dryness and the resulting syrup (0.029 g) was crystallized from ethanol-methanol; m.p. 187-188°, [α]D24 +22.6° (c 0.2, methanol); λmax MeOH 264 nm (ε 6310), 208 (6210); c.d. Δε+1.14 (λmax 274 nm, c 0.06, methanol), [θ]25274 +3777°, Δε-0.7 (λmax 243), [θ]243 2260°; n.m.r. data ((CD3)2SO): τ 3.22 (s, 1, H-6), 3.46, 3.75 (2s, 2, NH2, exchanges with D2O), 5.08 (d, 1, J1',2, 11 Hz, H-1'), 7.60 (t, 1, J2',3, 9.8 Hz, H-3'), 8.05 (s, 3, CH3).

Anal. Calc. for C12H17N3O7·H2O: C, 43.24; H, 5.75; N, 12.61. Found: C, 43.50; H, 5.58; N, 12.60.
1-(2',4',6-Tri-O-acetyl-3'-C-carbamoyl-3'-deoxy-\(\alpha\)-D-glucopyranosyl)-
\(\text{\(N^4\)}\)-acetylcytosine (167)

The glycosyl bromide (0.385) prepared in the same manner as in the synthesis of 165, was dissolved in anhydrous dichloromethane (5 ml) containing 2,4-bis(trimethylsilyl)-\(\text{\(N^4\)}\)-acetylcytosine (0.40 g) and the solvent removed under diminished pressure. This homogeneous syrup was then heated for 20 min. to 97° at 6 torr. Methanol saturated with sodium hydrogen carbonate (20 ml) was added after cooling, and the solution filtered through sintered glass. Removal of the solvent under diminished pressure yielded a brown syrup (0.4 g). Column chromatography of the product on t.l.c. silica (20 x 3 cm) with 1:1 ethyl acetate-ethanol, as developer, afforded 1-(2',4',6-tetra-O-acetyl-3'-C-carbamoyl-3'-deoxy-\(\beta\)-D-glucopyranosyl)-\(\text{\(N^4\)}\)-acetylcytosine (167), (0.255 g, 55%). An analytical sample of 167 was prepared by recrystallization from ethanol-petroleum ether (b.p. 30-60°); m.p. 163-164.5°, 
\([\alpha]_D^{25}+35^\circ\) (c 0.2, methanol); \(\lambda_{\text{max}}^{\text{MeOH}}\) 250 (ε 17,000), 208 (15,700), 298 nm (6850); c.d. \(\Delta\varepsilon+3.3\) (\(\lambda_{\text{max}}\) 275 nm, c 0.004, methanol), 
\([\theta]_{275}^{25}+10,890, \Delta\varepsilon-3.5\) (\(\lambda_{\text{max}}\) 235 nm), \([\theta]_{235}^{35}-11,600\); n.m.r. data ((CD\(_3\))\(_2\)SO): \(\tau\) 1.78 (d, 1, J\(_{5,6}\) 7.6 Hz, H-6), 2.78 (d, 1, H-5), 2.36-2.88 (broad s, 2, NH\(_2\), exchanges with D\(_2\)O), 3.99 (d, 1, J\(_{1',2'}\) 10 Hz, H-1'), 6.94 (t, 1, J\(_{2',3'}\) 10.4 Hz, H-3'), 7.82, 7.94, 7.96, 8.14 (4s, 12, OAc).

Anal. Calc. for C\(_{19}\)H\(_{24}\)N\(_4\)O\(_{10}\): C, 48.72; H, 5.16; N, 11.96. Found: C, 48.89; H, 5.00; N, 11.69.
1-(3-C^-Carbamoyl-3-deoxy-β-D-glucopyranosyl)cytosine (168)

The fully acetylated nucleoside 167 (0.05 g) was dissolved in anhydrous methanol (10 ml) and a catalytic amount of sodium methoxide solution was added (10 μl of a 0.3 mM solution). This solution was kept for 8 h at room temperature, after which time it was neutralized with IR-120 (H\(^+\)) resin. T.l.c. of the product on silica gel, developed with 1:1 methanol-ethyl acetate, showed two products, having R\(_f\) 0.45 and 0.37. After filtering of the resin, removal of the solvent left a clear syrup (0.04 g). Column chromatography of the product, with the same solvent, on silica gel (13 x 1 cm) afforded the major zone (0.020 g, 65%). The unprotected nucleoside 168 was purified by chromatography according to the procedure of Dekker. An analytical sample of 168 was crystallized from ethanol-methanol; m.p. 185.5-187°, \([\alpha]_D^{24}+20.4° \, (\text{c} \, 0.56, \text{methanol})\);

\(\lambda_{\text{max}}^{\text{MeOH}}\) 209 nm (\(\epsilon\) 6740), 237 nm (5620), 267 nm (5399); c.d. \(\Delta\epsilon +2.42\)

\(\lambda_{\max}^{274 \text{ nm}, \text{ c} \, 0.004, \text{ methanol}}, [\theta]_{274}^{25}+8000, \Delta\epsilon-1.22 \, (\lambda_{\max}^{236} \text{ nm})\),

\([\theta]_{236}^{25}=4045\); n.m.r. data (\(\text{D}_2\text{O}\)): \(\tau\) 2.10 (1, d, J\(_5\),\(_6\), 8 Hz, H-6), 3.70 (1, d, H-5), 3.9-4.1 (broad s, 2, NH\(_2\), exchanges slowly with \(\text{D}_2\text{O}\)), 4.33 (d, 1, J\(_1\),\(_2\), 9.5 Hz, H-1'), 6.10 (q, 1, J\(_2\),3', 10 Hz, H-2'), 7.06 (q, 1, J\(_2\),3', 10 Hz, H-3'). Irradiation at \(\tau2.10\) produced a singlet at \(\tau3.70\).

Anal. Calc. for C\(_{11}\)H\(_{16}\)N\(_4\)O\(_6\)·H\(_2\)O: C, 41.51; H, 5.70; N, 17.60.

Found: C, 41.61; H, 5.30; N, 17.00.
To a solution of 1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-ribofuranos-3-\(\alpha\)-D-glucopyranos (169, 20 g) in carbon tetrachloride (100 ml) and water (50 ml) containing sodium hydrogen carbonate (1 g) and ruthenium dioxide (0.10 g), was added a 5% solution of sodium metaperiodate with vigorous stirring. The metaperiodate solution was added slowly until the characteristic yellow-green colouration of ruthenium tetroxide was observed; no further metaperiodate was added until the solution had fully reverted to the black ruthenium dioxide stage. This process was repeated until all starting material had been consumed (10-20 h) as evidenced by t.l.c. on silica gel developed with 95:5 dichloromethane-ethyl acetate. Unreacted oxidant was decomposed by the addition of 3-4 drops of isopropanol. The reaction mixture was filtered and the carbon tetrachloride was layer separated from the aqueous solution which was extracted with chloroform (10 x 100 ml). The combined organic solutions were washed with 5% sodium thiosulfate solution (50 ml), dried with anhydrous sodium sulfate, filtered and evaporated to afford crystalline 170 (19 g, 95%). The ketose hydrate was recrystallized from hexane; m.p. 109-110°; (lit\textsuperscript{204b} 109-111°).
3-O-Acetyl-1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-erythro-hex-3-enofuranose (171)

To a solution of 1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-ribofuranos-3-ulose (170) (hydrate) (16 g) and anhydrous pyridine (130 ml) was added acetic anhydride (66.5 ml). The resulting solution was heated to 70-75° for 5 h after which time t.l.c. of the product developed with 95:5 benzene-ethyl acetate showed all of the starting material had disappeared. After cooling to room temperature, the reaction solution was concentrated by evaporation to a syrup and poured into ice water (300 ml) and stirred for 20 min. This aqueous suspension was extracted with dichloromethane (2 x 200 ml) and the organic layer washed with 5% aqueous sodium hydrogen carbonate, water (100 ml), dried over anhydrous sodium sulfate, filtered and the solvent evaporated to yield a syrup 171 (15 g, 90%). Pure 171 was obtained by recrystallization from ethanol-water; m.p.  60-61° (lit. 202 m.p. 62-63°).

Irradiation of 3-O-Acetyl-1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-erythro-hex-3-enofuranose (171)

As in the previously described irradiations, a mixture of compound 171 (10 g), formamide (30 ml), tert-butanol (15 ml), and acetone (15 ml) was added dropwise during 1 h to a mixture of formamide (200 ml), tert-butanol (10 ml) and acetone contained in the photolysis cell. Irradiation was continued during the addition
and prolonged for 48-72 h. After the solution was concentrated to remove tert-butanol and acetone by evaporation (30 torr and 50°C), the resulting mixture was diluted with saturated aqueous sodium chloride (200 ml). The resulting mixture was extracted with dichloromethane (7 x 150 ml). The combined dichloromethane extracts were concentrated to 200 ml and washed with a saturated sodium chloride solution (50 ml), dried over sodium sulfate, filtered, and evaporated under diminished pressure to yield a syrup (11 g). This syrup was chromatographed on t.l.c.-grade silica gel (40 x 11 cm), with 10:10:1 benzene-ethyl acetate-ethanol as developer, to afford starting material 171 (5 g), the amide 172 (3.75 g, 65%) and the amide 173 (1.55 g, 26%).

Compound 172 was recrystallized from ether-petroleum ether (b.p. 30-60°); m.p. 163-164°, [α]_D^{26} +54.5° (c 4.5, chloroform); i.r. (nujol) 3500, 3400 and 1695 cm\(^{-1}\) (CONH\(_2\)); n.m.r. data (CDCl\(_3\)): \(\delta\) 3.45 (d, 1, J\(_{1,2}\) 3.5 Hz, H-1), 4.66 (d, 1, J\(_{2,3}\) 5.5 Hz, H-3), 5.18 (q, 1, H-2), 5.22 (t, 1, J\(_{5,6}\) = 6.5 Hz, H-5), 5.86 (m, 2, H-6, H-6'), 7.86 (s, 3, OAc), 8.40, 8.60, 8.62, 8.64 (4s, 12, CH\(_3\)). Irradiation at \(\delta\)4.17 produced a doublet at \(\delta\)5.18.

Anal. Calc. for C\(_{15}\)H\(_{23}\)N\(_2\)O\(_8\): C, 52.17; H, 6.71; N, 4.06. Found: C, 52.56; H, 6.86; N, 3.76.

Compound 173 crystallized upon the slow evaporation of a chloroform solution; m.p. 68-70°, [α]_D^{24} +57.4° (c 1.16, chloroform); i.r. (film) 3450 and 1690 cm\(^{-1}\) (CONH\(_2\)); n.m.r. data (CDCl\(_3\)): \(\delta\) 3.57 (broad s, 2, CONH\(_2\), exchanges with D\(_2\)O), 4.12 (d, 1, J\(_{1,2}\) 4 Hz, H-1), 4.67 (d, 1, J\(_{1,2}\) 4 Hz, H-2), 5.5 (m, 1, H-5),
7.9 (s, 3, OAc), 8.45, 8.5, 8.62 (3s, 12, CH₃).

