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PART ONE: SYNTHESIS AND REACTIONS
OF CARBONYL SUGARS

PART TWO: SYNTHESIS AND MODIFICATION
OF NUCLEOSIDES

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By
David C. Baker, B.S.

* * * * *

The Ohio State University
1973

Reading Committee:
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Prof. R. Mayer
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Approved by

Adviser
Department of Chemistry
DEDICATION

To Mother, who endured the years with a chemistry lab under her kitchen;

To Dad, who suffered with an enthusiastic chemist, but a less-than-willing farmhand.
The author thanks Prof. Derek Horton for the opportunity to work in his laboratory and for his example—his abundant energies and enthusiasm for carbohydrate chemistry. Thanks are also extended to my fellow coworkers, especially Dr. Joe Wander, for their interests and contributions relative to this work. The secretarial staff, Mrs. Sally Sayre and Mrs. Donna Salzgaber, and Mr. Bill Rond and the technical personnel, are acknowledged for their support. A special acknowledgment is extended to the undergraduate team of Mr. Ron Arrick, Mr. Chuck Boeder, Mr. Dave Brown, Mr. Bob Nickol and Mr. Bill Weaver, who played a major role in this and related work. Appreciation is extended to the Graduate School for a most generous fellowship, to the Department of Chemistry for a teaching appointment, and to The Ohio State University Research Foundation for support on Projects 759 (National Institutes of Health Grant No. CA-03232-13S1), 1820 (National Institutes of Health Grant No. GM-11976) and 3443-A1 (National Science Foundation Grant No. GP-33524).
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PART ONE:
SYNTHESIS AND REACTIONS OF
CARBONYL SUGARS
I. INTRODUCTION AND HISTORICAL BACKGROUND

A. The Role of Carbonyl Sugars in Carbohydrate Chemistry and Biochemistry

The term "carbonyl sugar" refers to a large class of dicarbonyl carbohydrates in which one carbonyl group is derivatized in the form of an acetal or hemiacetal, whereas the other one exists either free, or, especially in an aqueous solution, hydrated as a gem diol. Because of the high degree of reactivity of the carbonyl functionality, these compounds have achieved importance as intermediates for the synthesis of amino sugars,¹ deoxy sugars,²-⁴ and branched-chain sugars.⁵ Certain dicarbonyl sugars were

---


early postulated\(^6\),\(^7\) as transient, highly reactive inter-

\begin{enumerate}
\item J. U. Nef, *Ann.*, 357, 214 (1907); 376, 1 (1910).
\end{enumerate}

mediates (3-deoxy-aldos-2-uloses) in the acid- and base-
catalyzed degradation of sugars. Many such compounds have
since been prepared\(^8\)-\(^{10}\) or isolated\(^\text{11}\) as improved techniques

\begin{enumerate}
(1960); *ibid.*, 25, 671 (1961).
\item E. F. L. J. Anet, *J. Amer. Chem. Soc.*, 82,
\item H. El Khadem, D. Horton, M. H. Meshreki and
M. A. Nashed, *Carbohyd. Res.*, 13, 317 (1970); *ibid.*, 17,
183 (1971); *ibid.*, 22, 381 (1972).
\end{enumerate}

have become available. An important reaction, which is
involved in the non-enzymic "browning" of many foodstuffs,
can be traced to the involvement of 3-deoxy-aldos-2-uloses
as intermediates in reactions of sugars with amino acids.\(^\text{12}\)

\begin{enumerate}
(1959).
\end{enumerate}

These particular compounds have also been of interest as
possible agents involved in carcinostasis.\(^\text{13-15}\)
Biological transformations of sugars, such as the interconversion by epimerization at C-4 of D-galactose and D-glucose, as well as certain dehydrations of sugars to produce their deoxy analogs are postulated to occur by way of transient, keto-sugar intermediates that are glycosyl esters of nucleoside pyrophosphates. These and related reactions are discussed in authoritative reviews.

Although the occurrence of carbonyl sugars in Nature as terminal metabolites is rather infrequent, a few noteworthy examples do exist. These are, for the most part,
constituents of antibiotics,\textsuperscript{20} such as $\beta$-deoxy-$\alpha$-arabino-

\[ \text{hexose-5-ulose (1), isolated from Hygromycin A;}\textsuperscript{21,22} \]

\[ \text{a novel disaccharide, "3-ketosucrose" (}$\alpha$-$\alpha$-\text{ribo-hexopyranosyl-}\]

\[ \text{3-ulose $\beta$-fructofuranoside, 2), a metabolite from} \]

\[ \text{1} \]

\[ \text{2} \]
Agrobacterium tumefaciens$^{23}$ and 4,6-dideoxy-hexos-2,3-

---


---

diulose (3), indicated to be a structural component of actinospectacin.$^{24}$ Branched-chain dialdoses, such as

---


---

L-streptose (4)$^{25,26}$ and its 4-C-hydroxymethyl analog,

---


---

L-hydroxystreptose (5)$^{25,26}$ are more common, especially

---

![Chemical structures](image)
in antibiotics produced by certain streptomycetes.\textsuperscript{5} Since 1972, a number of 3-\(\text{C}\)-acetyl branched-chain sugars\textsuperscript{27} have been identified in antibiotics of the quinocycline complex. A structurally most unusual sugar is aldgarose \textsuperscript{(6)},\textsuperscript{28} a component of aldgamycin E; aldgarose has a unique cyclic carbonate structure.

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

B. The Synthesis of Carbonyl Sugars

E. Fischer reported in 1888 the first synthesis of a carbonyl sugar, \(\alpha\)-\text{arabino-hexos-2-uloose},
Synthesis of $\text{D-arabino-hexos-2-ulo}$

which was formed by the acid-catalyzed hydrolysis of
"glucosazon" ($\text{D-arabino-hexulose phenylsazone}$). This

work initiated activity extending over half a century
that led to synthesis of many aldols-2-uloses (aldosulososes,
earlier "osones") from a variety of sugars. An

exchange reaction between an aldehyde, usually benzaldehyde,
and an arylosazone of the sugar has largely replaced
Fischer's original method and today remains the best route
for obtaining aldoses-2-uloses, and, especially, the 3-deoxyaldoses-2-uloses.

1. Oxidation of primary hydroxyl groups. --- Dialdoses constitute a group of dicarbonyl sugars in which the terminal hydroxymethyl group has been oxidized to an aldehyde group. As terminal aldehydes, these compounds have been prepared via the glycol cleavage of higher-carbon sugars.

Typically, pentodialdofuranoses may be readily prepared from suitably protected hexofuranoses, by cleavage of a terminal, extracyclic glycol group with either lead tetraacetate or periodic acid, the latter reagent being generally the one of choice.

