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BRANCHED-CHAIN SUGAR NUCLEOSIDES.
SYNTHESIS OF STRUCTURAL ANALOGUES OF PUROMYCIN

BY

DONALD ARTHUR BAKER

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Department of Chemistry

The University of British Columbia
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ABSTRACT

Several new routes to nitrogenous branched-chain sugars have been investigated and the preparation of several novel branched-chain sugar nucleosides having a structural relationship to puromycin has been described.

The cyanomethyl branched-chain sugars 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [LXXXVI], 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-gulofuranose [LXVII], and 5-O-benzyl-3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [LXXVIII] were prepared by condensation of diethyl cyanomethylphosphonate with 1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose [XVIII], 1,2:5,6-di-O-isopropylidene- α -D-xylo-hexofuranos-3-ulose [LXVII], and 5-O-benzyl-1,2-O-isopropylidene- α -D-erythro-pentofuranos-3-ulose [LXVIII], respectively, followed by stereoselective hydrogenation over palladium-on-charcoal of the intermediate unsaturated sugars. Reduction of the nitrile group of LXXXVI and LXXVIII gave the D-amino sugars, isolated as their acetamido derivatives, 3-C-(2'-acetamidoethyl)-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [XCII] and 3-C-(2'-acetamidoethyl)-5-O-benzyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [XCIII].

Selective hydrolysis of the 5,6-O-isopropylidene ketal of LXXXVII followed by sodium periodate degradation and sodium borohydride reduction afforded the L-cyanomethyl branched-chain sugar 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- β -L-lyxofuranose [XCVI]. Reduction of the nitrile group of this compound gave the L-amino sugar characterized

as its acetamido derivative 3-C-(2'-acetamidoethyl)-3-deoxy-1,2-O-isopropylidene- β -L-lyxofuranose [XCVI].

The carbamoylmethyl branched-chain sugar 3-C-carbamoylmethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [C] was prepared via three different routes. Hydrolysis of LXXXVI using alkaline hydrogen peroxide afforded C in 70 % yield. The same compound was also obtained by ammonolysis of 3-C-carbomethoxymethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [XXXIX] using liquid ammonia and ammonium chloride and by the stereoselective photoaddition of formamide to the methylene branched-chain sugar 1,2:5,6-di-O-isopropylidene-3-C-methylene- α -D-ribo-hexofuranose [XX].

A nitromethyl branched-chain sugar 1,2:5,6-di-O-isopropylidene-3-C-nitromethyl- α -D-glucofuranose [CV] was also prepared by condensing XVIII with nitromethane.

The cyanomethyl branched-chain sugar LXXXVI was the key intermediate in the synthesis of the branched-chain sugar nucleosides. Selective hydrolysis of LXXXVI to the 1,2-O-isopropylidene compound followed by benzylation, hydrolysis of the 1,2-isopropylidene ketal and acetylation yielded 1,2-di-O-acetyl-5,6-di-O-benzoyl-3-C-cyanomethyl-3-deoxy- β -D-allofuranose [CX]. Fusion of CX with 6-chloropurine followed by reaction with methanolic-aqueous dimethyl amine gave the branched-chain sugar nucleoside 6-N,N-dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy- β -D-allofuranosyl)-purine [CXXI]. Sodium metaperiodate oxidation of CXXI followed by sodium borohydride reduction gave the corresponding ribo nucleoside 6-N,N-dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy- β -D-

ribofuranosyl)-purine [CXXII].

In a separate procedure CXXII was obtained by fusion of 6-chloropurine with 1,2-di-O-acetyl-5-O-benzoyl-3-C-cyanomethyl-3-deoxy-β-D-ribofuranose [CXIII] (prepared from LXXXVI by selective hydrolysis of the 5,6-isopropylidene group followed by sodium periodate degradation, sodium borohydride reduction of the aldehyde intermediate, benzylation, hydrolysis of the 1,2-isopropylidene group and acetylation), followed by reaction with methanolic aqueous dimethylamine.

The corresponding unblocked cyanomethyl branched-chain ribo sugar nucleoside 6-N,N-dimethylamino-9-(3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXXXI] was obtained by fusion of CXIII with 6-chloropurine followed by reaction of the blocked nucleoside with anhydrous dimethylamine.

Pyrolysis of the N,N-dimethylcarbamoylmethyl ribonucleoside CXXII gave the novel lactone nucleoside 6-N,N-dimethylamino-9-(3'-C-carboxymethyl-2',3'-γ-lactone-3-deoxy-β-D-ribofuranosyl)-purine [CXXVIII]. Condensation of this compound with ammonia afforded 6-N,N-dimethylamino-9-(3'-C-carbamoylmethyl-3-deoxy-β-D-ribofuranosyl)-purine [CXXIX] and condensation of CVIII with ethyl glycinate gave the peptide nucleoside 6-N,N-dimethylamino-9-(3'-C-carbamoylmethyl-N-glycine ethyl ester-3'-deoxy-β-D-ribofuranosyl)-purine [CXXX].

Reduction of cyanomethyl branched-chain ribo-nucleoside CXXXI afforded an amino branched-chain sugar nucleoside which was characterized as its N-acetyl derivative 6-N,N-dimethylamino-9-(3'-C-(2"-acetamido-ethyl)-3'-deoxy-β-D-ribofuranosyl)-purine [CXXXIV].

Compounds CX and CXIII were also converted into the corresponding blocked adenyI nucleosides 6-benzamido-9-(2'-O-acetyl-5',6'-di-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-allofuranosyl)-purine [CXXXVI] and 6-benzamido-9-(2'-O-acetyl-5'-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXXXVII] by reaction with hydrogen bromide followed by condensation with chloromercuri-6-benzamido purine.

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I. OBJECTIVE:

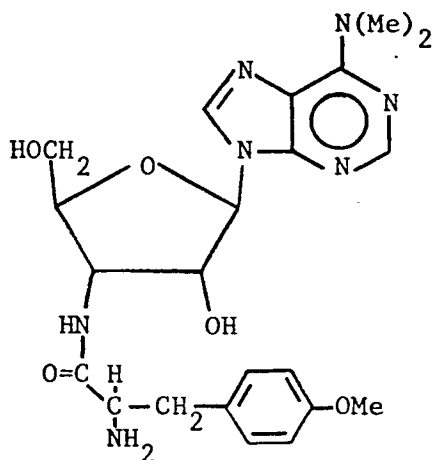
In recent years a wide variety of unusual nitrogen containing carbohydrate derivatives has been isolated from antibiotics (1). This has led to a great interest in the synthesis of compounds of this type as not only has there been the motivation of preparing materials having interesting biological activities but also, because of the high density of diverse functional groups present, their preparation has presented to the synthetic organic chemist intriguing challenges.

The first objective of this work was to explore ways of preparing carbohydrate derivatives containing deoxy-nitrogenous branched-chains. Although no carbohydrates having a nitrogenous branched-chain have as yet been encountered in nature, one nitro (10) and two amino (9,11) branched-chain sugars have been found to be components of antibiotics.

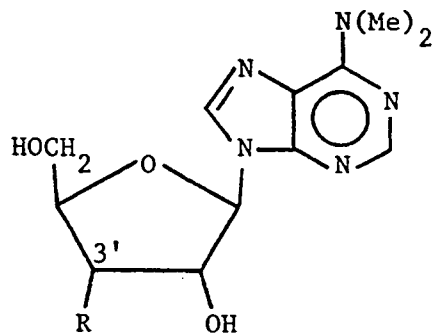
To attain the above objective three new methods of introducing nitrogenous branched-chains, the addition of the Wittig reagent diethyl cyanomethylphosphonate to several 3-ketoses, the condensation of nitromethane with ketoses and the photo-amidation of unsaturated sugars, were examined. During the completion of this work the condensation of nitromethane with carbohydrates to give branched-chain nitro methyl and amino methyl sugars was reported by several other groups (20,79,80).

The second objective of this work was to convert some of the 3-deoxy branched-chain sugars prepared via the above Wittig reaction into hexo- and, in particular, pento-furanosyl branched-chain sugar nucleosides.

The C-3' modified nucleosides prepared were mainly dimethylaminopurine derivatives. Dimethylaminopurine was chosen to be the heterocyclic base in these compounds in order that these branched-chain sugar nucleosides would be structural analogs of the antibiotic puromycin [I] (2a). The biological activity of puromycin and its analogs is known to be very dependent on the C-3' substituent. For example, the dimethylaminopurine nucleoside II, having a hydroxyl group at the 3' position, has been shown to be completely inactive (2b) while the corresponding C-3'-amino-C-3-deoxy-dimethylaminopurine nucleoside III (3) and various C-3' secondary amino nucleosides IV (4) show a range of antimetabolic activity (3,4). This suggests that dimethylaminopurine nucleosides having C-3' branched-chains bearing nitrogen substituents could be potential therapeutic agents.



[I]



- [II] R = OH
 [III] R = NH₂
 [IV] R = NHR

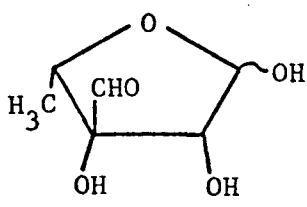
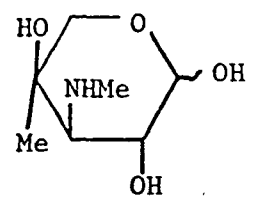
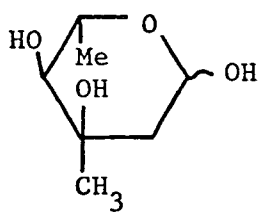
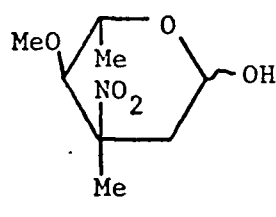
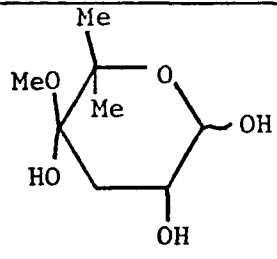
In order to provide a perspective for subsequent discussion, methods of synthesis of branched-chain sugars, Wittig reactions, nitroparaffin condensations, photo-additions of formamide to olefins and photo-additions to carbohydrates will all be briefly reviewed. In addition, some comments on methods of nucleoside synthesis and the biological activities of branched-chain sugar nucleosides will be made.

II. INTRODUCTION:

1. Branched-chain sugars

A branched-chain sugar is a carbohydrate in which a hydrogen or hydroxyl group is replaced by a carbon so as to lead to branching of the carbon skeleton. Over the years these modified sugars have been isolated from a number of natural products (5). However, it has been the relatively recent discovery that these unusual sugars are components of some important antibiotics that has led to a heightened interest in the preparation and properties of these compounds.

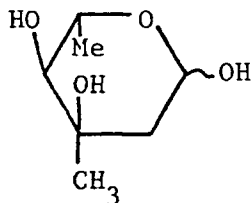
In Table I are shown some representative branched-chain sugars isolated from naturally occurring antibiotics. It can be seen that there exists a variety of branched-chains and unusual sugars. Of particular interest here are the branched-chain sugars garosamine [VIII] and evernitrose [IX] as these compounds are examples of nitrogen containing branched-chain sugars. Very recently another amino branched-chain sugar, sibirosamine (11), so far only identified as a 4,6-dideoxy-3-C-methyl-4-methylaminohexopyranose, has been isolated from the antibiotic sibiromycin. Grisebach and Schmid (12) have lately reviewed the chemistry and biochemistry of these unusual sugars.

TABLE I Branched-chain Sugars Isolated from Antibiotics			
Structure	Reference	Structure	Reference
 [V]	6	 [VIII]	9
 [VI]	7	 [IX]	10
 [VII]	8		

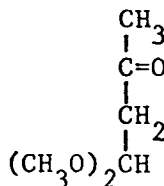
1.1 Synthesis of branched-chain sugars

There are two possible ways branched-chain sugars can be prepared. One can either construct the desired sugar in stages by condensing together small non-carbohydrate units, or one can introduce a branch-chain into an already pre-formed carbohydrate.

Because in the former method racemic mixtures result whenever asymmetric centers are produced, and carbohydrates generally have a high density of asymmetric centers, this has not been a popular approach for the preparation of branched-chain sugars. One notable exception, however, was in the synthesis of mycarose [VI] by Lemal and coworkers (13). As at the time there was no clear evidence for the relative configuration at C-3, C-4 and C-5 they devised a scheme whereby the four possible racemic mycarose isomers could be prepared. This was done by condensing the keto acetal X with the Grignard reagent 1-propynylmagnesium bromide followed by partial hydrogenation and cis hydroxylation. This gave a mixture of triols which were cyclized and separated as their methyl glycosides. In this way they were able to synthesize racemic mycarose and its 3-epimer.



[VI]



[X]

Methods used to date to introduce branching into the carbon skeleton of a pre-formed sugar are summarized in Table II. Although a wide variety of reactions has been employed in the majority of cases the branched-chains obtained are formally produced by

TABLE II	
Methods for Introduction of Branched-chains into Sugars	
Method	Reference
1. From Carbohydrate Ketoses	
(a) Acetonitrile addition	14
(b) Cyanohydrin reaction	15
(c) Diazomethane addition	16
(d) Enamine alkylation	17
(e) Grignard addition	18
(f) Methyl lithium addition	19
(g) Nitromethane addition	20
(h) Wittig reaction	21, 22
2. From Carbohydrate Epoxides	
(a) Addition of carbanions	23
(b) Methyl lithium addition	24
3. From Unsaturated Carbohydrates	
(a) Oxo reaction	25
(b) Photoamidation	26
4. Miscellaneous Approaches	
(a) Dimerization to branched-chain sugars	27
(b) Nitromethane addition to sugar dialdehydes	28
(c) Reduction of a lactone to a branched-chain sugar	29
(d) Ring contraction to a branched-chain sugar	30

substituting a branch-chain for a hydrogen atom in the carbon skeleton of the sugar. The other type of branched-chain sugars (deoxy branched-chain sugars), where a hydroxyl group is replaced by a branch-chain, are less readily available. Three reactions: Wittig additions, nitroparaffin additions and photo-additions, which do lead to deoxy branched-chain sugars, will be discussed in greater detail. But first, because the synthesis of many branched-chain sugars is dependent on the preparation of carbohydrate ketoses (see Table II), methods of oxidation of secondary hydroxyl groups of sugars will be reviewed.

2. Oxidations of secondary carbohydrate hydroxyl groups

Prior to about 1963 the means generally available for oxidation of secondary carbohydrate hydroxyl groups were: platinum oxide and oxygen (31), lead tetracetate-pyridine (32) and chromium trioxide-pyridine (33). Yields of ketones in blocked derivatives were often low and in some cases the reaction failed completely (34). Since then however, the addition of two new oxidizing agents, dimethyl sulfoxide (DMSO) and ruthenium tetroxide (RuO_4) and improvements in the older procedures have made available many new carbonyl carbohydrates. The application of all these reagents to carbohydrates has been reviewed (35) and only those reagents employed in this work (DMSO and RuO_4) will be considered further.

Dimethyl sulfoxide has proved to be a very powerful oxidizing agent for carbohydrate hydroxyl groups (36). Using this reagent a secondary alcohol is oxidized to a carbonyl and the DMSO is reduced

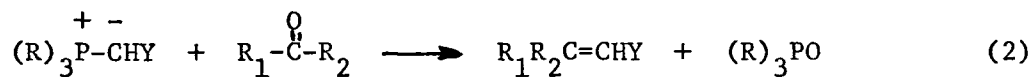
ruthenium tetroxide is generally preferred as it is simpler and only trace amounts (about 20 mg per g substrate) of costly ruthenium dioxide are used.

The source of supply of ruthenium dioxide used in this oxidation is very important (46). Commercial ruthenium dioxide is prepared in one of two ways, either by direct combination of ruthenium with molecular oxygen, or from ruthenium trichloride via the precipitation process (47). Using aqueous periodate solutions it is only possible to prepare ruthenium tetroxide from ruthenium dioxide prepared via the precipitation process.

Side products in ruthenium tetroxide oxidations usually result from over-oxidation (48) resulting in lactone formation.

3. The Wittig reaction

The Wittig reaction (49) is a method for preparing olefins from aldehydes or ketones. This reaction involves a condensation elimination between a phosphonium ylid and the carboxyl group of an aldehyde or ketone to form an olefin and a phosphine oxide (Equation 2).



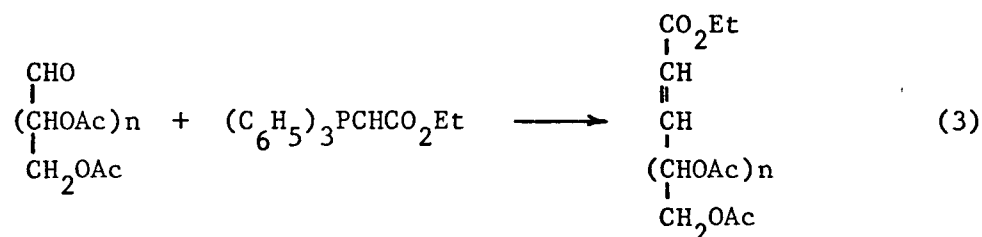
Y=H or electron withdrawing group

As this reaction is widely used by organic chemists, general reviews (50) and detailed discussions of the mechanism and stereochemistry (51) are available in the literature and therefore these features will not be reviewed here. The application of this reaction

to carbohydrates will be examined, however.

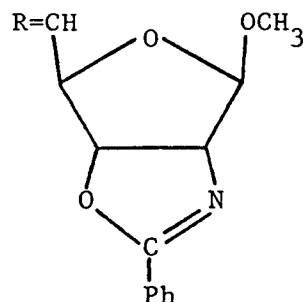
3.1 Application of the Wittig reaction to carbohydrates

The first application of the Wittig reaction in carbohydrate chemistry was reported in 1963 by Kochetkov et al. (52). These workers had undertaken to develop a general route to higher aldoses. The unsaturated aldonic esters obtained via a Wittig reaction (Equation 3) were key intermediates in their program. By means of



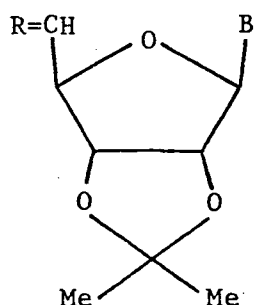
different Wittig reagents others have used the same strategy to obtain unsaturated higher ketoses (53), aldonic acids (54), deoxy sugars (55) and C glycosides (56).

The Wittig reaction has also been used to extend the carbon skeletons at the opposite end of the sugar chain. Condensation of the aldehyde XI (57) with either n-pentadecyltriphenyl phosphonium bromide or ethoxycarbonylmethylene triphenylphosphorane gave the expected unsaturated compounds XII and XIII respectively.



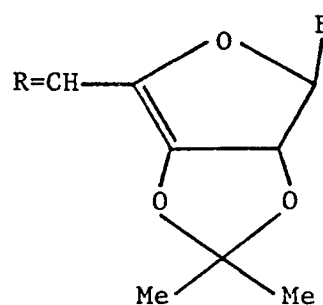
- [XI] R = O
 [XII] R = CH(CH₂)₁₁CH₃
 [XIII] R = CHCO₂Et

Nucleosides having a 5' aldehydo group have also been condensed with Wittig reagents. When pyrimidine nucleoside XIV (58) was reacted with the phosphorane ylid, generated in situ by the action of sodium ethoxide on (ethoxycarbonylmethyl) triphenylphosphonium bromide, a rapid reaction ensued which gave five products. These were subsequently identified as uracil, unsaturated acids XV and XVI and the ethyl esters of these acids.



[XIV] $R = O$

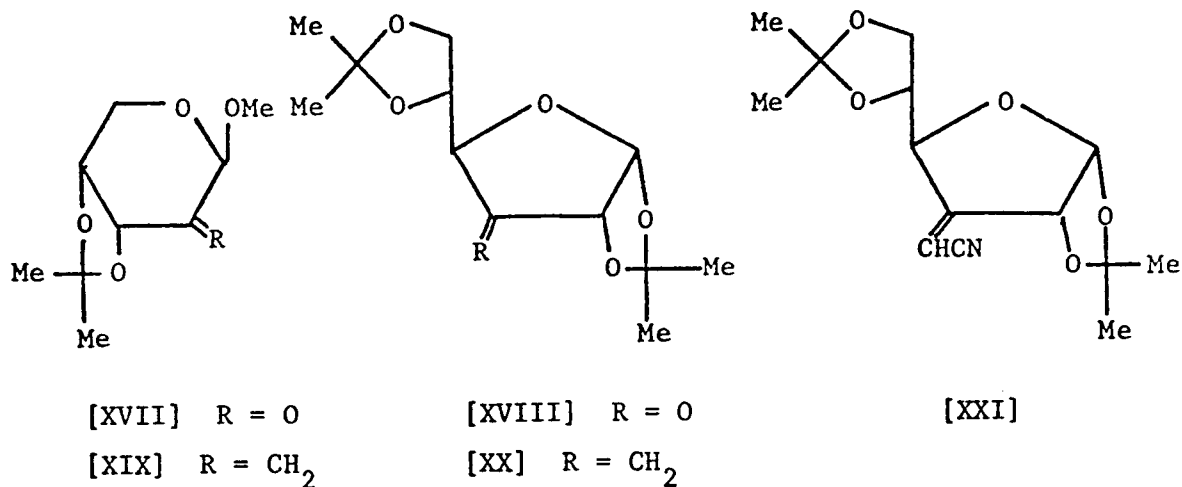
[XV] $R = \text{CHCO}_2\text{H}$



[XVI] $R = \text{CHCO}_2\text{H}$

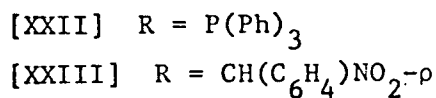
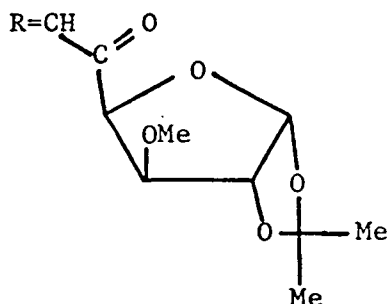
B = uracil

In this laboratory the Wittig reaction has been employed to prepare deoxy branched-chain sugars. Thus condensation of the basic Wittig reagent methyltriphenylphosphonium bromide with carbohydrate ketoses XVII and XVIII has been used by Rosenthal and Sprinzl to obtain the 2-C-2-deoxy- XIX (59) and 3-C-3-deoxy- XX (21) exocyclic methylene branched chain sugars. Compound XX has also been prepared under slightly different conditions by Jones et al. (60). Other branched-chain sugars prepared via a Wittig reaction have included the unsaturated cyano sugars XXI (61). These compounds were prepared by condensation of ketose XX with cyanomethylene-triphenyl phosphorane.



In all of the above examples the carbohydrates have served only as the carbonyl components of the Wittig reaction. However, Zhdanov and Polenov (62) have reversed this approach and prepared a Wittig reagent from a carbohydrate. This carbohydrate phosphorane XXII was found to react with activated aldehydes to give both cis and trans olefinic ketones.

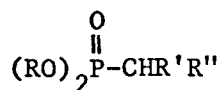
For example, reaction with *p*-nitrobenzaldehyde gave the cis and trans isomers of ketone XXIII.



3.2 The phosphonate modification of the Wittig reaction

As mentioned previously the Wittig reaction involves a condensation elimination between a phosphonium ylid and an aldehyde or ketone. It has been shown (63) that ylids can be obtained from any phosphorus system having a hydrogen atom adjacent to a phosphorus atom bearing a reasonable degree of positive charge.

One phosphorus system which meets the above criteria is the phosphonates XXIV and the condensation of ylids prepared from these compounds with aldehydes and ketones is referred to as the phosphonate modification of the Wittig reaction.

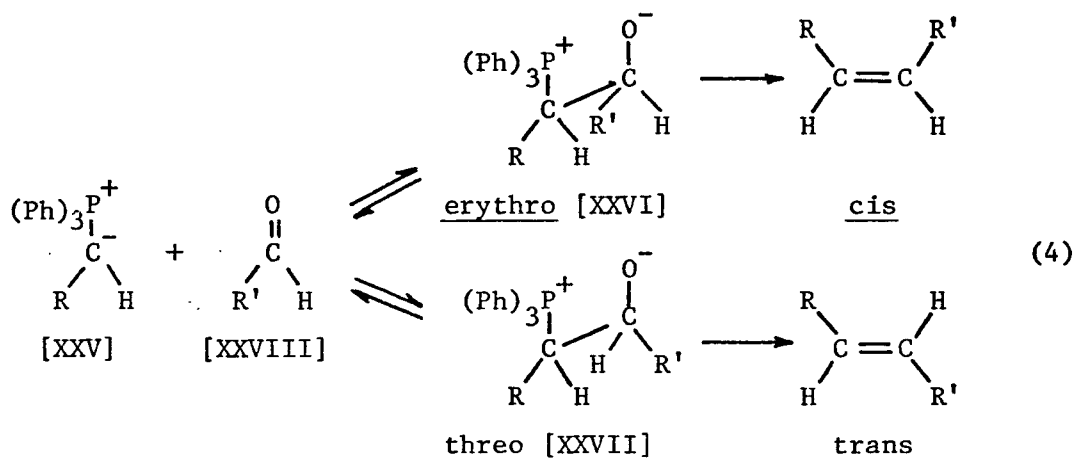


[XXIV]

The first reported reaction of this type was due to Horner and coworkers (64) who obtained triphenylethylene in quantitative yield by condensing benzophenone with the ylid prepared from diethylbenzylphosphonate. The use of phosphonates in Wittig-type reactions was thoroughly investigated by Wadsworth and Emmons (65) who found that in general compared to phosphonium ylids, the phosphonates were more reactive, and gave better yields of olefin. In addition, phosphonates are cheaper than phosphonium salts. Also, the phosphorus by-product from phosphonates is a water soluble phosphate ester which is easier to separate from the olefin than triphenylphosphine oxide, the usual by-product from the standard Wittig reaction.

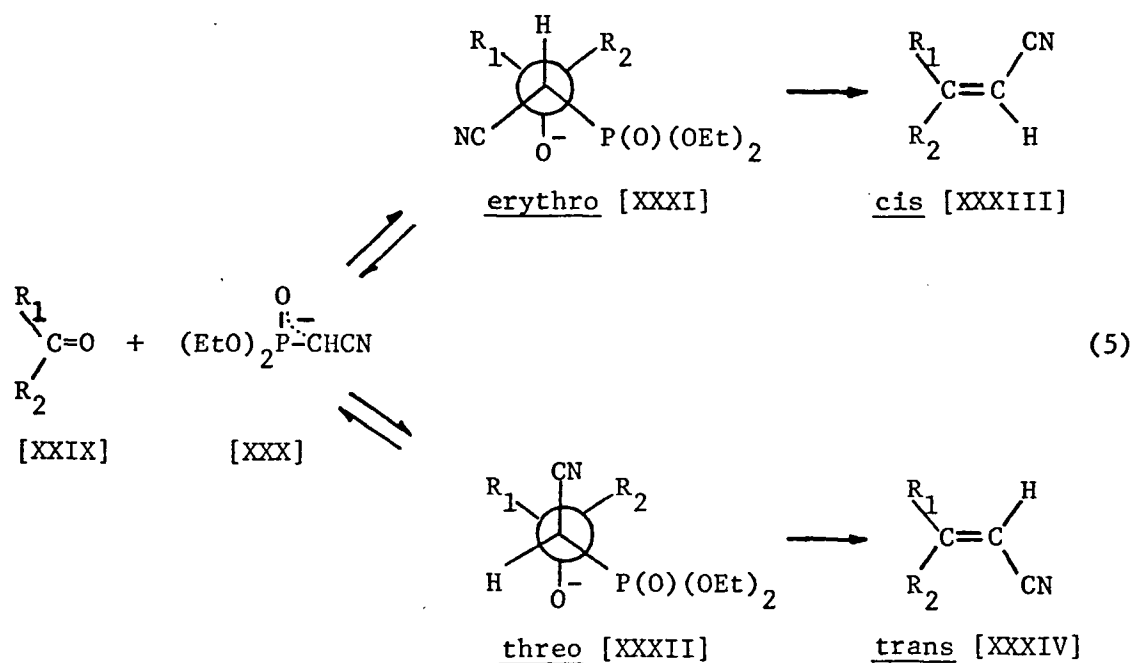
3.3 Mechanism and stereochemistry of the phosphonate modification of the Wittig reaction

The Wittig olefin synthesis is usually considered to proceed as shown below (Equation 4) (51) with the erythro-betaine XXVI leading to the cis olefin and the threo-betaine XXVII leading to the trans. For stabilized ylids (XXV, R = electron withdrawing group) reaction with aldehydes gave predominately trans olefins while non-stabilized ylids (XXV, R = alkyl) gave the cis isomers, particularly in salt-free non-polar solvents (66).



The reaction of phosphonate carbanions with aldehydes and ketones is also presumed to proceed as shown above for the phosphoranes. Although the stereochemistry of the products has not been as extensively studied as the products from the standard Wittig reaction, it would appear that in most instances both stabilized and non-stabilized anions give a predominance of the trans olefin (67). Fortuitously, the condensation of diethyl cyanomethylphosphonate anion with aldehydes and ketones has been the subject of two recent studies (68, 69). This is the modified Wittig reaction used in this work.

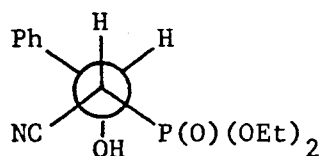
In the earlier investigation (68) the products arising from the reaction of alkylphenyl ketones with the carbanion generated from diethyl cyanomethylphosphonate and sodium hydride (Equation 5) were examined. It was found that when the phenyl group (R_1) was unsubstituted in the ortho-position and the alkyl group (R_2) was unbranched, a predominance of trans olefin (cis/trans ratio 0.1 - 0.2) resulted. However, if the alkyl group was secondary, substantial amounts of cis isomer were formed (cis/trans ratio 0.5 - 0.7), and if R_2 was a tertiary alkyl group the cis olefin was the major product. Ortho substitution in the phenyl ring also increased the proportion of cis isomer, whereas meta and para substitution did not appreciably affect the product composition.



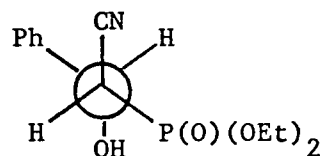
R_1 = substituted or unsubstituted phenyl

R_2 = alkyl or H

In the later study (69) the erythro XXXV and threo XXXVI diethyl-1-cyano-2-hydroxy-2-phenylethylphosphonates were prepared and separated. By studying the decomposition of these compounds in basic media, (sodium hydride in tetrahydrofuran), with and without the presence of competing aldehyde, the following conclusions were reached: (a) In this basic medium anions XXXI and XXXII (R_1 = phenyl, R_2 = H) partly reverted to benzaldehyde and anion XXX and partly interconverted directly (ie. $XXXI \rightleftharpoons XXXII$) without the formation of intermediates XXIX and XXX. (b) The cis-trans ratio of cinnamionitriles (cis/trans about 0.18) (cis XXXIII, trans XXXIV, R_1 = phenyl, R_2 = H) was very nearly the same no matter if the reaction was carried out using XXXV or XXXVI, with or without competing aldehyde, or directly using benzaldehyde and anion XXX. This indicated that the cis-trans ratio depended mainly on the relative rates of olefin formation from oxyanions XXXI and XXXII.



[XXXV]

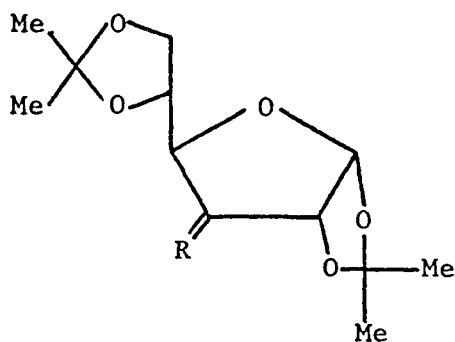


[XXXVI]

3.4 The modified Wittig reaction in carbohydrate chemistry

The first application of the phosphonate modification of the Wittig reaction to a carbohydrate ketose was reported by Rosenthal and Nguyen (22) in 1967. Here the ketose XVIII was condensed with the carbanion prepared by the action of potassium t-butoxide on

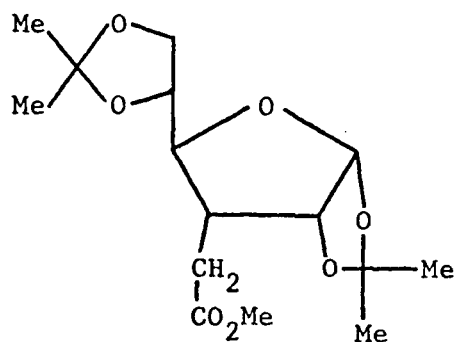
trimethylphosphonoacetate. This procedure gave as the major products a mixture of cis and trans unsaturated esters (XXXVII and XXXVIII). Hydrogenation of either isomer gave as the only product the same 3-deoxy allo branched-chain sugar XXXIX. Application of the same reaction to the 2-deoxy keto sugar XL afforded, after stereoselective hydrogenation, the 2,3-dideoxy branched-chain ribo sugar XLI (70).



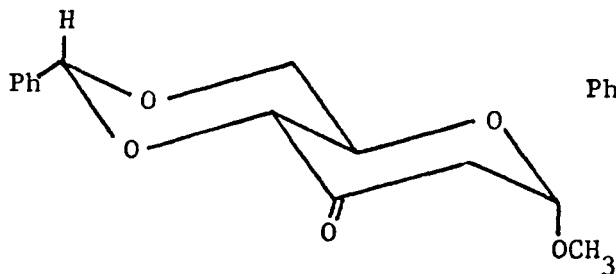
[XVIII] R = O

[XXXVII] R = C $\begin{matrix} \text{H} \\ \text{CO}_2\text{CH}_3 \end{matrix}$

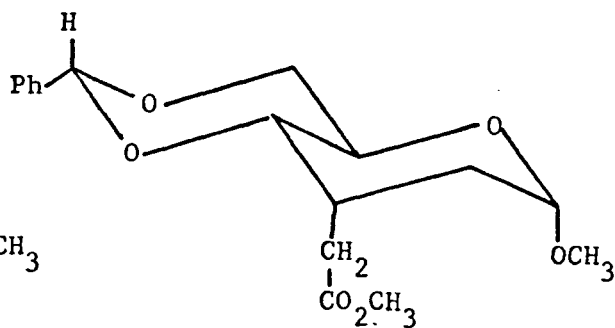
[XXXVIII] R = C $\begin{matrix} \text{CO}_2\text{CH}_3 \\ \text{H} \end{matrix}$



[XXXIX]

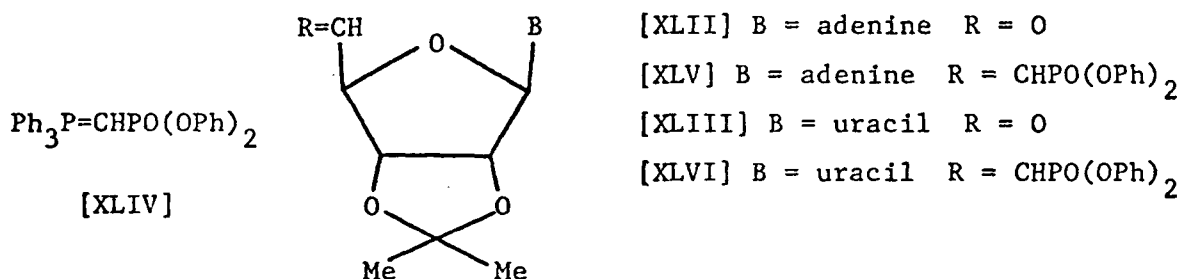


[XL]



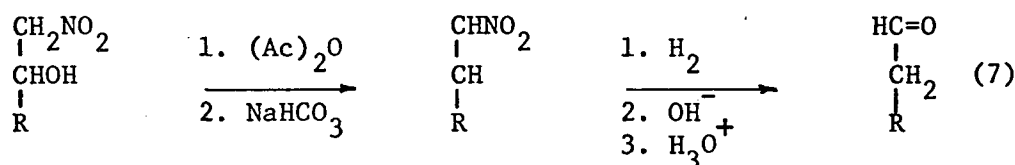
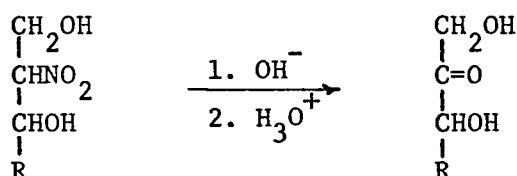
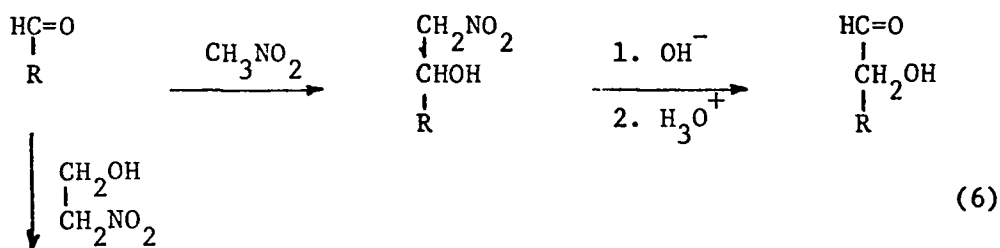
[XLI]

Protected 5'-aldehydo nucleosides XLII and XLIII have also been condensed with phosphonate Wittig reagents (71). Thus XLII when condensed with the carbanion from diphenyl triphenylphosphoronylidine-methylphosphonate [XLIV] gave the 5'-deoxy-5'-(dihydroxyphosphinylmethyl)-nucleoside XLV. Nucleoside XLIII condensed with the same reagent gave the corresponding uridine compound XLVI.