Anal. Calc. for C₁₅H₂₃N₂O₈: C, 52.17; H, 6.71; N, 4.06.
Found: C, 51.97; H, 6.70; N, 3.93.

4-C-Carbamoyl-1,2:5,6-di-O-isopropylidene-α-D-gulofuranose (174)

Compound 172 (0.3 g) was dissolved in anhydrous methanol (10 ml) containing a catalytic amount of sodium methoxide. After 2 h the sodium ions were removed by stirring with IR-120 (H⁺) resin, followed by filtration. The filtrate was evaporated to dryness and the resulting syrup (0.24 g, 93%) was crystallized from ethyl ether-petroleum (30-60°) to afford pure 174; m.p. 65°, [α]D²⁶ -1.3° (c 1.28, chloroform); n.m.r. data (CDCl₃): 3.2, 3.7 (2 broad s, 2, CONH₂), 4.18 (d, 1, J₂,₃ 2 Hz, H₁), 8.4, 8.6 (2s, 12, CH₃).

(N.m.r. data unobtainable upon D₂O addition).

Found: C, 51.26; H, 6.92; N, 4.54.

3-O-Acetyl-6-deoxy-1,2-O-isopropylidene-α-D-gulofuranose-4,6-carbolactone (176)

Compound 172 (0.5 g) was dissolved in methanol (25 ml) containing 5% aqueous hydrochloric acid (2.5 ml). This solution was stirred at room temperature for 12 h after which it was neutralized with Amberlite IR-45 (OH⁻) resin, filtered and the filtrate evaporated to dryness under diminished pressure to yield
a syrup (0.46 g). A minor impurity was removed by chromatography on t.l.c. silca (15 x 2 cm) eluted with 10:10:1 benzene-ethyl acetate-ethanol. This afforded crystalline 176 (0.31 g, 73%) which was recrystallized from ethyl ether-petroleum ether (b.p. 30-60°); m.p. 142-143°, $[\alpha]_{D}^{25}+35.6^\circ$ (c 1.01, chloroform); i.r. (CHCl₃ soln) 3550 cm⁻¹ (OH), 1795 cm⁻¹ ($\gamma$-lactone), 1750 cm⁻¹ (OAc); n.m.r. data (CDCl₃): $\tau$ 3.94 (d, 1, $J_{1,2}$ 3.5 Hz, H-1), 4.95 (d, 1, $J_{2,3}$ 4.8 Hz, H-3), 5.02 (q, 1, H-2), 5.15 (m, 1, H-5), 5.64 (m, 2, H-6, H-6'), 7.25 (broad s, OH, exchanges with D₂O), 7.89 (s, 3, OAc), 8.41, 8.70 (2s, 6, CH₃).

Anal. Calc. for C₁₂H₁₆O₈: C, 50.00; H, 5.59.
Found: C, 49.90; H, 5.51.

6-Deoxy-1,2-0-isopropylidene-α-D-gulofuranose-4,6-carbolactone (177)

Compound 176 (0.04 g) was dissolved in anhydrous methanol (1 ml) containing a catalytic amount of sodium methoxide. After standing for 15 min. at room temperature, the sodium ions were removed from the solution by stirring with Rexyn RG-51 (H⁺) resin followed by filtration. Evaporation of the filtrate gave crystalline 177 (0.032 g, 90%). Recrystallization of the product from ethanol gave pure 177; m.p. 171-173°, $[\alpha]_{D}^{25}$-13.6° (c 0.65, chloroform); i.r. (nujol) 3500, 3450 cm⁻¹ (OH), 1775 cm⁻¹ ($\gamma$-lactone); c.d. $\Delta e$-0.759 ($\lambda_{max}$ 225 n.m., c 0.0045, methanol), $[\beta]_{225}^{30}$-2507; n.m.r. data (CDCl₃ and (CD₃)₂CO): $\tau$ 3.95 (d, 1, $J_{1,2}$ 3.8 Hz, H-1), 5.03 (d, 1, $J_{2,3}$ 3.5 Hz, H-3), 5.53 (q, 1, H-2), 8.39, 8.62 (2s, 6, CH₃).
 Anal. Calc. for C_{10}H_{14}O_{7}: C, 48.78; H, 5.73.
Found: C, 48.45; H, 5.62.

3-O-Acetyl-6-deoxy-1,2-0-isopropylidene-5-0-tosyl-\(\alpha\)-D-gulofuranose-4,6-carbolactone (178)

Compound 176 (0.05 g) was dissolved in anhydrous pyridine (1 ml) at 0° and p-toluenesulfonyl chloride (0.066 g) was added and the resulting solution was heated to 50° for two days. After cooling the reaction mixture, the solution was diluted with ice-water (5 ml) and extracted with dichloromethane (2 x 10 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (10 ml) and dried over anhydrous sodium sulfate, filtered, and the resulting solution was evaporated under diminished pressure to afford a syrup (0.08 g). T.l.c. of the product developed with 4:1 benzene-ethyl acetate indicated the presence of some starting material. Chromatography of the mixture on t.l.c. silica (23 x 1 cm) developed with the same solvent afforded the pure tosylate 178 (0.037 g) in 61% yield based on consumed starting material. Recrystallization of the product from benzene gave an analytical sample; m.p. 160.5-161°, [\(\alpha\)]_{D}^{26} -48.9° (c 0.62, chloroform); n.m.r. data (CDCl_{3}): 7 2.05 (m, 2, H-2', H-6'), 2.6 (m, 2, H-3', H-5'), 3.93 (d, 1, J_{1,2} 3.7 Hz, H-1), 4.38 (q, 1, J_{5,6} 2 Hz, H-5), 4.82 (d, 1, J_{2,3} 4.5 Hz, H-3), 4.99 (q, 1, H-2), 5.46 (m, 2, H-6, H-6'), 7.58 (s, 3, CH_{3}), 7.88 (s, 3, OAc), 8.4, 8.67 (2s, 6, CH_{3}).
Anal. Calc. for $C_{19}H_{22}O_{10}S$: C, 51.58; H, 5.01.

Found: C, 51.43; H, 4.82.

6-Deoxy-$\alpha$-(and $\beta$)-D-gulofuranose-4,6-carbolactone (179)

Compound 177 (0.02 g) was dissolved in 80% aqueous trifluoroacetic acid (0.5 ml) and stirred at room temperature after which the solution was successively azeotroped with toluene (2 x 2 ml) to afford a mixture of $\alpha$ and $\beta$-anomers of 179 (0.012 g, 75%): i.r. (film) 1770 cm$^{-1}$ ($\gamma$-lactone); n.m.r. data ((CD)$_3$CO and D$_2$O): 4.70 (1, d, $J_{1\alpha,2}$ 4 Hz, H-1$\alpha$); 4.85 (1, d, $J_{1\beta,2}$ 1.5 Hz, H-1$\beta$).

Anal. Calc. for $C_7H_{10}O_7$: C, 40.78; H, 4.89.

Found: C, 40.61; H, 4.93.

3-$C$-Carbamoyl-1,2:5,6-di-$O$-isopropylidene-$\alpha$-D-allofuranose (180)

3-$O$-Acetyl-$3-C$-carbamoyl-1,2:5,6-di-$O$-isopropylidene $\alpha$-D-allofuranose (173) (0.10 g) was deacetylated as described above for the preparation of 174, to afford compound 180 (0.08 g, 90%); m.p. 156-157°, $[\alpha]_D^{26}$ -1.75 (c 0.6, chloroform); i.r. (CHCl$_3$ soln) 3575 cm$^{-1}$ (OH), 3450, 3300, and 1700 cm$^{-1}$ (CONH$_2$); n.m.r. data (CDC$_3$): $\tau$ 3.05, 3.6 (2 Broad s, NH$_2$), 4.0 (d, 1, $J_{1,2}$ 3.9 Hz, H-1), 5.34 (d, 1, H-2), 6.5 (s, 1, OH, exchanges with D$_2$O), 8.44, 8.60, 8.64, 8.7 (4s, 12, CH$_3$).

Anal. Calc. for $C_{13}H_{21}N_1O_7$: C, 51.48; H, 6.98; N, 4.62.

Found: C, 51.50; H, 6.79; N, 4.60.
3-O-Acetyl-3-C-carbamoyl-1,2-O-isopropylidene-α-D-allofuranose (181)

Compound 173 (0.60 g) was dissolved in methanol (50 ml) and 5% aqueous hydrochloric acid (1 ml). After 10 h at room temperature, the solution was neutralized by stirring with Amberlite IR-45 (OH⁻), filtered and the solution evaporated to yield 181 (0.49 g, 93%). Compound 181 could not be obtained in crystalline form: \([\alpha]_D^{26} +114.4° (c 1, chloroform)\); i.r. (CHCl₃ soln.) 3500-3300 cm⁻¹ (OH), 3200, 1695 cm⁻¹ (CONH₂), 1750 cm⁻¹ (OAc); n.m.r. data (CDCl₃): \(\delta 3.52\) (broad s, 2, NH₂), 4.1 (d, 1, \(J_{1,2} 4.2\) Hz, H-1), 4.2 (d, 1, H-2), 7.84 (s, 3, OAc), 8.48, 8.66 (2s, 6, CH₃).

3,5-Di-O-acetyl-1,2-O-isopropylidene-α-D-allo-pentodialdofuranose-3,5-N-acetylcarbolactam (183) and 3-0-Acetyl-5-deoxy-1,2-O-isopropylidene-β-L-talofuranose-3,5-carbolactam (187)

Compound 181 (0.03 g) was dissolved in methanol (1 ml) and added to water (2 ml) containing sodium hydrogen carbonate (0.01 g), and sodium metaperiodate (0.02 g). The resulting solution was stirred at room temperature for 15 min. after which time dichloromethane (2 ml) was added and the resulting solution filtered and concentrated by evaporation to yield a syrup (0.03 g). This syrup was chromatographed on t.l.c. silica gel (12 x 1 cm) developed with 1:1 benzene-ethyl acetate to afford 3-O-acetyl-1,2-O-isopropylidene-α-D-allo-pentodialdofuranose-3,5-carbolactam.
(182, 0.013 g) and 3-O-acetyl-5-deoxy-1,2-O-isopropylidene-β-L-talofuranose-3,5-carbolactam (187).

Compound 182 (0.012 g) was dissolved in anhydrous pyridine (1 ml) and acetic anhydride (1 ml) and left at room temperature for 10 h. The reaction mixture was evaporated to dryness and the residue dissolved in dichloromethane (2 ml) and extracted with water (1 ml) and the organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to afford crystalline 3,5-di-O-acetyl-1,2-O-isopropylidene-α-D-allo-pentodialdofuranose-3,5-N-acetylcarbolactam (183); m.p. 118-120°, [α]_D^30 -20.6° (c 0.12, chloroform); i.r. (CHCl₃ soln.) 1770 and 1720 cm⁻¹ (CONCO), 1750 cm⁻¹ (OAc); n.m.r. data (CDCl₃): τ 3.38 (s, 1, H-5), 4.14 (d, 1, J₂₄ Hz, H-1), 4.8 (d, 1, H-2) 5.44 (s, 1, H-4), 7.48 (s, 3, NAc), 7.82, 7.89 (2s, 6, OAc), 8.42, 8.62 (2s, 6, CH₃).