Direct oxidation of a primary alcoholic group in a sugar is often difficult to control. Partial oxidation beyond the aldehyde stage may occur, yielding the carboxylic acid, and complex mixtures of products can result because of concomitant oxidation elsewhere in the molecule.
However, in recent years the development of mild oxidation reagents \(^{36-38}\) has permitted the direct synthesis of sugar aldehydes (dialdoses) from suitable precursor alcohols. Of all these reagents, that of Pfitzner and Moffatt, \(^{39}\)

which makes use of a combination of methyl sulfoxide—dialkyl carbodiimide, is the most versatile for producing dialdoses in high yields. Applications of this reagent include a synthesis of a nucleoside 5'-aldehyde, \(^{39,40}\) as well as the preparation of aldehydes derived from suitably protected pyranose \(^{41,42}\) and furanose \(^{43}\) sugars. A limitation
of the reagent is the fact that formation of a (methylthio)methyl ether is generally a competing reaction, and yields of by-product amount to 5-10% (or more) of the total products with some non-hindered, primary alcohols. The conditions may be optimized for production of the aldehyde by using various acid catalysts, with both pyridinium trifluoroacetate and pyridinium phosphate being preferred over the free acids. Diisopropylcarbodiimide and diethylcarbodiimide, which, in the course of the reaction, generate organic-soluble and water-soluble ureas, respectively, greatly facilitate the isolation procedure in some instances. Also, sensitive aldehydes may be conveniently isolated as their crystalline 1,3-diphenylimidazolidine.
Several mechanistic studies of the Pfitzner—Moffatt oxidation have appeared. Generally, the mechanism as originally proposed has proven to be entirely consistent with subsequent interpretations. Further investigations have led to a plausible mechanism, that has been confirmed by isotope-labeling experiments, as outlined [Chart I]. Protonated carbodiimide (a) has been shown to form an adduct (c) with methyl sulfoxide (b); n.m.r. spectroscopy has demonstrated this reaction to be readily reversible. Subsequent attack by the electron-rich alcohol (d) on (c) leads to either an ionic species (e) [Path 1] or a tetracovalent intermediate (f) [Path 2] that decomposes with intramolecular hydrogen transfer to the sulfur ylid-ylene species (g). Subsequent decomposition of (g) leads to the carbonyl product (h), accompanied by the formation of dimethyl sulfide (i). The foregoing and
CHART I: Mechanism for the Pfitzner-Moffatt Oxidation Reaction
related mechanisms are discussed at length in an authori-
tative review.52

(52) J. G. Moffatt, Sulfoxide-Carbodiimide and
Related Oxidations, in "Oxidation," Vol. 2, ed. by J. M.
Augustine and D. J. Trecker, Marcel Dekker, New York, 1971,
Chapter 1.

Related methyl sulfoxide--based reagents, such as the
ones using acetic anhydride53,54 or phosphorus pentaoxide,55

30, 1107 (1965).

(54) J. D. Albright and L. Goldman, J. Amer. Chem.
Soc., 87, 4214 (1965); ibid., 69, 2416 (1967).

(55) K. Onodera, S. Hirano, and N. Kashimura,
J. Amer. Chem. Soc., 87, 4651 (1965); Carbohyd. Res., 6,
276 (1968).

although useful for oxidizing isolated, secondary hydroxyl
groups,56 have been generally found unsuitable for produc-

(56) D. Horton and J. S. Jewell, Carbohyd. Res., 2,
251 (1966).

tion of aldehydes, although the latter reagent has been used
to a limited extent, with careful control of conditions,
to give a formyl branched-chain sugar57 and an aldosulose58

16, 177 (1971).

from a suitably protected ketone. With both reagents formation of the (methylthio)methyl ether ether poses serious complications.\textsuperscript{36} The undesired products amount in some cases to the preponderant products\textsuperscript{43,59} isolable


from the reaction mixtures. The methyl sulfoxide—acetic anhydride reagent also leads, in an additional competing reaction, to formation of primary acetates.\textsuperscript{59} Although (methylthio)methyl ether formation has been shown to be minimal with methyl sulfoxide and sulfur trioxide—pyridine,\textsuperscript{60} the latter reagent has only occasionally been


used for the oxidation of sugar derivatives.\textsuperscript{61,62} Formation


of novel, but undesirable, elimination products\textsuperscript{61} is a serious problem in using the reagent.
An unusual ketene-imine derivative, \( \text{Ph}_2\text{C}=\text{C}=\text{N}^-\text{CH}_3 \) in methyl sulfoxide has been used to oxidize 2',3'-O-isopropylideneadenosine to its 5'-aldehyde, reportedly in good yield.\(^{63}\) For preparation of numerous sugar aldehydes, an alternative route that involves photolysis of primary azides is of value in both monosaccharide\(^{64,65}\) and polysaccharide\(^{66}\) systems.

2. Oxidation of secondary hydroxyl groups.— The oxidation of isolated, secondary hydroxyl groups in carbohydrate systems requires a special set of conditions in that the oxidant must (a) be powerful enough to effectively oxidize the secondary, often hindered, alcoholic functions, and (b) at the same time, leave unaffected the often sensitive protecting groups elsewhere in the molecule. Historically, this has been a difficult
task, but in recent years with the development of new reagents, the synthesis of keto sugars has become commonplace.

The controlled oxidation of secondary alcoholic functions, other than the classical "osone" synthesis of Fischer (see p. 8) has been generally effected either via platinum-catalyzed oxidations or by the use of some of the chromium(VI) oxide reagents. By the former method, the configuration and conformation of the sugar have been shown with many examples, to be of the utmost importance in determining the site of oxidation. Indeed, with the conformationally rigid 1,6-anhydroaldohexopyranoses, a distinct regiospecificity has been noted, whereby a single hydroxyl group is oxidized in otherwise unprotected sugars.

An ordering of reactivity was noted in the series of all eight 1,6-anhydrohexopyranoses, whereby the tendency for oxidation falls in the order: 3-ax. > 4-ax. > 2-ax. > 4-eq. > 2-eq. > 3-eq.
Oxidations with chromium(VI) oxide reagents have almost entirely been limited to the chromium(VI) oxide—pyridine complex\(^6\) as used by Sarett.\(^7\) Fair results have been obtained with this reagent; Wolfrom and Hanessian reported a yield of 50% in the oxidation of 3-0-benzyl-1,2-isopropylidene-\(\alpha\)-D-xylofuranose to the 5-ulose.\(^7\)

Other oxidations on either hydroxy groups in pyranose derivatives\(^2\) or on alcoholic exocyclic chains\(^7\),\(^5\),\(^6\)


have been reported, with variable results. Cyclic furanose systems are generally oxidized only at the anomeric center, and the procedure can be used to prepare aldonolactones\textsuperscript{77} in high yield. A degree of selectivity has been noted in the oxidation of sugars that have more than one free hydroxy group.\textsuperscript{78,79} The chromium(VI) oxide–pyridine complex is also useful for the oxidation of alditols, where the yield of product was found to be highly dependent on the stereochemical environment of the hydroxyl group.\textsuperscript{80} Configuration at the anomeric center has been shown to have an effect towards determining the success of the oxidation of alcoholic groups at C-2.\textsuperscript{81,82}


\textsuperscript{(78)} A. Assarsson and O. Theander, \textit{Acta Chem. Scand.}, 11, 1557 (1957); \textit{ibid.}, 12, 1507 (1958); \textit{ibid.}, 18, 727 (1964).