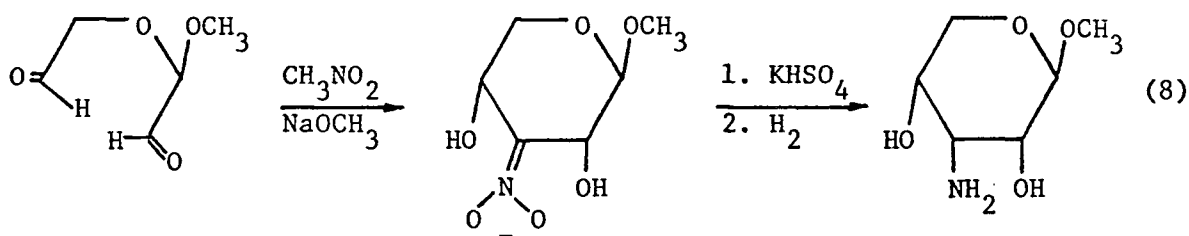


4 Nitroparaffin addition to carbohydrates

Nitroparaffin condensation reactions with carbohydrates have been extensively studied (72). Historically these condensations were used as a route to higher carbon aldoses or ketoses (Equation 6), the initial alkyl nitro condensation products being converted to aldehydes or ketones by the Nef reaction (73). A modification of this reaction (Equation 7) has provided a general route to the 2-deoxy aldoses. Thus acetylation of the initial nitromethane-aldose condensation products followed by a Schmidt - Rutz reaction (74) yields unsaturated nitro carbohydrates. Reduction of these compounds followed by a Nef reaction on the nitro-sugar yields the 2-deoxy aldoses.

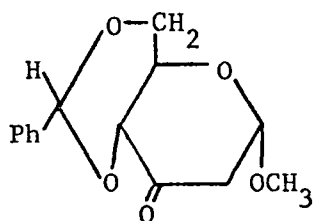


As well as these above reactions which serve to extend the sugar chain, nitroparaffin condensations have been used to prepare deoxyamino sugars (75), branched-chain deoxynitro sugars (28, 76) and dideoxy branched-chain dinitro sugar derivatives (77). The majority of these reactions were developed by H. H. Baer and coworkers at the University of Ottawa. The condensation of sugar dialdehydes with nitromethane (75) (Equation 8) is particularly interesting. Under the reaction conditions cyclization occurred and reduction of the aci nitro compound afforded deoxyamino sugars. By substituting nitroethane for nitromethane in this reaction deoxynitro branched-chain sugars have been prepared (28, 76).

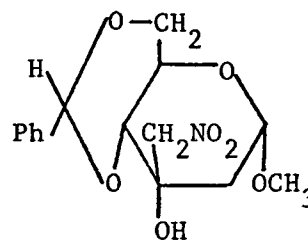


Despite this considerable body of work done on the addition of nitroparaffins to carbohydrates, until very recently no attempt had been made to condense nitromethane with carbohydrate ketoses in order to obtain branched-chain sugars. This situation changed, however, in 1969 when two groups (78, 79) independently reported the addition of nitromethane to keto sugars.

In the report from our laboratory (78) the 2-deoxy-3-keto-hexo-pyranose XLVII was condensed with nitromethane to afford the 2-deoxy-3-C-nitromethyl-D-ribo-hexopyranose XLVIII.

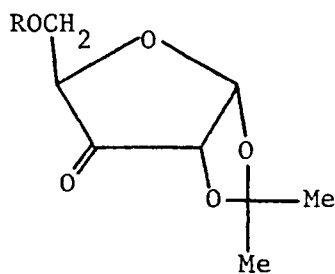


[XLVII]

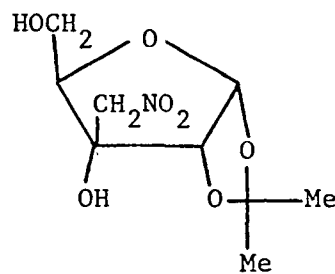


[XLVIII]

The second study dealt with the addition of nitromethane to the 3-keto furanoses XLIX (79). By this means the 3-C-nitromethyl-D-ribofuranose branched-chain sugar L was obtained.



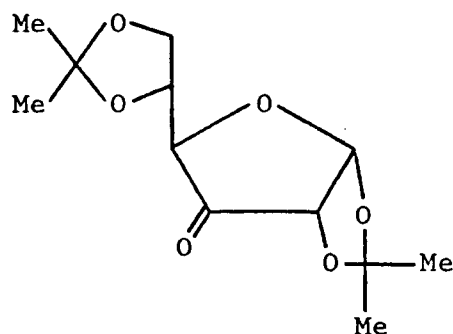
[XLIX]



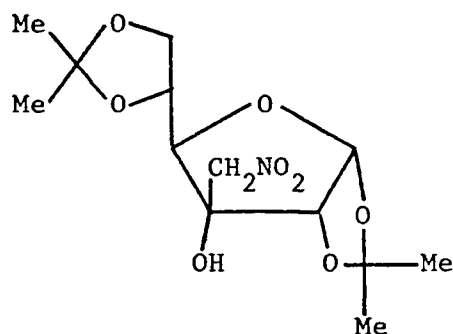
[L]

R = trityl or tosylate

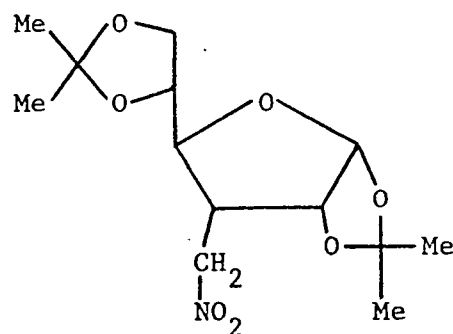
Shortly after these initial investigations appeared, Overend et al. (20) published an extensive study on the addition of nitromethane to methyl glycopyranosiduloses, and Albrecht and Moffat (80) announced the condensation of nitromethane with 3-keto-furanose XVIII to obtain the 3-C-nitromethyl-D-ribofuranose LI. This compound was converted by a Schmidt-Rutz reaction (74) followed by reduction to the deoxy nitromethyl branched-chain sugar LII from which were obtained 3-C-nitromethyl LIIIa and 3-C-amino methyl LIIIb branched-chain sugar nucleosides.



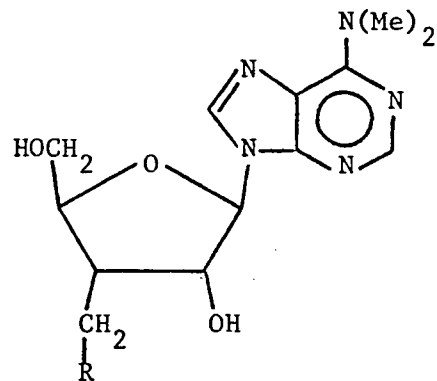
[XVIII]



[LI]



[LII]



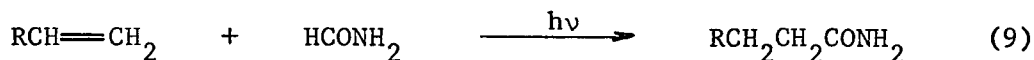
[LIIIa] R = NO₂

[LIIIb] R = NH₂

5. Photo-addition of formamide to olefins

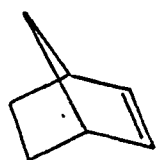
The photo-addition of formamide (81-84) to olefins was developed by Elad and Rokach as a general process for converting olefins to amides. It was found that in the absence of ketones the photo-addition of formamide required long irradiation periods and gave low yields. However, in the presence of ketones such as acetone, irradiation ($\lambda > 300$) of formamide solutions of olefins gave good (50-80%) yields of amides.

For terminal olefins (81) the photo-products were found to be mainly the 1:1 adducts resulting from anti-Markovnikov addition of formamide to the double bond (Equation 9). Minor side products

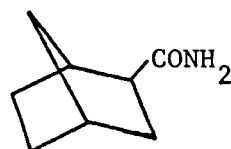


included non-terminal 1:1 formamide olefin adducts, acetone addition products and teleomeric material. Non-terminal olefins in this reaction were found to give primarily a mixture of 1:1 formamide olefin adducts. Reaction of α,β -unsaturated esters afforded mainly products where formamide addition had taken place at the β carbon (84).

Of particular interest in this reaction is the sensitivity of the addition to steric features of the olefin. As well as the nearly exclusive anti-Markovnikov addition discussed above for terminal olefins, it was found that the photo-condensation of formamide with norbornene [LIV] (82) gave only the single amide, norbornane-2-exo-carboxamide [LV].

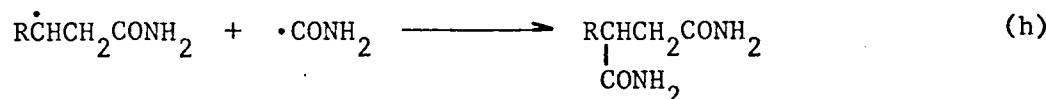
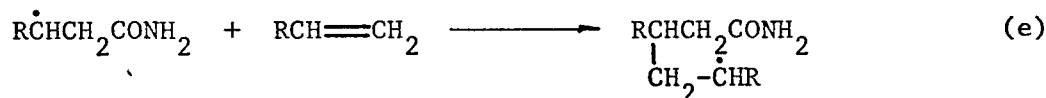
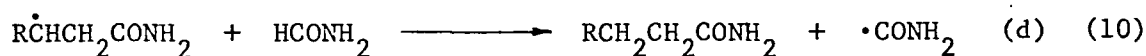
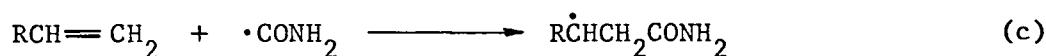
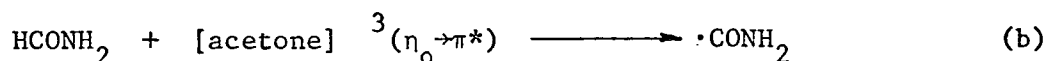
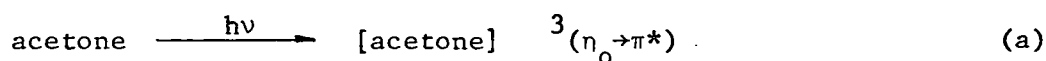


[LIV]



[LV]

The mechanism postulated by Elad and Rokach (82) for the acetone initiated photo-addition of formamide was as follows (Equation 10). They hypothesized that the carbamoyl radicals are generated either from the collapse of the photo-activated formamide molecule or through hydrogen atom abstraction from formamide by the excited triplet of acetone. The olefin then serves as a scavenger for the carbamoyl radicals thereby forming the formamide addition products. Chain propagation can continue as shown in equation 10 d-f. Termination



of the chain may occur in many different ways, as for example in equation 10h. Products resulting from the side reactions (10 e-h) were isolated in some instances (82,83).

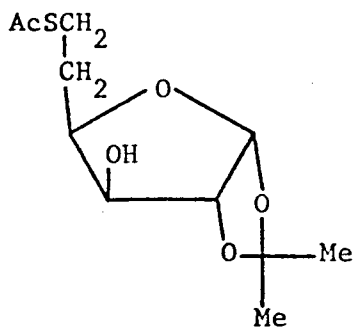
The exact role of acetone in this reaction was recently clarified (85). For a direct energy transfer between the $\eta_0 \rightarrow \pi^*$ triplet of acetone and the $\eta \rightarrow \pi^*$ first triplet of formamide to occur, the triplet energy of acetone (3.5 ev) (86) would have to be higher than that of formamide. When the energy of the $\eta_0 \rightarrow \pi^*$ first triplet of formamide was calculated it was found to be 4.2 ev. Therefore direct energy transfer to formamide from an acetone triplet is not possible and consequently the carbamoyl radicals in this photolysis must be produced by extraction of a formyl hydrogen from ground state formamide by a photo-activated acetone molecule.

5.1 Photo-additions to carbohydrates

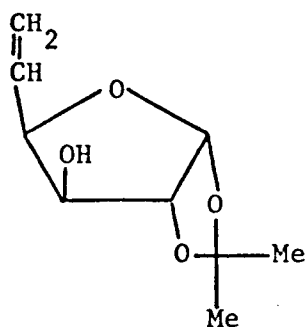
Although photo-degradation reactions of sugars have been well studied (87), there is only a limited number of instances of photo-additions to carbohydrates reported in the literature.

In 1966 Horton and Turner (88), while studying carbohydrates having heteroatoms other than oxygen in the ring, prepared the thioacetate LVI by photo-addition of thioacetic acid to the unsaturated sugar LVII. Other sulfur-containing sugar derivatives have been prepared (89) by the addition of thioacetic acid and benzyl mercaptan to the unsaturated sugar LVIII.

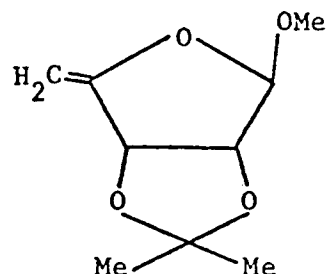
Various other reagents photo-condensed with unsaturated sugar LVII have included phosphine and phenylphosphine (90) and 1,3 dioxalan (91). With the exocyclic "ene" sugar XX photo-addition of



[LVI]

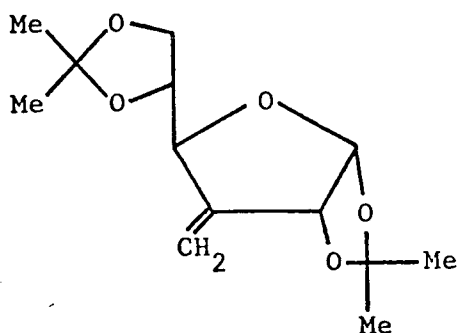


[LVII]

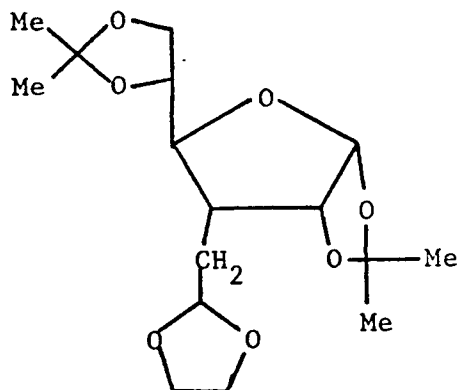


[LVIII]

dioxalan afforded the 3-deoxy-allo-branched-chain sugar LIX as the only product. More recently reports of photo-condensations of acetone with triacetyl-D-glucal [LX] (92), and 2,3 dimethylbut-2-ene with hexenopyranoses (93) have appeared.

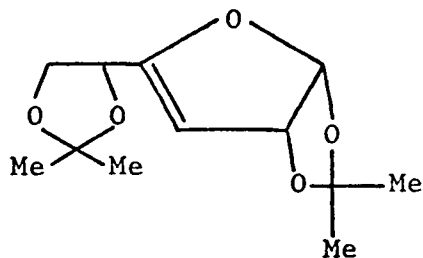
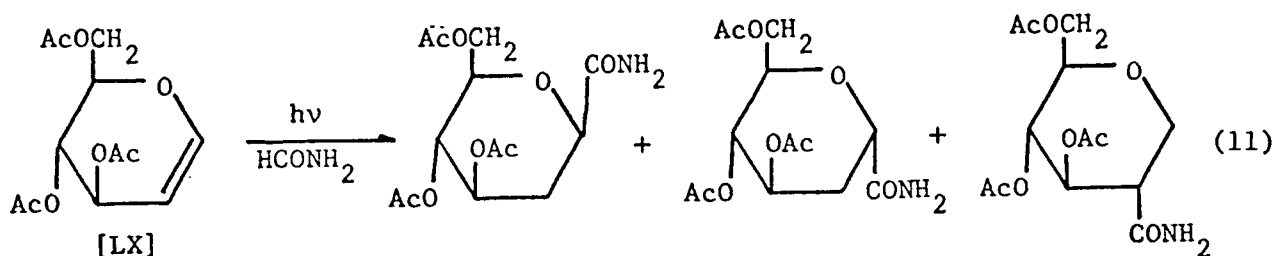


[XX]

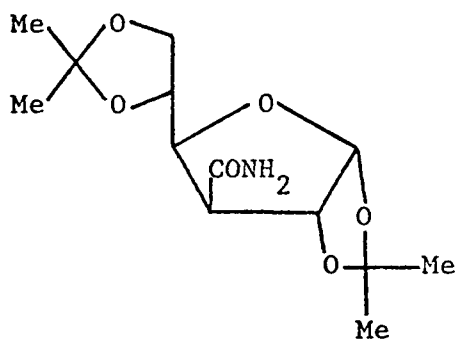


[LIX]

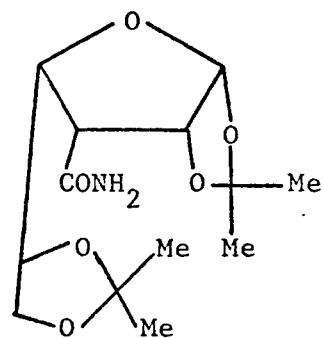
In this laboratory photo-amidation has been examined as a route to deoxy branched-chain amido and amino sugars. It was found that the acetone sensitized photo-addition of formamide to triacetyl-D-glucal [LX] (26) gave the mixture of amides depicted in equation 11 as well as trace amounts of acetone addition products. The same reaction applied to compound [LXI] (94) afforded the carbamoyl



[LXI]



[LXII]



[LXIII]

branched-chain sugars LXII and LXIII along with some products resulting from the photo-addition of acetone.

6. Nucleosides

The term nucleoside is used to denote compounds containing a nitrogen heterocycle (purine or pyrimidine and their close analogs) in glycosidic linkage with a carbohydrate moiety. For naturally

occurring nucleosides the heterocyclic bases are attached via β glycosyl linkages, with the most commonly occurring bases being the purines adenine and guanine and the pyrimidines cytosine, uracil and thymine. The carbohydrate portion is usually D-ribose or "2-deoxy-D-ribose" in the furanose form.

6.1 Nucleoside synthesis

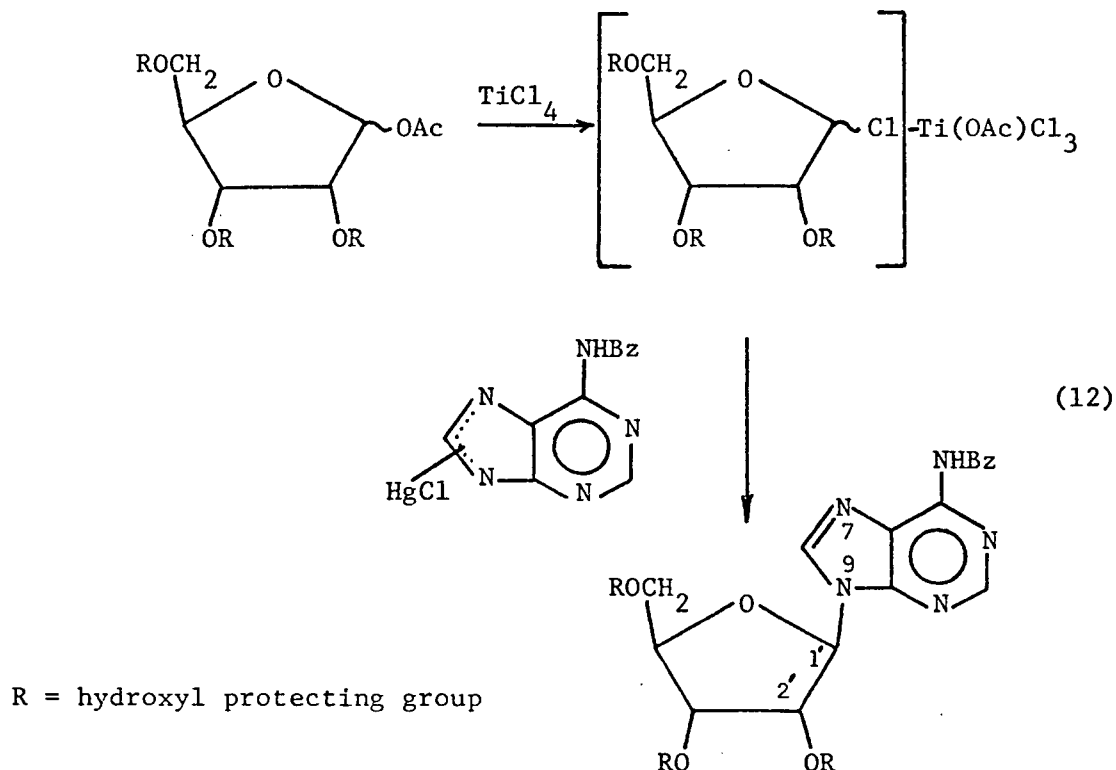
Rapid advances in nucleic acid chemistry have resulted in the development of many new methods of nucleoside syntheses. A complete review of the available methods is beyond the scope of this thesis; therefore only those methods of purine nucleoside synthesis used in this work will be discussed. For more complete surveys of the synthetic methods available see references (95) and (96).

6.2 Synthesis of purine nucleosides

Fischer and Helferich prepared the first purine glycosides (purine nucleosides) by condensing silver salts of some purine derivatives with acetylated glycosyl halides (97). Subsequent modifications of this procedure resulted in the replacement of the purine silver salts with chloromercuri derivatives (98) and the in situ generation of the glycosyl halide from the ester with titanium tetrachloride (99) [Equation 12].

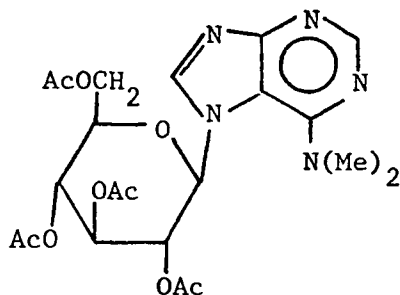
For sugars having at C-2 an ester hydroxyl protecting group, the anomeric (C-1') configurations of the nucleosides obtained by the above condensations are predicted by Baker's trans rule (100): "condensations of a heavy metal salt of a purine or pyrimidine with an acylated glycosyl halide will form a nucleoside with a C-1', C-2' trans

configuration in the sugar moiety regardless of the original configuration of C-1, C-2." The mechanistic considerations underlying this observation have been reviewed (101) and although some exceptions are known (102), in the vast majority of cases the C-1', C-2' cis configuration is not observed, or observed only in minor proportions. Experimentally the anomeric configuration of glycofuranosyl purine nucleosides have been determined from the sign of their Cotton effect (103); the 9-β-D-glycofuranosyl derivatives give negative Cotton effects (104) and the 9-α-D-compounds show positive Cotton effects.



Although in equation 12 the N-9 substituted nucleoside is depicted as being the only product formed, as it is in most instances, in some cases the N-7 isomer is produced, occasionally to the complete

exclusion of the N-9 form. A case in point occurred in the preparation of the puromycin analog LXIV. When α -bromoacetoglucose was condensed with the chloromercuri derivative of 6-dimethylamino purine (105) only the N-7 nucleoside LXIV was isolated. Fortunately, in the case of puromycin derivatives, the N-7 and N-9 isomers are easily differentiated on the basis of their ultraviolet spectra, N-9 isomers at pH-7 having a λ maximum at about 275 nm and N-7 isomers having a λ maximum at about 295 nm (105). At present there is still no completely satisfactory rule for predicting whether the N-9 or N-7 isomer will be formed in this reaction.



[LXIV]

A more recently developed method for purine nucleoside synthesis is the fusion procedure (106,107). Here the acetylated sugar, with or without an acid catalyst, is simply fused under reduced pressure with a purine derivative. The resultant nucleosides are usually the N-9 substituted isomers having anomeric configurations consistent with that which would be predicted by Baker's rule.

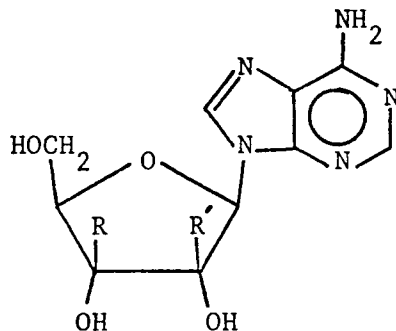
Aside from simplicity, the fusion procedure has the additional advantages that the relatively unstable glycosyl halide is not necessary as an intermediate and that the purine may be substituted with amino, oxo, or thio functionalities which need not be protected

during the reaction. Also this procedure results in nucleosides free of mercury contamination which is sometimes not possible using the above halo-mercuri method. This is important in cases where the biological activity of a nucleoside is to be evaluated as it has been shown (108) that mercuric ion concentration as low as 10^{-8} molar can lead to erroneous interpretations of biological activity.

6.3 Branched-chain sugar nucleosides

As branched-chain sugars had been isolated from a number of important antibiotics, in the middle years of the last decade a number of research groups independently began programs leading to the synthesis of nucleosides containing branched-chain sugars instead of the normal D-ribo furanoses in order that their potential as therapeutic agents could be evaluated.

The first report of a synthesis of a branched-chain sugar nucleoside came in 1966 from Walton et al. (109) working in the research laboratories of Merck, Sharp and Dohme. These workers reported the preparation of the 2'-C-methyl-D-ribofuranose LXV and 3'-C-methyl-D-ribofuranose LXVI analogs of adenosine.



[LXV] R = H R' = CH₃

[LXVI] R = CH₃ R' = H

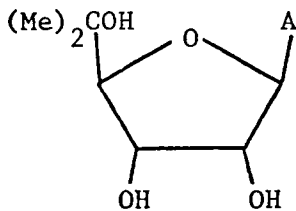
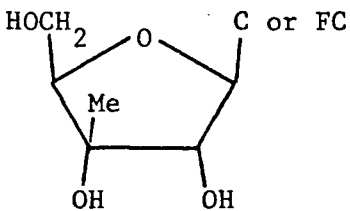
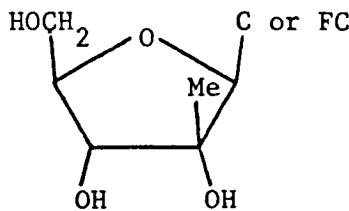
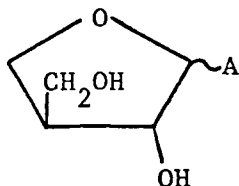
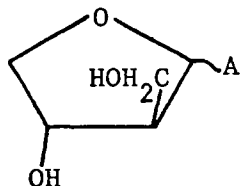
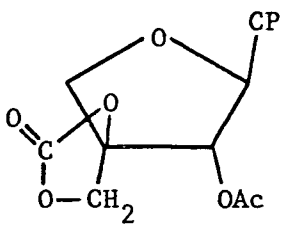
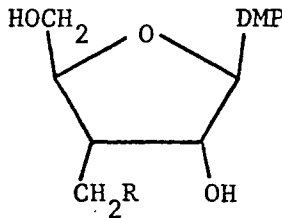
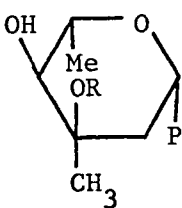
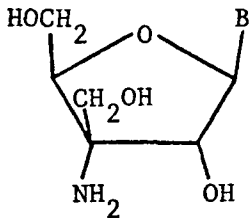
Since then, in addition to the 3'-deoxy-3'-C-hydroxyethyl (110), 3'-deoxy-3'-C-methyl (22) and 3'-deoxy-3'-C-hydroxymethyl (111) ribo and allo furanosyl adenine nucleosides prepared in this laboratory, numerous other branched-chain nucleosides (Table III) have been synthesized. The continuing interest of both academic and industrial research groups in the chemistry of these compounds has made this a very active area of research.

6.4 Biological activity of branched-chain sugar nucleosides

Although no studies have been published concerning the biological activity of all these modified nucleosides in a single system, the fragmentary reports which do exist in the literature indicate that some of these compounds might be developed into useful therapeutic agents. For example, the methyl branched-chain sugar nucleosides have been shown to inhibit the growth of KB cells in culture (112) and to be effective anti-neurovaccinia agents in mice (113). In addition, the 3'-amino-3'-hydroxymethyl derivative of adenosine has been shown to exhibit weak inhibition against vaccinia Dairen (118). It should be noted that where compounds have been assayed biologically those having branches at the 3' position (eg. LXVI) showed the greatest activity.

TABLE III

Synthesis of Branched-chain Sugar Nucleosides

 (112)	 (113)	 (113)
 (114)	 (114)	 (115)
 R = NO₂ or NH₂ (80)	 R = H or Me (116)	 B = A, DMP, G, C, U (117)

A = adenine; C = cytosine; CP = 6-chloropurine; DMP = 6-dimethylaminopurine
FC = 5-fluorouracil; G = guanine; P = purine.

The numbers in parentheses are the references for these compounds.

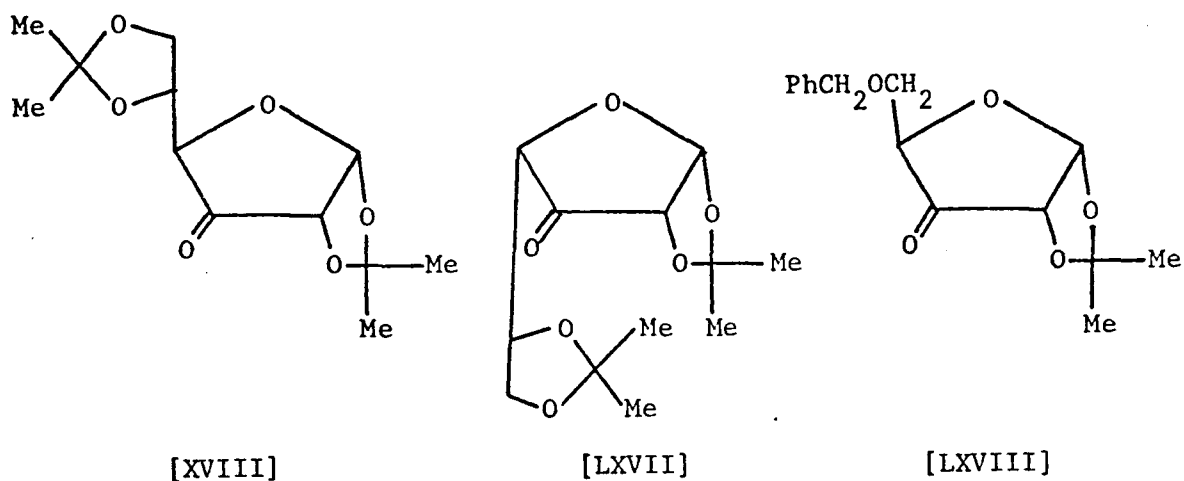
III. RESULTS AND DISCUSSION

1. Synthesis of branched-chain cyanomethyl sugars by a Wittig reaction

In the objective it was indicated that the first goal of the work described here was to explore various means for introducing deoxy-nitrogenous branched-chains into carbohydrates. As a modified Wittig reaction had been shown in this laboratory to be a useful way of preparing carbomethoxymethyl branched-chain sugars (22), it was decided to attempt the condensation of the phosphonate Wittig reagent diethyl cyanomethylphosphonate (68,69) with the carbohydrate 3-keto furanoses 1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose [XVIII], 1,2:5,6-di-O-isopropylidene-D- α -xylo-hexofuranos-3-ulose [LXVII] and 5-O-benzyl-1,2-O-isopropylidene- α -D-erythro-pentofuranos-3-ulose [LXVIII].

This particular Wittig reagent was chosen because it was felt that after reduction of the initial cyanovinyl addition products to cyanomethyl deoxy branched-chain sugars, these cyanomethyl compounds could be converted into various other nitrogenous branched-chain sugars such as aminomethyl and carbamoylmethyl derivatives. As the second objective was to use these branched-chain compounds to prepare branched-chain sugar nucleosides and to examine the biological activity

of these modified nucleosides, it was decided to use 3-keto-furanoses as the carbonyl component of this Wittig reaction. In this way the branched-chain sugars prepared would be in the furanose configuration (the carbohydrate configuration present in most naturally occurring nucleosides) and the branched-chain nucleosides prepared from these sugars would have 3'-branched-chains. As was pointed out in the Introduction (p.32) branching at this position appears to confer the greatest degree of biological activity.