Compound 187 was recrystallized from carbon tetrachloride-ethyl ether; m.p. 128-129°, [α]_D^26 -71° (c 0.1, chloroform); i.r. (CHCl₃ soln.) 1750 cm⁻¹ (OAc), 1720 cm⁻¹ (γ-lactam); n.m.r. data (CDCl₃): τ 4.12 (d, 1, J₁₋₂ 3.6 Hz, H-1), 4.43 (q, 1, J₁ NH,5 12 Hz, H-5), 5.05 (d, 1, J₆₋₆ 11 Hz, H-6), 5.19 (d, 1, H-2), 5.3 (d, 1, H-6'), 5.38 (d, 1, J₄₋₅ 4.5 Hz, H-4), 6.1 (broad d, 1, disappears upon the addition of D₂O, N-H), 6.4 (broad s, 1, disappears upon
the addition of D$_2$O, OH), 7.80 (s, 3, OAc), 8.2, 8.55 (2s, 6, CH$_3$). D$_2$O exchange collapsed the quartet at $\tau$4.43 to a doublet. Irradiation at $\tau$4.12 collapsed the doublet at $\tau$5.19 to a singlet. Irradiation at $\tau$4.43 collapsed the doublet at $\tau$5.38 to a singlet.

Anal. Calc. for C$_{12}$H$_{17}$NO$_7$·$\frac{1}{2}$H$_2$O: C, 48.64; H, 6.12; N, 4.72. Found: C, 48.35; H, 5.81; N, 4.38. Molecular weight by mass spectrometry 286.996. C$_{12}$H$_{17}$NO$_7$ requires 287.100. M$^+$+1 288.099 required 288.108.

5-Deoxy-1,2-0-isopropylidene-$\alpha$-D-allofuranose-3,5-carbolactone (185)

Compound 181 (0.09 g) was placed in a short path distillation apparatus (bulb to bulb) and heated to 140-150° at 0.2 torr until distillation of a syrup ceased. Crystals which had formed at the mouth of the exit tube were heated with warm air to force them into the exit. Separation of the exit tube from the collection bulb afforded pure acetamide (0.013 g); m.p. 81-82°, (lit. 240 m.p. 82.3°). The syrup (0.057 g, 79%) in the collection bulb was removed and recrystallized from ethanol to give pure 185; m.p. 129-132°, [\(\alpha\)]$_D^{26}$+29° (c 0.64, chloroform); i.r. (CHCl$_3$ soln.) 3600-3400 cm$^{-1}$ (OH), 1790 cm$^{-1}$ (\(\gamma\)-lactone); c.d. $\Delta\varepsilon+0.673$ ($\lambda_{\text{max}}$ 230 nm, c 0.0036, methanol), [\(\theta\)]$_{230}^{30}$+2223; n.m.r. data (CDCl$_3$):

4.11 (d, 1, J$_1$,2 4 Hz, H-1), 5.28 (d, 1, H-2), 6.04 (broad s, 2, OH, exchanges with D$_2$O), 8.4, 8.6 (2s, 6, CH$_3$).

Anal. Calc. for C$_{10}$H$_{14}$O$_7$: C, 48.78; H, 5.73. Found: C, 48.97; H, 5.60.
3,6-Di-O-acetyl-5-deoxy-1,2-O-isopropylidene-α-D-allofuranose-3,5-carbolactone (186)

Compound 185 (0.05 g) was dissolved in pyridine (1 ml) and acetic anhydride (0.5 ml) and the resulting solution left at room temperature for 24 h. The reaction mixture was concentrated by evaporation and the resulting residue dissolved in dichloromethane (2 ml) and washed with water (1 ml). The organic solution was dried with anhydrous sodium sulfate, filtered, and evaporated to afford a syrup (0.064 g, 95%) which was crystallized from benzene-petroleum ether (b.p. 30-60°); m.p. 116.5-117°, [α]D+6.4° (c 0.26, chloroform); n.m.r. data (CDCl₃): 4.05 (d, 1, J₁,₂ 4 Hz, H-1), 4.87 (d, 1, H-2), 5.21 (s, 1, H-4), 5.38 (q, 1, J₅,₆ 6 Hz, H-5), 5.62 (m, 2, H-6, H-6'), 7.8, 7.86 (2s, 6, OAc), 8.42, 8.58 (2s, 6, CH₃).

Found: C, 50.93; H, 5.48.

3-C-Hydroxymethyl-1,2-O-isopropylidene-α-D-allofuranose (188)

Compound 185 (0.042 g) was dissolved in methanol (1 ml) and water (1 ml) containing sodium borohydride (0.011 g). The resulting mixture was left at room temperature for 24 h and then neutralized with RG-51 (H⁺) resin, filtered and the resulting solution evaporated to yield a syrup. This syrup was successively azeotroped with methanol (3 x 5 ml) under diminished pressure, and
the residue dissolved in ethyl acetate, filtered and the solvent removed by evaporation to give a syrup (0.03 g, 70%); $[\alpha]_D^{25} +28.4^\circ$ (c 0.67, chloroform); (lit. 29 $[\alpha]_D^{20} +30^\circ$, chloroform).

3-C-Acetoxymethyl-5,6-di-O-acetyl-1,2-O-isopropylidene-$\alpha$-D-allofuranose (189)

The 3-C-hydroxymethyl compound 188 (0.01 g) was acetylated as described above for the preparation of 186, to afford 3-C-acetoxymethyl-5,6-di-O-acetyl-1,2-O-isopropylidene-$\alpha$-D-allofuranose (189) (0.015 g, 100%). Distillation of 189 at 140° and 0.2 torr gave an analytical sample; $[\alpha]_D^{28} +25.1^\circ$ (c 1.1, chloroform); n.m.r. data (CDCl$_3$): $\tau$ 4.22 (d, 1, $J_1$ 2 4.1 Hz, H-1), 4.72 (m, 1), 7.86, 7.92 (2s, 9, OAc), 8.4, 8.6 (2s, 6, CH$_3$).

Anal. Calc. for C$_{16}$H$_{24}$O$_{10}$: C, 51.06; H, 6.43.

Found: C, 51.31; H, 6.40.

5,3-Hemiacetal of 3-C-Hydroxymethyl-1,2-O-isopropylidene-$\alpha$-D-ribo-pentodialdose (190) 29

Compound 188 (0.06 g) was dissolved in water (1 ml) at 0° and sodium metaperiodate (0.005 g) dissolved in water (1 ml) was added. After 20 min. the reaction mixture was concentrated to approximately 1 ml, diluted with saturated aqueous sodium chloride (1 ml) and extracted with dichloromethane (2 x 2 ml). The organic solution was dried with anhydrous sodium sulfate, filtered and evaporated to give a syrup (0.0015 g, 30%); $[\alpha]_D^{28} +73^\circ$ (c 0.1,
chloroform), \((\text{lit}^{27} [\alpha]_D^{22}+72^\circ, \text{chloroform})\); \((\text{lit}^{29} [\alpha]_D^{20}+68^\circ, \text{chloroform})\); n.m.r. data \((\text{CHCl}_3)\): \(\tau\) 4.08 (d, 1, J1,2 3.9 Hz, H-1), 4.6 (s, 1, H-5), 5.55 (d, 1, H-2), 5.74 (1, s, H-4), 6.05 (d, 2, JAB 10 Hz, CH2), 8.39, 8.59 (2s, 6, CH3).

4-C-Hydroxymethyl-1,2-O-isopropylidene-\(\alpha\)-D-gulofuranose (191) and 4-C-Acetoxymethyl-3,5,6-tri-O-acetyl-1,2-O-isopropylidene-\(\alpha\)-D-gulofuranose (192)

A solution of the 4-S-6-spiro-\(\gamma\)-lactone 176 (0.4 g) dissolved in methanol (16 ml) and water (16 ml), containing sodium borohydride (0.04 g) was stirred for 12 h at room temperature. Neutralization of the solution by stirring with Rexyn RG-51 (H\(^+\)) resin followed by filtration, and successive azeotropic distillation with methanol (2 x 20 ml) under diminished pressure afforded a clear syrup 191 (0.26 g, 79%): \([\alpha]_D^{26}+15^\circ \ (\epsilon 1.1, \text{methanol})\); n.m.r. data \((\text{CD}_3)_2\text{CO})\): \(\tau\) 4.17 (d, 1, J1,2 4 Hz, H-1), 5.28 (q, 1, J2,3 5.8 Hz, H-2), 5.58 (d, 1, H-3), 5.8 (q, 1, J5,6 4 Hz, J5,6, 7 Hz, H-5), 6.1 (s, 2, CH2), 4.4 (m, 2, H-6, H-6'), 8.4, 8.6 (2s, 6, CH3). The 4-C-hydroxymethyl sugar 191 was further characterized as its tetraacetate derivative 192.

The 4-C-hydroxymethyl sugar (0.02 g) was dissolved in anhydrous pyridine (1 ml) and acetic anhydride (0.75 ml) and the solution left at room temperature for 10 h and then concentrated to dryness under diminished pressure. The residue was dissolved in dichloromethane (5 ml) and washed with water (2 ml). The organic solution was dried with anhydrous sodium sulfate, filtered
and concentrated to afford 4-C-acetoxymethyl-3,5,6-tri-O-acetyl-1,2-O-isopropylidene-α-D-gulofuranose (192, 0.03 g, 90%). An analytical sample of 192 was obtained by distillation at 150° and 0.5 torr; \([\alpha]_D^{26}+44.3^\circ (c 2.6, \text{chloroform})\); n.m.r. data (CDCl₃):

\[\begin{align*}
\tau & \quad \text{J} \\
4.19 & (d, 1, J_{1,2} 4 \text{ Hz}, H-1), \quad 4.36 (q, 1, J_{5,6} 2.6 \text{ Hz}, J_{5,6}^\gamma 7.7 \text{ Hz}, H-5), \quad 4.83 (d, 1, J_{2,3} 6 \text{ Hz}, H-3), \quad 5.15 (q, 1, H-2), \\
5.45 (q, 1, J_{6,6}^\gamma 12 \text{ Hz}, H-6), \quad 5.83 (s, 2, CH_2), \quad 5.93 (q, 1, H-6'), \quad 7.82, 7.90, 7.98 (3s, 12, OAc), \quad 8.39, 8.63 (2s, 6, CH_3).
\end{align*}\]

Found: C, 51.27; H, 6.40.