As with the synthesis of dialdoses, perhaps the best oxidation reagents for keto sugar synthesis have proven to be the methyl sulfoxide-based reagents. The Pfitzner-Moffatt reagent provides a route to 2'- and 3'-uloses of suitably protected nucleosides, although difficulty with elimination reactions in the oxidation of 2-deoxy nucleosides has severely limited the usefulness of the reagent in this field. With some furanose derivatives, for reasons which are not yet clear, the reagent has been claimed to fail to effect the desired oxidations (for an explanation in one example, see p. 30); however, in other instances with furanoid compounds (such as 5-deoxy-1,2-O-
isopropylidene-$\beta$-$\text{L}$-arabinofuranose,\textsuperscript{85} an intermediate in a synthesis of $\text{L}$-streptose (4)\textsuperscript{21,22,85} the oxidation proceeds without difficulty.

More potent than the Pfitzner–Moffatt reagent, a methyl sulfoxide–acetic anhydride\textsuperscript{53,54} combination is the more useful for the oxidation of isolated, secondary hydroxy groups, and it offers considerable procedural advantage in the isolation of products, as the reagents are easily lyophilized.\textsuperscript{56} The reagent has been found compatible with a variety of protecting groups, including sensitive benzeneboronic esters.\textsuperscript{86–88} Secondary hydroxyl groups,\textsuperscript{89,90} as well as hydroxyl functions in both

\begin{itemize}
  \item \textsuperscript{(88)} B. Lindberg, Methods Carbohydr. Chem., 6, 323 (1972).
\end{itemize}
Pyranoid\textsuperscript{56,91-100} and furanoid\textsuperscript{101-108} ring systems are


oxidized effectively. The oxidant is also suited for the oxidation of sterically congested, suitably blocked alditols,\textsuperscript{109,110} and has found use in polysaccharide oxidation.\textsuperscript{111}

In a majority of these examples, (methylthio)methyl ethers, and occasionally acetates, were noted as by-products, especially in pyranoid-ring systems possessing an equatorial hydroxy group. In one instance, the (methylthio)methyl ethers that formed served as useful blocking groups\textsuperscript{112} for further synthesis.

A noticeably higher yield of ketone could be obtained from the isomeric pyranose having the hydroxyl group...
axially, rather than equatorially, disposed.

Oxidations with a methyl sulfoxide-based reagent that contains 1.2–2.0 molar equivalents of phosphorus pentaoxide per mole of methyl sulfoxide are best performed with N,N-dimethylformamide as solvent, and have been shown superior to those performed with the Pfitzner–Moffatt reagent in some examples. Secondary alcohols of both furanoid and pyranoid systems, as well as exocyclic secondary alcoholic groups, have been oxidized by using this reagent.

Since oxidation of secondary, isolated, and often sterically hindered alcohols in carbohydrate systems requires a powerful oxidant that can be used in the presence of sensitive blocking groups, ruthenium tetroxide, a reagent that had prior to 1964 found application largely in the steroid field, has been shown to meet these

---


requirements admirably. The reagent has been successfully applied in furanoid systems, 119-130 pyranoid.


systems, 119, 120, 122, 123, 131-143 and with a suitably


protected adenine nucleoside. The oxidant is most

typically used in carbon tetrachloride, although chloroform and dichloromethane are also suitable, with some sacrifice in reaction rate.121 Ruthenium tetraoxide is readily generated from a hydrated, 50—60% preparation of ruthenium dioxide with sodium metaperiodate, and it may be extracted into the organic solvent and used directly. A most attractive procedure makes use of a catalytic amount of ruthenium tetraoxide that is continuously regenerated with an aqueous solution of periodate.118,122,123,134,135 For systems insensitive to base, a dilute solution of sodium hypochlorite145 may be used as the oxidant. A


serious limitation in oxidations with furanoid systems appears to be over-oxidation to form ring-expanded lactones,128 although, by carefully regulating conditions, and using the less-soluble potassium metaperiodate, the problem is minimized.123

In addition to chemical methods of oxidation, enzymes from various strains of Acetobacter are known to oxidize alditols to give ketoses in high yields.146 The bacterial

organisms are highly specific, producing enzymes that "recognize" certain structures within a molecule and selectively, through a dehydrogenase reaction, produce carbonyl derivatives. Acetobacter xylinum oxidizes a penultimate hydroxyl group, only in the cases where it is flanked on both sides with a secondary and a primary hydroxyl group of D- or L-erythro configuration.¹⁴⁷


Specificity is noted in the activity of Acetobacter suboxydans, where only a hydroxyl group in a D-erythro configuration are selectively oxidized.¹⁴⁸-¹⁴⁹ By proper choice of bacterial strain, selected transformations are possible for a wide range of alditols,¹⁴⁶ dithioacetals¹⁵⁰


and 2-acetamido-2-deoxyalditols.¹⁵¹

C. Synthesis and Reactions of 1,2:5,6-Di-\text{\textcopyright}isopropylidene-\text{\textcopyright}ribo-hexofuranos-3-ulose

1. Synthesis.-- Perhaps one of the most useful carbonyl sugars, from the standpoint of synthetic carbohydrate chemistry, is 1,2:5,6-di-\text{\textcopyright}isopropylidene-\text{\textcopyright}ribo-hexofuranos-3-ulose (8) [Chart II, p. 40], produced by the oxidation of 1,2:5,6-di-\text{\textcopyright}isopropylidene-\text{\textcopyright}glucofuranose ("diacetone glucose," 7). Early attempts to oxidize the sterically hindered 3-hydroxyl group of diacetone glucose (7), a compound known since 1895, had ended in failure. It was in 1964 that Theander reported the first synthesis of the 3-ulose (8), isolated as the crystalline hydrate (9) in 6% yield, by using the chromium(VI) oxide—pyridine reagent under carefully controlled conditions in acetic acid. With the development of new reagents for the oxidation of carbohydrates, improved syntheses for the 3-ulose 8 appeared rapidly in the ensuing years. Diacetone glucose was reported, although quite

(152) E. Fischer, Ber., 28, 1145 (1895).

erroneously,* not to be oxidized\textsuperscript{83} by the Pfitzner–Moffatt

\textsuperscript{*}The report\textsuperscript{83} was based on the observation that no carbonyl band was detected in the i.r. spectrum, and the fact that 8 rapidly hydrates to form 9 was not considered. Subsequent work has shown that the Pfitzner–Moffatt reagent converts 7 into 8 in essentially quantitative yield.\textsuperscript{52}

reagent;\textsuperscript{39} however, Sowa and Thomas\textsuperscript{101} found that the methyl sulfoxide–acetic anhydride reagent\textsuperscript{53,54} gives the desired 3-ulose in high yield. An improved, preparative-scale procedure that, under the conditions specified, is reported to give maximum yield of the ketone, with a minimum of the 1,2:5,6-di-O-isopropylidene-3-O-(methylthio)-methyl-a-D-glucofuranose by-product, has recently appeared.\textsuperscript{154}

\textsuperscript{(154) J. D. Stevens, Methods in Carbohydr. Chem., 6, 123 (1972).}

Methyl sulfoxide–phosphorus pentaoxide also gives acceptable yields of the product.\textsuperscript{55} However, the best, high-yielding procedurally simple method for the oxidation of diacetone glucose at least for small-scale preparations, appears to be an oxidation with ruthenium tetraoxide, as first described by Overend,\textsuperscript{119,120} and modified by Jones.\textsuperscript{123}
2. Reactions.--- The compound, 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose-3-ulose, (8), has been demonstrated to be synthetically useful for numerous structural modifications of D-glucose at C-3. Reductions with borohydride and lithium aluminum hydride have been reported to give compounds preponderantly of the D-allo configuration, although, one report cites the utility of 8 for the production, albeit in low yield, of C-3 tritium-labeled D-glucose. A facile, preparative route to the rare sugar, D-allose, recently shown to occur naturally in the Proteaceae family of plants, has been developed via the hydrolysis of 1,2:5,6-di-O-isopropylidene-α-D-allo-furanose, the major reduction product of compounds 8 or 9.