1.1 1,2:5,6-Di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose [XVIII]

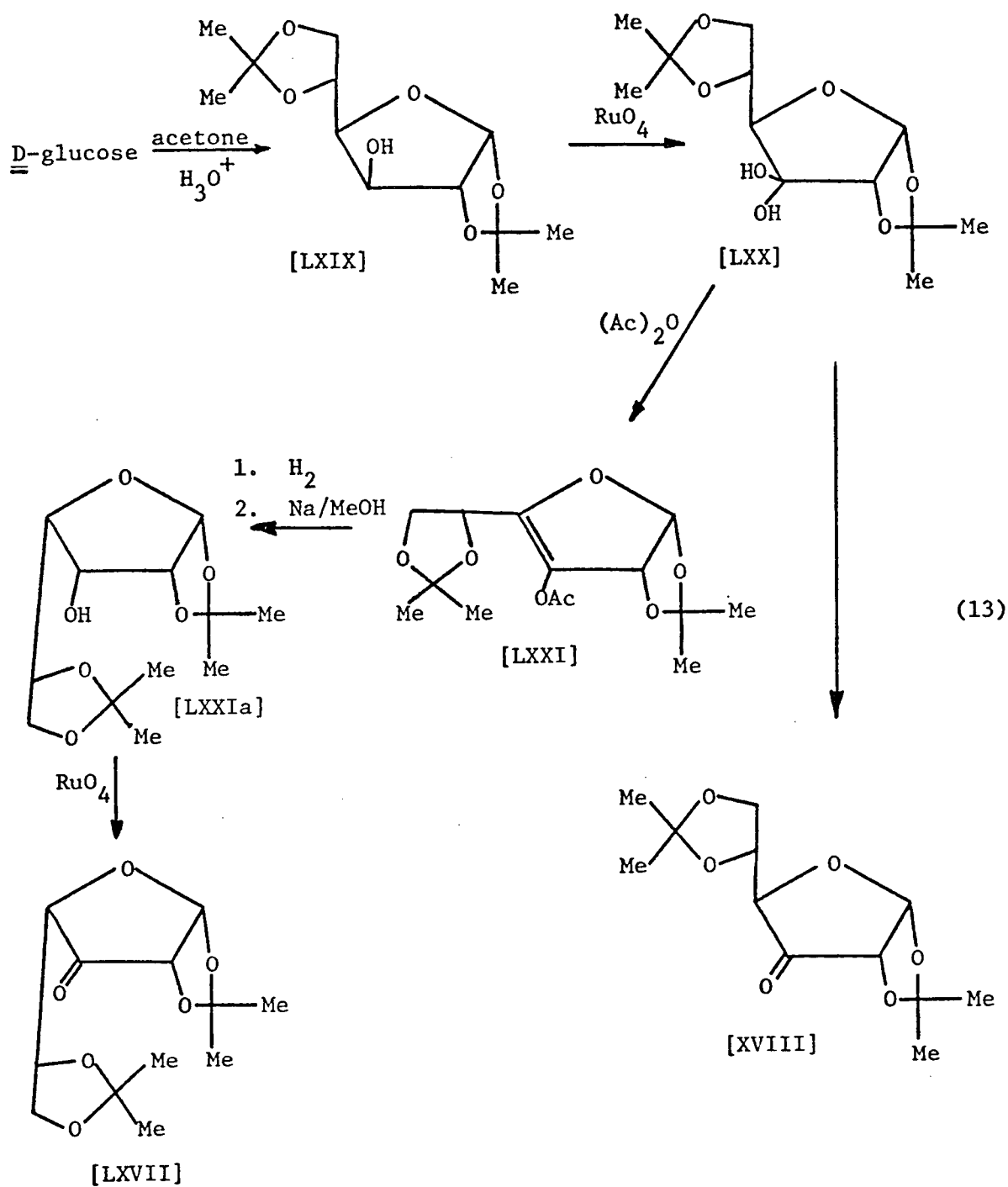
This compound was prepared from D-glucose by known procedures. Condensation of acetone with D-glucose in the presence of an acid catalyst (118) afforded 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose

[LXIX]. The secondary hydroxyl group of this compound was then oxidized to the hydrated 3-keto compound LXX (Equation 13) using sodium periodate and a "catalytic" amount of ruthenium dioxide (119). The water of hydration was removed from LXX by azeotropeing with toluene to afford ketose XVIII.

A point of technique frequently omitted in the discussion of the above oxidation is the necessity for carefully controlled addition of the periodate solution, particularly at the beginning of the reaction. Too rapid addition of periodate generally results in precipitation of the ruthenium catalyst as an insoluble complex on the walls of the reaction flask. The best yields of ketose were obtained by initiating the reaction by adding only a few drops of periodate solution. After several small additions of oxidant, it was added in larger portions (1-2 ml) and the colour changes in the reaction mixture were observed. The presence of the actual oxidant, ruthenium tetroxide was indicated by the reaction mixture taking on a green-black colour; when only ruthenium dioxide was present the solution appeared black. Additions of periodate were made only when all the ruthenium tetroxide generated by the previous addition of periodate had been consumed.

1.2 1,2:5,6-Di-O-isopropylidene- α -D-xylo-hexofuranos-3-ulose [LXVII]

This ketose was prepared from hydrated ketose LXX following the procedure of Slessor and Tracey (119) (Equation 13). Thus compound LXX was acetylated to afford the enol acetate LXXI which after hydrogenation over palladium-on-charcoal followed by removal of the



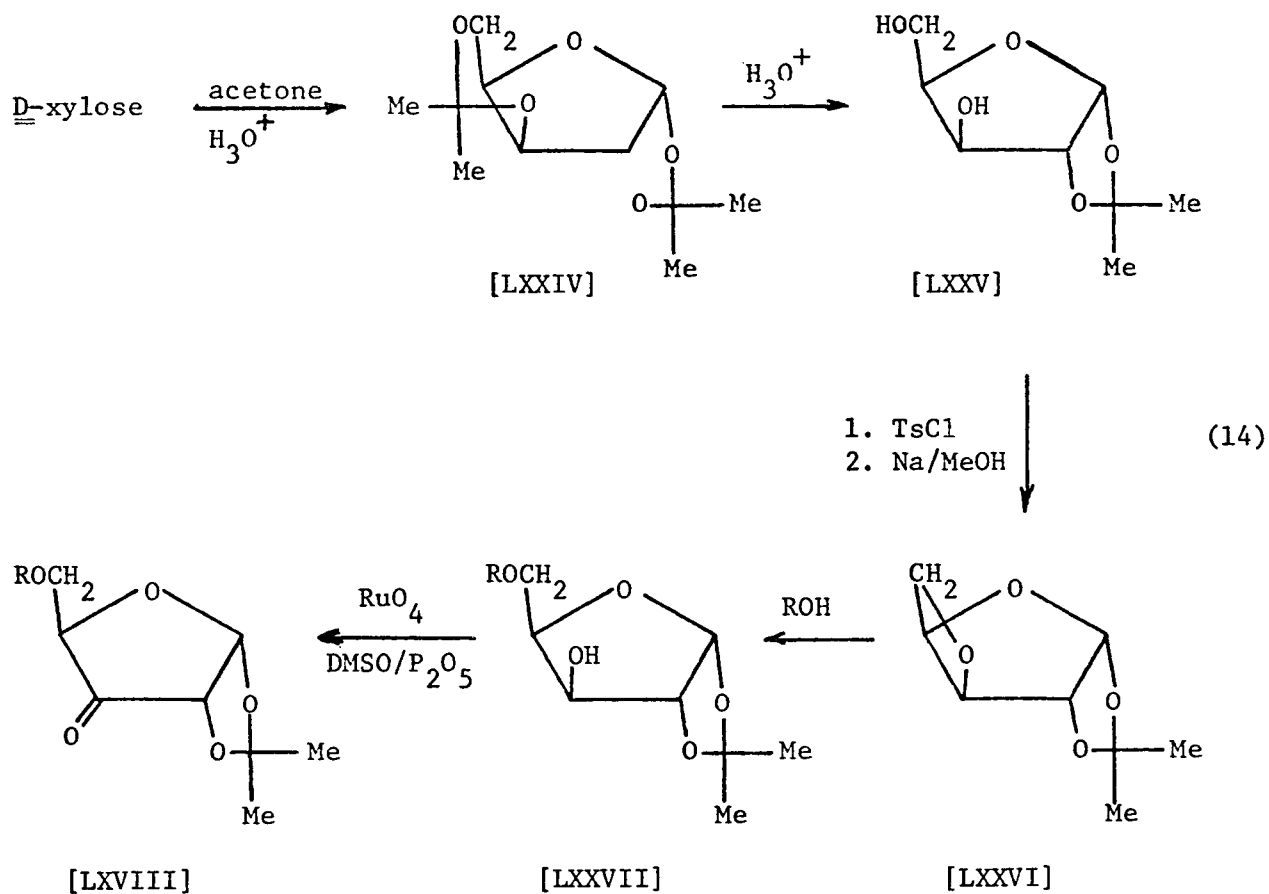
3-acetate using sodium methoxide and oxidation (with ruthenium tetroxide as before) gave the required 3-keto compound LXVII.

A point to note here for future discussion is the steric control exerted by the 1,2-O-isopropylidene group of enol acetate LXXI. Because of the directive effect exhibited by this group, hydrogenation of LXXI was stereoselective and resulted in formation of only one product [LXXIa].

1.3 5-O-Benzyl-1,2-O-isopropylidene- α -D-erythro-pentofuranos-3-ulose
[LXVIII]

This compound was obtained by a rather lengthy procedure (Equation 14) starting from D-xylose [LXXIII]. The di-O-isopropylidene compound LXXIV was prepared by the acid catalyzed condensation of acetone with D-xylose (120). The 3,5-isopropylidene group of LXXIV was then selectively cleaved with dilute acid to afford the mono-isopropylidene compound LXXV (120). Tosylation of the 5-hydroxyl group of LXXV (121) followed by treatment of the tosylate with sodium methoxide, gave the 3,5-anhydro sugar LXXVI (121). Opening of the 3,5-anhydro ring with benzyl alcohol and sodium afforded 5-O-benzyl-1,2-O-isopropylidene- α -D-xylo-furanose [LXXVII] (122). Preparation of this compound by direct monobenzylation of LXXV was not successful.

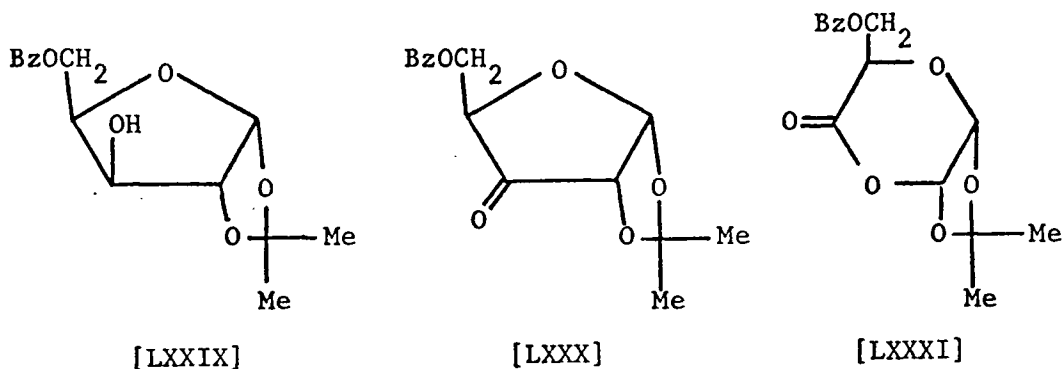
Two methods for the oxidation of the secondary hydroxyl group of alcohol LXXVII were examined. In the first method the oxidant was dimethyl sulfoxide with phosphorus pentoxide serving as the "activating" agent (40). This procedure afforded a 65% yield of 5-O-benzyl-1,2-O-isopropylidene- α -D-erythro-pentofuranos-3-ulose [LXVIII] as a homogeneous



syrup (R_f 0.76, benzene:methanol 4:1) having no hydroxyl absorption and a strong carbonyl absorption at 1760 cm^{-1} . Attempted chromatography of this ketose (on silica gel) led to decomposition so it was therefore characterized as its 2,4-dinitrophenylhydrazone derivative.

In the second method the oxidation of LXXVII was accomplished using ruthenium tetroxide generated as in the previous two oxidations from ruthenium dioxide and sodium periodate (119). This procedure gave very good yields (ca. 90%) of ketose LXVIII identical by tlc, ir and nmr with the product from the DMSO oxidation. Although this oxidation

required about twenty hours to complete, the yield of ketose was very good and none of the ring insertion lactone product was detected. In the oxidation of the related compound LXXIX with ruthenium tetroxide (123) (the ruthenium tetroxide being generated externally and added to a solution of alcohol LXXIX) the 3-ketose LXXX was isolated in about a 50% yield after a three hour reaction time. Longer reaction periods were found to give substantial amounts of the lactone side product LXXXI.



- 1.4 3-C-Cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [LXXXVI], 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-gulofuranose [LXXXVII] and 5-O-benzyl-3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [LXXXVIII]

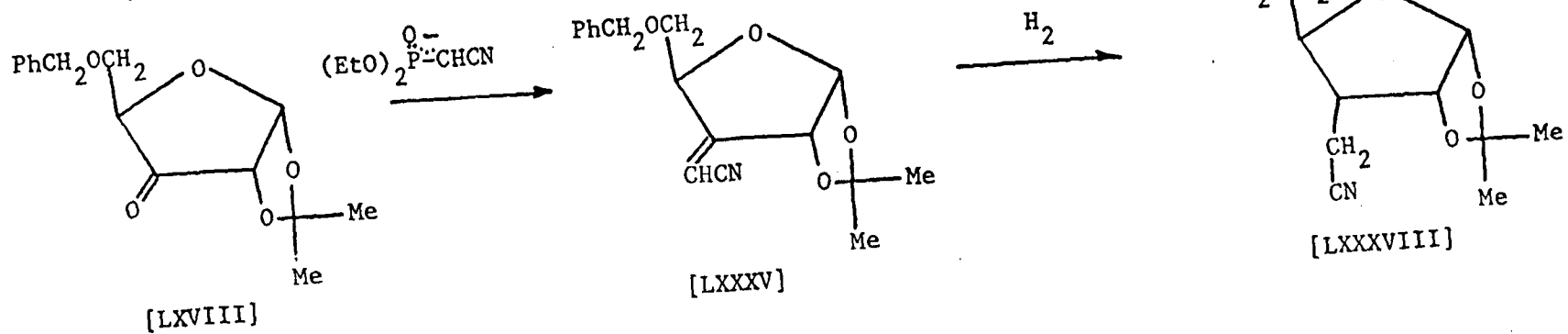
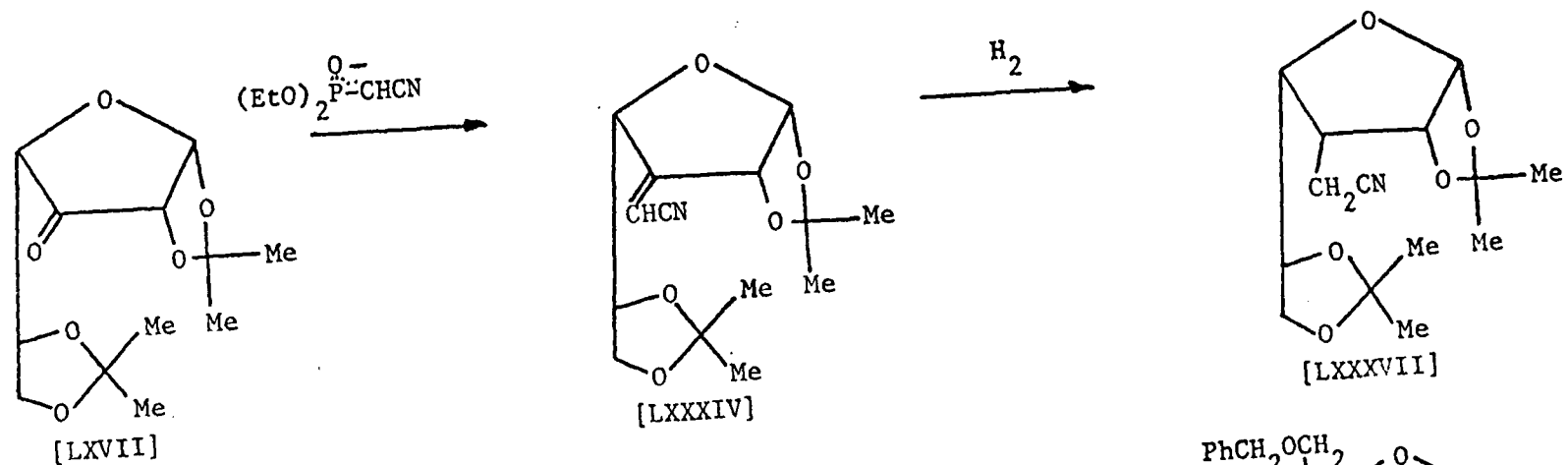
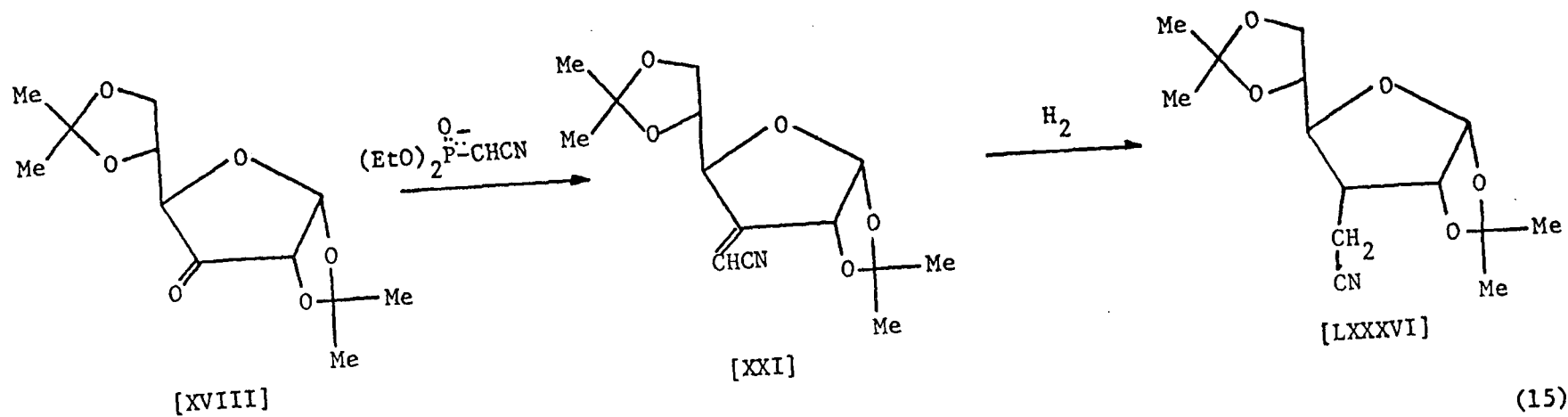
Having obtained the 3-ketoses just described the next step was to condense these compounds with the carbanion prepared from diethyl cyanomethylphosphonate and sodium hydride. The method followed here was essentially that utilized by Jones and Maissey (68) in the preparation of α,β -unsaturated nitriles from alkyl phenyl ketones. The only modifications to their procedure were that the reaction mixture was held

at 0° during addition of the ketose to the solution (this was found to eliminate the formation of side products) and that the initially produced α,β -unsaturated nitriles were hydrogenated (at atmospheric pressure using palladium on charcoal) without prior purification to afford the 3-C-cyanomethyl-3-deoxy branched-chain sugars.

Thus, the above reactions applied to 1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose [XVIII] afforded 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [LXVII] in 78% yield; 1,2:5,6-di-O-isopropylidene- α -D-xylo-hexofuranos-3-ulose [LXVIII] afforded 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-gulofuranose [LXXXVI] in 79% yield, and 5-O-benzyl-1,2-O-isopropylidene- α -D-erythro-pentofuranos-3-ulose [LXXXVII] afforded 5-O-benzyl-3-C-cyanomethyl-3-deoxy- α -D-ribofuranose [LXXXVIII] in 93% yield (Equation 15).

Although the intermediate α,β -unsaturated nitrile sugars XXI, LXXXIV and LXXXV were not characterized, it is presumed these were the initial condensation products as they are the expected reaction products and hydrogenation of these compounds gave the cyanomethyl branched-chain sugars as would be expected. Furthermore, in each case the ir spectra contained characteristic stretching absorptions for carbon-nitrogen triple bonds (ca. 2250 cm^{-1}) and the nmr spectra showed the presence of an olefinic proton (chemical shift about τ 4.1).

The palladium-on-charcoal atmospheric pressure hydrogenation of the olefinic bond proceeded smoothly in each instance, the uptake of hydrogen stopping spontaneously after absorption of about one equivalent. The stability of the 5-O-benzyl group of compound LXXXVIII in this

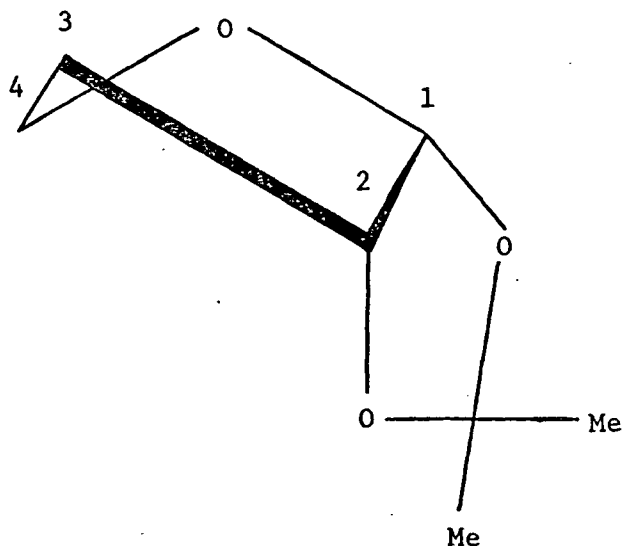


hydrogenation is somewhat surprising as these hydroxyl protecting groups are known to be hydrogenolyzed under mild conditions (124a); however, cases are known where hydrogenolysis of this group has required both heat and pressure (124b).

That this series of reactions did indeed lead to the cyanomethyl branched-chain sugars was clearly shown by the ir and nmr spectra. The presence of the nitrile group was confirmed by the characteristic $C\equiv N$ stretching absorption (ca. 2250 cm^{-1}) in the ir spectra and the presence of the methylene protons adjacent to the cyano group was confirmed by finding a two proton multiplet in the region 7.0-7.5 τ . In each instance the product after hydrogenation was judged homogeneous (by tlc and nmr). No trace of isomeric compounds having a C-3 cyanomethyl configuration epimeric with those shown in equation 15 was ever detected.

The configuration at C-3 of these cyanomethyl branched-chain sugars was determined by nmr spectroscopy in the following manner. It has been shown by Hall and coworkers (125) that for 1,2-O-isopropylidene- α -D-glucofuranose and of 1,2-O-isopropylidene- β -L-idofuranose compound in all cases the twist conformation LXXXIX is adopted. That is, C-2 lies below and C-3 above the plane formed by C-1, O and C-4. Assuming this conformation was adopted by the above 3-C-cyanomethyl branched-chain sugars and assuming a first order Karplus relationship (126), holds for H-1, H-2 and H-3, it is possible to make the following predictions:

(a) If the C-3 cyanomethyl substituent projects above the plane (opposite to the configuration shown in equation 15) the H-2 nmr signal



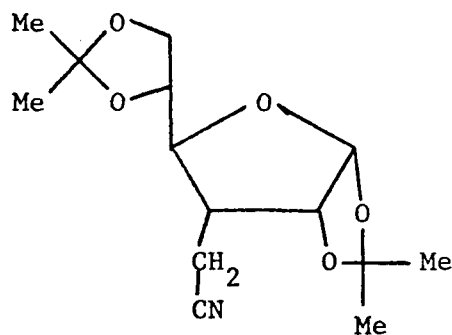
[LXXXIX]

should appear as a doublet ($J_{1,2} \approx 3-4$ Hz, $J_{2,3} < 0.5$ Hz).

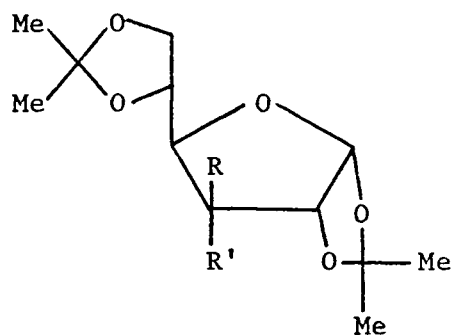
(b) If the C-3 substituent is as shown in equation 15 the H-2 resonance should appear as a triplet or quartet ($J_{1,2} = 3-4$ Hz, $J_{2,3} = 3-6$ Hz).

In Table IV are listed the H-2 chemical shifts and coupling constants for compounds LXXXVI, LXXXVII and LXXXVIII plus the same values for some representative 1,2-O-isopropylidene-furanoses. As can be seen from this Table, the H-2, H-3 coupling constant values indicate that the cyanomethyl branched-chain sugars have assumed the configurations depicted (i.e. the cyanomethyl branched chain is cis to the 1,2-isopropylidene group).

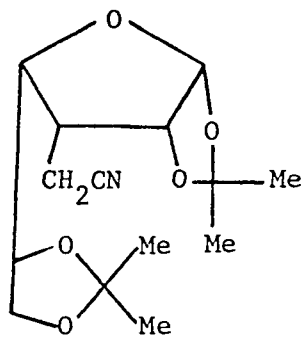
TABLE IV			
H-2 Chemical Shifts and Coupling Constants for Some 1,2-O-Isopropylidene-furanoses			
Compound	H-2 Chemical Shift	$J_{1,2}$	$J_{2,3}$
[LXXXVI]	5.23 τ CDCl_3	3.6	3.6
[LXXXVII]	5.27 τ CDCl_3	4.0	5.0
[LXXXVIII]	5.34 τ CDCl_3	3.6	3.9
[LXIX]	5.60 τ CCl_4 (146)	3.9	≈ 0
[LXIXa]	5.53 τ CCl_4 (146)	3.9	5.0



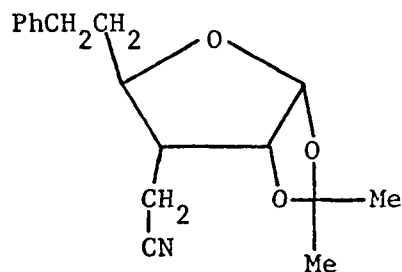
[LXXXVI]



[LXIX] R=OH, R'=H [LXIXa] R=H, R'=OH



[LXXXVII]



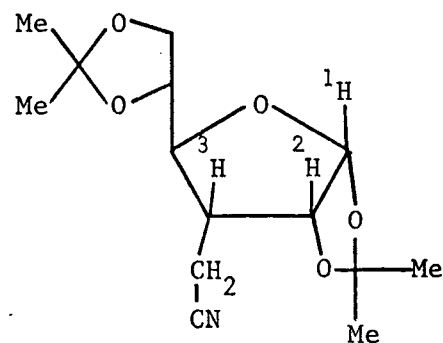
[LXXXVIII]

To illustrate the typical H-1, H-2 coupling pattern of these 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene branched-chain sugars the 100 MHz spectrum of compound LXXXVI is reproduced in Figure I. The hydrogen assignments for LXXXVI were made in the following way:

1. irradiation of the doublet at 4.13 τ (H-1) collapsed the triplet at 5.23 τ to a doublet indicating this was the H-2 resonance,
2. irradiation of the triplet at 5.23 τ collapsed the doublet at 4.13 τ to a singlet, confirming the previous assignment and altered the multiplet 7.6-7.8 τ indicating this was H-3 resonance.

Another factor corroborating the C-3 configurational assignment is the known directive effect of the 1,2-O-isopropylidene furanoses. As was previously noted (p. 38), the hydrogenation of enol acetate LXXI gave only one product LXXII. There is a generally observed trend that for compounds of this sort the bulky isopropylidene group blocking the C-1, C-2 hydroxyls interferes with the approach of reagents from the underside (cis to the 1,2-O-isopropylidene group) of the ring (80,123). Therefore, it was to be expected that catalytic hydrogenation of the unsaturated bond, took place via cis addition from the topside of the ring, thereby resulting in compounds having the proposed C-3 configuration.

Some time after our initial report on the preparation of cyanomethyl branched-chain sugars via the above modified Wittig reaction (127), Tronchet et al. (61) reported the synthesis of branched-chain unsaturated cyano sugars by reaction of the Wittig reagent cyanomethylene triphenylphosphorane with keto sugars. The unsaturated cyano sugars were cis-dihydroxylated (KMnO_4) to yield aldehydo branched-chain sugars (e.g. equation 16). This procedure gave compounds having the same branched-chain



[LXXXVI]

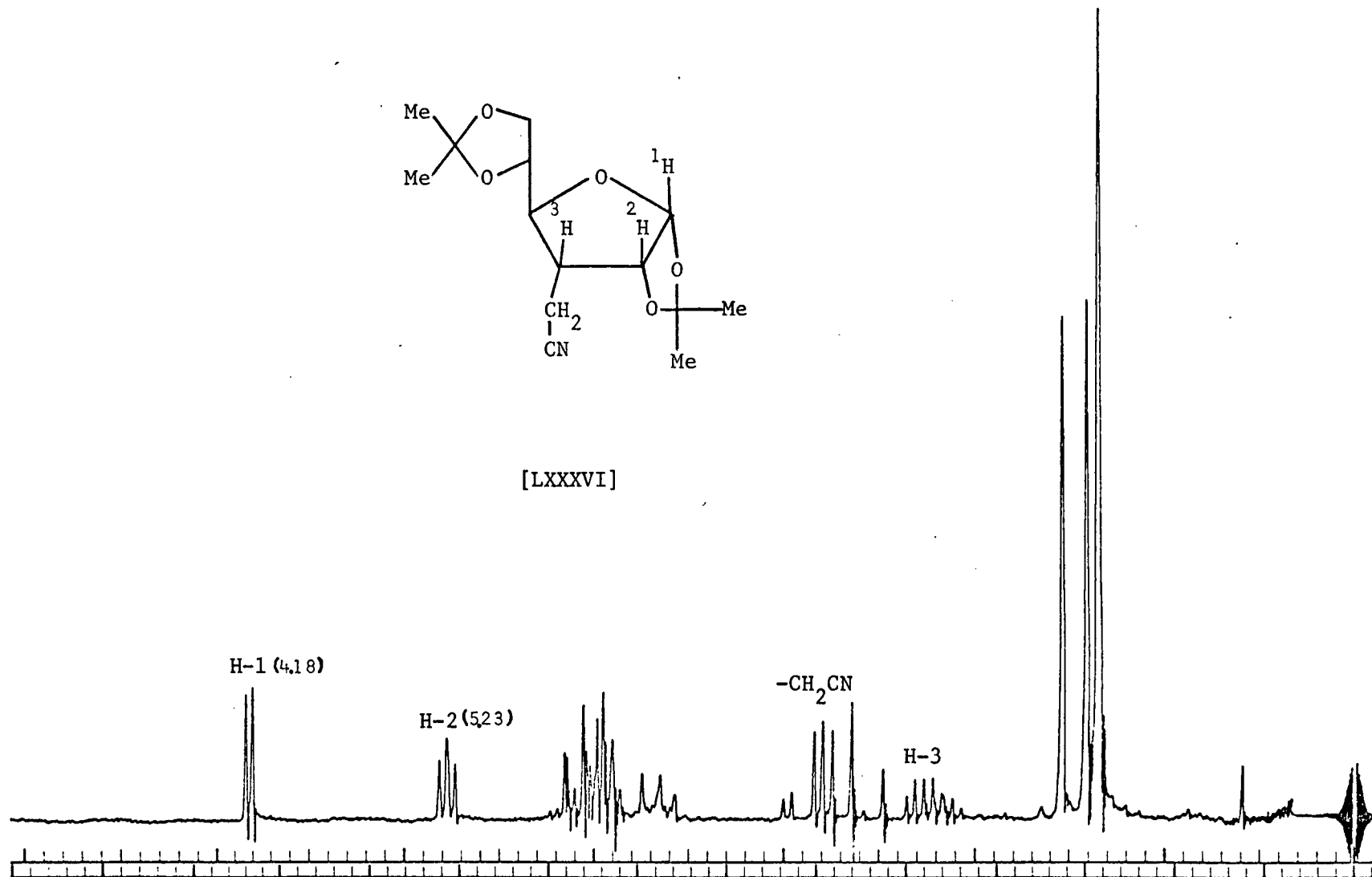
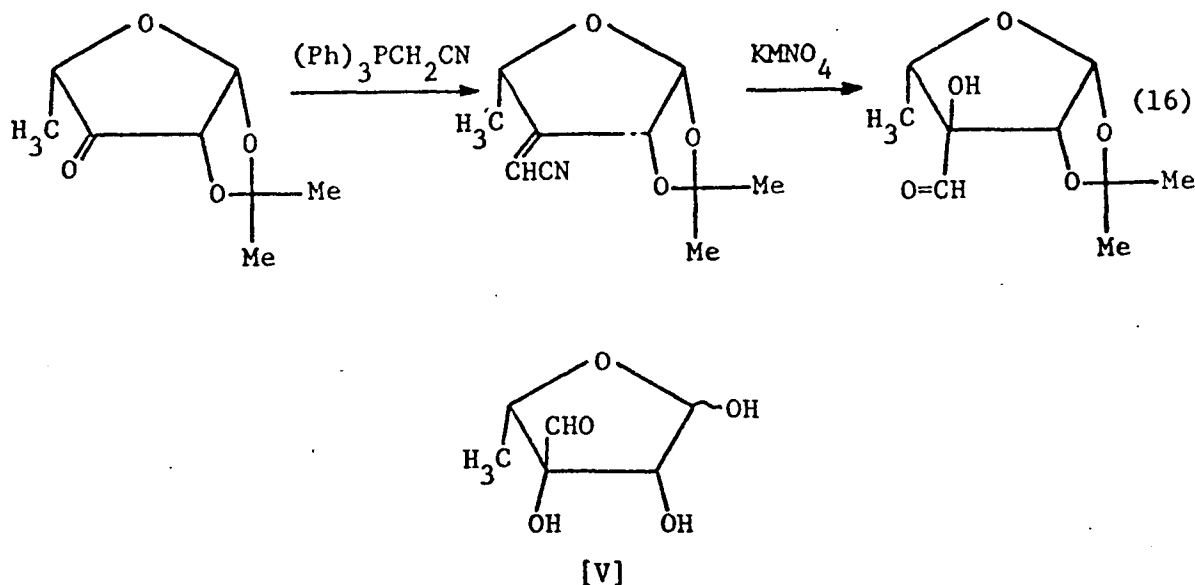


Figure 1. Proton magnetic resonance spectrum at 100 MHz in deuteriochloroform of 3-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [LXXXVI].

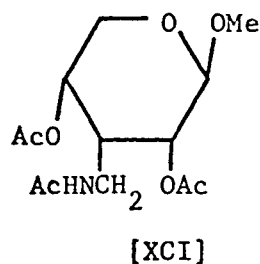
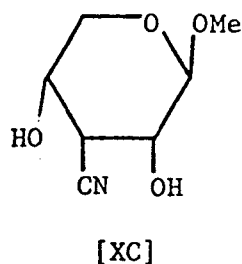


which occurs in the branched-chain sugar streptose [V].

2. Synthesis of branched-chain amino sugars by reduction of branched-chain cyano sugars

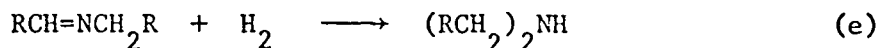
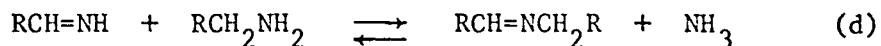
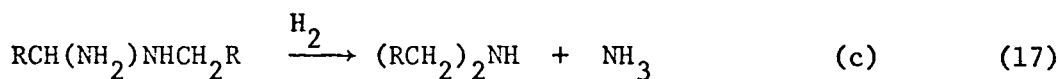
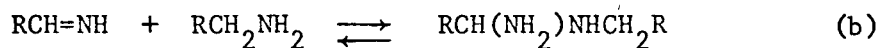
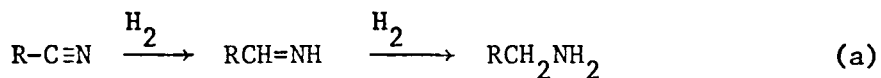
As it was desired to prepare branched-chain sugars having a variety of nitrogenous functionalities, the reduction of the previously described branched-chain cyanomethyl compounds to the corresponding aminoethyl branched-chain sugars.