4-C-Hydroxyethyl-1,2-O-isopropylidene-α-D-erythro-pentofuranose (194) and 4-C-Acetoxymethyl-3,5-di-O-acetyl-1,2-O-isopropylidene-α-D-erythro-pentofuranose (194)

A solution of the 4-C-hydroxymethyl sugar 193 (0.324 g) dissolved in methanol (6 ml) was added to a mixture of sodium metaperiodate (0.14 g) and sodium hydrogen carbonate (0.02 g) in water (6 ml). After 1 h t.l.c. of the product developed with 5:1 ethyl acetate-ethanol showed the reaction was complete and ethylene glycol (0.1 ml) was added followed by sodium borohydride (0.035 g). After 30 min., acetone (0.5 ml) was added and the solution evaporated under diminished pressure to yield a syrup (0.25, 88%); \([\alpha]_D^{28}+7^\circ (c 0.1, \text{methanol})\).
Compound 193 (0.25 g) was acetylated in a solution of acetic anhydride (3 ml) and pyridine (10 ml) and after 10 h at room temperature, the solution was concentrated by evaporation under diminished pressure and the residue dissolved in dichloromethane (10 ml) and the organic solution washed with water (5 ml). The organic solution was dried with anhydrous sodium sulfate, filtered and concentrated to afford the triacetate 194 (0.337 g, 90%). An analytical sample of 194 was obtained by distillation at 155-160° and 0.5 torr; \([\alpha]_D^{26} +47.6 (c 0.76, \text{chloroform})\); n.m.r. data (CDCl\(_3\)): 4.13 (d, 1, J\(_{1,2}\) 4 Hz, H-1), 4.85 (d, 1, J\(_{2,3}\) 5.8 Hz, H-3), 5.16 (q, 1, H-2), 5.55 (q, 2, J\(_{AB}\) 11 Hz, H-5, H-5'), 5.81 (q, 2, J\(_{AB}\) 12 Hz, H-5'', H-5'''), 7.87, 7.92 (2s, 9, OAc), 8.4, 8.67 (2s, 12, CH\(_3\)).

Anal. Calc. for C\(_{15}\)H\(_{22}\)O\(_n\): C, 51.98; H, 6.55.

Found: C, 52.02; H, 6.40.

4-\(-\text{Acetoxyethyl}-1,2,3,5\text{-tetra-0-acetyl-}\alpha-(\text{and } \beta)-\text{D-erythro-}
\text{pentofuranose (195)}\)

Compound 194 (0.1 g) was dissolved in 80% aqueous trifluoroacetate acid (1.5 ml) at 0°. After 15 minutes the solution was evaporated to dryness under reduced pressure and the residue diluted with toluene (2 ml) and the solvent removed under reduced pressure. The thoroughly dried residue was dissolved in pyridine (1 ml) and acetic anhydride (0.5 ml) and left at room
temperature for 10 h. After the reaction mixture was evaporated
to dryness, the residue was dissolved in dichloromethane (5 ml),
washed with water (2 ml) and the organic solution dried over
anhydrous sodium sulfate, filtered and the solvent removed under
diminished pressure to afford the α,β mixture of 195 (0.09 g, 80%).
An analytical sample of the anomeric mixture was obtained by
distillation of the product at 125-130° and 0.5 torr; \([\alpha]_D^{26}\) -21.5°
(c 0.68, chloroform); n.m.r. data (CDCl₃): δ 3.6 (d, 1, J₁α₂ 4 Hz,
H-1α), 3.8 (s, 1, H-1β), 7.92 (s, 15. OAc).

Found: C, 49.27; H, 5.80.

9-(4'-C-Hydroxymethyl-α-D-erythro-pentofuranosyl)adenine (196) and
9-(4'-C-Hydroxymethyl-β-D-erythro-pentofuranosyl)adenine (197)

An α,β mixture of 4-C-acetoxyethyl-1,2,3,5-tetra-O-
acetyl-D-erythro-pentofuranose (195) (0.1 g) was dissolved in
anhydrous dichloromethane (1 ml), and hydrogen bromide-saturated
glacial acetic acid (2 ml) was added at 0° with stirring. The
flask was sealed and allowed to stand at room temperature for 1 h.
The solution was then evaporated to dryness under diminished
pressure and any remaining acetic acid removed by successive
azeotroping with toluene (2 x 2 ml) under diminished pressure.
The resulting syrup was immediately dissolved in anhydrous
dichloromethane (5 ml) containing N⁶-benzoyl-N⁶,9-bis(trimethyl-
silyl) adenine\textsuperscript{197} (0.1 g) and the solvent removed under diminished pressure. This homogeneous syrup was heated to 130-135° at 15 torr for 30 minutes. T.l.c. of the product developed with benzene-ethyl acetate-ethanol showed the presence of three charring, u.v. absorbing components. Chromatography of this mixture on t.l.c. silica (20 x 2 cm), using the same solvent as above, afforded N\textsuperscript{6}-benzoyl-9-(4'-C-acetoxymethyl-2',3',5'-tri-O-acetyl-\alpha-D-erythro-pentofuranosyl) adenine (196, 0.029 g, 20%), N\textsuperscript{6}-benzoyl-9-(4'-C-acetoxymethyl-2',3'5'-tri-O-acetyl-\beta-D-erythro-pentofuranosyl) adenine (197, 0.029 g, 20%) and a third unknown component (0.007 g, 5%); n.m.r. data of 196 (CDCl\textsubscript{3}): \(\delta\) 0.9 (broad s, 1, N\textsuperscript{6}H), 1.2 (s, 1, H-2), 1.6 (s, 1, H-8), 1.95 (m, 2, o-aromatic protons), 2.42 (m, 3, m, p-aromatic protons), 3.36 (d, 1, J\textsubscript{2,3} = 4 Hz, H-T), 4.42 (d, 1, J\textsubscript{2,3} = 4 Hz, H-3'), 5.23 (t, 1, H-2'), 7.85, 7.94 (2s, 12, OAc). Irradiation at \(\delta\) 3.36 produced a doublet at \(\delta\) 5.23. Irradiation at \(\delta\) 5.23 produced singlets at \(\delta\) 3.36 and 4.42; n.m.r. data of 197 (CDCl\textsubscript{3}): \(\delta\) 0.85 (broad s, 1, NH), 1.23 (s, 1, H-2), 1.83 (s, 1, H-8), 2.0 (m, 2, o-aromatic protons), 2.61 (m, 3, p,m-aromatic protons), 3.73 (d, 1, J\textsubscript{1,2} = 5.8 Hz, H-1'), 3.83 (unresolved q, \(\delta\), J\textsubscript{2,3} = 5.5 Hz, H-2'), 4.1 (d, 1, H-3'), 5.58 (m, 4,), 7.87, 7.93, 7.95, 7.99 (4s, 12, OAc).

To a solution of compound 196 (0.02 g) in methanol (1 ml) was added a catalytic amount of sodium methoxide and the solution left to stand for 24 h. The sodium ions were removed
by stirring with Rexyn RG-51 (H⁺) resin followed by filtration. Evaporation of the solution under diminished pressure gave a residue which was dissolved in water, treated with charcoal, and filtered through sintered glass. Evaporation of the aqueous solution gave 9-(4-C-hydroxymethyl-α-D-erythro-pentofuranosyl) adenine (198) which was recrystallized from water; m.p. 262-263.5°, $[\alpha]_D^{26}+7^\circ (c 0.1, \text{water})$; $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 258 nm ($\varepsilon 9700$); c.d. $\Delta\varepsilon +0.448$ ($\lambda_{\text{max}}$ 255 nm, $c 0.0001$, water), $[\theta]_{255}^{30}+1480$; n.m.r. data ($D_2O$): $\tau1.07$ (s, 1, H-2); $1.15$ (s, 1, H-8); $3.31$ (d, 1, J 6.5 Hz, H-1'); $4.41$ (q, 1, J 2', 4 Hz, H-2').

Anal. Calc. for $C_{11}H_{15}N_5O_5\cdot2H_2O$: C, 39.64; H, 5.75; N, 21.30.
Found: C, 39.75; H, 6.13; N, 21.30.

Compound 197 was deacetylated in the same manner as described above to give 198, to afford 199 as a hard glass; $[\alpha]_D^{28}+1^\circ (c 0.1, \text{water})$; $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 258 nm ($\varepsilon 7,860$); c.d. $\Delta\varepsilon-0.335$ ($\lambda_{\text{max}}$ 255 nm, $c 0.0001$, water), $[\theta]_{255}^{30}-1650$; n.m.r. data ($CD_3OD$): $\tau1.5$ (s, 1, H-2), $1.67$ (broad s, 2, NH$_2$), $1.77$ (s, 1, H-8), $3.59$ (d, 1, J 2', 2.5 Hz, H-1'), $4.21$ (d, 1, J 2', 3, 6 Hz, H-3').

Anal. Calc. for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56.
Found: C, 44.75; H, 5.43; N, 23.33.
(E) and (Z)-3-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxy-carbonyl)methylene-α-D-ribo-hexofuranose (11) and (12)

The ketose hydrate 170 (p. 159) was dehydrated by azeotropic distillation with toluene, followed by removal of the solvent by evaporation under diminished pressure. The anhydrous ketose 10 (24 g) was reacted with phosphonoacetic acid trimethyl ester (20.1 g) and potassium t-butoxide (11 g) in N, N-dimethyl formamide (120 ml) at -20°. After allowing the reaction mixture to warm to room temperature, the mixture was maintained at 25° for 20 min. The solvent was then removed under diminished pressure. The residue was dissolved in ethyl ether (100 ml) and washed with water (2 x 50 ml). The organic solution was dried with anhydrous sodium sulfate and filtered. Removal of the solvent by evaporation gave a brown syrup (24 g). Chromatography of this syrup on t.l.c. silica (60 x 6.5 cm) using 4:1 benzene-ethyl acetate as developer gave a mixture of the E and Z-isomers 11 and 12 (17.5 g). Fractional crystallization of the mixture from hexane (b.p. 65-68°) afforded the pure Z-isomer 12 (8 g); m.p. 67-68° (lit. 219° 68-69°).

Irradiation of (E)(Z)-3-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-α-D-ribo-hexofuranose (11) and (12)

By a previously described procedure, a mixture of compound 11 and 12 (1 g), formamide (10 ml), tert-butanol (10 ml)
and acetone (5 ml) was slowly added to a solution containing formamide (200 ml), tert-butanol (10 ml) and acetone (15 ml). The solution was irradiated throughout the addition and continued for 24 h after which t.l.c. of the product using 10:5:1 benzene-ethyl ether-ethanol as developer showed the complete disappearance of the starting material. The reaction was worked up in the same manner as previously described (see p.146 or p.151) to afford a syrup (0.75 g) which was chromatographed on t.l.c. silica (29.5 x 3.5 cm) using the same solvent as above to yield an acetone addition product 202 (0.24 g, 21%) and two formamide addition products 200 and 201 (combined yield 0.5 g, 45%). Compound 200 was recrystallized from ethyl ether-petroleum ether (b.p. 30-60°); m.p. 105-107°, [α]_D^{20} +82° (c 0.15, chloroform); i.r. 1750 cm⁻¹ (C=O), 3520, 3420 and 1700 cm⁻¹ (CONH₂); n.m.r. data (CDCl₃): τ3.90 (broad s, 2, NH₂, exchanges with D₂O); 4.25 (d, 1, J₁,₂ 3.7 Hz, H-1), 5.08 (t, 1, J₂,₃ 3.7 Hz, H-2), 6.22 (s, 3, CH₃), 6.47 (d, 1, J₃',₃ 10 Hz, H-3'), 7.22 (q, 1, H-3), 8.48, 8.6, 8.65 (3s, 12, CH₃). Irradiation at 4.25 produced a doublet at τ5.08. Irradiation at τ5.08 produced a singlet at τ4.25 and a doublet at τ7.22. Irradiation at τ7.22 produced a doublet at τ5.08 and a singlet at τ6.47.