Nucleophilic alkylating reagents have been shown to add to the carbonyl group of \( \beta \), sometimes with a high degree of stereoselectivity, to give branched-chain sugars of the \( \beta \)-allo configuration. 1,3-Dithianyllithium effectively adds to give 3-C-(1,3-dithian-2-yl)-1,2:5,6-di-O-isopropylidene-\( \alpha \)-\( \beta \)-allofuranose\(^{159,160}\) in high yield.


Reformatsky-type condensations were found to lead exclusively to \( \beta \)-allo branched-chain compounds\(^{161}\), whereas,


in contrast, the addition of the conjugate base of nitromethane to \( \beta \) gives mixtures of C-3 epimeric products, the proportions varying with the conditions, as described in four separate reports\(^{161-164}\). The \( \beta \)-gluco isomer was found

to be the major isolable 3-epimer found in one study, a finding that is at variance with the concept of steric control exerted by the 1,2-O-isopropylidene group in most kinetically controlled reactions of 1,2-O-isopropylidene-α-D-furanos-3-ulose. Such an abnormal distribution of products has been established to be that of initial kinetic control to give exclusively the D-allo product; subsequent loss of water, with a base-promoted re-hydroxylation of the intermediate nitro-alkene can give rise to the analog having the D-gluco configuration. Pyridine-acetic anhydride treatment of 9 has been shown to give an enol acetate which, upon borohydride reduction, leads to 1,2:5,6-di-O-isopropylidene-α-D-gulofuranose from which the rare sugar, D-gulose, is readily prepared. Wittig syntheses have been demonstrated to provide
numerous 3-C-methylene compounds$^{161,169-173}$ that undergo
facile hydroxylation,$^{161,172,173}$ providing access to useful
3-C-branched sugars of the D-glucos configuration;
red$^{169-171,173}$ gives 3-C-branched-3-deoxy-D-allo products. An interesting alternative to the Wittig syn-
thesis that makes use of an α-metalated ethylisocyanico-
acetate has been employed in the synthesis of a 3-C-methylene
derivative which is useful for producing multifunctional
3-C-branched sugars.$^{174}$

Other chemical transformations of 1,2:5,6-di-O-
isopropylidene-α-D-ribo-hexofuranos-3-ulose ($\delta$) include:
the isolation of a product of its degradation, when exposed
either to water$^{175}$ or to heat,$^{176}$ the products of its
rearrangement under ultraviolet irradiation;\textsuperscript{177} a product that arises via deacetonation with mercury(II) chloride;\textsuperscript{176} and the Baeyer-Villiger synthesis of the lactone\textsuperscript{178} that is obtained as a by-product\textsuperscript{128} in the oxidation of 1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-glucofuranose (7) with ruthenium tetraoxide.
II. STATEMENT OF THE PROBLEM

The initial problem of this research was to investigate 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (8) as a synthetically useful intermediate for a large-scale production of D-allose (11), via the process outlined in Chart III (p. 45). Although numerous hydride reducing agents have been used for reduction of the ketone to give predominantly 1,2:5,6-di-O-isopropylidene-α-D-allofuranose, it was considered worthwhile to investigate in detail the stereoselectivity of the reduction with a number of hydride reducing agents, in order to devise a method which would optimize the yield of the D-allo product and to determine accurately the total steric course of the reduction. The most efficient process would then be applied to the large-scale synthesis of D-allose (11), while, hopefully, a less stereoselective reducing agent would be found that would provide the D-gluco epimer at C-3. Such an agent could provide the basis for a preparative route to 3-deuterated or 3-tritratated D-glucose, a labeled compound important for biochemical studies.
Secondly, the utility of the ketone $\mathcal{O}$ was to be investigated for the generation of a 3-C-chain-branched 1,2:5,6-di-O-isopropylidene-$\alpha$-D-allofuranose that could be further modified to give a 1-hydroxyethyl chain branch as found in aldagarose $^{28}$ (6) and related antibiotic sugars. $^{27}$

Thirdly, in an ever-widening search for new and useful methods for the controlled oxidation of derivatized carbohydrates for the synthesis of synthetically useful carbonyl sugars, a chromium(VI) oxide—dipyridine reagent $^{179-181}$ was to be investigated, and its usefulness evaluated in several systems.


III. DISCUSSION AND EXPERIMENTAL RESULTS

A. The Large-Scale Synthesis of D-Allose

1. General considerations.— D-Allose has been conventionally prepared via a Fischer—Kiliani synthesis from D-ribose.\textsuperscript{182} In addition to the difficulties involved in working with sodium cyanide, the route has the practical limitation in that D-ribose itself is an expensive sugar, and that the reaction also leads to D-altrose. D-Allose is isolated in only a 30% yield after a somewhat tedious reduction of the intermediate D-allono-1,4-lactone. The report of a facile synthesis of 1,2:5,6-di-O-isopropylidene-a-D-ribo-hexofuranos-3-ulose,\textsuperscript{123} and its reduction\textsuperscript{129} to 1,2:5,6-di-O-isopropylidene-a-D-allofuranose, which, upon hydrolysis gives D-allose,\textsuperscript{153} prompted a detailed study of the reduction of the ketone and application of these findings to a large-scale preparation of D-allose.

\textsuperscript{182} F. L. Humoller, Methods Carbohyd. Chem., 1, 102 (1962).
2. Large-scale oxidation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (7).— In a scaled-up modification\(^{122,123}\) of a procedure\(^{122,123}\) that had effectively been employed on one-gram portions of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (7), it was found that, with ordinary laboratory equipment, as much as 125 g of 7 could be oxidized in one batch. The procedure\(^{122,123}\) used was the version that employed a small portion of ruthenium dioxide suspended in a two-layer system of chloroform—water to dissolve respectively the organic compound to be oxidized and the potassium metaperiodate, an oxidant that continuously regenerates ruthenium tetraoxide. Thus with a bulky, heterogeneous system, effective stirring was of utmost importance. A Morton flask (a flask with indented sides) and a heavy-duty overhead stirrer were used to promote thorough agitation. A commercial grade of 50—60% ruthenium dioxide was found effective for the oxidation, and 2 g was found sufficient to oxidize up to 125 g of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (7); moreover, ruthenium dioxide could be recovered quantitatively at the end of the reaction. Generally, the reaction proceeded smoothly, going into a mildly exothermic stage 30—60 min after the reaction was initiated, and careful t.l.c. analysis showed the entire process to be complete after 10—15 h of vigorous
CHART II: Synthesis of β-D-Allose
stirring. Over-oxidation, known\(^{128}\) to be a problem in the oxidations of most furanose sugars, was minimized through usage of the less-soluble potassium metaperiodate and by prompt processing of the reaction mixture as soon as the t.l.c. indicated disappearance of the starting material. In this manner there was obtained a 90% yield of the crude ketone, as its crystalline hydrate \(\mathcal{Z}\). The hydrate was suitable for the direct reduction to 1,2:5,6-di-\(\alpha\)-isopropylidene-\(\alpha\)-\(D\)-allofuranose\(^{10}\). Analytically pure material could be obtained by simple recrystallization from ether—petroleum ether.