Although alkyl cyanides provide useful intermediates for the synthesis of alkyl amines, the cyano group being reduced by metal hydrides (128), by catalytic hydrogenation (129), or by diborane (130); there have been very few reports of successful conversion of carbohydrate cyanides into carbohydrate amines. Coxon and Fletcher (131) have reported the lithium aluminum hydride reduction of a galactopyranosyl cyanide to an amino heptitol and interestingly, the branched-chain cyano sugar XC (132) has reportedly been hydrogenated (no details given) to the corresponding amino sugar isolated as the tri-acetal derivative XCI.



2.1 3-C-(2'-Acetamidoethyl)-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [XCI]

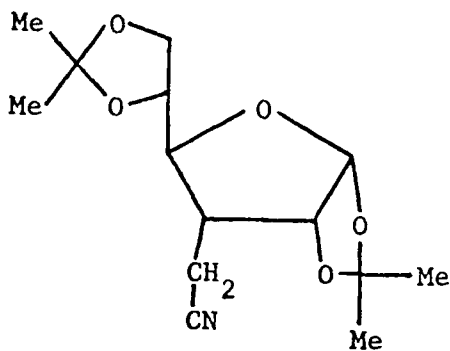
As a successful catalytic reduction of a nitrile branched-chain sugar had been reported (see above) it was decided to attempt the reduction of 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [LXXXVI] by catalytic hydrogenation. Catalytic hydrogenation of nitriles to amines has been assumed to proceed through an imine intermediate (128) (Equation 17a).



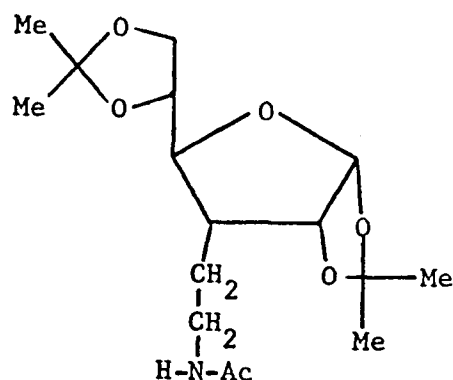
Complications in this reaction occur when the primary amine couples with the intermediate imine, (Equation 17b) giving a product from which a secondary amine may be formed by hydrogenolysis (Equation 17c) or by elimination of ammonia (Equation 17d) followed by hydrogenation (Equation 17e) of the resultant imine. Variations on this general scheme have been used to account for the formation of other observed side products (128).

The above coupling reactions have been prevented by either forming a derivative of the primary amine as soon as it was produced, this being done by hydrogenation in the presence of mineral acid (133) or acetic anhydride (134), or by hydrogenation in an ammonia saturated solution (135) which reverses the equilibrium in equation 17d. As nitrile branched-chain sugar LXXXVI contains the very acid labile 5,6-O-isopropylidene group, it was decided to hydrogenate LXXXVI in ethanol saturated with ammonia.

Accordingly LXXXVI in ethanol saturated with ammonia at 0° was hydrogenated at 60 psi for twenty hours at room temperature over 5% rhodium-on-alumina. Because of the presence of ammonia it was impossible to monitor the hydrogen uptake; however, the reaction was continued until no starting material remained (as evidenced by tlc). This procedure gave the expected aminoethyl branched-chain sugar characterized as its N-acetyl derivative 3-C-(2'-acetamidoethyl)-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [XCII] in 80% yield. The ir spectrum of this compound contained no C $\equiv$ N absorption but did show an N-H stretch at 3300 cm⁻¹ and a carbonyl absorption at 1640 cm⁻¹. The nmr spectrum



[LXXXVI]



[XCII]

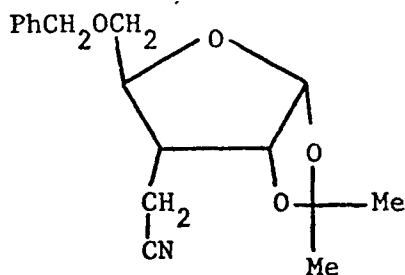
showed the presence of the N-H proton as a broad triplet at 3.27 τ and the N-acetate as a 3 proton singlet at 8.03 τ .

2.2 3-C-(2'-Acetamidoethyl)-5-O-benzyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [XCIII]

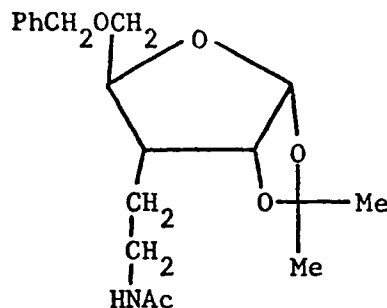
To reduce the nitrile group of the 5-O-benzyl cyanomethyl branched-chain sugar LXXXVIII catalytic hydrogenation procedures were judged to be inapplicable as the rather vigorous conditions involved would in all likelihood have hydrogenolyzed the 5-O-benzyl hydroxyl protecting group. Had this happened it would have then been necessary to reblock the 5-hydroxyl group to use this compound in nucleoside syntheses.

In view of this it was decided to attempt the reduction of the cyano group of LXXXVIII using lithium aluminum hydride in ether. Reduction to the pentose amino sugar proceeded smoothly with the product being characterized as before as the N-acetyl derivative 3-C-(2'-

acetamidoethyl)-5-O-benzyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [XCIII]. That the product of this reduction was the expected acetamidoethyl branched-chain sugar was confirmed by the NH and carbonyl absorptions found in the ir spectrum at 3300 cm^{-1} and 1650 cm^{-1} respectively and by the broad NH signal and the N-acetyl signal found in the nmr spectrum at 4-4.4 τ and 8.1 τ respectively.



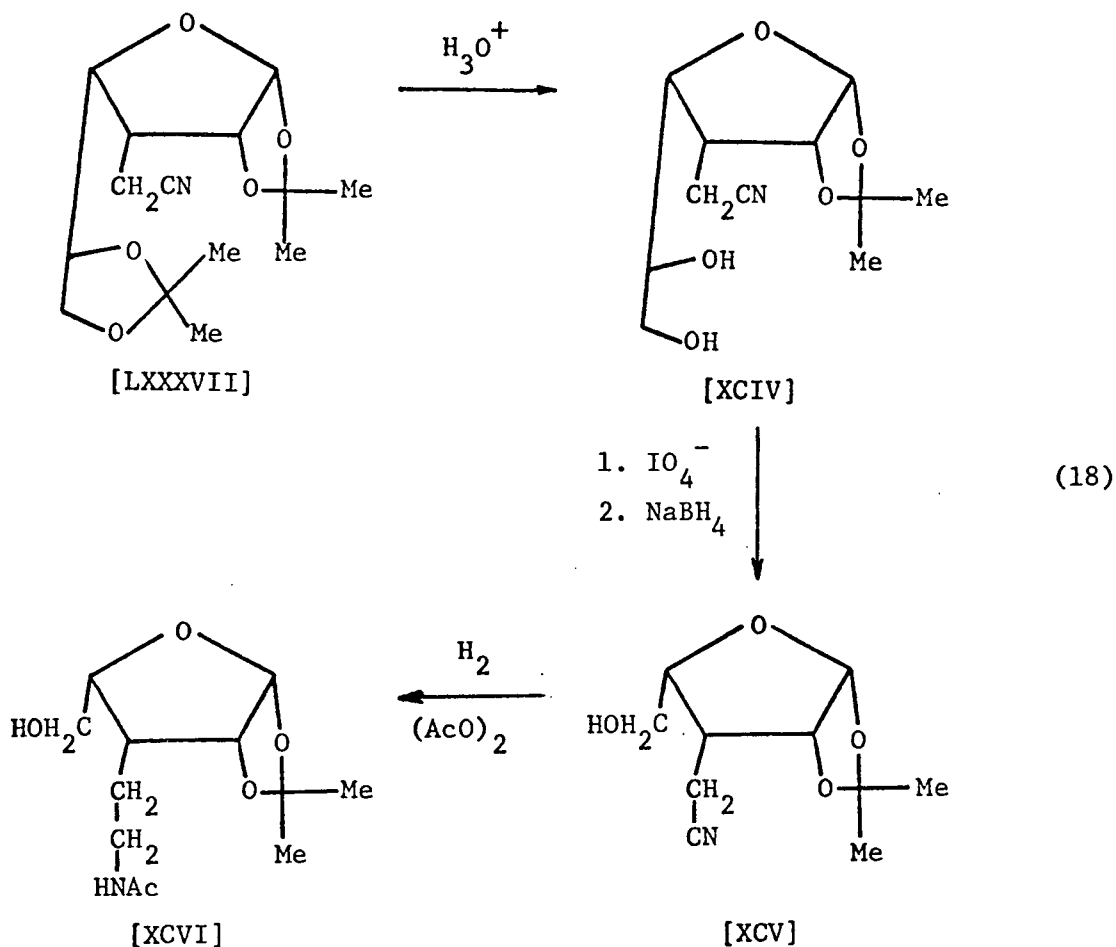
[LXXXVIII]



[XCIII]

2.3 3-C-Cyanomethyl-3-deoxy-1,2-O-isopropylidene- β -L-lyxofuranose [XCV] and 3-C-(2'-acetamidoethyl)-3-deoxy-1,2-O-isopropylidene- β -L-lyxofuranose [XCVI].

As various L-amino sugars are known to exist in Nature (136) it was decided to undertake the synthesis of the above cyanomethyl and acetamidoethyl branched-chain sugars. The manner in which this was done is illustrated in equation 18.



The first step in this sequence is the selective hydrolysis of the 5,6-isopropylidene group of LXXXVII. It has been widely observed that for 1,2:5,6-di-O-isopropylidene furanose derivatives the 5,6-isopropylidene ketal is hydrolyzed much more rapidly than the 1,2 isopropylidene moiety (137). The hydrolysis of 1,2,5:6-di-O-isopropylidene- α -D-glucofuranose [LXIX] provides an excellent example of the selectivity of this reaction. In this instance the 5,6-isopropylidene group is cleaved with dilute hydrochloric acid

some eighty times faster than the 1,2-isopropylidene (138). The 5,6-isopropylidene group has been selectively hydrolyzed using a variety of acidic conditions (138,139,140). In the present work this group was removed using an aqueous methanol solution containing sulfuric acid as in the case of the preparation of 1,2-O-isopropylidene glucose (140). The hydrolysis was conducted at room temperature for 7 hours to afford the mono-isopropylidene compound XCIV as a syrup in 88% yield. The nmr spectrum of this compound showed the presence of two hydroxyl groups and only two methyl groups (at 8.40 and 8.64 τ) belonging to the 1,2-isopropylidene group.

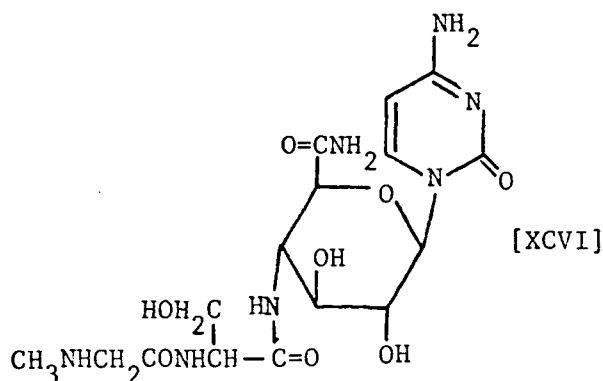
The L sugar 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- β -L-lyxofuranose [XCVI] was obtained from mono-isopropylidene compound XCIV by sodium periodate oxidative cleavage to the 5-aldehydo compound followed by sodium borohydride reduction of the 5-aldehydo group (21). This series of reactions is very frequently used in carbohydrate chemistry to prepare sugars having one carbon less than the starting compound. The best yields are usually obtained by reducing the intermediate aldehydo compound without isolation, as was done in this instance. That the cyanomethyl branched-chain of XCVI had survived the above operations was confirmed by the ir spectrum ($C\equiv N$ 2245 cm^{-1}).

Reduction of the cyanomethyl branched-chain sugar XCV to the corresponding acetamidoethyl compound XCVI was accomplished by catalytic hydrogenation. As hydrogenation is technically simpler than lithium aluminum hydride reduction, where possible it is the method of choice for reduction of the cyano moiety. In this instance the hydrogenation medium chosen was an acetic anhydride-ethanol 1:1 mixture.

As the 1,2-isopropylidene group is comparatively acid stable, there was no danger of hydrolysis in this weakly acid medium. In the presence of acetic anhydride the N-acetyl derivative is formed in situ preventing the previously discussed coupling reactions. Accordingly XCV was hydrogenated at 60 psi over platinum oxide for four and a half hours. A tlc examination of the reaction mixture after this time indicated that no starting material remained and showed the presence of only one product. Spectral data (nmr 3.8-4.3 τ , broad N-H, 8.02 τ singlet, N acetyl) confirmed the reduction had taken the expected course to afford crystalline 3-C-(2'-acetamidoethyl)-3-deoxy-1,2-O-isopropylidene- β -L-lyxofuranose [XCVI] in 93% yield.

3. Synthesis of branched-chain carbamoylmethyl sugars

In order that the variety of nitrogenous deoxy branched-chain sugars available might be increased, the preparation of carbamoyl branched-chain sugars was also examined. Although no branched-chain carbamoyl sugars have been reported as yet, the nucleoside antibiotic gougerotin [XCVII] (141a) is known to contain a C-6' carbamoyl group and 5'-carboxyamide adenosine analogs are used in the treatment of circulation disorders (141b).

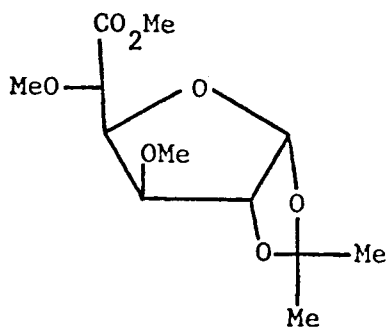


3.1 3-C-Carbamoylmethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [C]

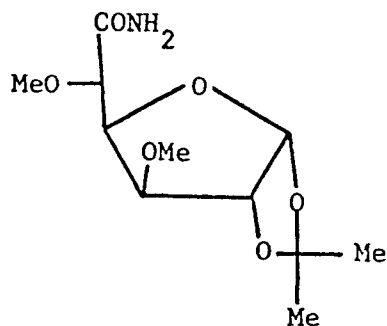
One method which has been utilized in carbohydrate chemistry for the preparation of amides involves ammonolysis of an ester by reacting it with liquid ammonia in the presence of ammonium chloride. Heynes and Baltes (142) had used this procedure to convert the C-6 methyl ester of compound XCVIII to the C-6 amide XCIX. Fortunately a 3-C-carbomethoxymethyl sugar XXXIX (22) had already been prepared in this laboratory (p. 18) so therefore it was only necessary to apply the above ammonolysis to this compound to obtain the desired carbamoylmethyl branched-chain sugar 3-C-carbamoylmethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [C].

Surprisingly under the conditions used by Heynes and Baltes (heating in a sealed tube at 50° for 6 hr in liquid ammonia containing ammonium chloride) only about 10% conversion (as evidenced by tlc) of XXXIX to C occurred. It was found that to obtain satisfactory yields it was necessary to allow the reaction to proceed at 60° for 24 hr. Under these conditions XXXIX was converted to C in 76% yield (Equation 19).

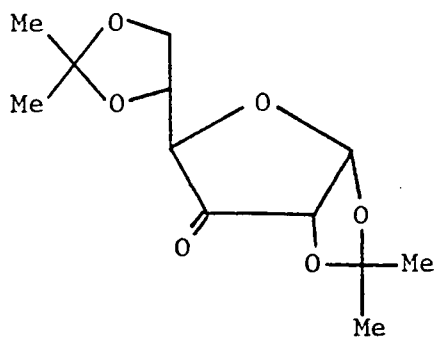
As an alternate route to carbamoylmethyl branched-chain sugars



[XCVIII]

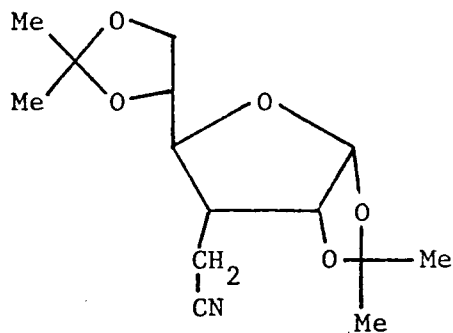


[XCIX]



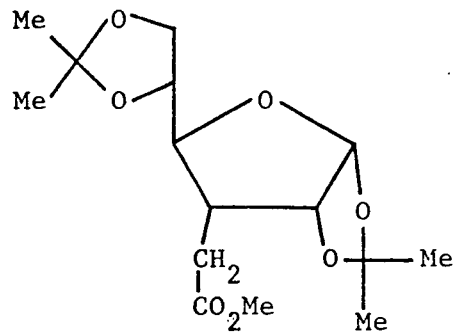
[XVIII]

1. $(\text{EtO})_2\text{POCH}_2\text{CN}$
2. H_2



[LXXXVI]

1. $(\text{MeO})_2\text{POCH}_2\text{CO}_2\text{Me}$
2. H_2

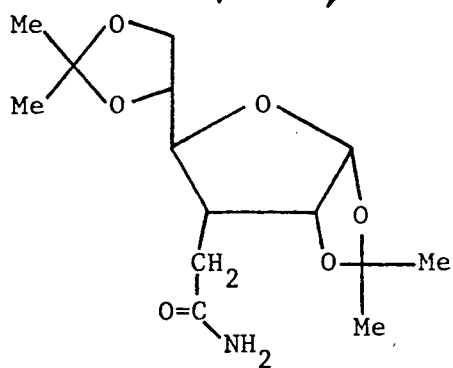


[XXXIX]

(19)

$\text{H}_2\text{O}_2/\text{OH}^-$

NH_3



[C]

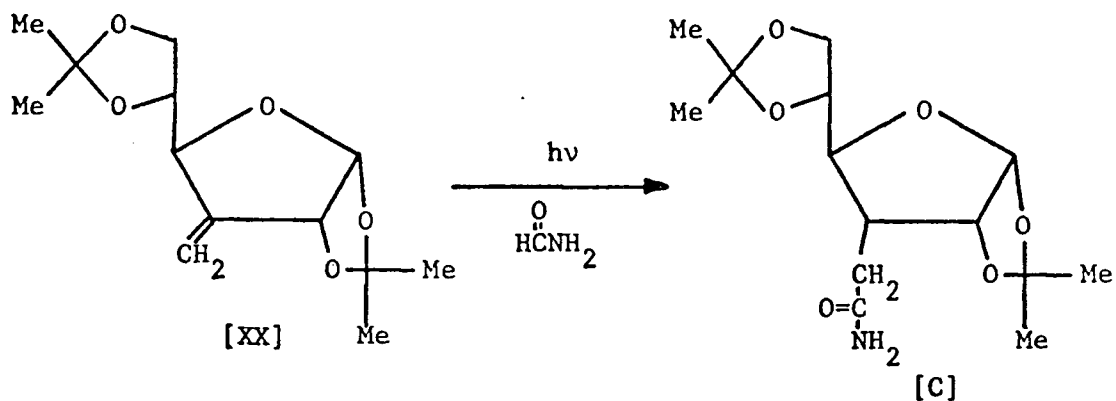
the base catalyzed reaction of cyanomethyl branched-chain sugar LXXXVI with hydrogen peroxide was examined. Although this reaction has been known for sometime (143) as a means of converting nitriles to the corresponding amides, to the best of our knowledge this reaction has not been previously applied to a carbohydrate nitrile.

When an ethanol solution of nitrile LXXXVI was reacted with hydrogen peroxide and 6 N sodium hydroxide at 50° for 6 hr, it was smoothly hydrolyzed to the carbamoylmethyl sugar C (70% yield) (Equation 19) identical (by nmr, ir, mixed m.p.) to the compound prepared via ammonolysis of ester XXXIX.

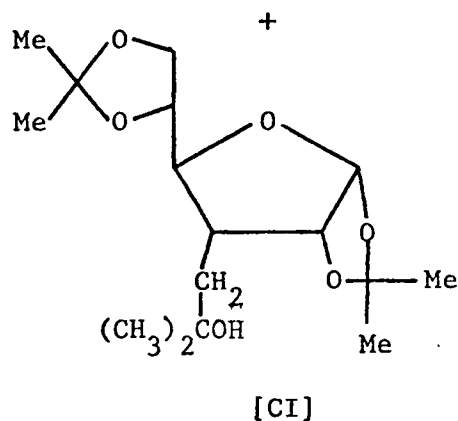
As well as providing two routes to the carbamoyl methyl sugars, the above procedures provide a means of interrelating the products of two different Wittig reactions (Equation 19). As both LXXXVI and XXXIX give the same amide both these compounds must have the same relative configuration. Since in connection with another problem an x-ray study of a derivative of compound XXXIX is underway, it was desirable to have a way of chemically relating the two Wittig products LXXXVII and XXXIX.

As a third route to these carbamoylmethyl branched-chain sugars the photoaddition of formamide to the exocyclic unsaturated sugar XX was undertaken. The preparation of compound XX and the mechanism of this photoamidation have already been dealt with in the Introduction (p. 12 and p. 24 respectively).

When compound XX was irradiated ($\lambda > 300$) for seven hours in an oxygen-free mixture of formamide, tertiary butanol and acetone products were isolated from the reaction mixture (Equation 20). The major product (50% yield) proved to be the carbamoylmethyl branched-chain



(20)



sugar C identical (ir, nmr, mixed m.p.) to the product isolated from the last two reactions. In view of the fact that photoaddition of formamide to terminal olefins is known to take place in an anti-Markovnikov manner (81), and as this reaction is known to be influenced by steric features of the olefin (82) (p. 23), it is not too surprising that the addition of formamide to XX takes place in a stereoselective manner to give only the allo carbamoylmethyl addition product of XX.

The minor product CI (11%) was not characterized but was tentatively assigned the structure CI on the basis of nmr evidence: H-2 appears as a triplet indicating an allo configuration, there is one exchangeable proton present in the molecule indicating the likely presence of a hydroxyl group, and there are six methyl signals, four belonging to the isopropylidene groups and presumably two for the methyl groups in the branched-chain. The formation of acetone addition in this reaction has been noted previously (81).

4. Synthesis of nitrogenous branched-chain sugars having a single carbon in the branched-chain

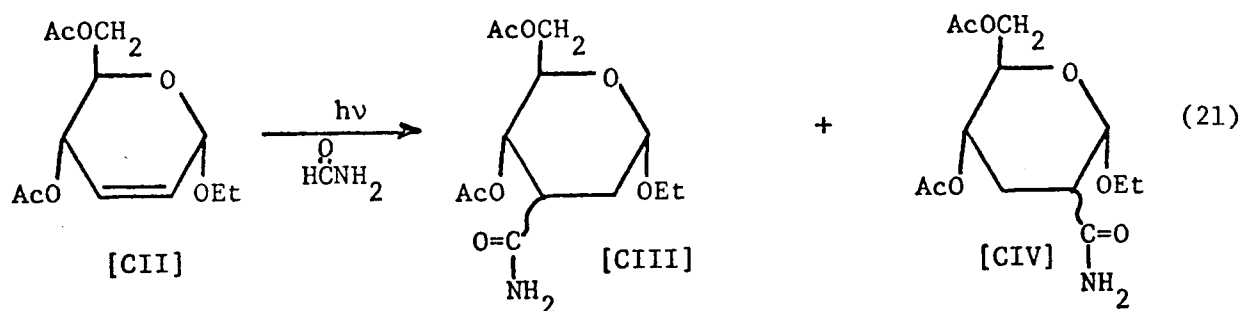
Concomitant with the program to develop routes to nitrogenous branched-chain sugars having two carbons in the branched-chain, the preparation of analogous compounds having only a single carbon in the branched-chain was attempted.

4.1 Photoamidation of 4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside [CII]

As the photoaddition of formamide to the exocyclic methylene sugar C just described had been relatively successful, it was decided to apply the same reaction to the unsaturated sugar 4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside [CII]. This compound was prepared from triacetyl-D-glucal by the method of Ferrier and Prasad (144).

It was anticipated that the photoaddition of formamide to this compound would result in 2- and/or 3-C-carbamoyl-2,3-dideoxy pyranosides

(Equation 21) which could hopefully be differentiated on the basis of their nmr spectra. Accordingly olefin CII dissolved in a de-oxygenated



mixture of formamide, t-butanol and acetone was irradiated ($\lambda > 300$) for 9 hr. After this time tlc examination showed that no starting material remained and that there were two product spots. These two components were separated by chromatography on silica-gel and examined.

The minor component (about 12% of the total product) was judged on the basis of its nmr spectra to be a mixture of acetone addition products and was not further investigated.

The major component, a syrup amounting to about 88% of the total product mixture had the following characteristics:

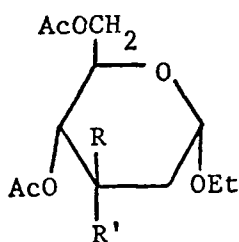
(a) The ir spectrum contained in addition to the usual C-H absorptions an absorption at 3400 cm^{-1} and a strong absorption at 1660 cm^{-1} .

(b) The nmr spectrum showed a broad low field 2 proton absorption at 3.47τ and a total of 21 protons present.

(c) The elemental analysis was consistent with that expected for the addition of the elements of formamide to olefin CII.

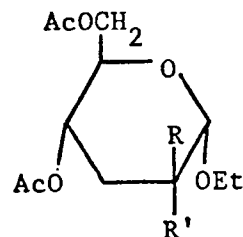
From the above data it was concluded that this product was a 1:1 formamide:olefin adduct. However, as the nmr spectrum showed several superimposed triplets for the methyl peaks of the ethyl glycoside, it was assumed that this product was a mixture of isomers. That this product was a mixture was further substantiated by finding that the de-acetylated (methanolic sodium methoxide) trimethylsilylated derivatives (145) showed the presence of four components in about equal amounts when examined by gas liquid chromatography. Despite repeated chromatography no single isomer could be separated in a pure form.

From the above it would appear that the major product of the photoamidation of CII is a mixture of all four possible formamide addition products CIIIa, CIIIb, CIVa, and CIVb. As it was apparent that it



[CIIIa] $R = \text{CONH}_2$, $R' = \text{H}$

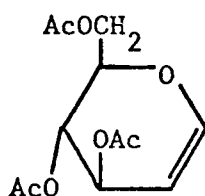
[CIIIb] $R' = \text{H}$, $R = \text{CONH}_2$



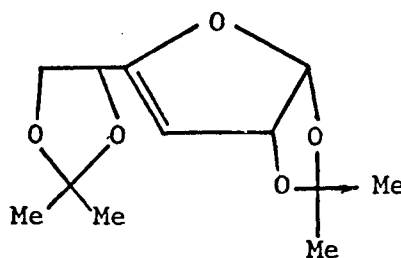
[CIVa] $R = \text{CONH}_2$, $R' = \text{H}$

[CIVb] $R' = \text{H}$, $R = \text{CONH}_2$

would be very difficult to prepare useful amounts of a single pure carbamoyl branched-chain sugar by this method, work along these lines was discontinued. In contrast to these results as indicated in the Introduction (p. 21) other workers in this laboratory have been able to apply this reaction with some success to the unsaturated sugars LX LXI. It is evident that photoaddition of formamide to carbohydrate



[LX]



[LXI]

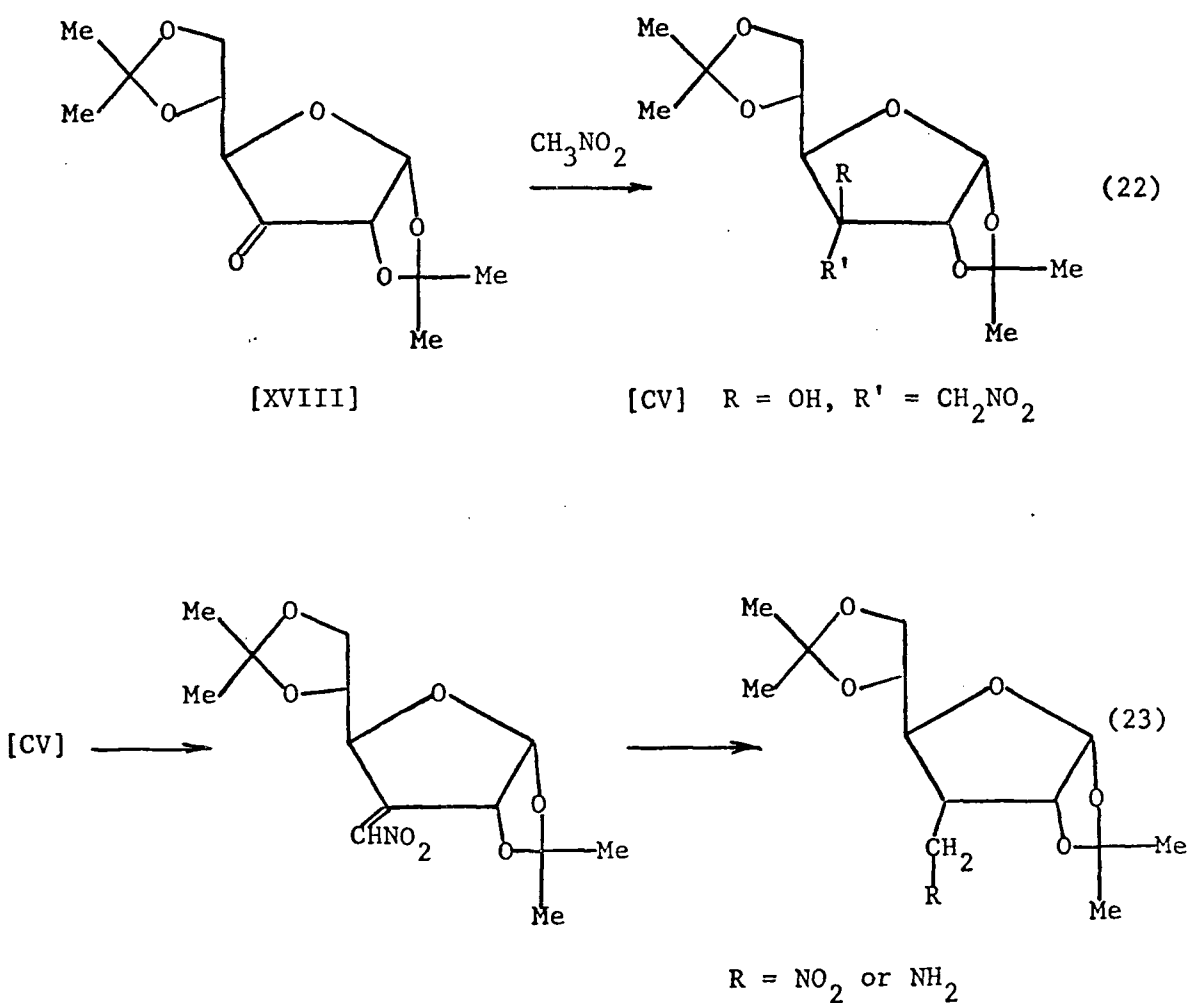
olefins is most useful when steric features of the olefin result in the preferential formation of a single product as was the case with compound XX.

4.2 Addition of nitromethane to 1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose [XVIII]

A second route investigated leading to nitrogenous branched-chain sugars having a single carbon in the branched-chain was the addition of nitromethane to carbohydrate ketoses. As was mentioned in the Introduction (p. 21) although the addition of nitroparaffins to

carbohydrates had been extensively investigated, when this work was begun there had been only two reports (78,79) (one of which (78) was from this laboratory) on the addition of nitromethane to carbohydrate ketoses to afford branched-chain sugars.

The manner in which this reaction was used is illustrated in equation 22. Condensation of ketose XVIII with the carbanion prepared



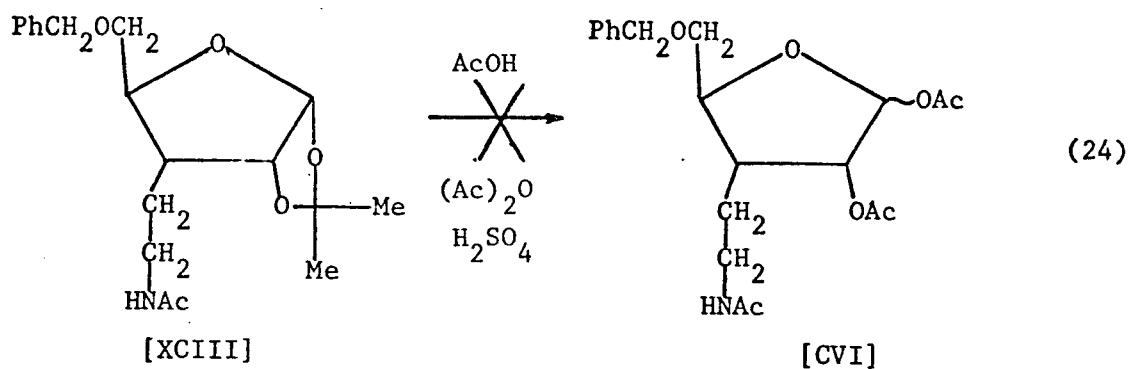
from nitromethane and sodium methoxide afforded the branched-chain nitro sugar 1,2:5,6-di-O-isopropylidene-3-C-nitromethyl- α -D-glucofuranose [CV]. It was planned to use this compound to prepare deoxy nitromethyl (by acetylation of the 3° hydroxyl group followed by a Schmidt-Rutz reaction (74) and reduction of the nitro-olefin double bond) and deoxy aminomethyl branched-chain sugars (Equation 23). However, shortly after the preliminary results concerning the addition of nitromethane to XVIII were published (148), a brief communication from Albrecht and Moffatt (80) reported their results on condensing nitromethane with the same ketose XVIII, the conversion of the initial nitromethane condensation product into deoxy nitromethyl and aminomethyl branched-chain sugars, and the conversion of these compounds into branched-chain sugar nucleosides. In view of this, further work here along these lines was discontinued and no further attempts were made to prepare branched-chain sugars of this type.

5. Nucleoside synthesis

Having synthesized the 3-deoxy, two carbon nitrogenous branched-chain sugars just described, the next step was to use these compounds to prepare the corresponding branched-chain sugar nucleoside derivatives. In order to utilize these compounds in standard nucleoside syntheses, it was necessary to convert them first into their 1,2-di-O-acetyl derivatives. As the procedures for preparation of amino sugar nucleosides had been extensively investigated (149), it was decided to attempt first the preparation of an amino branched-chain sugar nucleoside using the acetamidoethyl branched-chain sugar XCIII.

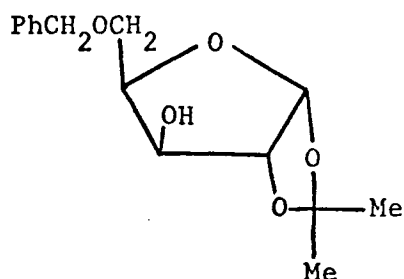
5.1 Attempted acetolysis of 3-C-(2'-acetamidoethyl)-5-O-benzyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [XCIII]

The preparation of the blocked branched-chain sugar 3-C-(2'-acetamidoethyl)-1,2-di-O-acetyl-5-O-benzyl-3-deoxy-ribofuranose [CVI] was first attempted. It was hoped that acetolysis by the normal procedure (150) using acetic acid, acetic anhydride, and sulfuric acid, would convert the 1,2-isopropylidene compound XCIII into the corresponding 1,2-di-acetyl derivative CVI (Equation 24).