Anal. Calc. for C₁₆H₂₅NO₃: C, 53.48; H, 7.01; N, 3.90.

Found: C, 53.29; H, 7.01; N, 3.60.

Compound 201 was recrystallized from ethyl ether-petroleum ether (b.p. 30-60°); m.p. 75-77°, [α]_D^{28} +25.2° (c 0.6, chloroform);
i.r. (CHCl₃ soln.) 3510, 3420, 1700 cm⁻¹ (CONH₂), 1750 cm⁻¹ (CO₂Me); n.m.r. data (CDCl₃): τ 3.8 (broad s, 2, NH₂, exchanges with D₂O), 4.2 (d, 1, J₁,₂ 4 Hz, H-1), 5.16 (t, 1, J₂,₃ 4 Hz, H-2), 6.22 (s, 3, CH₃), 6.36 (d, 1, J₃,₃ 8 Hz, H-3'), 7.3 (q, 1, H-3), 8.45, 8.57, 8.68 (3s, 12, CH₃). Irradiation at τ 4.2 produced a doublet at τ 5.16. Irradiation at τ 5.16 produced a singlet at τ 4.2 and a doublet at τ 7.3. Irradiation at τ 7.3 produced a doublet at τ 5.16 and a singlet at 6.36.


The acetone addition product was tentatively assigned structure 202 on the basis of its n.m.r. spectra; n.m.r. data (CDCl₃): τ 4.2 (d, 1, J₁,₂ 3.7 Hz, H-1), 5.13 (t, 1, J₂,₃ 3.7 Hz, H-2), 6.3 (s, 3, CH₃), 6.68 (broad s, OH, exchanges with D₂O), 7.02 (d, 1, J₃,₃ 9 Hz, H-3'), 7.63 (q, 1, H-3), 8.45, 8.59, 8.65 (3s, 12, OAc). Irradiation at τ 4.2 produced a doublet at τ 5.13.

**Attempted Hofmann Rearrangement of the Amides 200 and 201**

**Method A **

To a mixture of the two amides, 200 and 201 (0.025 g), dissolved in dimethoxyethane (1.5 ml) a 6% aqueous sodium hypochlorite solution (1.5 ml) was added at 0°C. The resulting mixture was heated to 40-50°C for 20 h. T.l.c. of the product on silica gel using 5:5:1 dichloromethane-ethyl acetate-ethanol as developer.
showed that no detectable reaction had taken place. Concentration of the solution under diminished pressure gave a syrup which was dissolved in dichloromethane (5 ml). The resulting solution was washed with water (2 ml), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The n.m.r. spectra of the residue was comparable with that of the starting amides.

**Method B:**

To a solution of compound 200 (0.1 g) in anhydrous methanol (1 ml) was added a sodium methoxide solution (0.6 ml of a 1 M solution) and bromine (0.08 ml) at 25°. The resulting solution was heated on a steam bath until the solution became colourless, and the heating continued for an additional 5 min. The solution was then neutralized with Rexyn IR-120 (OH) resin, filtered and the solvent removed under diminished pressure to afford a syrup (0.08 g). This syrup was dissolved in chloroform (2 ml) and filtered through sintered glass. The n.m.r. spectrum of this syrup was identical with that of compound 200.

**Method C:**

To a solution of a mixture of the two amides 200 and 201 (0.066 g) in anhydrous dimethyl formamide, was added purified lead tetraacetate (0.08 g) and the resulting solution stirred for 12 h. The solvent was removed under diminished pressure to yield a syrup (0.06 g). T.l.c. of the product on
silica gel using 10:5:1 benzene-ethyl ether-ethyl acetate as developer showed a complex mixture of four compounds of R_f 0.66, 0.59, 0.5 and 0.33. Chromatography on silica gel (10 x 2 cm) with the same solvent system led to the isolation of only starting material.

**Formation of 3',2-Carbolactones from the Amide 201**

The pure amide 201 (0.015 g) was dissolved in 66% aqueous acetic acid (1 ml) and left at room temperature for 12 h. The solvent was removed under diminished pressure and the resulting residue was dissolved in chloroform (3 ml) and the organic solution was washed with water (1 ml). After drying the organic solution with anhydrous sodium sulfate, filtering and removal of the solvent under diminished pressure, the residue was dissolved in pyridine (1 ml) and acetic anhydride (0.1 ml). After the solution was left standing for 30 min. at room temperature, the solvent was removed under diminished pressure. The residue was azeotropically distilled with toluene (1 ml) and the resulting syrup 203 (0.01 g) was then dissolved in 80% trifluoroacetic acid at 0°C. After allowing the solution to warm to room temperature, t.l.c. of the product using 5:5:1 benzene-ethyl acetate-ethanol as developer showed the presence of one spot of different R_f than the starting material. The solvent was removed under diminished pressure and any remaining trifluoro-
acetic acid removed by successive azeotroping with toluene (2 x 1 ml) under reduced pressure. The resulting syrup (0.008 g) was acetylated as described above to give two compounds which were separated by chromatography on t.l.c. silica (10 x 1 cm) developed with 1:1 benzene-ethyl acetate. This afforded separation of the minor component which was tentatively assigned as 1,5,6-tri-O-acetyl-2,3-dideoxy-3-C-[(R)-(methoxycarbonyl)methyl]-β-D-allofuranose-3',2-carbolactone (204) (0.005 g); \([\alpha]_D^{28} \approx -2.7^\circ\) (c 0.4, chloroform); i.r. (CHCl₃ soln.) 1795 cm⁻¹ (γ-lactone), 1742 cm⁻¹ (OAc); n.m.r. data (CDCl₃): τ 3.60 (s, 1, H-1), 4.93 (d, 1, J₂,₃ 6 Hz, H-2), 6.27 (s, 3, CH₃), 6.4 (q, 1, J₃,₃ 2 Hz, H-3), 7.86, 7.87, 7.94 (3s, 9, OAc).

The major component was tentatively assigned the structure of 1,5,6-tri-O-acetyl-2,3-dideoxy-3-C-[(S)-(carbamoyl)methyl]-α-(and β)-D-allofuranose-3',2-carbolactone (205) (0.001 g); \([\alpha]_D^{28} \approx -42^\circ\) (c 0.1, chloroform); i.r. (CHCl₃ soln.) 3480, 3270 and 1700 cm⁻¹ (CONH₂), 1780 cm⁻¹ (γ-lactone), 1745 cm⁻¹ (OAc); n.m.r. data (CDCl₃): τ 3.48 (d, 1, J₁α,₂ 4 Hz, H-1α), 3.6 (s, 1, H-1β), 4.35 (broad s, 2, NH₂); 6.18 (d, 1, J₃,₃ 4 Hz, H-3 β), 6.44 (q, 1, J₂,₃ 7 Hz, H-3 ), 7.86, 7.92 (2s, 9, OAc).

Addition of Hydrazoic Acid to \((Z)-3\text{-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methylene-}\alpha\text{-D-ribo-hexofuranose (12)}\) in the Presence of Sodium Azide

A mixture of the \((Z)-\)isomer 12 (10 g), sodium azide (5 g), hydrazoic acid (70 ml of a 1.6 M solution of HN\(_3\) in CHCl\(_3\)) and redistilled anhydrous dimethylformamide (400 ml) was stirred and heated to 55° for five days. After this time the solvent was evaporated under reduced pressure and the resulting syrup diluted with saturated aqueous sodium chloride (100 ml). The aqueous suspension was extracted with dichloromethane (2 x 100 ml) and the combined organic extracts dried over anhydrous sodium sulfate, filtered and the resulting solution evaporated under diminished pressure to yield a bright yellow syrup (11 g). Chromatography of this syrup on silica gel (51 x 7 cm) eluted with 2:1 benzene-ethyl acetate afforded unreacted starting material 12 (1 g), 3-azido-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl)methyl-\(\alpha\)-D-glucofuranose (206) (9 g, 80%), and 3-amino-3-deoxy-1,2:5,6-di-C-isopropylidene-3-C-[3' diazo(methoxycarbonyl)methyl]-\(\alpha\)-D-glucofuranose (207) (0.8 g, 7%). An analytical sample of 206 was obtained by distillation at 110-115° and 0.5 torr; \([\alpha]_D^{25} -26^\circ\) (c 1, chloroform); i.r. (film) 2137 cm\(^{-1}\) (N\(_3\)), 1745 cm\(^{-1}\) (CO\(_2\)CH\(_3\)); c.d. \(\Delta\varepsilon -0.035\) (\(\lambda_{\text{max}} 294 \text{ nm}, c 0.0046, \text{ methanol}\), \([\alpha]_D^{294} -118^\circ\); n.m.r. data (CDCl\(_3\)): \(\tau\) 4.05 (d, 1, \(J_{1,2} 3.8 \text{ Hz, H-1}\)), 4.93 (d, 1, H-2), 6.1 (s, 3, CH\(_3\)), 6.96 (q, 2, \(J_{AB} 18 \text{ Hz, H-3'}\)), 8.21, 8.52, 8.60...
(3s, 12, CH₃). Irradiation at τ4.05 produced a singlet at τ4.93.

Found: C, 50.53; H, 6.32; N, 11.30.

An analytical sample of 207 was obtained by distillation at 120-130° and 0.5 torr; [α]²⁵_D+16.2° (c 0.13, chloroform);
i.r. (film) 3410, 3350 cm⁻¹ (NH₂), 2101 cm⁻¹ (N₂), 1685 cm⁻¹
(CO₂CH₃); λ_max MeOH 269 nm (ε 7630), λ_max 213 nm (ε 5380); n.m.r.
data (CDCl₃): τ 4.12 (d, 1, J₁,₂ 4 Hz, H-1), 5.5 (d, 1, H-2), 6.21
(s, 3, CH₃), 7.95 (s, 2, NH₂, exchanges with D₂O), 8.50, 8.59,
8.63, 8.70 (4s, 12, CH₃). Irradiation at τ4.12 produced a
singlet at τ5.5.

Found: C, 50.71; H, 6.25; N, 11.71.

The Addition of Sodium Azide to (Z)-3-Deoxy-1,2:5,6-di-0-
isopropylidene-3-C-(methoxycarbonyl)methylene-α-D-ribo-hexofuranose
(12)

A mixture of the Z-isomer 1₂ (4.4 g), and sodium azide (3.5 g)
in anhydrous redistilled dimethylformamide (250 ml) was stirred
and heated to 55° for five days. After this time the reaction
mixture was treated in the same manner as described above to
yield a yellow syrup (3.5 g). Chromatography of this syrup on
t.l.c. silica gel (27x6 cm) using 2:1 benzene-ethyl acetate as
developer afforded unreacted starting material (1.07 g), a trace
of the 3-azido sugar 206 (0.2 g, 2%), and the 3-amino-diazo ester 207 (2.2 g, 45%).