3. Reduction of the ketone \(\mathcal{Z}\) and its hydrate \(\mathcal{Z}\).—Reduction of the hydrated ketone \(\mathcal{Z}\) with sodium borohydride, and examination of the products by gas—liquid chromatography (g.l.c.), revealed that the reduction was surprisingly stereoselective. Only a trace (< 0.5%) of any \(\beta\)-gluco product \(\mathcal{Z}\) could be found in the crude reaction mixture. Reduction with lithium aluminum hydride gave 97.3% of the \(\beta\)-allo product \(\mathcal{Z}\), with less than 3% of any \(\beta\)-gluco isomer \(\mathcal{Z}\). This result is at variance with a published report,\(^{155}\) whereby a 3:7 mixture of \(\beta\)-gluco (7) to \(\beta\)-allo (10) products was obtained. Such a distribution might have obtained had the ketone \(\mathcal{Z}\) contained a portion of unoxidized starting alcohol \(\mathcal{Z}\). No difference in product distribution was noted when the gem-diol \(\mathcal{Z}\) or the
free ketone 8 obtained via distillation of water from the compound under refluxing toluene was reduced under equivalent conditions. Similar results were obtained when sodium bis(2-methoxyethoxy)aluminum hydride ("Vitride") was used as the reductant; only 1.4 ±0.5% of the D-gluco (7) isomer was found in the product mixture.

Therefore, reduction with hydride reagents proceeds from the β-face of the molecule, giving the D-allo product 10 almost stereospecifically, and a preparative route to D-glucose labeled with isotopic hydrogen at C-3 was not achieved, although minute quantities of D-glucose-3-t have been obtained by a similar method. With these findings, sodium borohydride was employed for a preparative-scale reduction of the hydrated ketone 9. The reductant was slowly added, with cooling, to a solution of 9 in 3:7 water—ethanol to give the highly crystalline product 10, in 75% yield.

4. Hydrolysis of 10 to D-allose (11).— Hydrolysis of 10 to D-allose (11) was conveniently effected with a strong cation-exchange resin which was suspended in solution at 45°. D-Allose (11) was obtained as a syrup that slowly crystallized from 2:1 ethanol—water in 98.8% yield. A single dimorph (m.p. 141—142°) was obtained, and no lower-melting (m.p. 128°) material was encountered. A complex mutarotational equilibrium was noticed in which
the free sugar in solution had \([\alpha]_D^{25} -2.5^\circ (2 \text{ min}) \rightarrow +15.6^\circ (2.5 \text{ h}) \rightarrow +14.5^\circ \) (equilibrium). Such rotational properties have been noticed in this and other systems and may be accounted for on the basis of various ring forms present in the solution.


The residual syrup (0.45 g) from the preparative-scale reaction was \(\beta\)-(trimethylsilylated) and its sugar composition was analyzed by g.l.c. A 1:4 ratio of \(\beta\)-glucose to \(\beta\)-allose (\(\alpha\)- and \(\beta\)-anomers) was detected, indicating that there was 0.15% of the \(\beta\)-glucose in the total reaction products. This result corroborates well the findings in the analytical-scale reduction (see p. 41).

B. The Synthesis of Branched-Chain Sugars Related to \(\beta\)-Aldgarose

1. 3-C-Ethylation of \(1,2:5,6\)-Di-O-isopropylidene-\(\alpha\)-\(\beta\)-ribo-hexofuranos-3-\(\alpha\)-ulose. -- In a manner analogous to a number of chain-extension and chain-branching reactions that have been developed in this laboratory an
acetylenic chain-branch at C-3 was introduced into 1,2:5,6-di-O-isopropylidene-α-D-ribofuranos-3-ulose (8), through reaction with ethynylmagnesium bromide, to furnish a single product, 3-C-ethynyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (12) in a yield of 86% [Chart III, p. 45]. The reaction was shown by chromatography and n.m.r. analysis of the products to be stereospecific, giving the D-allo product (12), as expected from the general stereochemical control observed in 4-C-substituted 1,2-O-isopropylidene-α-D-xylo-tetrofuranose systems.

The D-allo configuration for 12 was confirmed by observing the effects, in the n.m.r. spectrum of product 12, of the addition of a lanthanide shift-reagent on the chemical shifts of the protons. The procedure, originally developed by Hinckley, has proven to have wide

CHART III: Synthesis and Reactions of 3-€-Ethynyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose 12
versatility\textsuperscript{190} for simplifying the proton n.m.r. spectra of various molecular types. Differentially induced chemical shifts that arise upon coordination of the bidentate lanthanide complex with relatively basic functionalities (namely, those groups that contain lone pairs of electrons) within the molecule, often permit direct, first-order elucidation of the n.m.r. spectrum that otherwise would be complex and second order. Spectral dispersion is achieved by moving upfield or downfield one or other signals of an overlapped multiplet, thereby exposing the fine structure previously concealed. Alternatively, an approach that makes use of a comparison of the grosser spectral changes of an unknown structure with those of similar, geometrically-defined molecules, may be sufficient to assign configuration at a tertiary center. This latter approach, which has already been applied in the carbohydrate field,\textsuperscript{191} was used for the present study. An n.m.r.


spectrum that was determined for compound $^{12}$ with incremental additions of tris[1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato]europium (III) $^{192}$ [Eu(fod)$_3$]


showed that both H-4 and H-2 were subjected to marked downfield shifts, whereas the shift-gradient for H-5 was relatively small [Figure 1, p. 43]. Similar results have been observed$^{193}$ with 1,2:5,6-di-O-isopropylidene-$\alpha$-


D-allofuranose (10), in sharp contrast to its D-gluco epimer. These findings have provided a convenient means for the assignment of the tertiary alcoholic centers in a series of conformationally similar compounds,$^{194}$ and these


results, when compared with the present data, clearly indicate the D-allo configuration for compound $^{12}$. A classical proof of the structure for compound $^{12}$ was obtained by ozonolysis and mild acid treatment of $^{12}$ to afford a lactone $^{15}$ [Chart III, p. 45]. The lactone $^{15}$
FIGURE 1: Lanthanide-Shift N.M.R. Spectrum of Compound 12
exhibited a carbonyl-stretching absorption at 1761 cm$^{-1}$ in the i.r. spectrum. Such an absorption is diagnostic for a 5-membered lactone ring, as opposed to that (1735 cm$^{-1}$) for a known 6-membered-ring lactone (3-$\text{C}$-carboxymethyl-1, 2-$\text{O}$-isopropylidene-$\alpha$-$\text{D}$-allofuranose-3, 5-lactone) of related structure. Furthermore, acetylation of 15 with pyridine—acetic anhydride gave the diacetate 17, in which the chemical shift of $H-6,6'$ was -0.6 p.p.m. to lower field than in the parent lactone 15, indicating the formation of a 6-$\text{O}$-acetyl derivative [see Table 1, p. 105]. Both compounds were isolated crystalline, and gave satisfactory elemental analyses and mass spectra [Table 2, p. 111].