Unfortunately, under these acetolysis conditions the C-5 benzyl ether group was cleaved. This was evidenced by the nmr spectrum of the major product which indicated that no aromatic protons were present in the molecule. Cleavage of the benzyl ether moiety was not desirable as this would allow the branched-chain sugar to revert to the unwanted but more stable pyranose configuration. That the benzyl ether was unstable to these acetolysis conditions was not entirely unexpected in view of the findings of Allerton and Fletcher (151) that

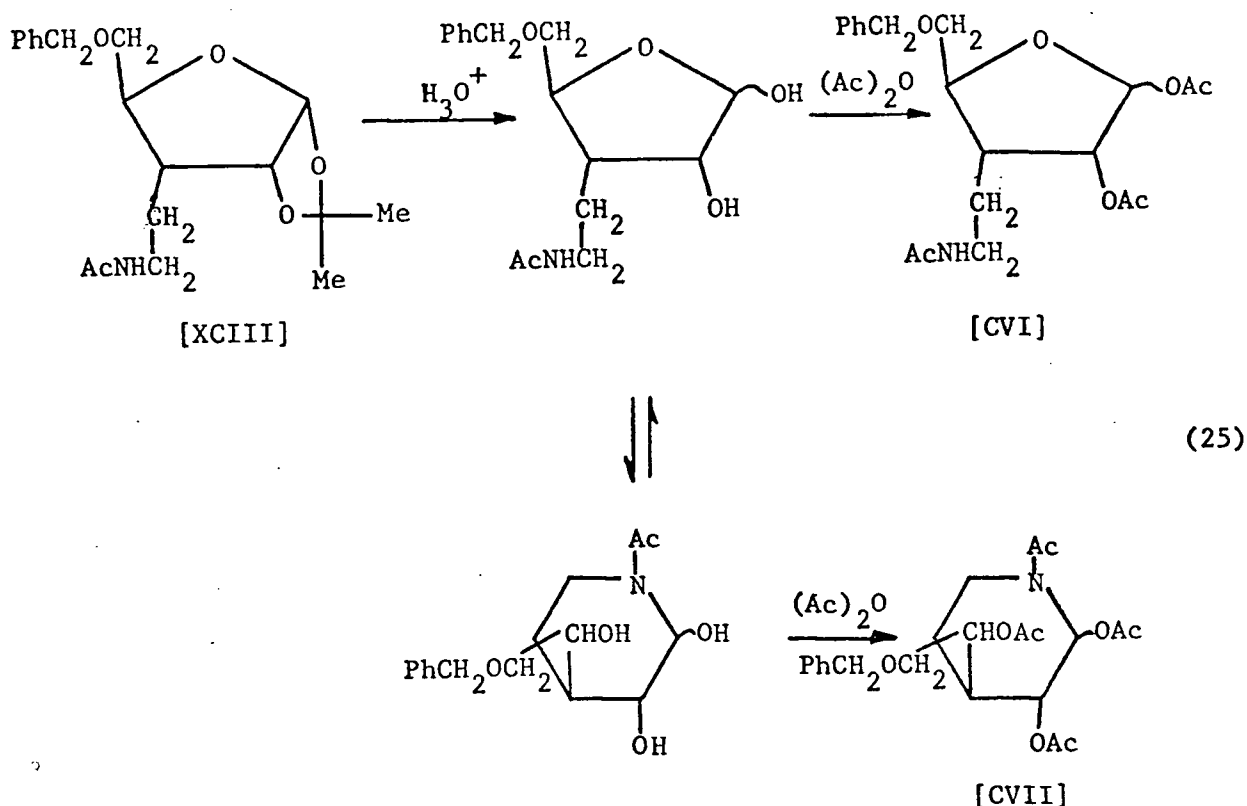
benzyl ethers are readily removed in acetolysis media. Acetolysis trials, on the model compound LXXVII, in which the percentage of sulfuric acid in the reaction medium was varied, revealed that the C-5 primary benzyl group of LXXVII was acetolyzed at about the same rate as the 1,2-isopropylidene ketal.



[LXXVII]

In view of this it was decided to prepare CVI by a two-step procedure. First XCIII was reacted with 90% trifluoroacetic acid to hydrolyze the isopropylidene ketal (152), and then the reaction product was acetylated with acetic anhydride and pyridine (Equation 25). This procedure resulted in the formation of a complex product mixture. A major component of this mixture was tentatively identified as the nitrogen heterocycle CVII. This conclusion was based on the observations that the nmr spectrum of this compound contained signals corresponding to one benzyl and four acetate groups and that the ir spectrum showed no NH absorption, and a low wavelength carbonyl absorption (1640 cm^{-1}) typical of 3° amides. The nmr spectrum of the desired 1,2-O-acetyl product CVI would be expected to show the presence of only three acetyl groups.

The formation of the nitrogen heterocycle CVIII was rationalized by postulating that after hydrolysis an equilibrium was set up between



the oxygen and the nitrogen heterocyclic compounds; subsequent acetylation of this mixture lead to compounds having both nitrogen and oxygen as the ring heteroatom (Equation 25). The rearrangement of C-4 and C-5 amino and amido monosaccharides to nitrogen heterocycles has been well studied (153). Normally where there is a competition for ring formation between a hydroxyl group and an acetamido group the oxygen heterocycle is formed predominantly even if it has the

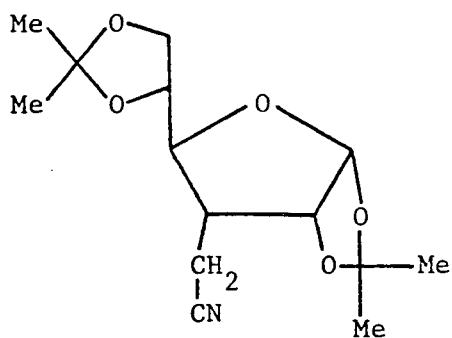
thermodynamically less favoured five membered ring structure (153). Thus it had been anticipated that CVII would not be a major constituent of the product mixture. Since this was not so, further attempts to prepare CVI were abandoned.

5.2 Conversion of 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene-
 α -D-allofuranose [LXXXVI] into 1,2-di-O-acetyl-5,6-di-O-
benzoyl-3-C-cyanomethyl-3-deoxy- β -D-allofuranose [CX] and 1,2-di-
O-acetyl-5-O-benzoyl-3-C-cyanomethyl-3-deoxy- β -D-ribofuranose [CXIII]

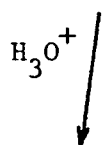
Since the preparation of amino branched-chain sugar derivatives suitable for nucleoside synthesis had been unsuccessful, it was decided to prepare an appropriate derivative from the cyanomethyl branched-chain sugar LXXXVI. To prepare the hexose derivative required the following steps:

- (1) selective hydrolysis of the 5,6-isopropylidene group;
- (2) blocking of the free 5,6-hydroxyl groups as the benzoate esters;
- (3) hydrolysis of the 1,2-isopropylidene group;
- (4) acetylation of the 1,2-hydroxyl groups.

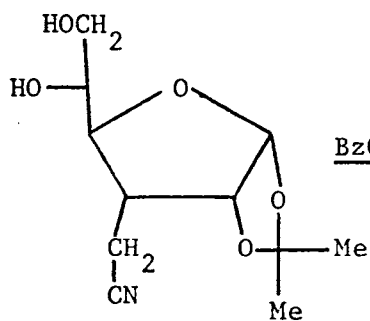
To prepare the pentose derivative required a modification of this procedure in that after step (1) a sodium periodate oxidative cleavage followed by sodium borohydride reduction was carried out to remove the C-6 hydroxymethyl group. The resultant pentose compound was then benzoylated and subjected to steps (3) and (4). The reaction scheme representing these steps is shown in equation 26.



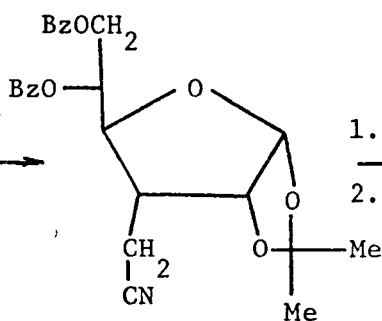
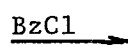
[LXXXVI]



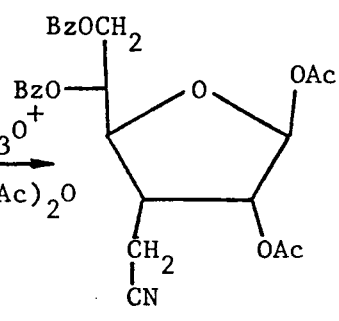
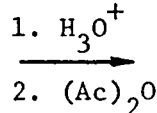
(26)



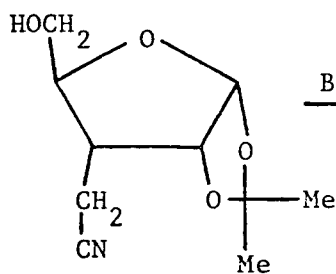
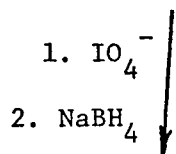
[CVIII]



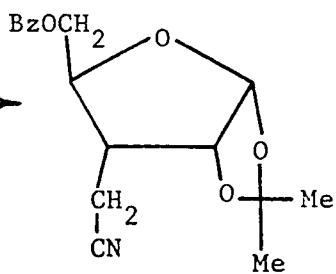
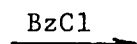
[CIX]



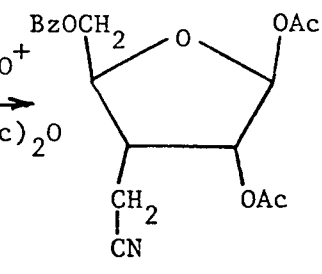
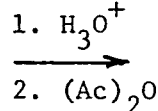
[CX]



[CXI]



[CXII]



[CXIII]

The selective hydrolysis of a 5,6 isopropylidene ketal and the removal of a C-6 hydroxymethyl group by oxidative cleavage, followed by reduction, were discussed previously in the preparation of compound XCVI and will not be considered in detail again. Suffice it to say that treatment of LXXXVI with an aqueous methanol solution containing a small amount of sulfuric acid selectively hydrolyzed the 5,6-isopropylidene group of LXXXVI to afford CVIII as a syrup in nearly quantitative yield. Compound CXI was obtained as a crystalline solid in 90% yield by cleavage of the 5,6-hydroxyl groups of CVIII with sodium periodate followed by reduction of the 5-aldehyde group with sodium borohydride (21).

The hydroxyl groups of compounds CVIII and CXI were benzoylated using the method of Molau (154). In this procedure the compound to be benzoylated is dissolved in anhydrous benzene to which is added only a slight excess of the amount of benzoyl chloride necessary for esterification and two equivalents of pyridine. Work up consists of filtering the reaction mixture through a short column of grade II alumina (a ratio of about 5:1 alumina to compound was used), evaporation of the filtrate and removal of traces of pyridine by azeotropeing with toluene. Applying this procedure to compound CVIII afforded a 90% yield of crystalline benzoate CIX and a 93% yield of crystalline benzoate CXII from CXI. The chief advantage of this procedure lies in the fact that no opportunity for benzoic anhydride contamination of the product arises. Standard benzylation procedures in carbohydrate chemistry sometimes result in the contamination of the benzoylated product with benzoic anhydride produced during the addition of water during work up (155).

Attempted acetolysis (150) of the 1,2-isopropylidene ketal of CIX using a mixture of acetic acid, acetic anhydride and sulfuric acid for twenty four hours at room temperature led to a complex mixture of products. The major component of this mixture (about 30% based on starting material) was isolated by column chromatography on silica. Elemental analysis of this material showed that it contained no nitrogen, indicating that the nitrile group on the branched-chain was apparently unstable to these conditions.

It was therefore decided to proceed as before and use a two-step procedure; first hydrolysis of the isopropylidene ketal with trifluoroacetic acid followed by acetylation with acetic anhydride in pyridine. Several exploratory runs using different acid concentrations were performed in order that the optimal conditions for hydrolysis might be found. For compound CIX reaction with 80% aqueous trifluoroacetic acid for 45 minutes at room temperature was found to give the best yield; for compound CXII it was found to be more advantageous to use a greater percentage of acid (90%) and run the hydrolysis for a shorter time (22 minutes).

Acetylation, using acetic anhydride and pyridine, of the hydrolysis product from CIX gave after chromatography on silica gel 1,2-di-O-acetyl-5,6-di-O-benzoyl-3-C-cyanomethyl-3-deoxy- β -D-allofuranose [CX] as a crystalline solid in 69% yield.

The anomeric (H-1) hydrogen of this compound appeared in the nmr spectrum as a singlet at 3.77 τ . As there was no measurable coupling between H-1 and H-2 it was concluded that a trans relationship existed between these two protons and that therefore CX had a β anomeric

configuration. Because of the conformational mobility of furanose systems (125a) it is not generally possible to definitely assign anomeric configurations on the basis of H-1, H-2 coupling constants alone. However, in instances where there is no appreciable coupling between two neighbouring protons it can be fairly safely assumed that a trans relationship exists between them (156).

Acetylation of the hydrolysis product from CXII, using the same conditions as above, gave after column chromatography on silica gel two components.

The major component isolated as a crystalline solid in 69% yield proved to be the expected acetylated cyanomethyl branched-chain sugar 1,2-di-O-acetyl-5-O-benzoyl-3-C-cyanomethyl-3-deoxy- β -D-ribofuranose [CXIII]. The β -configuration was tentatively assigned as before from the nmr spectrum (H-1 appeared as a singlet at 3.80 τ).

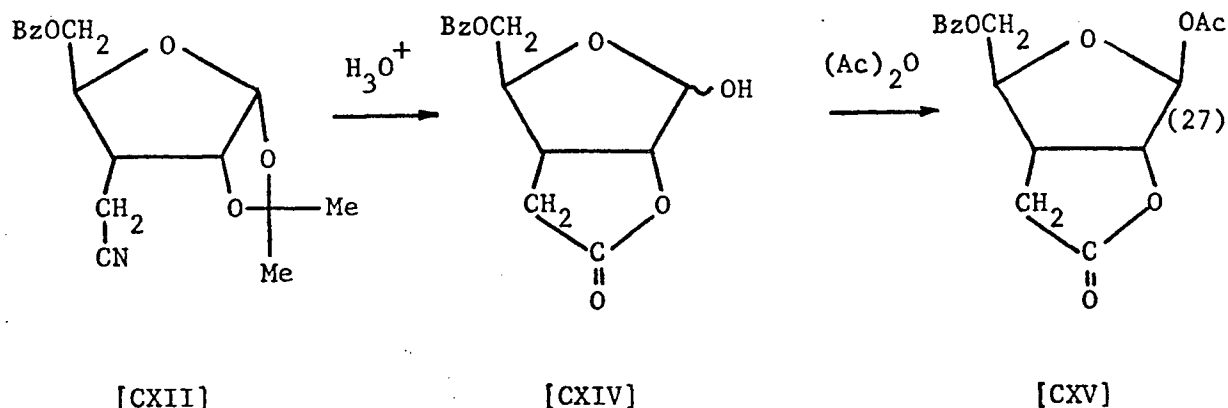
The minor product, isolated in about 5% yield as a crystalline solid, gave the following data upon examination:

(1) the nmr spectrum indicated that only one benzoate and one acetate ester were present;

(2) the infrared spectrum showed no nitrile absorption and three carbonyl absorptions.

From the above it was concluded that this compound was the lactone 1-O-acetyl-5-O-benzoyl-3-C-carboxymethyl-2,3- γ -lactone-3-deoxy- β -D-ribofuranose [CXV]. The elemental analysis of this compound was found to be in agreement with the proposed structure. The β -anomeric configuration was again assigned on the basis of the nmr spectrum (H-1 was observed as a singlet at 3.6 τ).

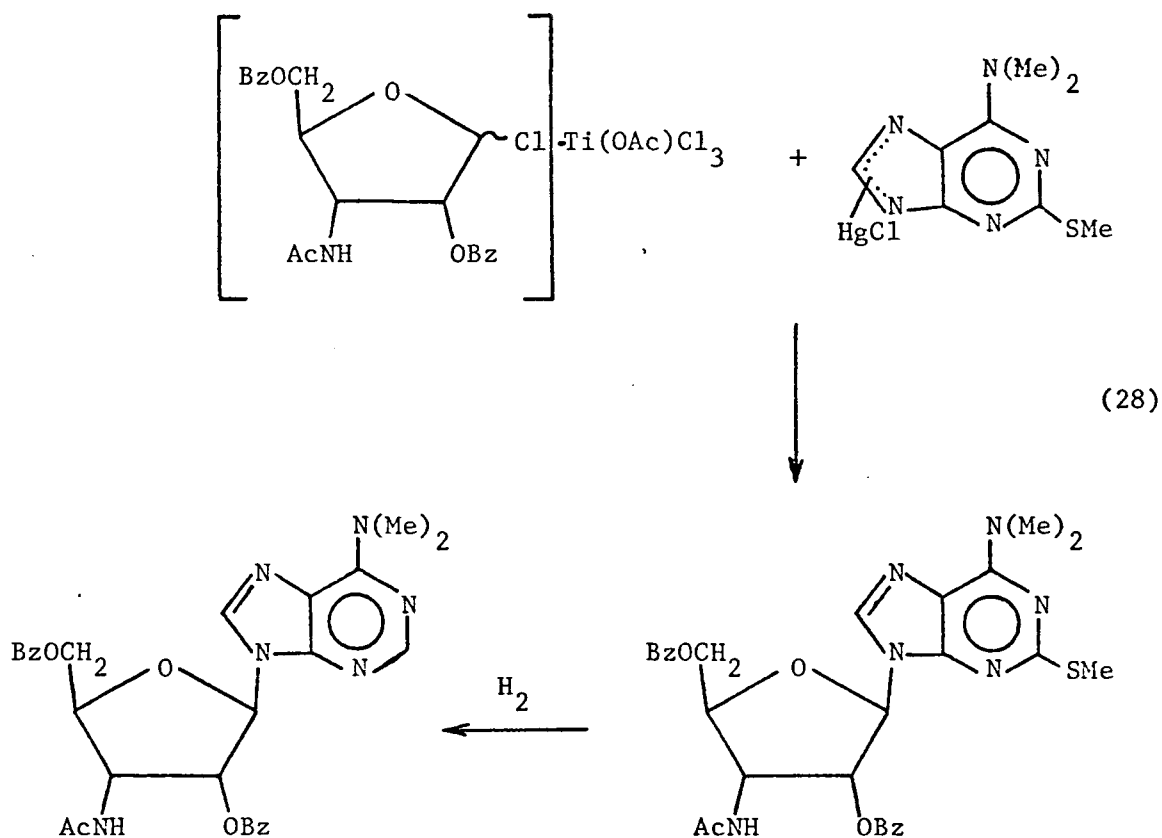
It is probable that the above side product arose as is illustrated in equation 27. During the trifluoroacetic acid hydrolysis of compound CXII the nitrile group in the branched-chain underwent partial hydrolysis to the carboxylic acid which lactonized to afford compound CXIV. Acetylation of this material would then lead to CXV.



5.3 6-Chloro-9-(2'-O-acetyl-5',6'-di-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-allofuranosyl)-purine [CXVI] and 6-chloro-9-(2'-O-acetyl-5'-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXVIII]

As it was desired to obtain 6-N,N-dimethylaminopurine nucleoside derivatives of the previously described cyanomethyl branched-chain sugars, the methods used for the preparation of dimethylaminopurine nucleosides were examined. B.R. Baker and coworkers (157), in their classic synthesis of puromycin, formed the carbon nitrogen glycosidic bond by condensation of the titanium-amino sugar complex with

chloromercuri-2-methylmercapto-6-dimethylaminopurine. Raney nickel desulfurization of the purine then gave the 6-dimethylaminopurine nucleoside (Equation 28). While a 6-dimethylaminopurine nucleoside was obtained by this method several steps were required and the yield in the desulfurization was only fair.



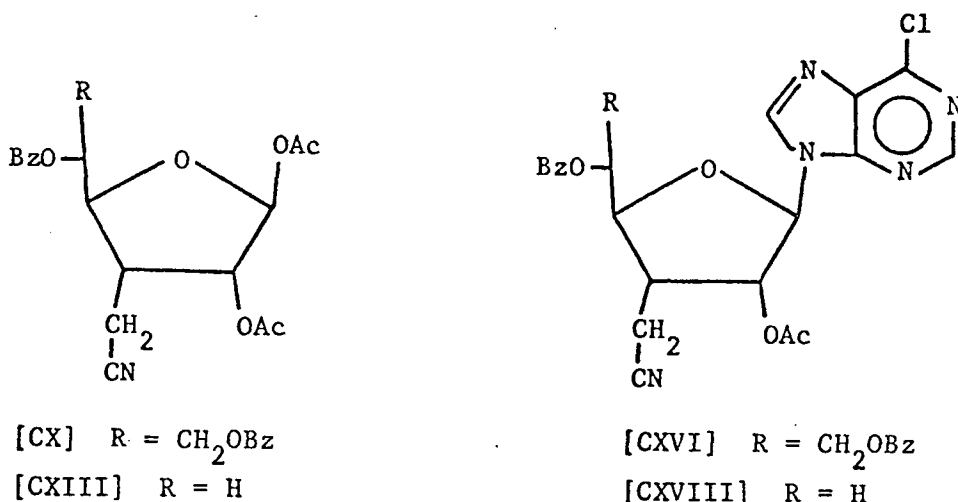
An alternate route to these nucleosides has been devised by R.K. Robins (158). Here a 6-mercaptapurine nucleoside (159) was first prepared and then this compound was reacted with dry chlorine gas to afford the 6-chloropurine nucleoside. This chloropurine nucleoside was then converted to the 6-dimethylaminopurine nucleoside with aqueous dimethylamine. The chief disadvantage of this procedure is the number of manipulations of the base required to obtain the

6-dimethylaminopurine compound.

This disadvantage has been overcome by the relatively recently developed fusion procedure (106). Using this method the 6-chloropurine nucleosides were prepared directly by fusion of a C-1 acetylated sugar with 6-chloropurine. The 6-dimethylamino functionality was then introduced as above, by reacting the 6-chloropurine nucleoside with aqueous dimethylamine. In view of its simplicity, and the fact that the nucleosides prepared are free of mercury contamination, this procedure was selected for the preparation of dimethylaminopurine nucleosides from the cyanomethyl branched-chain sugars.

Accordingly CX was fused with 6-chloropurine at 155-160° under reduced pressure for 45 minutes. Chromatography on silica gel afforded as the only nucleoside product 6-chloro-9-(2'-O-acetyl-5',6'-di-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-allofuranosyl)-purine [CXVI] in 69% yield. Similarly fusion of CXIII with 6-chloropurine under the same conditions gave 6-chloro-9-(2'-O-acetyl-5'-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXVIII] in 66% yield.

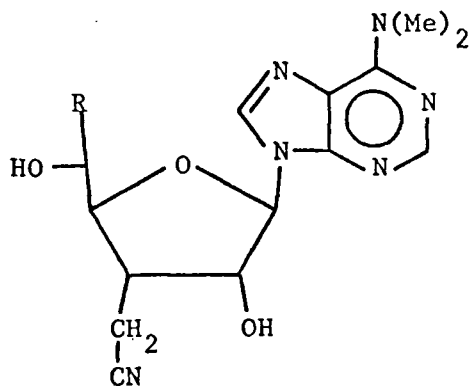
The β-anomeric configuration was tentatively assigned to these nucleosides on the basis of their small H-1', H-2' coupling constants (CXVI $J_{1',2'} = 2$ Hz; CXVIII $J_{1',2'} = 1$ Hz). This assignment was later confirmed by the circular dichroism (cd) spectra of the unblocked nucleosides. A thorough examination of all the reaction products did not reveal the presence of any other nucleoside indicating as expected that there was no appreciable formation of the α-anomer.



5.4 6-N,N-Dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy-β-D-allofuranosyl)-purine [CXXI] and 6-N,N-dimethylamino-9-(3'-C-N,N-dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXXII]

The second step in the preparation of the 6-dimethylaminopurine nucleosides was the reaction of the above 6-chloropurine blocked nucleosides with aqueous dimethylamine. This procedure was intended to remove the ester hydroxyl protecting groups and replace the 6-chloro group by a dimethylamino functionality thereby resulting in the formation of the cyanomethyl branched-chain nucleosides CXIX and CXX. When the chloropurine nucleoside CXVI was reacted for four hours with an aqueous methanol solution of dimethylamine and the products were separated by chromatography on silica gel a single crystalline nucleoside was isolated in 78% yield.

The nmr spectrum in dimethyl sulfoxide- d_6 of this nucleoside is reproduced in Figure 2. Some features of this spectrum were readily interpreted: the two low field singlets at 1.69 and 1.88 τ were assigned to the H-2 and H-8 protons of the heterocyclic base; the doublet at 4.08 τ is the H-1' signal; the two doublets at 4.28 and 4.64 τ which disappeared on addition of deuterium oxide were assigned to the secondary hydroxyl groups of C-2' and C-5', not necessarily respectively; a third hydroxyl group is superimposed on the C-2' signal at 5.48 τ ; the large singlet at 6.74 τ was assigned to the six protons of the N,N-dimethyl group of the heterocyclic base, a small water peak was superimposed on this signal. However, the two singlets at 7.02 τ and 7.20 τ which integrate for three protons each were not consistent with the expected nmr spectrum of the cyanomethyl branched-chain sugar nucleoside CXIX.



[CXIX] R = CH_2OH

[CXX] R = H

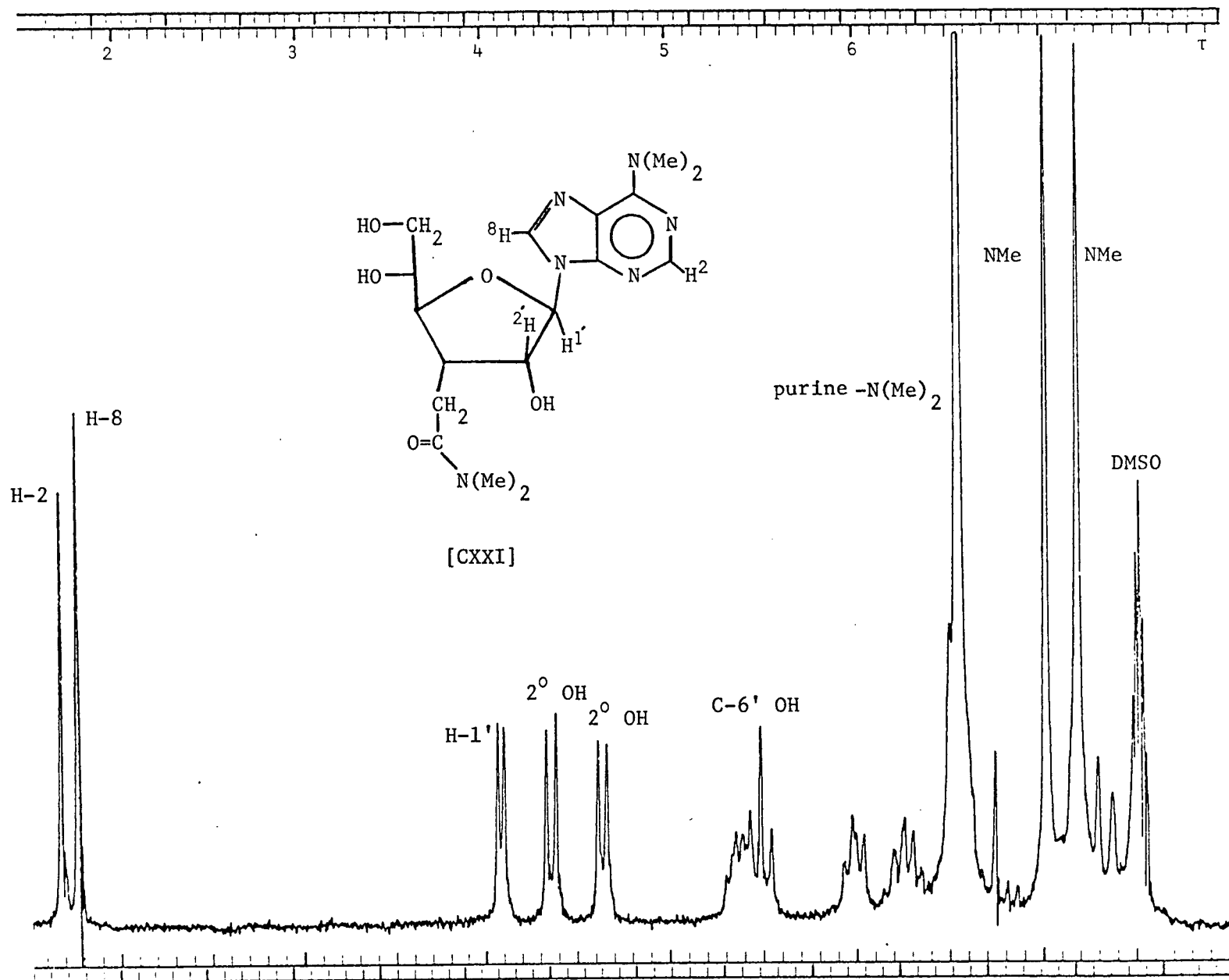


Figure 2. Proton magnetic resonance spectrum at 100 MHz in dimethyl sulfoxide- d_6 of 6-N,N-dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy- β -D-allofuranosyl)-purine [CXXI].

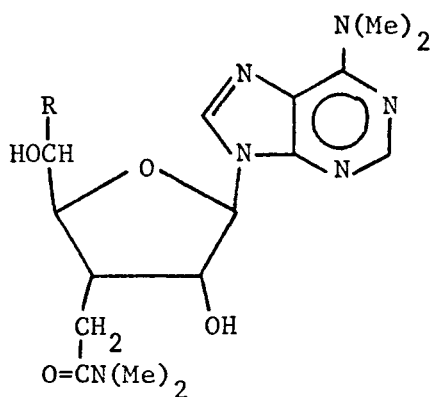
A point to note here was the method of assigning the hydroxyl signals in this spectrum. In dimethyl sulfoxide it is possible to differentiate between primary, secondary and tertiary hydroxyl groups on the basis of their couplings with adjacent protons. Primary hydroxyl groups generally appear as a triplet because of coupling to the two adjacently methylene protons; secondary hydroxyl groups appear as a doublet, and tertiary hydroxyl groups appear as a singlet. This simple method of differentiating hydroxyl groups was frequently used in this work.

Further investigation of the above nucleoside provided the following information: the ultraviolet absorption ($\lambda_{\text{max}} = 275 \text{ nm}$) indicated that the position of attachment of the base to the sugar was at N-9 (105); the circular dichroism (cd) spectrum showed a negative Cotton effect confirming that this nucleoside had the expected β -anomeric configuration (104); the ir spectrum contained no nitrile absorption but did show an unexpected carbonyl absorption (1610 cm^{-1}); the nmr spectrum in deuteriochloroform showed the molecule contained about 26 hydrogens; the mass spectrum gave a value of $m/e = 394$ for the highest non-isotopic fragment, and no fragment at $m/e = 348$, which would correspond to the molecular ion of CXIXa was found. On the basis of the above data it was concluded that this compound was the dimethyl-carbamoylmethyl branched-chain sugar nucleoside 6-N,N-dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy- β -D-allofuranosyl)-purine [CXXI].

That this structure for CXXI was in agreement with the observed data is readily apparent. The two singlets at 6.78 and 6.86 τ were assigned to the N,N-dimethyl moiety in the branched-chain; the carbonyl absorption

at 1610 cm^{-1} is typical of tertiary amides and the mass spectral m/e value of 394 was consistent with the molecular formula $\text{C}_{17}\text{H}_{26}\text{N}_6\text{O}_5$ obtained from this structure.

Reaction of the pentose chloropurine nucleoside CXVIII with the same methanol aqueous dimethylamine mixture afforded the analogous pentose nucleoside 6-N,N-dimethylamino-9-(3'-C-N,N-dimethylcarbamoyl methyl-3'-deoxy- β -D-ribofuranosyl)-purine as a syrup in 72% yield after chromatography on silica gel. Although CXXII appeared homogeneous



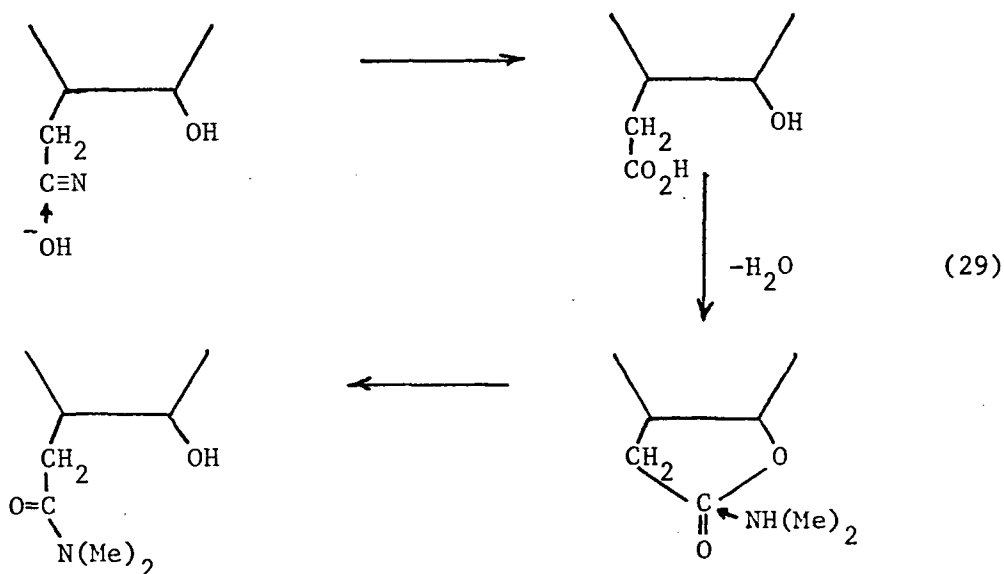
[CXXI] R = CH_2OH

[CXXII] R = H

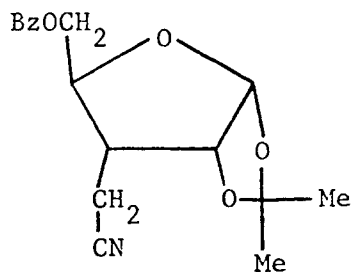
by nmr, tlc and paper chromatography, it could not be obtained crystalline, nor could a satisfactory elemental analysis be obtained. Consequently this compound was characterized as its 2',5'-di-O-acetyl derivative. To further verify the structure of nucleoside CXXII, the previously described sodium periodate, oxidative cleavage sodium borohydride reduction (59) was used to remove the C-6'-hydroxymethyl group from

nucleoside CXXI. This procedure afforded a homogeneous syrup in 69% yield identical by ir and nmr with the product obtained from the reaction of aqueous dimethylamine with chloropurine nucleoside CXVIII.

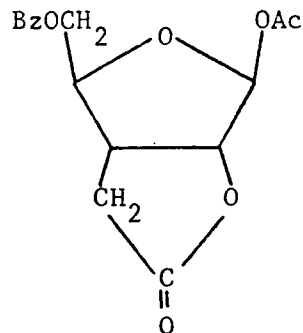
To account for the formation of the above nucleosides it was initially postulated that in the basic aqueous dimethylamine medium the nitrile group on the branched-chain underwent hydrolysis to give the carboxylic acid, followed by lactonization and addition of dimethylamine to the lactone (Equation 29). The hydrolysis of nitriles



to carboxylic acids is known to be catalyzed by both acids and bases; however, as a rule hydrolysis proceeds faster in acidic media (160). It should be recalled here that in the trifluoroacetic acid hydrolysis of the 1,2-isopropylidene ketal of CXII, that after acetylation a small amount of lactone CXV was recovered.