3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxycarbonyl) methyl-α-D-glucofuranose (208)

A solution of 206 (0.9 g) in methanol (5 ml) was added to prehydrogenated 5% palladium on charcoal (0.15 g) in methanol (50 ml). This mixture was hydrogenated at atmospheric pressure for 12-15 h at which time t.l.c. of the product using 1:1 benzene-ethyl acetate as developer showed that all of the starting material had disappeared. The catalyst was removed by filtration and evaporation of the solvent under diminished pressure afforded 208 (0.8 g, 96%) as a clear syrup which could not be induced to crystallize. Distillation of this syrup at 135-140° and 0.5 torr gave an analytical sample; [α]D26+39.7° (c 1.07, chloroform); i.r. (film) 3400-3100 cm⁻¹ (NH₂), 1740 cm⁻¹ (CO₂CH₃), 1650-1550 cm⁻¹ (NH₂); n.m.r. data (CDCl₃): 4.15 (d, 1, J₁,₂ 3.7 Hz, H-1), 5.47 (d, 1, H-2), 6.33 (s, 3, CH₃), 7.2 (q, 2, J₅,₆ 18 Hz, H-3'), 8.24 (s, 2, NH₂, exchanges with D₂O), 8.52, 8.60, 8.68, 8.71 (4s, 12, CH₃). Irradiation at 4.15 produced a singlet at 5.47.

3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(hydroxycarbonyl) methyl-α-D-glucofuranose (209)

To a solution of 208 (0.055 g) in methanol (2 ml) was added 4% sodium hydroxide in methanol (1 ml) and the resulting mixture was refluxed for 30 min. The reaction mixture was then passed through a short column (10 x 0.5 cm) of Rexyn RG-51 (H⁺) resin. Collection of the charring fractions and evaporation of the solvent under diminished pressure afforded 209 (0.04 g, 85%) as a crystalline mass. An analytical sample of 209 was prepared by sublimation at 210° and 0.5 torr; [α]₂₅° +25° (c 0.12, chloroform); i.r. (nujol) 3200-2600 cm⁻¹ (CO₂H), 1640 cm⁻¹ (C=O), n.m.r data (CDCl₃): 4.1 (d, 1, J₁,₂ 3.9 Hz, H-1), 5.5 (d, 1, H-2), 6.30 (q, 2, Jₐ,ₐ 8 Hz, H-3'), 8.0-8.2 (broad s, 2, NH₂, exchanges with D₂O), 8.55, 8.62, 8.69, 8.73 (4s, 12, CH₃).

Anal. Calc. for C₁₄H₂₃N₁O₇:  C, 52.99; H, 7.31; N, 4.41. Found:  C, 52.97; H, 7.15; N, 4.20.

3-Acetamido-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-(methoxy-carbonyl)methyl-α-D-glucofuranose (210)

A solution of 208 (2 g) in anhydrous pyridine (20 ml) and acetic anhydride (2 ml) was stirred for 20 h at ambient temperature. After this time, the solution was poured into ice water (20 ml) and stirred for 10 min. This solution was extracted with dichloromethane (2 x 50 ml) and the organic layers combined,
dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to yield a crystalline mass (2.2 gm, 98%),

3-acetamido-3-deoxy-1,2:5,6-di-O-isopropylidene-3-C- (methoxy-carbonyl) methyl-α-D-glucofuranose (210). An analytical sample of 210 was prepared by sublimation at 115-120°C and 0.5 torr; 

\[ [\alpha]_D^{26} +22.8^\circ \text{ (c 1.05, chloroform); i.r. (film) 3500, 3400, 1695 cm}^{-1} \text{ (-CONH-), 1740 cm}^{-1} \text{ (CO}_2\text{CH}_3); n.m.r. \text{ data (CDCl}_3\text{): } \tau \text{ 3.8 (s, 1, NH), 3.92 (d, 1, J }_{1,2} \text{ 4 Hz, H-1), 4.68 (d, 1, H-2), 6.29 (s, 3, CH}_3\text{), 7.0 (s, 2, H-3'), 8.0 (s, 3, NAc); 8.45, 8.52, 8.62 (3s, 12, CH}_3\text).} \]

Anal. Calc. for C\text{17}H\text{27}NO\text{8}: C, 54.68; H, 7.29; N, 3.75. Found: C, 54.76; H, 7.25; N, 3.88.

3-Acetamido-5-O-benzoyl-3-deoxy-1,2-O-isopropylidene-3-C- (methoxy-carbonyl)methyl-α-D-xylofuranose (213)

A solution of 210 (2.1 g) in 66% acetic acid (5 ml) was stirred at ambient temperature for 23 h after which toluene (25 ml) was added and the solvent removed under diminished pressure to afford a light yellow syrup (1.8 g) which was homogenous on t.l.c. developed with 5:5:1 benzene-ethyl acetate-ethanol, \( R_f \) 0.13. Distillation of the diol at 150-160° and 0.5 torr gave the pure compound 211 in near quantitative yield; 

\[ [\alpha]_D^{26} +51.5^\circ \text{ (c 1.14, chloroform); i.r. (CHCl}_3 \text{ soln.) 3600-3400 cm}^{-1} \text{ (OH), 1735 cm}^{-1} \text{ (CO}_2\text{CH}_3\text{), 1675 cm}^{-1} \text{ (NAC); n.m.r. \text{ data (CDCl}_3\text): } \tau \text{ 3.32 (s, 1, NH), 4.13 (d, 1, J }_{1,2} \text{ 3.8 Hz, H-1), 5.12 (d, 1, H-2), 7.98 (s, 3, NAC), 8.55, 8.73 (2s, 6, CH}_3\text).} \]
To a solution of 211 (1.7 g) in methanol (40 ml) was added a solution of sodium periodate (1.09 g) in water (70 ml) and a saturated sodium bicarbonate solution (2 ml). After the mixture was left standing for 15 min. a drop of ethylene glycol was added, followed by sodium borohydride (0.120 g) and the resulting solution stirred for 0.5 h. The solution was then filtered through sintered glass and the solvent removed under reduced pressure. The resulting residue was taken up in water (25 ml) and extracted with dichloromethane (4 x 100 ml). The combined organic layers were dried with anhydrous sodium sulphate, filtered and evaporated to dryness to yield a hard glass (1.3 g, 85%). Distillation at 150-160° and 0.5 torr gave pure 212; 
\([\alpha]_D^{26} +19.0^\circ \text{ (c 1.44, chloroform); i.r. (CHCl}_3 \text{ soln.) 3600 cm}^{-1} \text{ (OH), 3400 cm}^{-1} \text{ (NH), 1735 cm}^{-1} \text{ (CO}_2\text{CH}_3\text{), 1685 cm}^{-1} \text{ (NAc); n.m.r. data (CDCl}_3\text{): 2.32 (s, 1, NH, exchanges with D}_2\text{O), 4.15 (d, 1, J}_1\text{, 2 Hz, H}-1\text{), 4.93 (d, 1, H-2), 6.35 (s, 3, CH}_3\text{), 8.01 (s, 3, NAc), 8.52, 8.7 (2s, 6, CH}_3\text{).}

Compound 212 (1.2 g) was dissolved in anhydrous benzene (15 ml) to which was added dropwise a solution of benzoyl chloride (0.5 ml) and pyridine (1 ml). After stirring at ambient temperature for 8 h, the solution was passed through a short column of alumina (5 g) and the charring fractions combined and evaporated to dryness to yield 213 (1.39 g). T.l.c. of the product on silica using 10:10:1 benzene-ethyl acetate-ethanol as
The developer indicated the presence of mostly one spot, \( R_f \) 0.25 and a very minor impurity. Purification of the product was achieved by chromatography on t.l.c. silica gel (23 x 3 cm) eluted with 10:10:1 benzene-ethyl acetate-ethanol. This afforded pure \( \text{213} \) (1.08 g) in an overall 50% yield from \( \text{210} \).

An analytical sample of \( \text{213} \) was obtained by distillation at 200-210° and 0.5 torr; \([\alpha]_D^{26}+28.4^\circ \) (c 1.1, chloroform); i.r. (CHCl\(_3\) soln.) 3500-3300 cm\(^{-1}\) (NH); n.m.r. data (CDCl\(_3\)): \( \tau \) 1.8-2.1 (m, 2, o-aromatic protons), 2.4-2.6 (m, 3, p,m-aromatic protons), 3.39 (broad s, 1, NH), 4.05 (d, 1, \( J_{1,2} \) 3.5 Hz, H-1), 4.92 (d, 1, H-2), 4.38 (s, 3, CH\(_3\)), 4.71 (s, 2, H-3'), 8.08 (s, 3, OAc), 8.48, 8.65 (2s, 6, CH\(_3\)).

Anal. Calc. for \( \text{C}_{20}\text{H}_{25}\text{N}_1\text{O}_8 \): C, 58.96; H, 6.19; N, 3.44. Found: C, 58.60; H, 6.30; N, 3.21.

3-Acetamido-1-O-acetyl-5-O-benzoyl-2,3-dideoxy-3-C-methyl-\( \alpha \)-(and \( \beta \))-D-xylofuranose-3',2-carbolactone (215) and (216)

Compound \( \text{213} \) (1 g) was dissolved in 80% trifluoroacetic acid (50 ml) and the mixture stirred at room temperature for 1 h after which the solvent was removed under reduced pressure and the residue azeotroped with toluene (2 x 25 ml) to remove the last traces of acid. The resulting syrup (0.84 g) was dissolved in pyridine (6 ml) and acetic anhydride (4 ml) and left for 20 h. The solution was then poured in ice water (20 ml) and stirred for
20 min. Extraction of the mixture with dichloromethane (2 x 50 ml) followed by drying over sodium sulfate and evaporation of the solvent under reduced pressure gave a syrup 214 (0.9 g, 90%). Chromatography of the anomeric mixture on t.l.c. silica gel (29 x 4 cm) eluted with 5:5:1 benzene-ethyl acetate-ethanol afforded the pure α and β-acetates 215 and 216. An analytical sample of 215 was prepared by distillation at 140-145° and 0.5 torr; [α]$_D^{26}$+75° (c 0.69, chloroform); i.r. (CHCl$_3$ soln.) 1800 cm$^{-1}$ (γ-lactone), 1680 cm$^{-1}$ (CONH); n.m.r. data (CDCl$_3$): τ 1.8-2.1 (m, 2, o-aromatic protons), 2.3-2.6 (m, 3, p,m -aromatic protons), 3.41 (d, 1, J$_{1,2}$ 5 Hz, H-1), 3.75 (broad s, 1, NH, exchanges with D$_2$O), 4.71 (d, 1, H-2), 4.8 (q, 2, J$_A,B$ 18 Hz, H-3'), 7.85 (s, 3, NAc), 7.95 (s, 3, OAc).

Anal. Calc. for C$_{18}$H$_{19}$N$_1$O$_3$: C, 57.29; H, 5.08; N, 3.71. Found: C, 57.23; H, 4.93; N, 3.57.