When initial reaction mixture for the Grignard reaction was not saturated with acetylene, a by-product, amounting to 25—30% of the total products, was obtained and was isolated by column chromatography on silica gel. The obvious similarity of the n.m.r. spectrum of this by-product with that of the major product 12, together with the mass-measured peak for the ($\text{M}^+ - \text{CH}_3$) ion (m/e 527.2137 daltons), which furnished the formula $\text{C}_{25}\text{H}_{35}\text{O}_{12}$ (527.2128 daltons) for the fragment, led to the assignment of the structure as 1,2-bis(1,2:5,6-di-$\text{O}$-isopropylidene-$\alpha$-$\text{D}$-allofuranos-3-yl)acetylene (13). These data were supported by a correct elemental analysis and the absence of any acetylenic $\text{C}-\text{H}$ or $\text{C}=$C absorptions in
the i.r. spectrum. Direct ozonolysis—acid treatment of 13 gave the lactone 15, but only in low yield, as determined by t.l.c. However, reduction of the acetylenic linkage to the trans olefin 18 with lithium aluminum hydride, followed by ozonolysis—reduction, gave 3-C-hydroxymethyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (16) in good yield. This product was identical with a product obtained from the ozonolysis—reduction of 1,2:5,6-di-O-isopropylidene-3-C-vinyl-α-D-allofuranose (14) (see p. 51).

2. Vinylation of 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose-3-ulose (8).—By the same general route as the ethynylation reaction that produced 12, the reaction of 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose-3-ulose (8) with vinylmagnesium chloride gave, although in lower yield, the corresponding alkene 14, a product that was identical by i.r., m.p. and X-ray powder diffraction data with the product obtained by the lithium aluminum hydride reduction of 12. These results suggest that the better route to the 3-C-vinyl compound 14 is by reduction of the acetylenic analog 12, rather than by direct vinylation of the ketone 8. Similar findings have been previously noted in other systems, in which the route

Ozonolysis of 1,2:5,6-di-O-isopropylidene-3-C-vinyl-α-D-allofuranose (14) at low temperature, followed by reduction of the product with sodium borohydride, gave crystalline 3-C-hydroxymethyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (16), which differed in m.p. and $[\alpha]_D$ from the epimeric 3-C-hydroxymethyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose that has been previously reported. The i.r. spectrum exhibited hydroxy absorptions at 2.88, 7.91, and 9.38 μm, and also other absorptions that were in accord with the assigned structure 16. The n.m.r. spectrum revealed a series of complex, overlapping resonances in the $r 5.8-6.8$ region [Table 1, p. 105], and few definite assignments could be made. However, the spectrum did give satisfactory integrals for eight (8) hydrogen atoms ($r 5.8-6.8$) for protons H-3,3', H-4, H-5, H-6,6', plus two OH signals. Two of these signals were of protons exchangeable with deuterium oxide (OH protons). An acceptable elemental analysis and mass spectrum [Table 2, p. 111] were obtained for the compound.

In order to differentiate compound 16 more clearly from the known $p$-gluco epimer, and perhaps afford a more interpretable n.m.r. spectrum, compound 16 was treated with phosgene in dry pyridine, and the cyclic carbonate 19
was obtained. On the basis of m.p. and $[\alpha]_D$, an unambiguous differentiation could be made: whereas the known $\beta$-gluco analog\(^{172}\) was an oil having $[\alpha]_D +16.2^\circ$, compound 19 was crystalline, as confirmed by X-ray powder diffraction, had m.p. 116—116.5\(^\circ\) and $[\alpha]_D +40.2^\circ$. The n.m.r. spectrum of compound 19, although also displaying overlapping resonances, exhibited the anticipated integrals (7 protons, H-2—H-6,6', inclusive) in the $5.5—6.6$ region. A broad singlet (integral 2 H), at lower field than in the parent diol, could be attributed to the 3,3\(^{\alpha}\) methylene protons. A useful item of confirmatory evidence for the structure was a strong carbonyl absorption in the i.r. spectrum, at 5.42 and 5.50 $\mu$m (doublet), indicative\(^{196}\)


of a spiro cyclic carbonate structure as in 19. An acceptable elemental analysis was obtained, and mass spectral data [Table 2, p. 111] support the assigned structure.

3. Synthesis of the Epimeric 3-C-(1'-Hydroxyethyl)-1,2:5,6-di-O-isopropylidene-$\alpha$-$D$-allofuranoses (22a and 22b).—

To synthesize the 1'-hydroxyethyl chain branch, 3-C-ethynyl-1,2:5,6-di-O-isopropylidene-$\alpha$-$D$-allofuranose (12) was subjected to a modification\(^{197}\) of a mild, relatively
non-acidic hydration procedure\textsuperscript{198,199} that employs mercury(II) acetate in a medium of ethyl acetate. The products that were identified after prolonged reaction time were 3-C-acetyl-3-O-acetyl-1,2:5,6-di-O-isopropylidene-a-P-allofuranose (20) and 1,2-O-isopropylidene-[3\textsuperscript{1}-C, 5-O,6-O-(methylmethylidyne)]-a-P-allofuranose (21) [Chart IV, p. 54].

The structure of compound 20 was assigned on the basis of the n.m.r.-spectral data, together with i.r. spectroscopy and mass spectrometry. The i.r. spectrum showed two carbonyl absorptions (at 5.71 and 5.82 \( \mu \text{m} \)) and no hydroxyl-absorptions (in the 2.8–3.2 \( \mu \text{m} \) region) were observed. In the n.m.r. spectrum of 20, two singlets (at 7.75 and 7.82) integrating for three protons each, were in accord with their assignment to a C-acetyl and an acetoxy group, respectively. Furthermore, the two isopropylidene acetal groups remained, as indicated by
CHART IV: Synthesis and Reactions of 3-O-Acetyl-3-O-acetyl-1,2:5,6-di-
O-isopropylidene-α-D-allofuranose 20
the presence of three singlets at 8.48, 8.52 and 8.67 that integrated for twelve protons. Therefore, the structure obtained upon hydration of the acetylene 12 must be 3-\textsubscript{C}-acetyl-3-\textsubscript{O}-acetyl-1,2:5,6-di-\textsubscript{O}-isopropylidene-\textsubscript{a}-\textsubscript{D}-allofuranose (12), a product in which the tertiary hydroxyl function had become acetylated. The structural assignment was further substantiated by the mass spectrum of 20 [Table 2, p. 111], with exhibited a (M\textsuperscript{+} - CH\textsubscript{3}) fragmentation, together with other fragments that strongly support the structure as assigned. An acceptable elemental analysis was also obtained on a sample of 20.