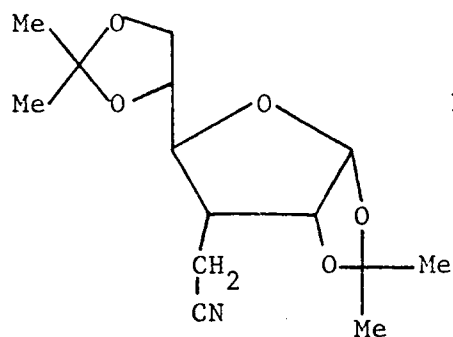
[CXII]



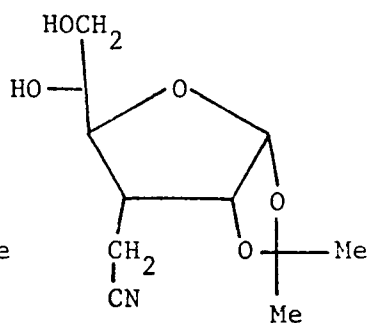
[CXV]

In order to examine the reactivity of the nitrile group in these branched-chain sugars towards aqueous dimethylamine, compounds LXXXVI CVIII and XCIV were subjected to the same hydrolysis conditions as the above chloro nucleosides. In each instance there was no detectable hydrolysis (even after twenty-four hours) and the starting materials were recovered unchanged. Furthermore, it was found that the nitrile group of the chloro-nucleoside CXXIII (161) under the same conditions was not hydrolyzed and only the branched-chain cyanomethyl nucleoside CXXIV was obtained. Obviously, therefore, the hydrolysis of the nitrile moiety in branched-chain nucleosides CXXI and CXXII was unusually facile.

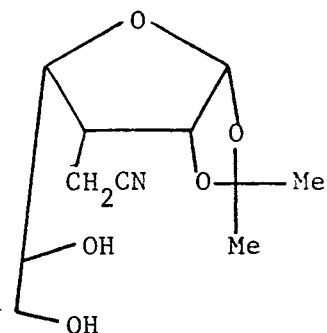
Although the alkaline hydrolysis of nitriles having adjacent hydroxyl groups has not been extensively studied some example which could have a bearing on these results were found in the literature. For example, the addition of hydrogen cyanide (usually via aqueous sodium cyanide) to reducing sugars (Kiliani syntheses (162), equation 30) is a classical method for extending sugar chains. After addition of the



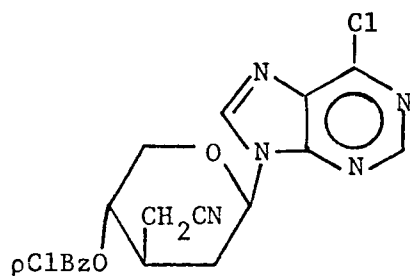
[LXXXVI]



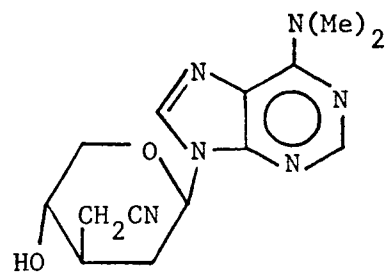
[CVIII]



[XCIV]

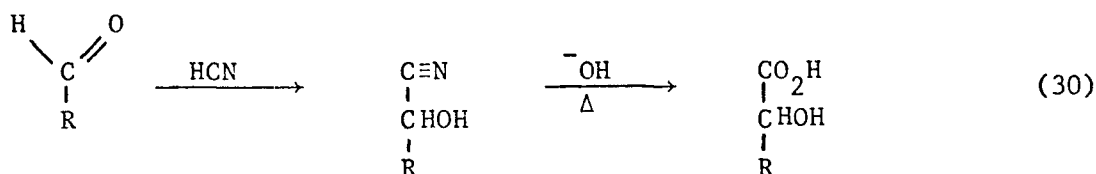


[CXXIII]

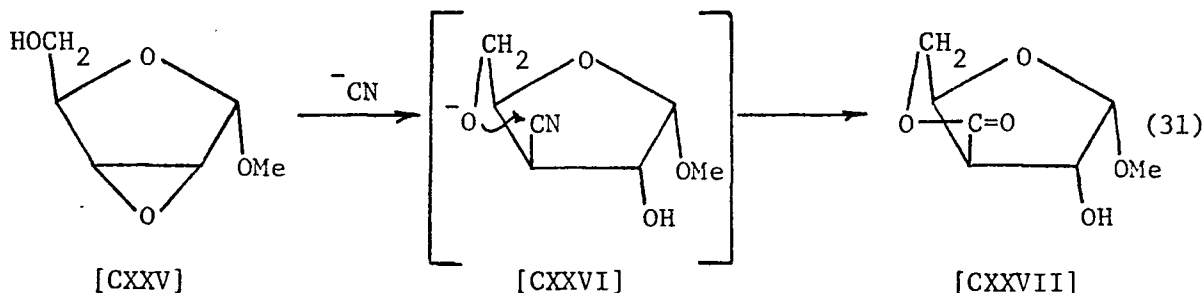


[CXXIV]

hydrogen cyanide the alkaline solution of nitrile was heated to 60-100° to effect hydrolysis. It has been found, however, that for some sugars (e.g. 2-deoxy-ribose and ribose (163)) hydrolysis of the nitrile proceeded spontaneously under very mild conditions (room temperature in a carbonate buffered solution).

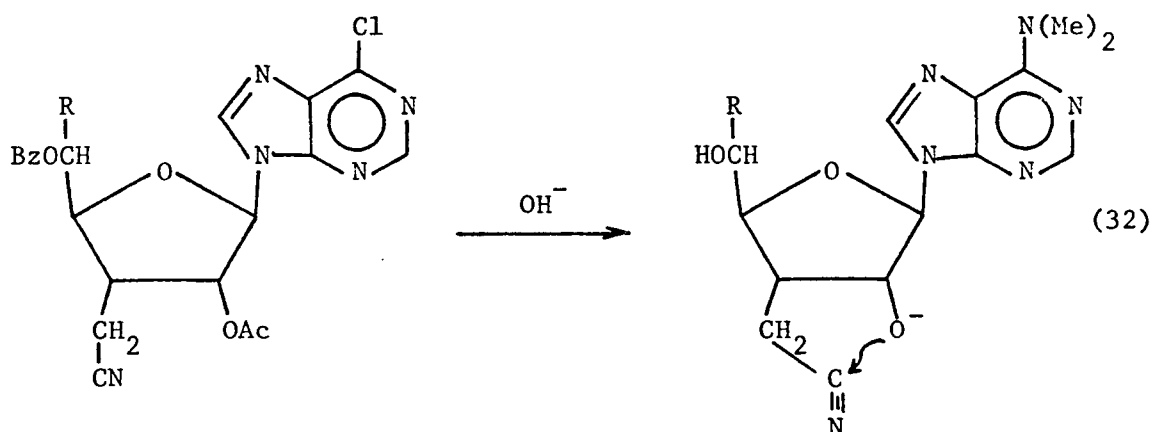


Another pertinent instance of nitrile hydrolysis was found in the addition of cyanide to epoxide CXXV (164). When this epoxide was heated to 100° in aqueous potassium cyanide solution no cyano addition products (e.g. CXXVI) were isolated, but rather only the lactone CXXVII. In rationalizing this result the authors postulated that the intermediate nitrile addition product CXXVI underwent intramolecular hydrolysis by attack of the C-5 alkoxide anion on the C-3 cyano group (Equation 31).



If it is assumed that intramolecular hydroxyl group participation can aid in the hydrolysis of a nitrile group it is possible to rationalize the facile hydrolysis of the nitrile group in nucleosides CXVI and CXVIII as the C-2 hydroxyl ion formed after acetate cleavage, is in a position to participate in hydrolysis of the nitrile (Equation 32). However, this theory does not account for the

resistance of the nitrile group compounds XCIV and CXXIV to hydrolysis, as it would be expected that intramolecular hydroxyl group participation leading to hydrolysis of the nitrile moiety would be possible with these compounds also. Apparently there are other factors involved here and the full explanation awaits further investigation.



[CXVI] R = CH₂OBz

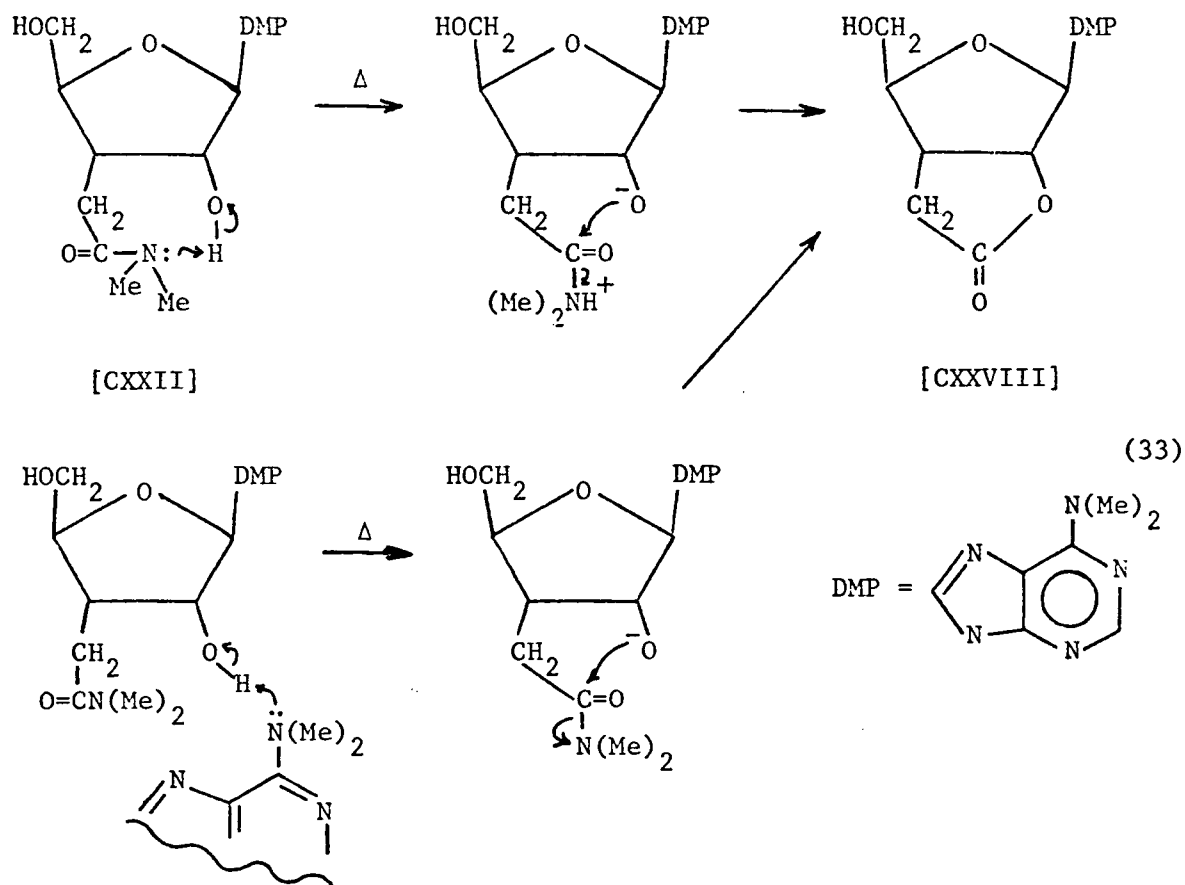
[CXVIII] R = H

5.5 6-N,N-Dimethylamino-9-(3'-C-carboxymethyl-2',3'-γ-lactone-3-deoxy-β-D-ribofuranosyl)-purine [CXXVIII]

In an attempted purification of the branched-chain nucleoside CXXII it was sublimed at 200-205° and 0.1 mm. This procedure afforded a crystalline nucleoside in 73% yield. It was immediately obvious, however, that during sublimation nucleoside CXXII had undergone decomposition as the ir spectrum of the sublimed nucleoside had a

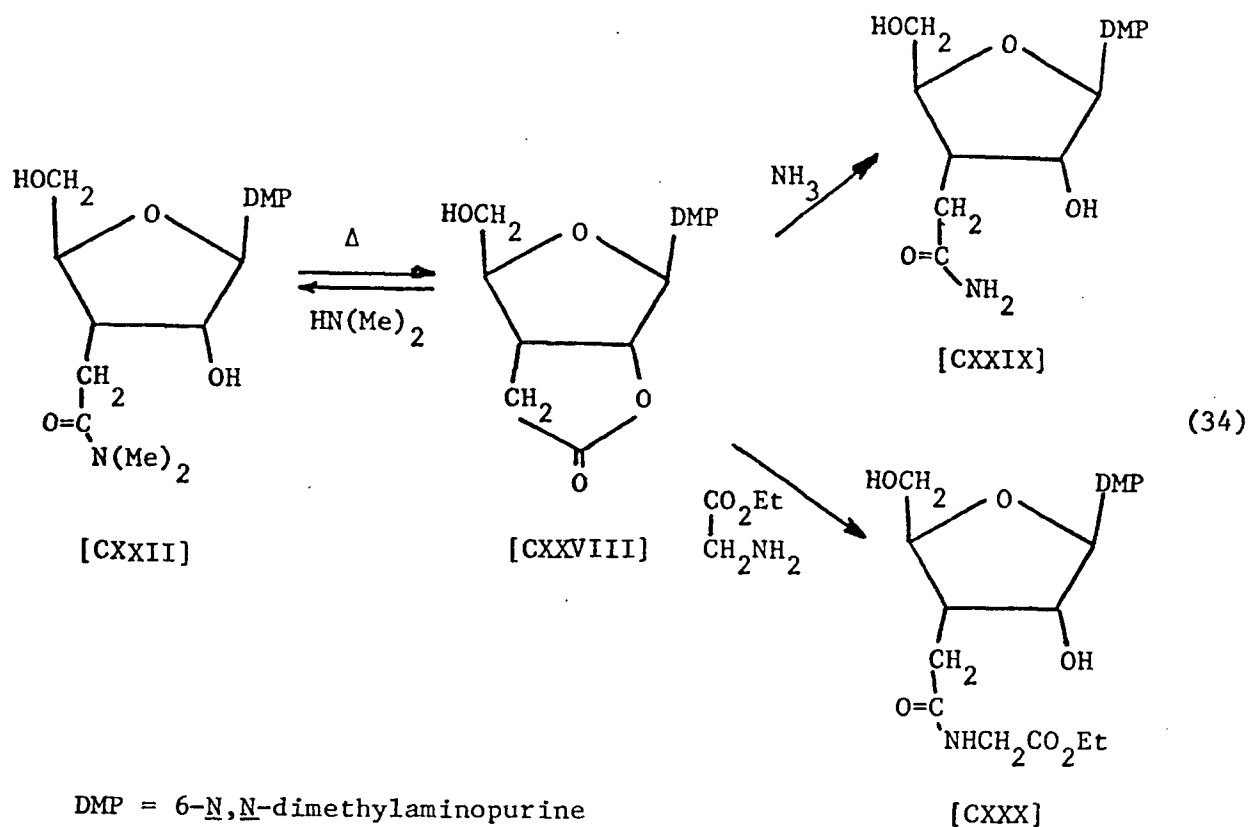
distinctly different carbonyl absorption (1770 vs. 1610 cm^{-1} for CXXII) and the nmr spectrum in $\text{DMSO-}d_6$ indicated that there was now only a single (primary) hydroxyl group present and that the molecule no longer contained the N,N-dimethyl group on the branched-chain. That nucleoside CXXII had undergone deamination was further substantiated by the finding that the highest nonisotopic fragment in the mass spectrum occurred at m/e 319. This implied that the new nucleoside had a molecular weight 45 units less than CXXII corresponding to the loss of dimethylamine from CXXII. On the basis of the above information it was determined that this new compound was the novel lactone nucleoside 6-N,N-dimethylamino-9-(3'-C-carboxymethyl-2',3'- γ -lactone-3-deoxy- β -D-ribofuranosyl)-purine [CXXVIII].

The deamination of CXXII under these conditions was not surprising, as amides having a neighboring hydroxyl group which can participate in the displacement of an amine from an amide have been shown to be easily deaminated (165) in acidic, neutral, or basic media. Presumably, the C-2' hydroxyl group of branched-chain tertiary amide nucleoside CXXVIII (Equation 33) assists in displacement of dimethylamine to give lactone CXXVIII. It is also possible that this reaction was further facilitated by intermolecular catalysis by the heterocyclic base of the nucleoside.



5.6 Conversion of 6-N,N-dimethylamino-9-(3'-C-carboxymethyl-2',3'- γ -lactone-3-deoxy- β -D-ribofuranosyl)-purine [CXXVIII] to 6-N,N-dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy- β -D-ribofuranosyl)-purine [CXXII], and 6-N,N-dimethylamino-9-(3'-C-carbamoylmethyl-3'-deoxy- β -D-ribofuranosyl)-purine [CXXIX] and 6-N,N-dimethylamino-9-(3'-C-carbamoylmethyl-N-glycine ethyl ester-3'-deoxy- β -D-ribofuranosyl)-purine [CXXX]

The lactone nucleoside CXXVIII proved to be a very useful compound for preparing amido branched-chain sugar nucleosides. The reaction of this nucleoside with a variety of amines is illustrated in equation 34.



Reaction of CXXVIII with dimethylamine for four hours at zero degrees centigrade afforded the N,N-dimethylcarbamoylmethyl branched-chain nucleoside CXXII as a syrup in quantitative yield. This compound was identical by nmr and ir with the compound prepared by reaction of dimethylamine with chloropurine nucleoside CXVIII. Using ammonia (166) in place of dimethylamine afforded the carbamoylmethyl nucleoside CXXIX as a crystalline solid in 95% yield.

As the above condensation of lactone nucleoside CXXVIII with ammonia

and dimethylamine were successful it was decided to undertake the preparation of a peptide nucleoside using this compound. Lately interest has increased in nucleosides containing non-hydroxyl linked peptides. This has come about partly because commercially important antibiotics such as the polyoxins (167), gougerotin (141), blasticidin S (168), and puromycin (2a) have been shown to be nucleoside peptide derivatives with the aminoacyl moiety attached through an amino group of the sugar, and partly because amino acids which are not removed by the usual deproteinization procedures have been found in highly purified samples of ribonucleic acid (169) and deoxy ribonucleic acid (170). The group of investigators led by R.K. Robins at the ICN Nucleic Acid Research Institute have been at the forefront in the preparation of these nucleoside peptides. These workers have made use of the active ester (171) and N,N'-dicyclohexylcarbodiimide (172) methods of peptide synthesis to prepare various 5'-N-aminoacyl-5'-amino-ribofuranosyl purine nucleosides (173).

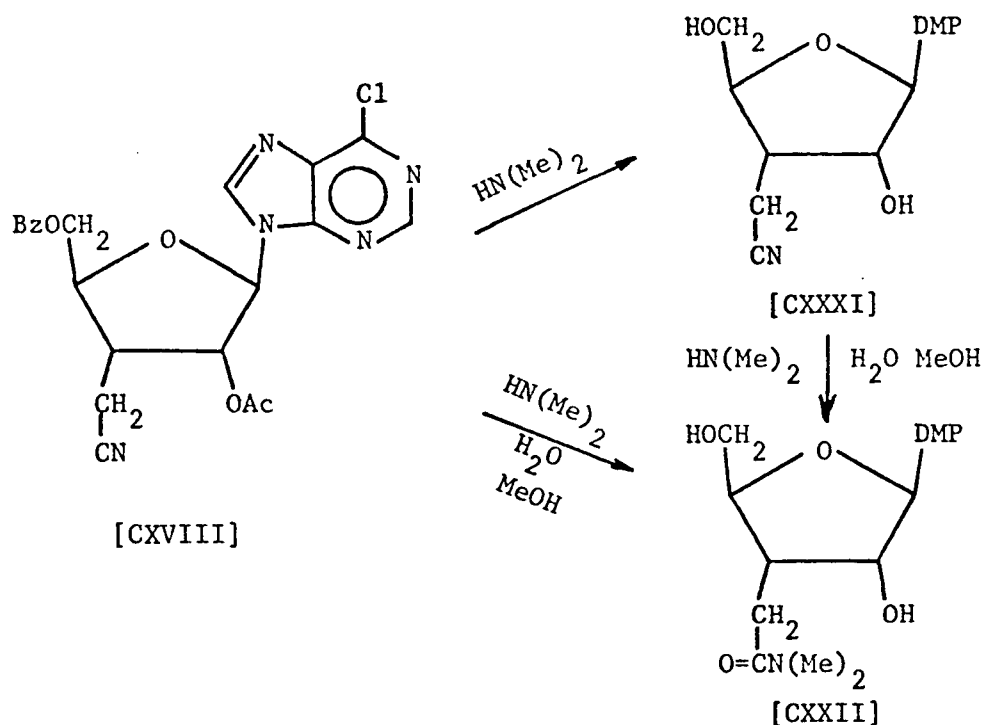
The method chosen here to prepare a peptide nucleoside, analogous with the above reactions of the lactone nucleoside with amines, was to simply condense glycine ethyl ester (174) with lactone nucleoside CXXVIII (Equation 34). Thus a mixture of glycine ethyl ester and nucleoside CXXVIII in dimethylformamide were stirred at room temperature for 30 hours. After removal of the solvent and chromatography on silica gel the peptide nucleoside 6-N,N-dimethylamino-9-(3'-C-carbamoylmethyl-N-glycine ethyl ester-3'-deoxy- β -D-ribofuranosyl)-purine [CXXX] was isolated as a crystalline solid in 72% yield. That the condensation had taken place as expected was easily verified by the

ir spectrum which showed the characteristic amide carbonyl absorption at 1650 cm^{-1} as well as an ester carbonyl absorption at 1780 cm^{-1} .

5.7 6-N,N-Dimethylamino-9-(3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-
purine [CXXXI]

In order to prepare the cyanomethyl branched-chain nucleoside CXXXI it was necessary to prevent the previously discussed hydrolysis of the nitrile moiety in the branched-chain which occurred during reaction of the blocked chloropurine nucleosides with aqueous dimethylamine. Although the fine points of the mechanism for the above hydrolysis had not been definitely elucidated, by simply comparing the reactants and products it was apparent that in anhydrous dimethylamine conversion of the nitrile functionality to the tertiary amide was not possible.

Consequently the chloropurine branched-chain sugar nucleoside CXVIII was dissolved in anhydrous dimethylamine and allowed to stand at -10° for twenty days. Upon removal of the solvent and trituration of the reaction mixture with ether, a portion of the desired cyanomethyl branched-chain sugar nucleoside CXXXI crystallized out. Chromatography of the remaining material gave a further portion of nucleoside CXXXI (total yield 78%). That this compound was the desired nucleoside 6-N,N-dimethylamino-9-(3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXXXI] was confirmed by spectral data. The ir spectrum contained hydroxyl and nitrile absorptions at $3200\text{--}3400\text{ cm}^{-1}$ and 2230 cm^{-1} , respectively, and no carbonyl absorptions, indicating that no hydrolysis of the nitrile had taken place and that the ester hydroxyl protecting groups had been completely removed. The nmr



spectrum and elemental composition were also consistent with the above structure.

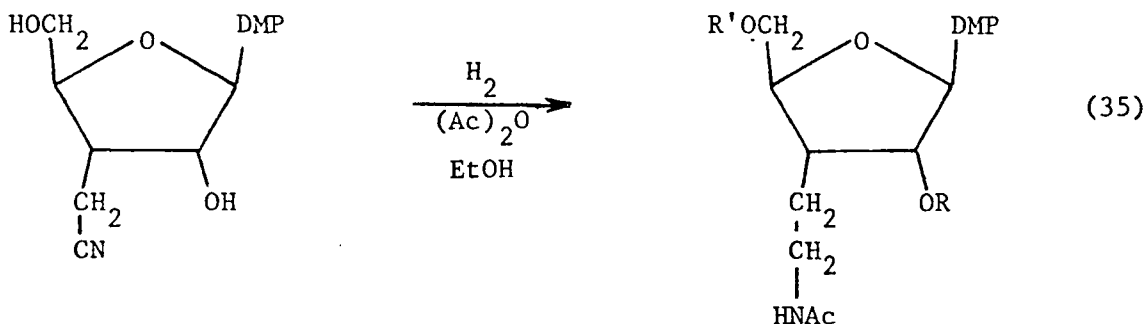
It is interesting to note that when this compound was dissolved in an aqueous dimethylamine-methanol mixture hydrolysis to the amide branched-chain sugar nucleoside CXXII took place but proceeded at a much slower rate (12 hr for complete hydrolysis) than the hydrolysis of chloropurine nucleoside CXVIII to CXXII.

5.8 6-N,N-Dimethylamino-9-(3'-C-(2"-acetamidoethyl)-3'-deoxy-β-D-ribofuranosyl)-purine [CXXXIV]

The preparation of an aminoethyl branched-chain sugar nucleoside was initially attempted by reduction of the amido branched-chain nucleoside CXXIX with lithium aluminum hydride in pyridine (175). Pyridine was chosen as the reaction solvent because of the negligible

solubility of nucleoside CXXI in ethers. Unfortunately using these conditions no appreciable reduction took place and the starting material was recovered unchanged.

An alternate approach to the desired aminoethyl nucleoside through reduction of the nitrile moiety of nucleoside CXXXI was then investigated. Hydrogenation at room temperature and 60 psi of this compound over platinum oxide in a 1:1 mixture of acetic anhydride and ethanol gave after four hours two products (R_f 0.18 and 0.10 on silica gel with dichloromethane:ethyl acetate:ethanol as developer). These were separated by column chromatography on silica gel and their nmr spectra in dimethyl sulfoxide- d_6 were examined. The spectra of both compounds exhibited a single low field broad triplet (2.14 τ for the faster moving component and 2.22 τ for the slower moving one) characteristic of a N-H acetamido proton. This indicated that reduction of the nitrile had taken place. However, surprisingly the faster moving component CXXXII had no hydroxyl absorptions and 3 methyl singlets (7.85 τ , 8.04 τ , 8.20 τ); the slower moving component CXXXIII on the otherhand, showed one hydroxyl absorption (a doublet at 4.18 τ indicating a secondary hydroxyl group) and two methyl singlets (7.98 τ and 8.17 τ). From this it was concluded that as well as reduction of the nitrile group acetylation of some of the hydroxyl groups had taken place to give as the reduction products an approximately 50:50 mixture of compounds CXXXII and CXXXIII (Equation 35). Presumably it is the heterocyclic base of the nucleoside which catalyzes the acetylation of the hydroxyl groups in the nucleoside. This is somewhat remarkable in view of the low concentration of base present in the reaction mixture.

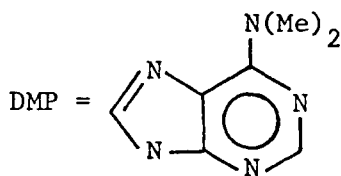


[CXXXI]

[CXXXII] R = R' = Ac

[CXXXIII] R' = Ac, R = H

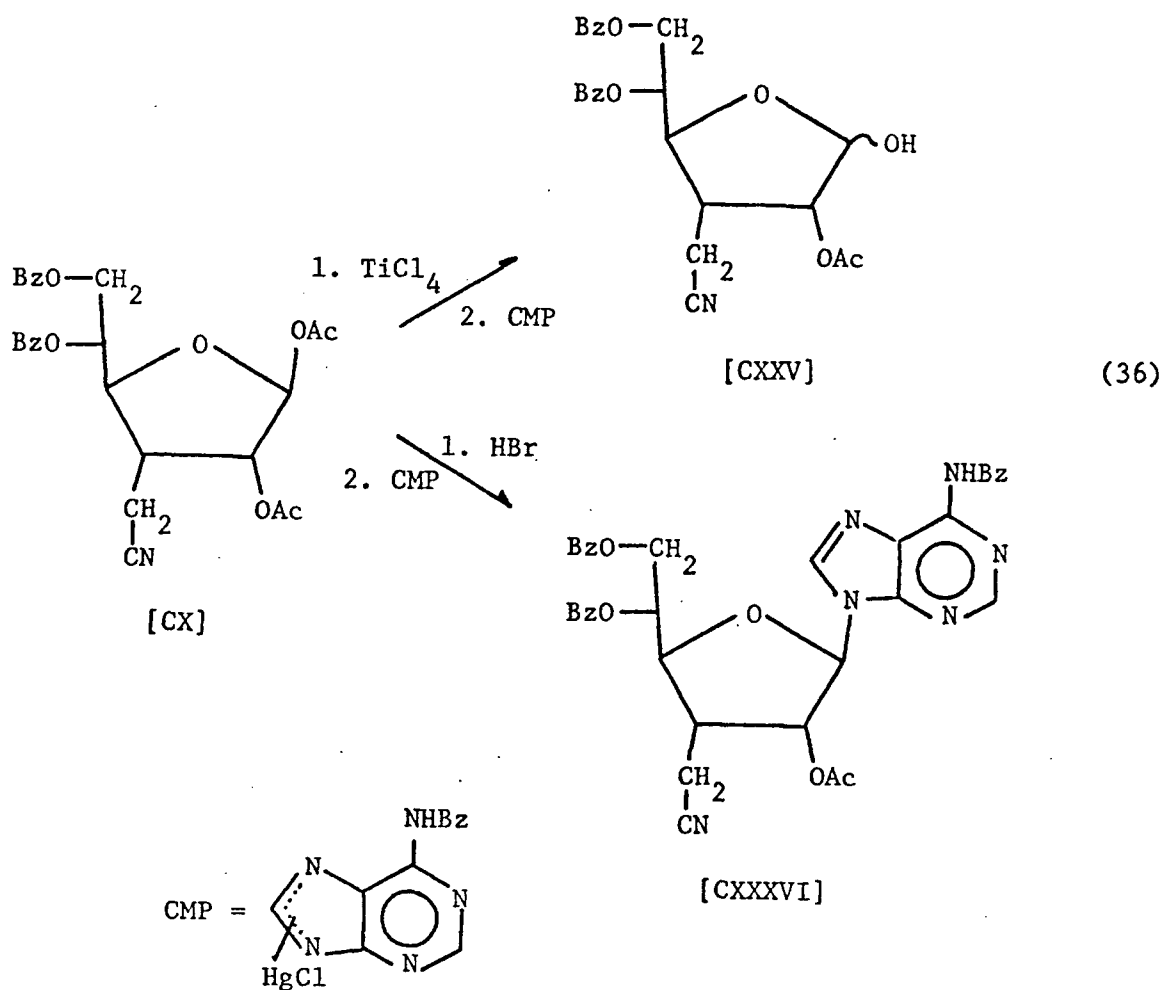
[CXXXIV] R = R' = H



These two compounds were de-O-acetylated by reaction with aqueous dimethylamine to give the same acetamidoethyl branched-chain sugar nucleoside 6-N,N-dimethylamino-9-(3'-C-(2''-acetamidoethyl)-3'-deoxy-β-D-ribofuranosyl)-purine [CXXXIV] as a crystalline solid.

5.9 6-Benzamido-9-(2'-O-acetyl-5',6'-di-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-allofuranosyl)-purine [CXXXVI] and 6-benzamido-9-(2'-O-acetyl-5'-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXXXVII]

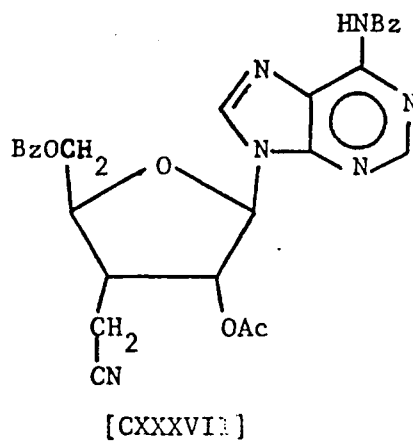
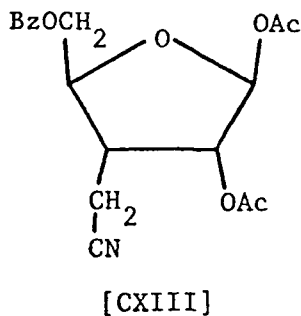
In order to extend the utility of cyanomethyl branched-chain sugars in nucleoside synthesis the preparation of nucleosides using the standard glycosyl halide, chloromercuri purine method (98,99) was briefly examined. When the titanium tetrachloride, chloromercuri-6-benzamido-purine method (176) was used with CX (Equation 36) no appreciable yield



of nucleoside was obtained. The main product of this reaction appeared from spectral data to be the C-1 hydrolysis product CXXXV, indicating that the glycosyl halide had been formed but that it had not undergone condensation with the base, but rather had been hydrolyzed to CXXXV probably during workup.

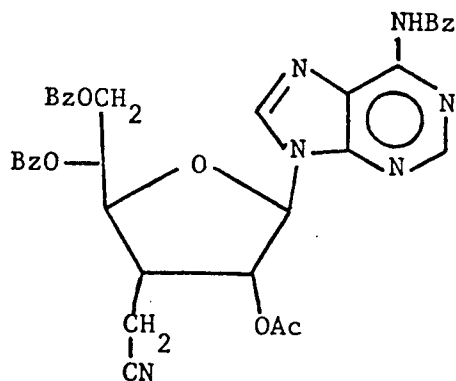
In view of the above result it was decided to prepare the more reactive glycosyl bromo derivative and to condense this compound with chloromercuri-6-benzamido purine. Thus the glycosyl bromide of CX was synthesized by reacting this compound with a saturated solution of

hydrogen bromide in dichloromethane (177). The unstable bromo-glycoside obtained after evaporation of the solvent was immediately added to a suspension of chloromercuri 6-benzamido purine in toluene at 65° (176). After the usual work up and chromatography on silica gel this procedure afforded the blocked adenylyl nucleoside 6-benzamido-9-(2'-O-acetyl-5',6'-di-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-allofuranosyl)-purine [CXXXVI] as a syrup in 60% yield. The assignment of the β-configuration to this compound was based on Baker's trans rule (100) and the small H-1', H-2' coupling constant ($J_{1',2'} = 1$ Hz). Application of the above procedure to CXIII gave the corresponding pentose nucleoside 6-benzamido-9-(2'-O-acetyl-5'-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXXXVII]. The anomeric configuration was deduced as before from Baker's rule and the fact that the anomeric proton appeared as a singlet at 3.95 τ.

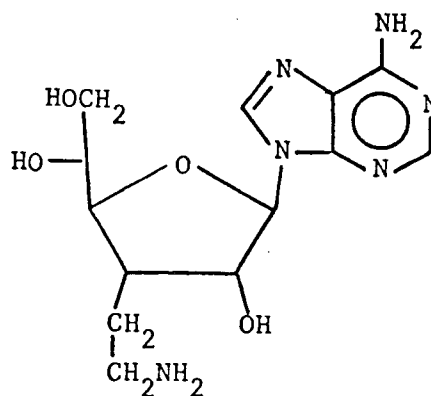


5.10 9-(3'-C-Aminoethyl-3'-deoxy-β-D-allofuranosyl)-adenine [CXXXIX]

In order to reduce the nitrile group in the branched-chain of the blocked adenyI nucleoside CXXXVI catalytic hydrogenation at 60 psi in acetic anhydride with platinum oxide catalyst was initially attempted. However under these conditions no detectable reduction took place after 24 hours at room temperature. It was therefore decided to reduce this compound using lithium aluminum hydride in tetrahydrofuran (131). Using this procedure the desired aminoethyl nucleoside CXXXIX was obtained as a crystalline solid albeit in low (20%) yield. Although the compound was purified by passage through an ion exchange resin (Dowex 50W-X2 (NH₄⁺ form)) and crystallized several times from methanol, the product always remained contaminated with a trace of inorganic material. This tendency of nucleosides to complex with metals was noted before (108). Wherever possible, reaction conditions which could introduce such contamination should be avoided, especially if the compounds are to undergo biological testing.