An analytical sample of 216 was prepared by distillation at 150-155° and 0.5 torr; [α]$_D^{26}$-57° (c 0.18, chloroform); i.r. 1800 cm$^{-1}$ (γ-lactone), 1690 cm$^{-1}$ (CONH); n.m.r. data (CDCl$_3$): τ 1.89-2.01 (m, 2, o-aromatic protons), 2.4-2.6 (m, 3, p,m-aromatic protons), 2.8 (s, 1, NH, exchanges with D$_2$O), 3.82 (d, 1, J$_{1,2}$ 1 Hz, H-1), 4.93 (d, 1, H-2), 5.20 (t, 1, J$_{4,5}$ = J$_{4,5}$, 5 Hz, H-4), 5.5 (d, 2, J$_{4,5}$ 5 Hz, H-5'), 6.91 (q, 2, J$_{AB}$ 19 Hz, H-3'), 8.01 (s, 6, NAc, OAc).

Anal. Calc. for C$_{18}$H$_{19}$N$_1$O$_3$: C, 57.29; H, 5.08; N, 3.71. Found: C, 57.65; H, 5.34; N, 3.58.
N-Benzoyl-9-(3'-acetamido-5'-O-benzoyl-2',3'-dideoxy-3'-C-methyl-α- (and β)-D-xylofuranos-3'',2-carbolactone-yl)adenine (217) and (218)

An anomeric mixture of 215 and 216 (0.15 g) was dissolved in anhydrous dichloromethane (2 ml) and hydrogen bromide-saturated glacial acetic acid (2 ml) was added at 0°. The flask was sealed and allowed to warm to room temperature and was stirred for an additional 2 h. The solution was then evaporated to dryness under diminished pressure and any remaining acetic acid removed by successive azeotroping with toluene (2 x 2 ml) under diminished pressure. The resulting syrup was immediately dissolved in anhydrous dichloromethane (5 ml) containing N^6-benzoyl-N^6,9-bis(trimethylsilyl)adenine^197 (0.2 g) and the solvent removed under diminished pressure. This homogenous syrup was then heated to 170° at 15 torr for 25 min. Ethanol saturated with sodium hydrogen carbonate (10 ml) was added after cooling, and the resulting suspension filtered through sintered glass. Removal of the solvent under diminished pressure gave a brown syrup (0.2 g). Column chromatography of the product on t.l.c. silica gel (23 x 2 cm) with 5:5:1 dichloromethane-ethyl acetate-ethanol as the developer afforded N-benzoyl-9-(3'-acetamido-5'-O-benzoyl-2',3'-dideoxy-3'-C-methyl-β-D-xylofuranos-3'',2'-carbolactone-yl) adenine (218) (0.075 g, 36%) and N-benzoyl-9-(3'-acetamido-5'-O-benzoyl-2',3'-dideoxy-3'-C-methyl-α-β-D-xylofuranos-3'',2'-carbo-
lactone-yl)adenine (217) (0.03 g, 14%). An analytical sample of
217 was recrystallized from methanol; m.p. 154-156°, \([\alpha]_D^{26} = -13.9°
(\epsilon 0.8, \text{chloroform}); \lambda_{\text{MeOH}}^{\text{max}} 202 (\epsilon 22,200), 227 (\epsilon 19,800), 277 nm
(16,700); \text{i.r. (CHCl}_3 \text{ soln.) 1800 cm}^{-1}(\gamma\text{-lactone}); \text{n.m.r. data (CDCl}_3): \tau 0.6
(broad s, 1, NHBz, exchanges with D}_2\text{O), 1.5 (s, 1, H-2), 1.8
(s, 1, NHAc), 1.86 (s, 1, H-8), 2.0-2.2 (m, 4, o-aromatic
protons), 2.4-2.7 (m, 6, p,m-aromatic protons), 3.12 (d, 1, J_1',2',
4 Hz, H-1'); 4.45 (d, 1, H-2'), 5.0 (m, 1, H-4'), 5.2-5.6 (m, 2,
H-5'), 6.75 (s, 2, H-3"), 8.06 (s, 3, NAc).

\text{Anal. Calc. for } C_{28}H_{24}N_{6}O_7: C, 58.55; H, 4.55;
N, 14.61. Found: C, 58.60; H, 4.46; N, 14.77.

Compound 218 was obtained as an amorphous solid; \([\alpha]_D^{30}
+42.6° (\epsilon 0.22, \text{methanol); } \lambda_{\text{MeOH}}^{\text{max}} 202 (\epsilon 22,900), 227 (\epsilon 19,490),
278 nm (\epsilon 16,000); \text{i.r. (CHCl}_3 \text{ soln.) 1800 cm}^{-1}(\gamma\text{-lactone}); \text{n.m.r. data (CDCl}_3): \tau 0.32
(broad s, 1, NHBz, exchanges with D}_2\text{O), 0.74 (broad s, 1, NHAc, exchanges with D}_2\text{O), 1.22 (s, 1, H-2),
1.8 (s, 1, H-8), 1.9-2.1 (m, 4, o-aromatic protons), 2.3-2.7 (m,
6, p,m-aromatic protons), 3.99 (d, 1, J_1',2', 0.8 Hz, H-1'),
4.5 (d, 1, H-2'), 5.1 (q, 1, J_4'=5', 6 Hz, H-4'), 5.6 (m, 2, H-5'),
6.58 (q, 2, J_{AB} 18 Hz, H-3"), 7.84 (s, 3, NAc).

\text{Anal. Calc. for } C_{28}H_{24}N_{6}O_7: C, 58.55; H, 4.55;
N, 14.61. Found: C, 58.69; H, 4.43; N, 14.37.
9-(3'-Acetamido-2',3'-dideoxy-3'-C-methyl-α-D-xylofuranos-3''-2',-carbolactone-yl)adenine (219)

The fully blocked nucleoside 217 (0.1 g) was dissolved in anhydrous methanol (4 ml) and a catalytic amount of sodium methoxide was added (5 ml of a 0.02 mM solution). After 20 h at room temperature the solution was neutralized with IRC-50 (H⁺) resin. The solution was filtered and the solvent removed to yield a clear syrup. The residue was dissolved in water (3 ml) and extracted with ethyl ether (1 ml). The aqueous layer was evaporated to dryness under diminished pressure to afford an amorphous solid (0.04 g, 65% yield). 219 was recrystallized from methanol; m.p. 162-163°, [α]D30 -37.4° (c 0.12, methanol); i.r. (nujol) 1796 cm⁻¹ (γ-lactone); λH₂O max 205 nm (ε 23,300), 258 nm (ε 14,250); n.m.r. data (CDCl₃): c.d. δε+1.0 (λmax 255 nm, c 0.00015, water), [α]D30 +3300°; n.m.r. data (D₂O): τ 1.8 (2s, 2, H-8, H-2), 3.45 (d, 1, J₁,2, 4 Hz, H-1'), 4.45 (d, 1, H-2'), 6.75 (q, 2, Jₐ,₈ 10 Hz, H-3''), 7.95 (s, 3, NAc).

Anal. Calc. for C₁₄H₁₆N₆O₅·MeOH: C, 47.36; H, 5.28; N, 22.12. Found: C, 47.83; H, 5.29; N, 22.32.

9-(3'-Acetamido-2',3'-dideoxy-3'-C-methyl-β-D-xylofuranos-3'',2'-carbolactone-yl)adenine (220)

Compound 218 was deacetylated by the same procedure as used for the preparation of 219 to afford the free β-nucleoside 220
(0.12 g, 79%) which was recrystallized from ethanol-acetone; m.p. 159-162°, [α]D28 -11° (c 0.3, methanol); i.r. (nujol) 1790 cm⁻¹ (γ-lactone); λmax H₂O 205 nm (ε 14,800), λmax 258 (ε 11,300); c.d. Δε-0.5 (λmax 260 nm, c 0.00013, water), [θ]D30 1650°; n.m.r. data ((CD₃)₂CO): τ 1.57 (s, 1, H-2), 1.63 (s, 1, H-8), 1.98 (broad s, 1, NH, exchanges with D₂O), 3.8 (d, 1, J₂₁ , 2' 2 Hz, H-1'), 4.3 (d, 1, H-2'), 7.8 (s, 3, NAc).

Anal. Calc. for C₁₄H₁₆N₀₅·CH₃OH: C, 47.36; H, 5.38; N, 22.12. Found: C, 48.05; H, 5.00; N, 22.21.

3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-spiro-2'[(R) and (S)-(methoxycarbonyl)methyl aziridine] (221) and (222)

A solution of 207 (0.36 g) and anhydrous copper sulfate (0.05 g) in anhydrous cyclohexane (45 ml) was vigorously stirred and refluxed until t.l.c. on silica gel developed with 2:1 benzene-ethyl acetate showed all of the starting material had disappeared. The solution was filtered through sintered glass and the solvent was removed under diminished pressure to yield a clear syrup (0.278, 87%).

The n.m.r. spectrum showed the product to be comprised of two components which could not be chromatographically separated. An analytical sample of the mixture of aziridines 221 and 222 was obtained by distillation at 140° and 0.5 torr; i.r. (film) 3600-3200 cm⁻¹ (NH), 1730 cm⁻¹ (CO₂CH₃).
Anal. Calc. for C$_{15}$H$_{23}$NO$_7$: C, 54.70; H, 7.04; N, 4.25.

Found: C, 54.47; H, 7.09; N, 4.00.

Hydrogenation of the R,S-Aziridine Mixture

A solution of the aziridine mixture (0.04 g) in methanol (2 ml) was hydrogenated at atmospheric pressure with Raney nickel. After 4 h, the solution was filtered to remove the catalyst, and the resulting solution was evaporated to dryness under diminished pressure to give a clear syrup (0.039 g) which gave n.m.r. and i.r. spectra which were indistinguishable from those of the previously described 3-amino sugar 208.

Treatment of a Mixture of the Aziridines 221 and 222 with Trifluoroacetanhydride in Pyridine

The mixture of aziridines (0.05 g) was dissolved in a solution of anhydrous dichloromethane (2 ml) and pyridine (0.5 ml) and cooled to 0°. Trifluoroacetic anhydride (0.1 ml) was added and the stirred solution was allowed to warm to room temperature and maintained at that temperature for 30 min. T.l.c. of the product on silica gel developed with 2:1 benzene-ethyl acetate showed the presence of two spots, R$_f$ 0.61 and 0.31. The product composition did not change (as observed by t.l.c.) regardless of varying quantities of anhydride or pyridine or length of reaction time. The solution was evaporated under diminished pressure to
yield a clear syrup (0.066 g). Chromatography of the product on t.l.c. silica gel (10 x 1.5 cm) developed with 2:1 benzene-ethyl acetate afforded pure 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-spiro-2'–[(S)-(methoxycarbonyl)methyl-N-trifluoroacetyl aziridine] (223, 0.026 g) and 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-spiro-2'–[(R)-(methoxycarbonyl)-methyl aziridine] (221) (0.02 g). An analytical sample of 223 was prepared by distillation at 120-130° and 0.5 torr; $[\alpha]_{D}^{25} +142.2^\circ$ (c 0.18, chloroform); i.r. (film) 1728 cm$^{-1}$ ($CO_2CH_3$), 1714 cm$^{-1}$ (COCl$_3$), 1221 cm$^{-1}$ (CF); n.m.r. data (C$_6$D$_6$): $^\tau$ 4.1 (d, 1, J$_{1,2}$ 3.6 Hz, H-1), 4.80 (d, 1, H-2), 5.38 (m, 1, H-5), 5.88 (s, 1, H-2'), 6.68 (s, 3, CH$_3$), 8.66, 8.74, 8.93, 9.20 (4s, 12, CH$_3$); Fluorine n.m.r. (CDCl$_3$, CFCI$_3$ internal standard)-76 p.p.m. (s, CF$_3$).