By the foregoing data, the methyl ketone derived by the mercury(II) acetate—initiated hydration of 12 was unexpectedly found to be the acetylated species 20. Furthermore, examination of the crude reaction mixture by g.l.c.—mass spectrometry revealed none of the non-acetylated analog of 20. A similar acylation has been recorded in the steroid literature, where a sterically accessible tertiary hydroxyl group was acetylated in the course of a mercury(II)-mediated hydration of a propargylic alcohol; a cyclic mechanism involving a mercury complex has been proposed.\textsuperscript{197}

Together with compound 20, roughly one molar equivalent of a material was isolated that by i.r. spectroscopy showed a hydroxyl stretching-absorption at
but no other distinctive features that would indicate a prominent group, such as a carbonyl or an acetylenic function. The n.m.r. spectrum [Table 1, p. 105] indicated that one O-isopropylidene group had been removed from the molecule, so that only a C-methyl singlet (ν 8.42, 6 protons) remained; furthermore, only one exchangeable proton was observed in the spectrum upon addition of deuterium oxide to the sample. These data, together with an accurate measurement of the molecular ion by mass spectrometry (measured: 244.0949 daltons), led to the assignment of the structure as the internal cyclic acetal 21 (theory: 244.0947 daltons for C11H16O6). Elemental analyses accorded with this proposed structure.

A formal proof for the structure of 21 was furnished by the sequence as indicated (20 → 21) in Chart IV. Compound 20 could be O-deacetylated under rather harsh conditions (refluxing methanolic sodium methoxide) to give a product whose mass spectrum exhibited a highest mass at 287 daltons (16% intensity, assignable to M^+ + CH3.) and 101 daltons (100%, base peak, showing formation of a fragment C5H9O2^+, typical of 5,6-O-isopropylidene-

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aldohexofuranose functions), among other fragments that indicated the O-deacetylation of 20 [see Experimental Section]. Treatment of the O-deacetylated product dilute acetic acid to hydrolyze selectively the 5,6-O-isopropylidene acetal, and finally heating in ethanol under dehydrating conditions afforded a product that had identical properties with authentic 21 when examined by t.l.c. (three solvent systems) and g.l.c. A mass spectrum of the foregoing product was superposable upon that of authentic 21.

It is to be noted that, unlike compound 20, compound 21 possesses a non-acetylated 3-hydroxyl group; in addition, no 3-acetylated analog of 21 could be detected when the crude product mixture from the mercury(II)-mediated hydration reaction was examined by g.l.c.—mass spectrometry. The formation of compound 21 might well be envisaged to occur via a 5,6-deacetonation of the acid—labile 5,6-O-isopropylidene functionality, with formation of an intramolecular acetal. Whether the reaction sequence is an acid—mediated process, or whether the reactions are promoted by a mercury—acytylenic complex, known to catalyze acetal formation, 201 remains unclear. The

mercury(II) acetate—ethyl acetate system, although demonstrated to be mild and useful in the presence of cyclic acetals,\textsuperscript{197} is not entirely acid-free, as shown by the stoichiometry of the processes.\textsuperscript{198} However, in view of the fact that rather vigorous conditions [see Experimental Section] were necessary to effect the intramolecular acetalation process to produce 21, even in low (\(-35\%\)) yield, an orderly, energetically favorable process, possibly arising from an organo-mercury intermediate, is favored to explain the almost 1:1 ratio of 20 to 21 isolated from the hydration reaction.

Trial reductions on 3-\(\alpha\)-acetyl-3-\(\beta\)-acetyl-1,2:5,6-di-\(\alpha\)-isopropylidene-\(\alpha\)-D-allofuranose (20) were conducted with milligram quantities, and the results from reductions with three different metal hydrides were evaluated by g.l.c.—mass spectrometry. Of the three hydrides, sodium borohydride, sodium bis(2-methoxyethoxy)aluminum hydride, and lithium aluminum hydride, only the latter was found to effect the desired, high-yielding reduction of the ketonic carbonyl group, with concomitant cleavage of the tertiary ester group. Preparative-scale experiments, with an excess of lithium aluminum hydride, and prolonged periods of heating under reflux, gave nearly quantitative yields of the epimeric diols, 22a and 22b, in \(-2:1\) proportion, respectively. The epimers were separable by both t.l.c.
and by column chromatography on silica gel. Also, the two compounds could be differentiated on the basis of their optical rotations, which showed a difference of 12.5°; their melting points, which differed by 21.5° (mixed m.p. 87—90°); their X-ray powder diffraction patterns, and also by their i.r. and n.m.r. spectra.

The n.m.r. spectrum [Table 1, p. 105] for the minor isomeric diol, 22b, was largely first-order, allowing a straightforward interpretation of the data. For 22b, the n.m.r. signals for H-1 and H-2 appeared as doublets (r4.22 and 5.48, J1,2 4.2), with the signal for H-5 overlapping that of H-2. The signal for H-4 was a wide doublet at r6.08. The H-6,6'—H-5 protons gave rise to signals that essentially represent an A2X pattern: H-6,6', doublet (J5,6 6.5 Hz); H-5, multiplet. The methylene protons on the side chains, as expected, gave rise to a quartet (r5.71, J31,32 7 Hz), with the terminal methyl group appearing as a doublet (r8.83). The n.m.r. spectrum of compound 22a, on the other hand, showed that the signals for H-31 (quartet) overlapped with the A2X pattern expected for H-6,6' and H-5, producing a complex set of resonances; furthermore, H-5 appeared to overlap with the signal for H-2. In both cases, the correct numbers of protons were found upon integration of the spectra, and two hydrogen atoms for each compound were found to be exchangeable with deuterium oxide. As expected, 22a and 22b gave identical mass
spectra [Table 2, p. 111]. Both isomers gave correct elemental analyses and i.r. spectra that supported the assigned structures.

The stereochemistry for the epimeric centers on the side chains of compounds 22\(a\) and 22\(b\) remains unresolved. The optical rotation data, especially since the \([\alpha]_D^\circ\) differs by only 12.5°, provides little information about the stereochemical disposition at the asymmetric center. As noted in the preceding section, the n.m.r. spectra differ markedly for 22\(a\) and 22\(b\); however, too little is known about the conformation of the furanoid ring system to determine the configuration at C-3\(^1\).

In an effort to synthesize the diols 22\(a\) and 22\(b\) directly and thereby avoid the reduction of compound 20\(\_\_\), an oxymercuration reaction was attempted on the vinyl analog 14\(\_\_\), by the procedure of Brown and Geoghegan.\(\_\_\)202

\(\_\_\)


However, the conversion of alkene 14\(_\_\) into 22\(a\) and 22\(b\) could not be achieved under a variety of conditions, and the starting material was recovered intact. The 3-C-\(\_\_\)-vinyl functionality is apparently highly sterically hindered, and the formation of an organo-mercury complex is inhibited.
4. Synthesis of the epimeric 3,1\(^1\)-O-carbonyl-3-C-(1\(^1\)-hydroxyethyl)-1,2:5,6-di-O-isopropylidene-a-D-allofuranoses (23a and 23b).— Carboxylation of each diol, 22a and 22b, was effected cleanly with phosgene in anhydrous pyridine to give the isomeric cyclic carbonates, 23a and 23b. Both isomers showed the typical cyclic carbonate carbonyl absorption at 5.5 \(\mu\)m. Despite the fact that the specific rotation for 23a and 23b differed by only \(-1^\circ\), and their o.r.d. spectra were very similar down to 240 nm, the two isomers could be distinguished on the basis of their melting points, which differed by more than 50\(^\circ\), and by their X-ray powder diffraction, in addition to marked differences in their n.m.r. spectra. The n.m.r. spectrum of 23b, as with its precursor diol, 22b, was largely first order, and the assignments [Table 1, p. 105] were relatively straightforward. However, isomer 23a exhibited a set of overlapping resonances that remain unassigned. Both compounds gave integrations for the correct number of protons, and, as expected, the mass spectra for 23a and 23b were identical. Elemental analyses support the assigned structures. A mixture of 23a and 23b melted at 125—128\(^\circ\).