[CXXXVII]



[CXXXIX]

6. Biological activity evaluation of branched-chain sugar nucleosides

All the nucleosides whose preparation is described herein (with the exception of the last mentioned compound CXXXIX) are currently undergoing biological testing at the United States National Cancer Institute, Bethesda, Maryland. The means being used to evaluate the activity of these nucleosides is the Leukemia L 1210 system, as this type of compound generally shows its greatest activity in this system (178).

IV. EXPERIMENTAL:

1. General Methods

Unless otherwise specified all solvent evaporations were done in vacuo at prevailing aspirator pressure and a bath temperature less than 50°. Circular dichroism (cd) spectra were recorded on a Jasco ORD/UV-5 spectropolarimeter or a Jasco J-20 automatic recording spectropolarimeter. Optical rotations were measured with a Perkin Elmer model 141 polarimeter. Infrared (ir) spectra were recorded on a Perkin Elmer model 137 spectrophotometer. Sixty MHz nuclear magnetic resonance (nmr) spectra were measured on a Varian T-60 spectrometer; 100 MHz spectra were recorded on a Varian HA-100 or XL-100 spectrometer. Absorptions are given in τ units with tetramethylsilane as internal standard (set at τ 10). The following abbreviations are used: (b) = broad, (d) = doublet(s), (s) = singlet(s), (t) = triplet(s), (p) = proton(s). Mass spectra were recorded on an A. E. I. MS 9 spectrometer. Elemental analyses were performed by Mr. Peter Borda at the University of British Columbia.

2. Chromatography

2.1 Column

Silica gel column chromatography was accomplished using either silica gel 60-200 mesh, Davidson commercial grade H, indicated in the

experimental as "silica gel", or silica gel for tlc D O Mondray Ltd., indicated as "tlc silica gel." For silica gel column chromatography the ratio of material to absorbent was about 1 to 70. Grade II activity indicates that 10% of water has been added to the absorbent. For tlc silica gel column chromatography the ratio of material to absorbent was about 1 to 200 and columns were run under a positive pressure of 2 to 7 psi. Alumina column chromatography was done using aluminum oxide Woelm neutral, the desired activity grade being prepared according to the directions on the container.

2.2 Thin Layer Chromatography

All thin layer chromatography (tlc) was performed using silica gel for tlc D 5 Mondray Ltd. containing 1% electronic phosphor. Compounds were detected either by ultraviolet absorption or by spraying with ca. 20% sulfuric acid followed by heating on a hot plate.

2.3 Paper Chromatography

Paper chromatograms were developed on Whatman No. 1 paper. Nucleosides were detected with ultraviolet light.

2.4 Gas Liquid Chromatography

Gas liquid partition chromatographic separations (glc) were performed using a Varian aerograph model 1525 with the following columns: column A is a stainless steel column (10' x 3/8") packed with 5% butane diol succinate on Chromosorb W-AW-DMCS 60-80 mesh; column B is a stainless steel column (8' x 1/4") packed with 8.5%

SF 96 on Chromosorb W.

3. Photolysis Reactions

The light source in these reactions was a Hanovia 450 w type L lamp. Large scale (internal) photolyses were carried out by placing the lamp, and filter if required, inside a water cooled quartz immersion well apparatus which was placed inside a 3-necked pyrex vessel (capacity with lamp about 300 ml). Small scale (external) photolyses were performed by placing the solution to be photolysed in a pyrex tube (capacity about 80 ml) and clamping this tube to the outside of the quartz immersion well. The immersion well and photolysis tube then were placed in a water bath in order that the solution being photolysed would remain at room temperature. In both of the above procedures in order to prevent accidental exposure to ultraviolet radiation and to make the most efficient use of the radiation source, the whole photolysis apparatus was wrapped in aluminum foil. All photolysis solvents were reagent grade, distilled and dried before use. Photolysis solutions were deoxygenated with Matheson prepurified nitrogen.

1,2:5,6-Di-O-isopropylidene- α -D-glucofuranose [LXIX]

To an efficiently stirred suspension of α -D-glucose (300 g) in absolute acetone (2l) was added pulverized anhydrous zinc chloride (280 g) and 85 % phosphoric acid (15 g). The mixture was allowed to shake at room temperature for two days. The unreacted sugar (108 g) was removed by filtration and the filtrate was made slightly alkaline

with sodium hydroxide (170 g in 170 ml of water). The insoluble inorganic material was removed by filtration and washed with acetone. The filtrate and washings were concentrated under reduced pressure. The residue was dissolved in water (300 ml) and extracted with chloroform (300 ml x 3). The combined chloroform extracts were washed again with water, then dried over sodium sulfate. Evaporation of the solvent yielded a solid residue, which was recrystallized from cyclohexane to afford crystalline LXIX (220 g, 80% yield based on D-glucose consumed), m.p. 109°. Reported (179): m.p. 110-111°.

5-O-Benzyl-1,2-O-isopropylidene- α -D-xylofuranose [LXXVII]

This compound was synthesized following known procedures. Starting with 100 g of D-xylose [LXXIII], diacetone xylose [LXXIV] was prepared following a procedure given by Baker and Schaub (120); yield 104 g (73%) b.p. 97 - 98° (0.25 mm). Reported (120): 90 - 92° (0.2 mm). The diacetone xylose (104 g) was then hydrolyzed to monoacetone xylose (120) by dilute sulfuric acid; yield 95 g (95%). The monoacetone xylose [LXXIV] (75 g) was converted to 1,2-O-isopropylidene-5-O-tosyl- α -D-xylofuranose; yield 71 g (52%), m.p. 135 - 136°. Reported (121): m.p. 133 - 134°. Treatment of the tosylate (60 g) with sodium methoxide converted it to 1,2-O-isopropylidene-3,5 anhydro- α -D-xylofuranose [LXXVI]; yield 24.5 g (83%) b.p. 48 - 50° (about 0.05 mm). Reported (121): 63 - 65° (0.1 mm). Finally the anhydro sugar LXXVI (23 g) was allowed to react with benzyl alcohol and sodium (122) to afford 5-O-benzyl-

1,2-O-isopropylidene- α -D-xylofuranose [LXVIII] (32.5 g, 87%), m.p. 63-64°. Reported (122): m.p. 63-65°.

1,2:5,6-Di-O-isopropylidene- α -D-gulofuranose [LXXIa]

This compound was prepared by known procedures (119) from the hydrate of 1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose [LXX].

The hydrate of LXX (6.5 g) was reacted with acetic anhydride and pyridine to afford 3-O-acetyl-1,2:5,6-di-O-isopropylidene- α -D-erythro-hex-3-enofuranose [LXXI] (3.1 g), m.p. 56-57°. Reported (119): m.p. 62°. Hydrogenation of LXXI (3 g) over 5% palladium-on-charcoal (1 g) gave 3-O-acetyl-1,2:5,6-di-O-isopropylidene- α -D-gulofuranose [LXXII] (2.4 g). De-acetylation of this material with methanolic sodium methoxide afforded the title compound (2.01 g, 33% yield based on LXX), m.p. 105°. Reported (119): 105-106°.

1,2:5,6-Di-O-isopropylidene- α -D-ribofuranos-3-ulose [XVIII]

To a solution of 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose [LXIX] (5 g) in carbon tetrachloride (80 ml) was added water (15 ml), sodium bicarbonate (1 g) and finely powdered ruthenium dioxide (80 mg). To this solution was added with vigorous stirring a few drops of 10% sodium periodate solution. After approximately 5 min another small addition of periodate was made. This process was then repeated several times while gradually increasing the volume of periodate solution added. Addition was discontinued when the solution appeared a greenish-black, which indicated the presence of ruthenium tetroxide, and was

restarted when the solution appeared black, which indicated only ruthenium dioxide was present. The reaction was stopped when tlc examination indicated that no more starting material remained (the total volume of periodate solution added was about 50 ml). Any residual ruthenium tetroxide was then destroyed by addition of isopropyl alcohol (0.5 ml) and the ruthenium dioxide removed by filtration. The carbon tetrachloride layer was separated and the water layer extracted with chloroform (10 x 20 ml). The combined organic extracts were dried over sodium sulfate and the solvent evaporated to yield the ketose hydrate LXX (4.8 g, 97%) m.p. 109-110°. Reported (119): m.p. 109-111°. The hydrate was suspended in dry toluene (200 ml) and 50 ml was distilled off at atmospheric pressure. The remaining toluene was then removed by flash evaporation using a rotary evaporator connected to an oil pump. The crude ketose was then distilled, in an apparatus having a very short distillation path (bulb-to-bulb), (150°, 0.1 mm) to afford XVIII (4.5 g, 90%) as a syrup. The ir spectrum showed a carbonyl absorption at 1760 cm^{-1} and no hydroxyl absorption.

1,2:5,6-Di-O-isopropylidene- α -D-xylo-furanos-3-ulose [LXVII]

1,2:5,6-Di-O-isopropylidene- α -D-gulofuranose (5 g) was oxidized with sodium periodate and ruthenium dioxide as previously described for compound [XVIII]. Only five extractions with chloroform were necessary to remove the ketose from the water layer. The product crystallized from petroleum ether (65-110°) to give the ketose LXVII (3.9 g, 78%), m.p. 75°. Reported (119): m.p. 76-77°.

5-O-Benzyl-1,2-O-isopropylidene- α -D-erythro-pentofuranos-3-ulose
[LXVIII]

Method A:

A solution of 5-O-benzyl-1,2-O-isopropylidene- α -D-xylofuranose [LXXVII] (10 g in anhydrous dimethyl sulfoxide (60 ml)) was cooled in an ice bath until frozen. Phosphorus pentoxide (4 g) was then added and after one hour at 0° the mixture was slowly allowed to come to room temperature. After twenty-four hours tlc examination of the reaction mixture indicated that all the starting material had been consumed (R_f LXVIII 0.76; R_f LXXVII 0.47, benzene methanol (4:1)). The reaction mixture was then added with stirring to a cold saturated sodium bicarbonate solution (100 ml) and after filtration, the filtrate was extracted with chloroform (7 x 50 ml). The chloroform extract was washed once with sodium bicarbonate solution (10 ml) and once with water and dried over magnesium sulfate. The majority of the solvent was then removed by evaporation and the residue dried by dissolving it in anhydrous benzene (50 ml) and distilling off 25 ml at atmospheric pressure. The remainder of the benzene and residual DMSO was removed by evaporation on a rotary evaporator connected to a vacuum pump (pressure about 1 mm) leaving 6.5 g of ketose LXVIII as a viscous yellow oil. The ir spectrum of this material showed no hydroxyl absorbtion and a strong carbonyl absorbtion at 1760 cm^{-1} . This compound was characterized as its 2,4-dinitrophenylhydrazone derivative which was crystallized from acetone water, m.p. 143-144°, $[\alpha]_D^{22} +140^\circ$ (c 2, in chloroform).

Anal. Calcd. for $C_{21}H_{22}O_8N_4$: C, 55.02; H, 4.84; N, 12.22. Found: C, 55.25; H, 5.03; N, 12.08.

Method B:

To a solution of 5-O-benzyl-1,2-O-isopropylidene- α -D-xylofuranose [LXXVII] (5 g) in carbon tetrachloride (80 ml) was added ruthenium dioxide (80 mg), water (10 ml), and sodium bicarbonate (1 g). While the mixture was being vigorously stirred about 0.25 ml of 10% sodium metaperiodate solution was added dropwise. After 5 minutes another 0.5 ml of 10% sodium metaperiodate solution was added and after a further 5 minutes more periodate solution was added until the solution was observed to turn a green-black colour (indicating the presence of ruthenium tetroxide). Addition of periodate solution was then continued at intervals whenever the solution turned black (indicating only ruthenium dioxide was present). When tlc examination indicated that all the starting material had been oxidized (this required about 1.3 equivalents of sodium periodate) a few drops of isopropyl alcohol were added to the reaction mixture to decompose any unreacted ruthenium tetroxide and the ruthenium dioxide was filtered off. The carbon tetrachloride layer was then separated and the aqueous layer extracted with chloroform (3 x 75 ml). The combined organic extracts were then dried over magnesium sulfate and the solvent evaporated. After drying with benzene as previously described there remained 4.8 g of ketose LXVII (90% of theoretical) identical by nmr and ir to the product from the DMSO oxidation.

3-C-Cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose

[LXXXVI]

1,2:5,6-Di-O-isopropylidene- α -D-ribofuranos-3-ulose [XVIII]
(14.7 g, 0.057 mole) dissolved in 1,2-dimethoxy ethane (DME) (250 ml) was added dropwise with stirring to a solution (kept at 0°) of diethyl cyanomethylphosphonate carbanion (prepared as in the synthesis of LXXXVIII from sodium hydride (1.64 g, 0.0685 mole) and diethyl cyanomethylphosphonate (12.1 g, 0.0685 mole)) in DME (50 ml). After addition was complete the reaction mixture was allowed to come to room temperature and after 4 hr it was diluted with ice water (100 ml) and the product extracted with ether (3 x 200 ml). The combined ether extracts were washed with water (3 x 20 ml), dried (sodium sulfate) and evaporated. The residue after evaporation of the solvent was bulb-to-bulb distilled (190°, 0.1 mm) to afford 13.6 g of a colourless syrup (R_f 0.68, benzene:methanol (19:1)); ir (film) 2250 cm^{-1} (C $\equiv$ N); τ^{CDCl_3} 3.9-4.1 (m, 2p, H-1 and olefinic proton).

Hydrogenation of this material in ethanol (150 ml) at ambient pressure and temperature over 5% palladium-on-charcoal (4 g) (1.01 equivalents of hydrogen absorbed) gave, after removal of the catalyst by filtration and evaporation of the solvent, 13.6 g of syrup.

Crystallization of this material from ether-petroleum ether 30-60°, afforded the branched-chain sugar LXXXVI (12.6 g, 78%), m.p. 109°, $[\alpha]_D^{22} +91^\circ$ (c 2, in chloroform); ir (nujol) 2270 cm^{-1} (C $\equiv$ N); τ^{CDCl_3} 4.18 (d, 1p, H-1, $J_{1,2} = 3.6\text{ Hz}$), 5.23 (t, 1p, H-2, $J_{2,3} = 3.6\text{ Hz}$).

Irradiation of LXXXVI at the H-1 signal collapsed H-2 into a doublet.

Anal. Calcd. for $C_{14}H_{15}N O_5$: C, 59.3; H, 7.47; N, 4.94. Found: C, 59.26; H, 7.35; N, 4.81.

3-C-Cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-gulofuranose
[LXXXVII]

1,2:5,6-Di-O-isopropylidene- α -D-xylohexafuranos-3-ulose [LXVII] (290 mg) dissolved in DME (20 ml) was added dropwise with stirring to a solution (kept at 0°) of diethyl cyanomethylphosphonate carbanion (prepared as in the synthesis of LXXXVIII from sodium hydride (30 mg)) and diethylcyanomethyl phosphonate (220 mg) in DME (15 ml). After addition was complete the reaction mixture was allowed to come to room temperature and after 4 hours it was diluted with ice water (20 ml) and the product was extracted with ether (3 x 25 ml) as previously described. Crystallization from ether-pet. ether 30-60° afforded 260 mg (80%) of the unsaturated cyano branched-chain sugars 3-C-cyanovinyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-xylofuranose [LXXXIV], m.p. 98°; ir (nujol) 2260 cm^{-1} (C $\equiv$ N); τ^{CDCl_3} 4.06-4.33 (m, 2p, H-1 and olefinic proton).

Hydrogenation of LXXXIV (260 mg in 10 ml ethanol) at ambient pressure and temperature over 5% palladium-on-charcoal (100 mg) (1 equivalent of hydrogen absorbed) gave the title branched-chain sugar LXXXVII (260 mg, 79%) which was crystallized from ether-petroleum ether 30-60°, m.p. 112°, $[\alpha]_D^{25}$ -28.6° (c 2.3, in chloroform); ir (nujol) 2280 cm^{-1} (C $\equiv$ N); τ^{CDCl_3} 4.17 (d, 1p, H-1, $J_{1,2} = 4.0\text{ Hz}$), 5.27 (broad t, 1p, H-2, $J_{2,3} = 5.0\text{ Hz}$). Irradiation of H-1 collapsed H-2 to a doublet.

Anal. Calcd. for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.33; H, 7.63; N, 4.69.

5-O-Benzyl-3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [LXXXVIII]

To a suspension of sodium hydride (NaH) (0.36 g, 15 mmole) in anhydrous 1,2-dimethoxyethane (DME) (20 ml) was added a solution of diethyl cyanomethylphosphonate (2.7 g, 15 mmole) in DME (20 ml). When evolution of hydrogen had ceased the mixture was filtered (all the above operations were performed in a dry box under nitrogen atmosphere) and the solution of phosphonate carbanion cooled to 0°. To this solution was then added dropwise 5-O-benzyl-1,2-O-isopropylidene- α -D-erythro-pentofuranos-3-ulose [LXVIII] (2.8 g, 10.1 mmole) in DME (60 ml). When the addition was complete the reaction mixture was allowed to come to room temperature and after four hours the solution was diluted with ice water (75 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water (3 x 5 ml), dried (magnesium sulfate) and evaporated. The remaining residue was dissolved in benzene (50 ml) and decolourized with charcoal. Evaporation of the solvent gave 3 g of syrup. Hydrogenation of this syrup in ethanol (25 ml) at ambient pressure and temperature over 10% palladium-on-charcoal (1 g) (1.05 equivalents of hydrogen absorbed) gave after removal of the catalyst and evaporation of the solvent the title compound LXXXVIII as a homogeneous syrup (3 g, 93%); $[\alpha]_D^{23} +50^\circ$ (c 3, in chloroform); ir (nujol) 2270 cm^{-1} (C $\equiv$ N); $\tau_{CDCl_3}^{13} 4.2$ (d, 1p, H-1, $J_{1,2} = 3.6\text{ Hz}$), 5.34 (t, 1p, H-2, $J_{2,3} = 3.9\text{ Hz}$).

Irradiation of the H-1 signal of LXXXVIII collapsed H-2 into a doublet.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.45; H, 7.20; N, 4.78.

3-C-(2'-Acetamidoethyl)-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [XCII]

The 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [LXXXV] (1 g) dissolved in absolute ethanol (70 ml) saturated with ammonia was hydrogenated over 5% rhodium-on-alumina (200 mg) at room temperature and 60 psi for 20 hr. The catalyst was then removed by filtration and the solvent evaporated. The resulting syrup was acetylated with a mixture of acetic anhydride (3.5 ml) and pyridine (3.5 ml) for 24 hr at room temperature. The mixture was then diluted with ice water (20 ml) and the product extracted with dichloromethane (3 x 20 ml), washed with water (2 x 5 ml) and dried over sodium sulfate. Evaporation of the solvent afforded 0.92 g (80%) of the above amide XCII as a syrup; $[\alpha]_D^{23} +41^\circ$ (c 1, in chloroform); ir (film) 3300 cm^{-1} (N-H), 1640 cm^{-1} (N-C=O); $\tau_{\text{CDCl}_3}^{13} 3.27$ (broad t, 1p, H-N), 4.30 (d, 1p, H-1 $J_{1,2} = 4.0\text{ Hz}$), 5.30 (t, 1p, H-2), 8.03 (s, 3p, Ac).

Anal. Calcd. for $C_{16}H_{27}N_1O_6$: C, 58.34; H, 8.20; N, 4.25. Found: C, 58.27; H, 8.44; N, 4.00.

3-C-(2'-Acetamidoethyl)-5-O-benzyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [XCIII]

A solution of 5-O-benzyl-3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [LXXXVIII] (7 g in anhydrous ether (50 ml)) was added dropwise to a suspension of lithium aluminum hydride (LAH) (2.03 g) in anhydrous ether (100 ml). After two hours unreacted LAH was decomposed by the slow addition of ethyl acetate (35 ml) in ether (50 ml) followed by water (2 ml). The solution was then filtered and the filtrate was evaporated. The residue was taken up in chloroform (100 ml) and the chloroform solution was washed with water (3 x 10 ml), dried (sodium sulfate) and evaporated. The remaining material was acetylated by treatment with a mixture of acetic anhydride (10 ml) and anhydrous methanol (19 ml) for 3 hours. The mixture was then poured into ice water (50 ml) and the product extracted with chloroform (3 x 75 ml). The combined chloroform extracts were washed with 5% sodium bicarbonate solution (2 x 10 ml) and water (2 x 10 ml) and dried (sodium sulfate). Evaporation of the filtrate gave 6.6 g of syrup which was chromatographed on silica gel using benzene:ethyl acetate (2:1) as developer to afford amide XCIII as a syrup (5.5 g, 68.5% from LXXXVIII); $[\alpha]_D^{22} +39^\circ$ (c 3, in chloroform); ir (film) 3300 (N-H), 1650 cm^{-1} ($\overset{\text{O}}{\parallel}\text{-C-N}$); τ^{CDCl_3} 4.2 (d, 1p, H-1), 4-4.4 (b, 1p, N-H), 8.1 (s, 3p, N-Ac).

Anal. Calcd. for $\text{C}_{19}\text{H}_{27}\text{N}_1\text{O}_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.60; H, 8.02; N, 3.87.

Acetolysis of 3-C-(2'-acetamidoethyl)-5-O-benzyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [XCIII]

Concentrated sulfuric acid (0.25 ml) was added dropwise to a cooled (0°) solution of 3-C-(2'-acetamidoethyl)-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose (500 mg) in acetic anhydride (0.5 ml) and glacial acetic acid (5 ml). After addition was complete the reaction mixture was allowed to come to room temperature and let stand for one day. Workup was accomplished by pouring the reaction mixture into ice water (30 ml) and extracting the product with chloroform (3 x 25 ml). A tlc examination of the chloroform extract showed the presence of five products (R_f 0.0, 0.1, 0.45, 0.61 and 0.75, benzene:methanol (9:1)) in about equal amounts.

3-C-Cyanomethyl-3-deoxy-1,2-O-isopropylidene- β -L-lyxofuranose [XCV]

To a solution of 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-gulofuranose [LXXXVII] (160 mg in 9 ml methanol) was added 0.7 M sulfuric acid (1.5 ml) and the mixture left to stand for 7 hours. The hydrolysis mixture was then neutralized with solid sodium bicarbonate and extracted with chloroform (4 x 15 ml). The combined chloroform extracts were dried (sodium sulfate) and evaporated to afford 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-gulofuranose [XCIV] (121 mg, 88%) as a syrup; τ_{CDCl_3} 4.07 (d, 1p, H-1), 5.23 (broad t, 1p H-2), 7.0-7.5 (m, 5p, CH_2C N, H-3, C-5 OH, C-6 OH), 8.40, 8.64 (2s, 6p, 1p). Upon addition of D_2O two absorbtions in the region τ 7.0-7.5 disappeared. The above diol XCIV (121 mg) was reacted with sodium periodate and sodium borohydride as described for the preparation

of XCI to afford the title branched-chain sugar XCV (105 mg, 87% based on LXXXVII) which was crystallized from ether, m.p. 81° , $[\alpha]_D^{24} +10.4^{\circ}$ (c 1.6, in chloroform); ir (nujol) 3500 (OH, 2245 cm^{-1} (C $\equiv$ N); τ^{CDCl_3} 4.10 (d, 1p, H-1, $J_{1,2} = 4\text{ Hz}$), 5.23 (t, 1p, H-2, $J_{2,3} = 4.5\text{ Hz}$), 8.43, 8.67 (2 s, 6p, 1p).

Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{N}_1\text{O}_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.22; H, 7.05; N, 6.50.

3-C-(2'-Acetamidoethyl)-3-deoxy-1,2-O-isopropylidene- β -L-lyxofuranose
[XCVI]

A solution of 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- β -L-lyxofuranose [XCV] (18 mg) dissolved in acetic anhydride (2 ml) and ethanol (2 ml) and containing platinum oxide (19 mg) was hydrogenated at room temperature and 60 psi for 4.5 hrs. A tlc examination at this time indicated that the reaction was complete (R_f XCV 0.47, R_f XCVI 0.05, dichloromethane:ethyl acetate:ethanol (5:5:1)). The catalyst was then removed by filtration and the solvent evaporated to afford the title compound XCVI (20 mg) (92%) which crystallized on standing (R_f 0.59 dichloromethane:methanol 9:1); m.p. 133° $[\alpha]_D^{25} +1.50^{\circ}$ (c 1.6, in chloroform); ir (KBr) 1630 cm^{-1} ($\overset{\text{O}}{\parallel}\text{C-N}$); τ^{CDCl_3} 3.8-4.3 (b, 1p, N-H), 4.17 (d, 1p, H-1, $J_{1,2} = 4\text{ Hz}$), 5.35 (t, 1p, H-2, $J_{2,3} = 5\text{ Hz}$), 8.0 (s, 3p, N-Ac).

Anal. Calcd. for $\text{C}_{12}\text{H}_{21}\text{N}_1\text{O}_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.72; H, 8.27; N, 5.10.

3-C-Carbamoylmethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose

[C]

To a solution of 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [LXXXVI] (0.566 g in 6 ml ethanol) was added 30% hydrogen peroxide (0.8 ml) and 6 N sodium hydroxide. (0.8 ml). The mixture was then stirred at 50° for 6 hrs. Any unreacted hydrogen peroxide was then decomposed by the addition of a few milligrams of platinum oxide, and the solution was filtered and evaporated to dryness. The residue after evaporation, was extracted with dichloromethane (40 ml) and the dichloromethane extract washed with water (5 ml) and dried over sodium sulfate. Evaporation of the solvent gave a solid which was recrystallized from ether to afford the title compound C (0.40 g, 70%), m.p. 138°; $[\alpha]_D^{24} +81^\circ$ (c 2, in chloroform); ir (nujol) 3490, 3250 (NH), 1650 cm^{-1} (C=O); τ^{CDCl_3} 3.8-4.4 (b, 2p, NH_2).

Anal. Calcd. for $\text{C}_{14}\text{H}_{23}\text{N}_1\text{O}_6$: C, 55.8; H, 7.69; N, 4.47. Found: C, 55.7; H, 7.91; N, 4.57.

Preparation of C from XXIX

3-C-(Carbomethoxymethyl)-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [XXIX] (150 mg) and ammonium chloride (15 mg) were dissolved in liquid ammonia (3 ml) and heated in a sealed stainless steel tube at 60° for 24 hrs. The ammonia was then evaporated and the residue dissolved in ether. Insoluble material was removed by filtration and the filtrate was evaporated. The remaining material was taken up in a minimum amount of ether and stored at 0° for 24 hrs. A portion of the title amide C (90 mg) crystallized from this solution and was removed by

filtration; a further 18 mg of C (total yield 76%) was obtained by concentrating the mother liquor and allowing it to stand at 0° for a further 24 hrs. The amide prepared by this procedure was identical (ir, nmr, melting point, and mixed melting point) with the amide prepared from LXXXVI.

Preparation of C from XX

A de-oxygenated solution of 1,2:5,6-di-O-isopropylidene-3-C-methylene- α -D-ribo-hexofuranose [XX] in formamide (40 ml), t-butanol (20 ml) and acetone (5 ml) was photolyzed externally in a pyrex vessel for 7 hrs. The volatile solvents were then evaporated and the remaining solution diluted with saturated sodium chloride solution. Extraction of this solution with dichloromethane (3 x 35 ml) afforded (after drying over sodium sulfate and evaporation of the solvent) 300 mg syrup. Column chromatography of this material on tlc silica gel using benzene:ethyl acetate:ethanol (5:5:1) as developer gave amide C (152 mg, 50%) identical (by ir, nmr, and mixed m.p.) to the product prepared from LXXXVI and some uncharacterized acetone addition product (35 mg, 11%). The nmr spectrum of the acetone addition product contained the following signals: τ^{CDCl_3} 4.23 (d, 1p, H-1), 5.27 (t, 1p, H-2), 8.0 (s, 1p, OH), 8.5-8.8 (m, 18p, 6Me). Upon addition of D₂O the singlet at τ 8.0 was removed.

Ethyl 4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside [CII](144)

Tri-O-acetyl-D-glucal (5 g) was dissolved in anhydrous benzene (20 ml, dried over molecular sieves) and distilled anhydrous ethanol

(1.8 ml). Boron trifluoride-ether (1 ml) was added to the mixture under anhydrous conditions. Vigorous stirring was maintained at room temperature for twenty-five minutes, after which time anhydrous sodium carbonate (5 g) was quickly added. Stirring was then continued for a further fifteen minutes so as to ensure the complete neutralization of any excess boron trifluoride. The solid sodium carbonate was removed by filtration. Upon evaporation of the solvents, the resulting syrupy residue crystallized spontaneously. Recrystallization from ether-petroleum ether afforded CII (4 g, 80%), m.p. 78-79°. Reported (144): m.p. 78-79°.

Photo-addition of formamide to ethyl-4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside [CII]

Ethyl 4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside [CII] (0.500 g) was dissolved in a mixture of freshly distilled formamide (190 ml), t-butanol (70 ml) and acetone (17 ml) and the solution purged with oxygen-free nitrogen for ten hrs. Irradiation (pyrex filter $\lambda > 300$) was then commenced. After 1 1/2 hr a further 2.5 g of CII in oxygen-free t-butanol (20 ml) and acetone (3 ml) was added dropwise over a three hour period. Examination of the reaction mixture by tlc (95:5 benzene:methanol R_f CII 0.50, R_f products ≈ 0 and 0.1) indicated that after 9 hrs no more starting material remained. The volatile solvents were then removed by evaporation and the remainder of the solution diluted with saturated sodium chloride solution (200 ml) and extracted with chloroform (4 x 100 ml). The combined chloroform

extracts were washed with water (3 x 20 ml), dried over sodium sulfate and evaporated to yield 3.1 g of syrup. Column chromatography of this material on silica gel grade II (benzene:ethyl acetate:ethanol 10:10:1) gave two components: 0.33 g of the first eluted component and 2.1 g of the second eluted component.

The first eluted component proved to be a mixture of acetone addition products: τ CDCl_3 7.66 (s, 1p, OH), 7.94 (s, 6p, 2Ac), 8.80 (t, 3p, CH_3 of ethyl glycoside) 8.80 (s, 6p, 2 methyl peaks of acetone addition branched-chain). Glc column A: 2 unresolved peaks, retention time 24-26 min at 200°. Column B: 2 unresolved peaks, retention time 15 1/2-18 1/2 min at 210°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{26}\text{O}_7$: C, 56.59; H, 8.23. Found: C, 56.31; H, 8.00.

The second component proved to be the amide addition product
ir (film) 3400 cm^{-1} (NH_2), 1740 cm^{-1} ($\text{C}=\text{O}$), 1660 cm^{-1} ($\text{C}-\text{N}$; τ CDCl_3
3.47 (b, 2p, $\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{NH}_2$), 7.90 (s, 6p, Ac), 8.74 (t, 3p, methyl peak of ethyl glycoside).

Anal. Calcd. for $\text{C}_{13}\text{H}_{21}\text{N}_1\text{O}_7$: C, 51.47; H, 6.97; N, 4.61. Found: C, 51.93; H, 6.67; N, 4.20.

1,2:5,6-Di-O-isopropylidene-3-C-nitromethyl- α -D-glucofuranose [CV]

A solution of one M sodium methoxide in methanol (1.95 ml, 1.95 mmoles) was added dropwise with stirring to a solution of 1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose [XVIII] (0.5 g, 1.95 mmoles) in 5 ml of nitromethane. The reaction mixture was stirred for 16 hr at room temperature and then deionized, and the filtrate then

evaporated to a syrup. Crystallization from petroleum ether (b.p. 60-110°) gave 0.430 g (71% of pure, crystalline nitro derivative CV, m.p. 138-140°, $[\alpha]_D^{22} +31^\circ$ (c 2, chloroform); ir (CCl₄) 3650 (s) (OH) 1560 cm⁻¹ (NO₂); τ^{CDCl_3} 4.05 (d, H-1, $J_{1,2}$ 3.5 Hz), 5.13 (an AB system, $J_{a,b}$ 12.5 Hz, methylene protons a and b on C-1'), 5.38 (d, H-2, $J_{1,2}$ 3.5 Hz), 5.5-6.3 (m), 6.50 (OH), 8.40, 8.55 (2s, 6p, Ip) 8.62 and 8.66 (2s, 6p, Ip).

Anal. Calcd. for C₁₃H₂₁NO₈: C, 48.89; H, 6.63; N, 4.39. Found: C, 48.73; H, 6.49; N, 4.54.

3-C-Cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-allofuranose [CVIII]

To a solution of 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-allofuranose [LXXXVI] (6.5 g) in methanol (300 ml) was added 1 N sulfuric acid (30 ml). The hydrolysis mixture was left to stand at room temperature until tlc indicated that all the starting material was gone (about 4 hr), then neutralized with solid sodium bicarbonate and extracted with chloroform (3 x 200 ml). The combined chloroform extracts after drying (over sodium sulfate) were evaporated to afford compound CVIII (5.5 g) as a syrup in nearly quantitative yield: $[\alpha]_D^{25} +99.4^\circ$ (c 1.67, in chloroform); ir (film) 3500 cm⁻¹ (OH), 2280 cm⁻¹ (C $\equiv$ N); τ^{CDCl_3} 8.17, 8.33 (2s, 6p, Ip).

Anal. Calcd. for C₁₁H₁₇N₁O₅: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.01; H, 7.21; N, 5.56.

5,6-Di-O-benzoyl-3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-allofuranose [CIX]

To a solution of 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-allofuranose [CVIII] (6.0 g in anhydrous benzene (30 ml)) was added dropwise a mixture of benzoyl chloride (3.2 ml) and pyridine (4.5 ml). After 14 hrs at room temperature the reaction mixture was filtered through a short column of grade II alumina (25 g) and the column washed with benzene (150 ml). Evaporation of the combined eluents gave the title ester CIX which was crystallized from ether-petroleum ether 30-60° to give 10.0 g (90%) of product; m.p. 71-72°, $[\alpha]_D^{24} +48.2^\circ$ (c 1.3, in chloroform).

Anal. Calcd. for $C_{25}H_{25}N_1O_7$: C, 66.6; H, 5.57; N, 3.10. Found: C, 66.33; H, 5.54; N, 2.95.

5-O-Benzoyl-3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [CXII]

To a solution of 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [CXI] (4.75 g, 22.3 mmole in anhydrous benzene (25 ml)) was added dropwise a mixture of benzoyl chloride (2.9 ml, 24.8 mmole) and pyridine (4 ml). After 20 hr at room temperature the reaction mixture was filtered through a short column of grade II alumina (20 g) and the column was washed with benzene (100 ml). Evaporation of the solvent from the eluent gave the title ester CXII which was crystallized from ether-petroleum-ether 30-60°: (6.55 g, 93%), m.p. 110°, $[\alpha]_D^{22} +59^\circ$ (c 1.8, in chloroform).

Anal. Calcd. for $C_{17}H_{19}N_1O_5$: C, 64.34; H, 6.03; N, 4.45. Found: C, 61.11, H, 5.93; N, 4.31.