Anal. Calc. for C$_{17}$H$_{22}$NO$_7$F$_3$: C, 47.99; H, 5.21; N, 3.29. Found: C, 47.93; H, 5.21; N, 3.08.

The second component 221 readily crystallized from benzene-petroleum ether (b.p. 30-60°); m.p. 95.5-96°, $[\alpha]_{D}^{25}$ -8.8° (c 0.17, chloroform); i.r. (film) 3300 cm$^{-1}$ (NH), 1716 cm$^{-1}$ (CO$_2$CH$_3$); n.m.r. data (CDCl$_3$): $^\tau$ 4.05 (d, 1, J$_{1,2}$ 4.4 Hz, H-1), 5.24 (d, 1, H-2), 6.23 (s, 3, CH$_3$), 6.7-7.2 (broad s, H-2', sharpens upon addition of D$_2$O), 7.6-8.2 (broad s, 1, NH, exchanges with D$_2$O), 8.5, 8.6, 8.67 (3s, 12, CH$_3$).

Anal. Calc. for C$_{15}$H$_{23}$NO$_7$: C, 54.70; H, 7.04; N, 4.25. Found: C, 54.47; H, 6.90; N, 3.95.
Deamination of 3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-gluco-
franose-3-spiro-2′-[(R)-(methoxycarbonyl)methyl aziridine] (221)
with Iso-amyl Nitrite

The R-aziridine 221 (0.012 g) was dissolved in anhydrous
tetrahydrofuran (0.5 ml), cooled to -15°, and an excess of
freshly distilled iso-amyl nitrate (0.03 ml) was added. After
allowing the solution to stand for 30 min., the pale yellow
solution was heated to 40-50° until decolourization occurred.
The resulting clear solution was evaporated under diminished
pressure to afford a colourless syrup (0.009 g) which was homogenous
by t.l.c. on silica gel developed with 4:1 benzene-ethyl acetate,
R_f 0.51. The p.m.r. spectrum of this compound was identical with
that of the known compound (E)-3-deoxy-1,2:5,6-di-O-isopropylidene-
3-C-(methoxycarbonyl)methylene-α-D-ribo-hexofuranose (11); n.m.r.
data (CDCl_3): δ 3.80 (m, 1, H-3'), 4.1 (d, 1, J_1,2 4.5 Hz, H-1),
4.9 (m, 2, H-2, H-4), 6.24 (s, 3, CH), 8.58, 8.6, 8.68, 8.72
(4s, 12, CH_3).

Attempted Ring Opening of 3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-
glucofuranose-3-spiro-2′[(S)-(methoxycarbonyl)methyl-N-trifluoro-
acetyl aziridine] (223) with Sodium Azide

A solution of the aziridine 223 (0.04 g), sodium
azide and ammonium chloride (0.02 g) in anhydrous dimethyl
formamide (4 ml) was refluxed for 25 h and the course of the
reaction followed by t.l.c. on silica gel developed with 2:1 benzene-ethyl acetate. No reaction was observed to occur. Longer reaction times led only to slow decomposition to some unidentified material.

Attempted Ring Opening of 3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-spiro-2\'[(R)-(methoxycarbonyl)methyl aziridine] (221)

Application of the same procedure as described above in the attempted ring opening of compound 223 when applied to the R-aziridine, gave no identifiable products.

Hydrogenation of 207 to Afford 208 and 3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-3-α-methoxalyl-α-D-glucofuranose hydrazone (224)

The β-amino-α-diazo ester 207 (0.2 g) was hydrogenated in methanol (15 ml) with prehydrogenated 5% palladium on charcoal (0.05 g) for 3 h after which time, t.l.c. of the product using 10:10:1 benzene-ethyl acetate-ethanol as developer, showed the presence of two products of Rf 0.43 and 0.26. Chromatographic separation of these components was achieved on t.l.c. silica gel (15 x 2 cm), using the same solvent as above, to afford the previously described β-amino ester 208 (0.084 g, 45%), and 3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-3-α-methoxalyl-α-D-glucofuranose hydrazone (224) (0.056 g, 28%). An analytical
sample of the hydrazone 224 was obtained by recrystallization from ethyl acetate; m.p. 110-112°, [α]$_D^{25}$ +89.5° ($c$ 0.42, chloroform); i.r. (nujol) 3490, 3350 cm$^{-1}$ (NH$_2$), 1690 cm$^{-1}$ (CO$_2$CH$_3$); λ$_{max}^{MeOH}$ 270 nm ($c$ 10,400); n.m.r. data (CDCl$_3$): δ 1.75 (s, 2, NH$_2$, exchanges with D$_2$O), 4.05 (d, 1, J$_{1,2}$ 4 Hz, H-1), 5.15 (d, 1, H-2), 6.18 (s, 3, CH$_3$), 8.4 (broad s, 4, NH$_2$, exchanges with D$_2$O), 8.6, 8.65, 8.72 (4s, 12, CH$_3$).

Anal. Calc. for C$_{15}$H$_{25}$N$_3$O$_7$: C, 50.13; H, 7.01; N, 11.69.

Found: C, 50.10; H, 7.01, N, 11.41.

Hydrogenation of 224 to Afford Methyl-2- D- and 2-L-(3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl)glycinate

(225) and (226)

A solution of the hydrazone 224 (0.05 g) in methanol (5 ml) and water (1 ml) was treated with freshly activated Raney nickel and hydrogen at 50 psi and 30° for 5 h to afford a mixture of the D and L-glycosyl α-amino esters 225 and 226 (0.044 g, 91%).

Anal. Calc. for C$_{15}$H$_{26}$N$_2$O$_7$: C, 52.01; H, 7.57; N, 8.09.

Found: C, 52.01; H, 7.02; N, 7.64.

Chromatographic separation of these products could not be achieved. However, treatment of the mixture of amino esters (0.03 g) dissolved in anhydrous dichloromethane (1 ml) with pyridine (0.5 ml) and trifluoroacetic acid (0.1 ml) at 0° for 5 min. afforded a quantitative yield of the di-trifluoroacetamido derivatives 227 and 228. Chromatographic separation of these
trifluoroacetates, achieved on t.l.c. silica gel (24 x 1.2 cm) using 2:1 benzene-ethyl acetate as a developer, afforded methyl-2-\(\alpha\)-D-(3-trifluoroacetamido-3-deoxy-1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-glucofuranos-3-yl)-N-trifluoroacetylglycinate (227) (0.018 g, 41%); \([\alpha]_D^{28} +35.4^\circ (c 1.8,\) chloroform); n.m.r. data (CDCl\(_3\)):
\[
\begin{align*}
\tau & \quad \text{(broad d, 1, } J_{\text{NH,H-1}}, 10 \text{ Hz, NH, exchanges slowly with } D_2O), \\
3.1 & \quad \text{(broad s, 1, NH, exchanges slowly with } D_2O), \\
J_{1,2} & \quad 3.4 \text{ Hz, H-1), } \\
4.42 & \quad \text{(d, 1, H-2), } \\
4.6 & \quad \text{(d, 1, H-1'), } \\
6.2 & \quad \text{(s, 3, CH\(_3\)), } \\
8.4, 8.53, 8.57, 8.59 & \quad \text{(4s, 12, CH\(_3\)); Fluorine n.m.r. (CDCl\(_3\), CFCl\(_3\) internal standard): } -76 \text{ p.p.m. (s, CF\(_3\)).}
\end{align*}
\]
and methyl-2-L-(3-trifluoroacetamido-3-deoxy-1,2:5,6-di-O-isopropylidene-\(\alpha\)-L-glucofuranos-3-yl)-N-trifluoroacetylglycinate (228) (0.018 g, 41%); \([\alpha]_D^{28} +66^\circ (c 1.04,\) chloroform); n.m.r. data (CDCl\(_3\)):
\[
\begin{align*}
\tau & \quad \text{(broad d, 1, } J_{\text{NH,H-1}}, 8 \text{ Hz, NH, exchanges slowly with } D_2O), \\
2.8 & \quad \text{(broad s, 1, NH, exchanges slowly with } D_2O), \\
3.9 & \quad \text{(d, 1, } J_{1,2} 4 \text{ Hz, H-1), } \\
4.58 & \quad \text{(d, 1, H'), } \\
4.58 & \quad \text{(d, 1, H-2), } \\
6.19 & \quad \text{(s, 3, CH\(_3\)), } \\
8.45, 8.5, 8.58 & \quad \text{(3s, 12, CH\(_3\)); Fluorine n.m.r. (CDCl\(_3\), CFCl\(_3\) internal standard): } -76 \text{ p.p.m. (2s, CF\(_3\)).}
\end{align*}
\]
2-\(\alpha\)-D-(3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-glucofuranos-3-yl)glycine (229)

Treatment of the \(\alpha\)-isomer 227 (0.018 g) with a 1% aqueous methanolic solution (1 ml) (1:1 methanol - 1% aqueous sodium hydroxide) followed by removal of the sodium ions by stirring with RG 51 (H\(^+\)) resin and filtration afford the free
amino-acid \textit{229} (0.11 g, 99%); which was recrystallized from methanol; m.p. 134-136°, $[\alpha]_D^{28}+26^\circ$ (c 1.2, methanol); c.d. $\Delta\varepsilon$-0.57 ($\lambda_{\text{max}}$ 215 nm, c 0.0014, methanol), $[\theta]_{215}^{30}$-1880°; n.m.r. data (CD$_3$OD): $\tau$ 3.9 (d, 1, J$_{1,2}$ 4 Hz, H-1), 4.75 (d, 1, H-2), 8.58, 8.60, 8.62 (3s, 12, CH$_3$).

Anal. Calc. for C$_{14}$H$_{24}$N$_2$O$_7$: C, 50.60; H, 7.28; N, 8.43.
Found: C, 50.20; H, 6.95; N, 8.21.

\textbf{2-L-(3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-\textalpha-D-glucofuranos-3-yl)glycine (230)}

Compound \textit{228} (0.03 g) was unblocked using the same procedure described for the preparation of \textit{229} to afford compound \textit{230}, m.p. 110-112°, $[\alpha]_D^{28}+35.8^\circ$ (c 0.53, methanol); c.d. $\Delta\varepsilon$+3.3 ($\lambda_{\text{max}}$ 215 nm, c 0.0014, methanol); $[\theta]_{215}^{30}$+11,090°; n.m.r. data (CD$_3$OD): $\tau$ 4.2 (d, 1, J$_{1,2}$ 4 Hz, H-1), 8.45, 8.51, 8.60, 8.65 (4s, 12, CH$_3$).
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