Attempted acetolysis of CIX

5,6-Di-O-benzoyl-3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-allofuranose CXII (350 mg) was dissolved in a mixture of acetic acid (4 ml) and acetic anhydride (0.4 ml). To this solution was added dropwise concentrated sulfuric acid (0.4 ml). After 24 hr the reaction mixture was diluted with ice water (20 ml) and extracted with chloroform (3 x 15 ml). Tlc examination of the chloroform extract showed three products; (R_f 0.65 major, 0.3, and 0.1, benzene:methanol (9:1)). The chloroform extract was dried (over sodium sulfate) and evaporated to a syrup which was chromatographed on a column of grade II silica gel using benzene:ethyl acetate (4:1) as developer. The major component was recovered (100 mg). Elemental analysis of this product showed that it contained no nitrogen.

Found: C, 64.40; H, 5.03.

1,2-Di-O-acetyl-5,6-di-O-benzoyl-3-C-cyanomethyl-3-deoxy- β -D-allofuranose

[CX]

5,6-Di-O-benzoyl-3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-allofuranose [CIX] (4.5 g) was allowed to react with an 80% solution of trifluoroacetic acid (60 ml) at room temperature for 45 minutes. The reaction mixture was then neutralized with solid sodium bicarbonate, filtered, and the filtrate was extracted with methylene chloride (6 x 50 ml). Evaporation of the combined methylene chloride extracts

afforded a syrup (4.1 g) which was acetylated with acetic anhydride (15 ml) and pyridine (15 ml). After 20 hrs the reaction mixture was poured into ice water (100 ml) and worked up in the usual way to obtain 4.4 g of syrup. Column chromatography of this material on grade II silica gel using benzene-ethyl acetate (3:1) as developer yielded after crystallization from ether 3.3 g (69%) of acetate CX, m.p. 110°, $[\alpha]_D^{23} -31^\circ$ (c 2, in chloroform); ir (KBr) 2230 cm^{-1} (C $\equiv$ N); $\tau_{\text{CDCl}_3}^{13\text{C}}$ 1.8-2.8 (m, 10p, 2 Bz), 3.77 (s, 1p, H-1), 7.87, 7.97 (2s, 6p, 2 Ac).

Anal. Calcd. for $\text{C}_{26}\text{H}_{25}\text{N}_1\text{O}_9$: C, 63.00; H, 5.08; N, 2.81. Found: C, 63.00; H, 4.97; N, 2.65.

3-C-Cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose [CXI]

To a solution of 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene- α -D-allofuranose [CVIII] (1.5 g, 6.2 mmole, in ethanol (40 ml)) was added with stirring saturated sodium bicarbonate solution (2 ml) and sodium periodate (1.32 g, 6.2 mmole, dissolved in water (70 ml)). After the solution was left stand for 3 hr in the dark at room temperature a few drops of ethylene glycol were added to destroy any unreacted periodate. Sodium borohydride (120 mg) was then added followed after 4 hr by acetone (0.5 ml) and the mixture stirred for an additional 0.5 hr. After filtration the solution was extracted with methylene chloride (4 x 100 ml) and the organic extracts were combined and dried over sodium sulfate. Evaporation of the solvent gave a syrup which was crystallized from ether to afford CXI (1g, 90%), m.p. 70°, $[\alpha]_D^{23} +97^\circ$ (c 1.1, in chloroform); ir (nujol) 3500 (OH), 2250 cm^{-1} (C $\equiv$ N).

Anal. Calcd. for $C_{10}H_{15}N_1O_4$: C, 56.4; H, 7.05; N, 6.57. Found: C, 56.6; H, 6.99; N, 6.67.

1,2-Di-O-acetyl-5-O-benzoyl-3-C-cyanomethyl-3-deoxy-β-D-ribofuranose
[CXIII]

5-O-Benzoyl-3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose [CXII] (7 g) was dissolved in 90% trifluoroacetic acid (42 ml) and let stand at room temperature for 22 minutes. The reaction mixture was then diluted with toluene (100 ml) and the solvent evaporated under vacuum (about 1 mm). The last traces of acid were removed by a second distillation of toluene from the product and the remaining material (6.1 g) was then acetylated with acetic anhydride (20 ml) and pyridine (20 ml) for 24 hr at room temperature. The acetylation mixture was poured into ice water and worked up as described for compound CX. The syrupy product (7 g) was dissolved in ethanol and allowed to stand at 0° overnight during which time some of the title acetate CXIII (3.5 g, 44% based on CXII) crystallized.

The mother liquor was concentrated to a syrup and chromatographed on a silica gel column using benzene:ethyl acetate (3:1) as developer to afford an additional 2 g of acetate CXII (25%) and a slightly faster moving component (0.4 g). The main component was crystallized from ethanol to afford 1,2-di-O-acetyl-5-O-benzoyl-3-C-cyanomethyl-3-deoxy-β-D-ribofuranose [CXII], m.p. 117°; $[\alpha]_D^{24}$ -21.9° (c 1.5, in chloroform); ir (nujol) 2260 cm^{-1} (C≡N); τ_{CDCl_3} 1.8-2.7 (m, 5p, Bz), 3.80 (s, 1p, H-1), 4.66 (d, 1p, H-2), 5.46 (d, 2p, C-5 CH₂), 5.6-6.0 (m, 1p, H-4), 7.2-8 (m, 3p, CH₂-C≡N and H-3), 8.43, 8.63 (2s, 6p, 2 Ac).

Anal. Calcd. for $C_{18}H_{19}N_1O_7$: C, 59.82; H, 5.31; N, 3.81. Found: C, 59.56; H, 5.17; N, 3.53.

The minor component was crystallized from ethanol to give 1-O-acetyl-5-O-benzoyl-3-C-carboxymethyl-2,3-γ-lactone-3-deoxy-β-D-ribofuranose [CXV], m.p. 137°, $[\alpha]_D^{24} -95.7^\circ$ (c 1.6, in chloroform); ir (nujol) 1700-1780 cm^{-1} (C=O); $\tau_{CDCl_3}^{13} 1.9-2.7$ (m, 5p, Bz), 3.6 (s, 1p, H-1), 5.0 (d, 1p, H-2), 5.5-5.9 (m, 3p, C-5CH₂ and H-4), 6.7-7.5 (m, -CH₂-C-O and H-3), 8.0 (s, 3p, Ac).

Anal. Calcd. for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found: C, 59.80; H, 5.18.

6-Chloro-9-(2'-O-acetyl-5',6'-di-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-allofuranosyl)-purine [CXVI]

A thoroughly dried, finely powdered intimate mixture of 1,2-di-O-acetyl-5,6-di-O-benzoyl-3-C-cyanomethyl-3-deoxy-β-D-allofuranose [CX] (1 g) and 6-chloropurine (350 mg) was heated in an oil bath at 160° and 30 mm pressure for 5 minutes, followed by further heating at 160° and 0.1 mm for an additional 40 minutes. The melt was then cooled to room temperature and extracted with dichloromethane (50 ml). Filtration and evaporation of the dichloromethane extract gave a yellow foam which was chromatographed on a column of grade II silica gel using benzene:ethyl acetate (1:1) as developer to afford two fractions. The first eluted component proved to be unreacted starting material (150 mg) and the second component was the title nucleoside CXVI (700 mg, 69% yield). This nucleoside remained as an amorphous foam and could not be crystallized: $[\alpha]_D^{22} -13^\circ$ (c 1.7, in chloroform);

ir (film) 2230 cm^{-1} ($\text{C}\equiv\text{N}$); τ^{CDCl_3} 1.42, 1.74 (2s, H-2, H-8), 3.9 (d, 1p, H-1', $J_{1',2'} = 2\text{ Hz}$), 7.2 (d, 2p, $\text{CH}_2\text{C}\equiv\text{N}$).

Anal. Calcd. for $\text{C}_{29}\text{H}_{24}\text{Cl}_1\text{N}_5\text{O}_7$: C, 59.19; H, 4.10; N, 11.87.
Found: C, 59.46; H, 4.35; N, 11.47.

6-Chloro-9-(2'-O-acetyl-5'-O-benzoyl-3'-C-cyanomethyl-3'-deoxy- β -D-ribofuranosyl)-purine [CXVIII]

A thoroughly dried mixture of 1,2-di-O-acetyl-5-O-benzoyl-3-C-cyanomethyl-3-deoxy- β -D-ribofuranose [CXIII] (722 mg) and 6-chloropurine (325 mg) was fused as described for compound CXVI. Chromatography of the material isolated after fusion on a column of tlc silica gel using benzene:ethyl acetate:ethanol (10:10:1) as developer afforded the title nucleoside CXVIII (600 mg, 66%) after crystallization from ethanol, m.p. $136.5\text{--}137^\circ$; $[\alpha]_{\text{D}}^{23} +15.5^\circ$ (c 1.5, in chloroform); ir (nujol) 2250 cm^{-1} ($\text{C}\equiv\text{N}$); τ^{CDCl_3} 1.5, 1.74 (2s, 2p, H-2, H-8), 3.96 (d, 1p, H-1', $J_{1',2'} = 1\text{ Hz}$), 7.2 (d, 2p, $\text{CH}_2\text{C}\equiv\text{N}$), 7.78 (s, 3p, Ac).

Anal. Calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_5\text{O}_5\text{Cl}$: C, 55.33; H, 3.98; N, 15.35.
Found: C, 55.00; H, 3.6; N, 15.14.

6-N,N-Dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy- β -D-allofuranosyl)-purine [CXXI]

To a solution of 6-chloro-9-(2'-O-acetyl-5',6'-di-O-benzoyl-3'-C-cyanomethyl-3'-deoxy- β -D-allofuranosyl)-purine [CXVI] (450 mg in 20 ml methanol) was added dropwise 25% aqueous dimethylamine solution (10 ml) and the mixture left to stand at room temperature for four hrs. After

evaporation of the solvent the remaining syrup was chromatographed on a column of tlc silica gel using dichloromethane:methanol (93:7) as developer to afford the title nucleoside (240 mg, 78% yield) which was crystallized from a methanol-ether mixture, m.p. 184-185°, $[\alpha]_D^{23}$ -66° (c 1.8, in methanol); uv $\lambda_{\max}$ 275 nm (ϵ 20,000 in methanol); cd $\lambda_{\max}$ 275 nm (θ -11,000, c 0.0047, in methanol); ir (KBr) 1630 cm^{-1} (C=O); τ^{CDCl_3} 2.0, 2.17 (2s, 2p, H-2, H-8), 6.57 (s, 6p, N(Me)₂), 6.93, 7.04 (2s, 6p, OCN(Me)₂); $\tau^{\text{DMSO-d}_6}$ 4.28, 4.64 (2d, 2p, C-2'OH, C-5'OH). Molecular weight Calcd: 394. Found by mass spectrometry: 394.

Anal. Calcd. for C₁₇H₂₆O₅N₆: C, 51.79; H, 6.64; N, 21.31. Found: C, 51.69; H, 6.71; N, 21.28.

6-N,N-Dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXXII]

To a solution of 6-chloro-9-(2'-O-acetyl-5'-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXVIII] (102 mg in methanol (7 ml)) was added dropwise a 25% aqueous solution of dimethylamine (2 ml). After 4 hr the solvent was evaporated and the residue chromatographed on a column of tlc silica gel using dichloromethane:methanol (93:7) as developer to afford the title amide nucleoside CXXII (64 mg, 72% yield) as a syrup. This compound was homogeneous by chromatography on paper (R_f 0.68 butanol:ethanol:water, 40:19:11), and on silica gel (R_f 0.42 dichloromethane:methanol 9:1); τ^{CDCl_3} 1.80 (s, 2p, H-2, and H-8), 6.10 (d, 1p, H-1'), 6.43 (b, 2p, C-5'OH and C-2'OH), 5.2-6.5 (m, 4p, H-2, H-4, and C-5'CH₂), 6.53 (s, 6p, N(Me)₂),

6.97, 7.08 (2s, 6p, $\overset{\text{O}}{\underset{\text{||}}{\text{CN}}(\text{Me})_2}$). This compound could not be induced to crystallize; $[\alpha]_{\text{D}}^{25} -31.2^\circ$ (c 1.37, in water); uv λ_{max} 275 nm (ϵ 14,300, in water) ir (film) 3200-3500 cm^{-1} (OH), 1640 cm^{-1} (C=O).

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{N}_6\text{O}_4$: C, 52.74; H, 6.65; N, 23.06. Found: C, 50.86; H, 6.43; N, 22.40

6-N,N-Dimethylamino-9-(2',5'-di-O-acetyl-3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy- β -D-ribofuranosyl)-purine

A solution of CXXII (50 mg) in pyridine (0.5 ml) and acetic anhydride (0.5 ml) was stored at room temperature for 20 hrs. After this time the reaction mixture was diluted with ice water (10 ml) and extracted with chloroform (3 x 20 ml). The chloroform extracts were dried over sodium sulfate and evaporated. The material remaining after evaporation was chromatographed on a column of tlc silica to yield 55 mg (40%) of the title nucleoside as a syrup; $[\alpha]_{\text{D}}^{25} -25.2^\circ$ (c 1, in chloroform).

Anal. Calcd. for $\text{C}_{20}\text{H}_{28}\text{N}_6\text{O}_6$: C, 53.64; H, 6.29; N, 18.74. Found: C, 53.90; H, 6.31; N, 18.65.

Preparation of 6-N,N-Dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy- β -D-ribofuranosyl)-purine [CXXII] from CXXVIII

6-N,N-Dimethylamino-9-(3'-C-carboxymethyl-2',3'- γ -lactone-3'-deoxy- β -D-ribofuranosyl)-purine [CXXVIII] (30 mg) was dissolved in dimethylamine (3 ml) and allowed to stand at 0° for 4 hr. After evaporation of the dimethylamine from the reaction mixture, the branched-chain N,N-dimethylcarbamoylmethyl nucleoside CXXII (34 mg,

quantitative yield) was recovered, having ir and nmr spectra identical to those of the product obtained by treatment of CXVIII with aqueous dimethylamine.

Preparation of CXXII from CXXI

Sodium periodate (152 mg) was added to a solution of 6-N,N-dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy- β -D-allofuranosyl)-purine [CXXI] (275 mg in 21 ml water, 14 ml ethanol and 0.5 ml saturated sodium bicarbonate solution) and the mixture was stirred in the dark for 2.5 hrs. Sodium borohydride (212 mg) was then added and the reaction mixture was stirred for an additional 3 hrs. Unreacted borohydride was destroyed by the addition of a few drops of glacial acetic acid and the solvent was then evaporated. The residue was taken up in methanol, refluxed for five minutes and the methanol evaporated. The remaining material was dissolved in dichloromethane and inorganic material removed by filtration. The material remaining after evaporation of the filtrate was chromatographed on a column of tlc silica gel using dichloromethane:methanol (93:7) as developer to afford the pentose amide nucleoside CXXI (170 mg, 68% yield) as a syrup identical by nmr and ir with the product obtained by treatment of CXVIII with dimethylamine.

Preparation of 6-N,N-dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy- β -D-ribofuranosyl)-purine [CXXII] from CXXXI

6-N,N-Dimethylamino-9-(3'-C-cyanomethyl-3'-deoxy- β -D-ribofuranosyl)-purine [CXXXI] (20 mg) was dissolved in a mixture of methanol (4 ml)

and 25% aqueous dimethylamine (2 ml). After the reaction mixture had stood at room temperature for 12 hrs the solvent was evaporated to yield CXXII (23 mg, quantitative yield) as a syrup identical by ir and nmr with the product obtained by treatment of CXVIII with aqueous dimethylamine.

6-N,N-Dimethylamino-9-(3'-C-carboxymethyl-2',3'-γ-lactone-3-deoxy-β-D-ribofuranosyl)-purine [CXXVIII]

Sublimation of 6-N,N-dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXXII] (30 mg) at 210° and 0.1 mm afforded, after crystallization from ethyl acetate, the title lactone nucleoside CXXVIII (19 mg, 73%); m.p. 198-199° (with sublimation); $[\alpha]_D^{22}$ -57.5° (c 1.1, in chloroform); uv $\lambda_{\max}$ 274 nm (ϵ 14,500, in methanol); cd $\lambda_{\max}$ 274 nm (θ -10,000, c 0.004 in methanol); ir (KBr) 1770 cm^{-1} (C=O); τ^{CDCl_3} 1.73, 2.23 (2s, 2p, H-2, H-8), 6.48 (s, 6p, N(Me)₂); $\tau^{\text{DMSO-d}_6}$ 4.93 (t, 1p, C-5'OH). The hydroxyl absorption disappeared on addition of D₂O. Molecular weight Calcd: 319. Found by mass spectrometry: 319.

Anal. Calcd. for C₁₄H₁₇N₅O₄: C, 52.65; H, 5.37; N, 21.93. Found: C, 52.43; H, 5.54; N, 21.83.

6-N,N-Dimethylamino-9-(3'-C-carbamoylmethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXXIX]

6-N,N-Dimethylamino-9-(3'-C-carboxymethyl-2',3'-γ-lactone-3-deoxy-β-D-ribofuranosyl)-purine [CXXVIII] (30 mg) was dissolved in liquid ammonia (3 ml) and the ammonia was allowed to evaporated slowly during

a period of six hrs. The resultant residue was crystallized from ethanol to afford the title nucleoside CXXIX (30 mg, 95%), m.p. 207°, $[\alpha]_D^{23}$ -29.9° (c 0.5, in water); ir (nujol) 1650 cm^{-1} (C=O); $\tau^{\text{DMSO-d}_6}$ 2.60, 3.13 (b, 2p, $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{NH}_2$), 4.08 (d, 1p, C-2'OH), 4.83 (t, 1p, C-5'OH); uv λ_{max} 275 nm (ϵ 14,100 in water); cd λ_{max} 275 nm (θ -6,000, c 0.0057, in water).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_6\text{O}_4$: C, 49.99; H, 5.99; N, 24.98. Found: C, 49.59; H, 5.94; N, 24.72.

6-N,N-Dimethylamino-9-(3'-C-carbamoylmethyl-N-glycine ethyl ester-3'-deoxy- β -D-ribofuranosyl)-purine CXXX]

6-N,N-Dimethylamino-9-(3'-C-carboxymethyl-2',3'- γ -lactone-3-deoxy- β -D-ribofuranosyl)-purine [CXXVII] (40 mg) was dissolved in a mixture of N,N-dimethylformamide (0.75 ml) and ethyl glycinate (0.25 ml) and stirred at room temperature for 30 hr. Volatile material was removed by distillation (50°, 0.1 mm) and the remaining residue column chromatographed on tlc silica gel using dichloromethane:methanol (9:1) as developer to afford, after crystallization from ethyl acetate, the title nucleoside CXXX (38 mg, 72%), m.p. 155-7°, $[\alpha]_D^{25}$ -48.8° (c 1.3, in chloroform); uv λ_{max} 275 nm (ϵ 14,600, in water); cd λ_{max} 275 nm (θ -8,550, c 0.0043, in water); ir (KBr) 1730 (C=O ester), 1650 cm^{-1} (C=O amide); τ^{CDCl_3} 1.83, 2.00 (2s, 2p, H-2, H-8); 1.8 (b, 1p, NH), 4.10 (d, 1p, H-1), 8.70 (t, 3p, CH_3 of ethyl ester).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_6\text{O}_6$: C, 51.1; H, 6.21; N, 19.89. Found: C, 50.92; H, 6.19; N, 19.61.

6-N,N-Dimethylamino-9-(3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-
purine [CXXXI]

6-Chloro-9-(2'-O-acetyl-5'-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXVIII] (268 mg) was dissolved in anhydrous dimethylamine (30 ml) and stored at -10° for twenty days. The dimethylamine was then evaporated and the residue triturated with ether (5 ml). The material remaining after the ether was decanted was taken up in ethanol and allowed to stand at 0° for twenty four hrs. A portion of the title nucleoside (94 mg) crystallized directly out of this solution and a further 60 mg (total yield 78%) was obtained by chromatography of the mother liquor on a column of tlc silica gel using dichloromethane:ethanol (93:7) as developer. Nucleoside CXXXI was crystallized from ethanol, m.p. 206° with sublimation, $[\alpha]_D^{25}$ -39.4° (c 0.6, in ethanol); uv $\lambda_{\max}$ 275 nm (ϵ 15,800, in water); cd $\lambda_{\max}$ 275 nm (θ -6,100, c 0.0048, in water); ir (KBr) 2230 cm^{-1} (C≡N); $\tau^{\text{DMSO-d}_6}$ 1.70, 1.76 (2s, sp, H-2, H-8), 3.98 (d, 1p, H-1'), 6.80 (s, 6p, N(Me)₂).

Anal. Calcd. for C₁₄H₁₈N₆O₃: C, 52.82; H, 5.70; N, 26.40.
Found: C, 52.64; H, 5.64; N, 26.42.

6-N,N-Dimethylamino-9-(3'-(2''-acetamidoethyl)-3'-deoxy-β-D-ribofuranosyl)-
purine [CXXXIV]

6-N,N-Dimethylamino-9-(3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)-purine [CXXXI] (32 mg) was dissolved in a mixture of acetic anhydride (2 ml) and absolute ethanol (2 ml) and hydrogenated over platinum oxide

(20 mg) at 60 psi for four hrs. The catalyst was then removed by filtration and the solvent evaporated to afford 40 mg of syrup. Examination of this product by tlc showed that it contained two components (R_f 0.18 and 0.10, R_f CXXI 0.62 in dichloromethane:ethyl acetate:ethanol 5:5:1). These two components were separated by column chromatography on tlc silica gel using the above developer, to afford 17 mg of the faster component, $\tau^{\text{DMSO-d}_6}_6$ 2.14 (broad t, 1p, N-H), 7.85, 8.04, 8.20 (3s, 9p, 3Ac), no hydroxyl signals and 19 mg of the slower component, $\tau^{\text{DMSO-d}_6}_6$ 2.22 (broad t, 1p, N-H), 4.18 (d, 1p, C-2'OH), 7.98, 8.17 (2s, 6p, 2Ac).

The slower moving component was dissolved in 25% aqueous dimethylamine solution for 3 hrs. After evaporation of the solvent the remaining material crystallized on trituration with dichloromethane. Reaction of the faster moving component under the same conditions afforded the identical product. The above two products were combined and recrystallized from an isopropanol water mixture to yield CXXIV (23 mg, 63%) which crystallized as the hemi-hydrate, m.p. 193-194°, $[\alpha]_D^{25}$ 1.0 ($\underline{c}$ 0.9, in ethanol); uv λ_{max} 274 nm (ϵ =23,900 water); $\tau^{\text{DMSO-d}_6}_6$ 1.56, 1.76 (2s, 2p, H-2, H-8), 2.19 (t, 1p, N-H), 4.0 (s, 1p, H-1'), 8.23 (s, 3p, N-Ac).

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{N}_6\text{O}_4 \cdot 1/2\text{H}_2\text{O}$: C, 51.47; H, 6.74; N, 22.47.
Found: C, 51.38; H, 6.39; N, 22.07.

Chloromercuri-6-benzamidopurine

To a stirred solution of 7.8 g (0.028 mole) of mercuric chloride in 100 ml of 50% aqueous ethanol was added 6.8 g (0.028 mole) of 6-benzamidopurine. To the resulting suspension, 10.3 ml of 10% aqueous

sodium hydroxide (0.028 mole) was added dropwise with stirring. The yellow mixture was stirred 1 hr and then allowed to stand at room temperature for a period of 20 hr. The white solid was filtered, washed with 25 ml of cold 50% aqueous ethanol and dried in vacuo over phosphorus pentoxide: yield, 13g (96%). Reported (176): yield 96%.

6-Benzamido-9-(2'-O-acetyl-5',6'-di-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-allofuranosyl)-purine [CXXXVI]

Hydrogen bromide was bubbled into a solution of 1,2'-di-O-acetyl-5,6-di-O-benzoyl-3-C-cyanomethyl-3-deoxy-β-D-allofuranose [CX] (1 g, 2.02 mmole) in anhydrous dichloromethane (50 ml) at 0° for fifteen minutes. After the reaction mixture was left to stand at 0° for 1 hr and then at room temperature for 15 minutes, the solution was evaporated to a syrup and the last traces of hydrogen bromide were removed by co-evaporation with dry toluene. The syrup, dissolved in dry toluene (40 ml), was immediately added to a suspension of chloromercuri-6-benzamidopurine (960 mg, 2.02 mmole) and Celite (300 mg) in dry toluene (30 ml). After refluxing for 45 minutes the hot solution was filtered and evaporated. The residue after evaporation was taken up in dichloromethane (120 ml) and washed successively with aqueous potassium iodide (30%, 2 x 20 ml) and water (2 x 20 ml). The dried (sodium sulfate) solution was evaporated and the resultant material chromatographed on silica gel (60 g, benzene:ethyl acetate (1:1) as developer) to give the title nucleoside CXXXVI (900 mg, 60% yield) as an amorphous foam; $[\alpha]_D^{22}$ -37° (c 1.5, in chloroform); ir film 2230 cm^{-1} (C≡N); τ_{CDCl_3} 0.8 (b, 1p, NH), 1.38 (s, 1p, H-2), 1.9-2.8

(m, 16p, 3 Bz and H-8), 7.25 (d, 2p, $\text{CH}_2\text{C}\equiv\text{N}$).

Anal. Calcd. for $\text{C}_{36}\text{H}_{30}\text{N}_6\text{O}_8$: C, 64.07; H, 4.45; N, 12.47. Found: C, 63.76; H, 4.72; N, 12.08.

Attempted preparation of CXXXVI using titanium tetrachloride
chloromercuri-6-benzamido-purine method (176)

A mixture of CX (100 mg), chloromercuri-6-benzamidopurine (105 mg), Celite (100 mg) and anhydrous xylene (15 ml) was dried by distilling off the xylene under reduced pressure (about 50 mm). To the resulting residue was added anhydrous ethylene chloride (25 ml) and 15 ml of the solvent was distilled. The mixture was then cooled to 30° and titanium tetrachloride was (30 μl) added and the reaction mixture was heated under reflux for 16 hrs. The cooled reaction mixture was poured into saturated sodium bicarbonate solution and stirred vigorously for 30 min. and then filtered. The filter cake was washed with dichloromethane (10 ml) and the combined organic extracts were washed with 30% aqueous potassium iodide solution (5 ml) and water (3 x 5 ml). The organic extract was then dried over sodium sulfate and the solvent evaporated. The remaining residue was chromatographed on a column of silica gel to yield 50 mg of a homogeneous syrup;
 τ^{CDCl_3} 1.8-2.8 (m, 10p, 2 Bz), 7.80 (s, 3p, Ac). The compound did not contain a purine moiety.

6-Benzamido-9-(2'-O-acetyl-5'-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-
β-D-ribofuranosyl)-purine [CXXXVII]

Hydrogen bromide was bubbled into a solution of 1,2-di-O-acetyl-5-O-benzoyl-3-C-cyanomethyl-3-deoxy-β-D-ribofuranose [CXIII] (500 mg) in anhydrous dichloromethane (25 ml) at 0° for 15 minutes. After being kept at 0° for 1 hr and at room temperature for 15 minutes, the solution was evaporated to a syrup and the last traces of hydrogen bromide were removed by co-evaporation with dry toluene. The resultant syrup was redissolved in toluene (10 ml) and added to a suspension of chloromercuri-6-benzamidopurine (658 mg) and Celite (500 mg) in toluene (50 ml) at 65°. (The above Celite, chloromercuri-6-benzamidopurine mixture had been previously dried by distilling off 20 ml of toluene from the mixture.) When addition was completed the mixture was refluxed for one hr and then worked up as previously described for compound CXXXVII. The material resulting from this procedure (508 mg) was chromatographed on silica gel using benzene:ethyl acetate:ethanol (5:5:1) as developer to afford nucleoside CXXXVII (298 mg, 40% yield) as an amorphous foam; $[\alpha]_D^{25} +3.1^\circ$ (c 1.2, in chloroform); ir (film) 2250 cm^{-1} (C≡N); $\tau_{\text{CDCl}_3}^{13\text{C}}$ 0.75-1.00 (b, 1p, NH) 1.46 (s, 1p, H-2 or H-8), 7.26 (d, 2p, -CH₂-C≡N), 7.83 (s, 3p, Ac).

Anal. Calcd. for C₂₈H₂₄N₆O₆: C, 62.22; H, 4.48; N, 15.55. Found: C, 61.99; H, 4.80; N, 15.50.

9-(3'-C-Aminoethyl-3'-deoxy-β-D-allofuranosyl)-adenine [CXXXIX]

To a suspension of LAH (210 mg, 5.5 mmole) in tetrahydrofuran (150 ml) was added dropwise a solution of 6-benzamido-9-(2'-O-acetyl-

5',6'-di-O-benzoyl-3'-C-cyanomethyl-3'-deoxy- β -D-allofuranosyl)-purine [CXXXVI] (826 mg, 1.23 mmole) in THF. After 0.5 hr at room temperature and 2 hr reflux the excess reagent was destroyed by slow addition of water (10 ml), ethanol (10 ml), and 5 N NH_4OH (10 ml). The resulting precipitate was removed by filtration and washed with ethanol (50 ml). The residue obtained by evaporation of the combined filtrate and washings was partitioned between dichloromethane (10 ml) and water (75 ml). Examination of the dichloromethane extract showed that it contained no nucleoside, nor any material giving a positive test with ninhydrin. The water extract was evaporated to dryness and the remaining material (700 mg) taken up in ethanol and left at 0° overnight. From this solution was obtained 200 mg of crystalline product having an ultraviolet spectrum similar to that of adenosine. The ultraviolet spectrum of the mother liquor indicated that it contained a negligible amount of nucleoside.

The above crystalline material was dissolved in 2% acetic acid (2 ml) and chromatographed on 5 ml of Dowex 50 W-X2 (NH_4^+ form) resin. The column was first washed with 100 ml water and then with 5% ammonium hydroxide to afford after crystallization of the main component from methanol nucleoside CXXXIX (80 mg, 20%), m.p. 170-171°, $[\alpha]_D^{25}$ -59.1° (c 1.2, in water); uv λ_{max} 261 nm (ϵ 15,000, in water); $\tau_{\text{DMSO-d}_6}$ 1.66, 1.82 (2s, 2p, H-2, H-8), 2.70 (b, 2p, NH_2), 4.10 (d, 1p, H-1'), 4.2-4.6 (b, 2p, NH_2), 5.28 (t, 1p, H-2').

Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{N}_6\text{O}_4$: C, 48.14; H, 6.62; N, 25.91. Found: C, 44.45; H, 5.41; N, 21.69. The sample contained some inorganic material which could not be removed.

ADDENDA

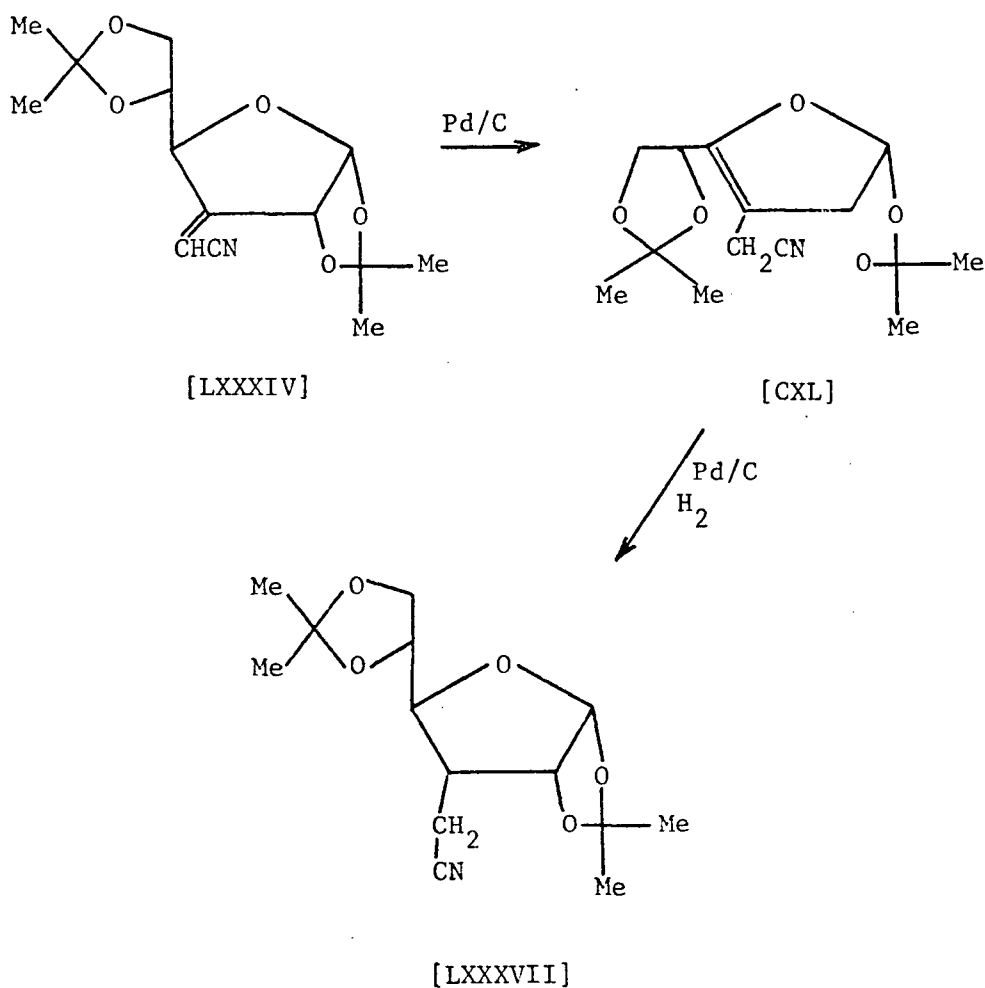
An interesting rearrangement of cyanovinyl sugar LXXXIV was discovered too late to be included in the body of this thesis and is therefore added as a brief note here.

When a sample of LXXXIV (1 g, R_f 0.49 benzene:methanol 9:1) was hydrogenated at ambient pressure and temperature over 5% palladium-on-charcoal (500 mg), it was observed that reduction was very slow (0.19 equivalents of hydrogen absorbed in 24 hours). Apparently in this case the catalyst had been inadvertently poisoned as normally this hydrogenation was completed in about two hours. A tlc examination of the hydrogenation mixture after 24 hours indicated the presence of three components (R_f 0.57 major, R_f 0.49 and R_f 0.35 benzene:methanol 9:1). The catalyst was then removed by filtration, the solvent was evaporated and the remaining material was chromatographed on tlc silica gel (with benzene:ethyl acetate 4:1 as developer). This procedure afforded three compounds.

Two of these products were readily identified, one being the unreduced starting material LXXXIV (170 mg, R_f 0.49) and the other being the expected reduction product LXXXVII (140 mg, R_f 0.35). Surprisingly the third component was identified on the basis of nmr evidence as the unsaturated sugar CXL (τ^{CDCl_3} 3.97 (d, 1p, H-1, $J_{1,2} = 5$ Hz), 4.71 (broad d, 1p, H-2), 5.28 (broad t, 1p, H-5), 5.6 - 6.2 (m, 2p, C-6 methylene), 6.55 (d, 2p, CH_2CN). These nmr values should be compared with those obtained from enol acetate LXXI (τ^{CDCl_3} 3.97 (d, 1p, H-1), 4.60 (d, 1p, H-2), 5.30 (t, 1p, H-5),

5.97 (d, 2p, C-6 methylene). Hydrogenation at ambient pressure and temperature of CXL over active 5% palladium-on-charcoal afforded as the only product the cyanomethyl sugar LXXXVII.

A palladium catalyzed rearrangement of a double bond has been noted by Slessor and Tracy (119) in the hydrogenation of enol acetate LXXI. Further investigation of the palladium catalyzed rearrangements of these branched-chain sugars is underway.



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