As with the parent diols, the stereochemistry at the epimeric center of the side chains for compounds 23a and 23b remains unresolved. O.r.d. spectra yielded little
information, as both showed virtually the same, positive curves [see Experimental Section], and the n.m.r. spectra, although clearly defined shift differences were observed, no definitive assignments could be made.

C. Preparation of Aldehydo and Certain Keto Sugars via Oxidation with the Chromium(VI) Oxide—Dipyridine Complex

Reported successes of the extremely mild oxidant, chromium(VI) oxide—dipyridine complex of Collins179,180 as modified by Ratcliffe and Rodehorst,181 for oxidation of a wide variety of hydrocarbon alcohols, prompted an investigation into the utility of this reagent for the oxidation of a number of protected sugars. Especially attractive was the fact that this reagent provides a synthesis of aldehydes from primary alcohols, with little or no further oxidation to the carboxylic acids.

1. Oxidation of primary hydroxyl groups.-- Thus the oxidation of methyl 2,3-O-isopropylidene-β-D-ribofuranoside (24) [Chart V, p. 63] with a 12:1 molar ratio of chromium(VI) oxide—dipyridine, prepared in situ in dichloromethane by the established method,181 afforded a synthesis of the terminal aldehyde (25) in 75% yield as a crystalline product, ~99%, pure by g.l.c., that had m.p. and [α]D in agreement with those published.40,43 Experimentally,
CHART V: Oxidations Using Chromium(VI) Oxide–Dipyridine:

Synthesis of ω-Aldehydo Sugars
the 12:1 ratio of oxidant to substrate was found necessary for oxidation of >99% of the substrate alcohol \( \text{24} \), as determined by g.l.c. Whenever 6:1 and 9:1 ratios were employed, incomplete oxidation of the alcohol resulted, as indicated by g.l.c. analysis. This fact is at variance with the reported \( ^{179-181} \) 6:1 ratio of oxidant to alcohol necessary for complete oxidation of hydrocarbon alcohols. The basis for this higher oxidant requirement remains unclear; the fact that a coordination complex with the heterocycle could form and account for an additional mole of oxidant complex is a possibility. All in all, the oxidation proved to be a highly efficient, procedurally simple, method for producing the methyl 2,3-\( \text{O} \)-isopropylidene-\( \text{a-D-ribo} \)-pentodialdo-1,4-furanoside (25), a useful intermediate\(^{43}\) for chain-extension reaction in the sugar series. The yields compare favorably with those obtained\(^{40,43}\) using methyl sulfoxide—dicyclohexylcarbodiimide. The chromium(VI) oxide—dipyridine method, in most hands, involves fewer purification steps than other methods, and no observable by-products contaminate the aldehyde.

From the results of the foregoing experiments, a general oxidation procedure was developed that was applied to various types of carbohydrate alcoholic functions. A similar primary alcohol, 1,2:3,4-di-\( \text{O} \)-isopropylidene-\( \text{a-D-galactopyranose} \) (26) was oxidized cleanly to give a 62%
yield of 1,2:3,4-di-O-isopropylidene-α-D-galacto-
hexodialdo-1,5-pyranose (27) that was >99% pure by g.l.c. The syrupy product was distilled to give an analytically pure sample whose n.m.r. spectrum was identical with that of a product\(^{41}\) produced by the Pfitzner—Moffatt procedure, although the present sample differed considerably in physical constants (b.p. and \([\alpha]_D\)) from those reported.\(^{41}\) Hydration of the aldehyde, known to be a facile process in such systems,\(^{203}\) might account for the discrepancy in optical rotation data. A \(p\)-nitrophenylhydrazone was prepared, which gave a m.p., \([\alpha]_D\), and X-ray diffraction pattern which was identical with an authentic sample from the original preparation, despite some discrepancies recorded in the literature.\(^{41}\)

Since the oxidant was found to be effective for conversion of primary alcohols into aldehydes, the reagent was applied to the synthesis of an aldosulose form a suitably protected ketose 28 [Chart VI, p. 66]. 2,3:4,5-
Di-O-isopropylidene-α-D-fructopyranose (28) was oxidized by the general procedure to give a distillable, syrupy product that, by i.r. spectroscopy gave absorptions at 3.48 and 5.70 \(\mu m\), which are indicative of C-H and C=O
CHART VI: Oxidation Using Chromium(VI) Oxide—Dipyridine: Synthesis of an Aldosulose,

2,3:4,5-Di-O-isopropylidene-\(\alpha\)-\(\beta\)-arabino-hexosulo-2,6-pyranose
stretching modes, respectively, of an aldehyde group; other i.r.-spectral features were also supportive of the structure 29. An n.m.r. spectrum [Table 3, p. 116] revealed among other interpretable resonances, an aldehydic proton resonance at 0.49. The mass spectrum, [see Experimental Section] although showing no molecular ion, gave an \([\text{M}^+ - \text{CH}_3]^{-}\) fragment along with \([\text{M}^+ - \cdot \text{CHO}], \) and \([\text{M}^+ - \cdot \text{CH}_3 - \text{C}_2\text{H}_2\text{O}]\) that are diagnostic for the structure 29. An acceptable elemental analysis, together with the foregoing data, supports the structure as assigned.

In the literature, two published reports describe other syntheses of the foregoing compound, but provide little characterization data. An uncharacterized oil that was obtained upon oxidation of 28 with methyl sulfoxide—sulfur trioxide is reported\(^6^2\) to give an n.m.r. aldehyde-proton absorption at 0.46. In another preparation\(^5^8\) a product that was an analytical sample gave an i.r. spectrum having absorptions very similar to compound 29; an \([\alpha]_D\) that was reported\(^5^8\) was -41.2° as opposed to -72° for compound 29.

The foregoing syrup was characterized on a crystalline basis as its (p-nitrophenyl)hydrazone, 30, which gave an acceptable elemental analysis, as well as i.r. and n.m.r. data [Table 3, p. 116] that fully supported the structure as 30.
Having demonstrated the potential of the reagent for the synthesis of the aldosulose 22, the oxidation of 2,3:4,6-di-O-isopropylidene-α-L-sorbofuranose was attempted. However, repeated trials, with varying reaction times, temperatures, and ratios of oxidant to substrate, led either to incomplete oxidation of the alcohol or to a complex mixture of products. The reagent appears, therefore, not to be a general oxidant for aldosulose synthesis.

2. Oxidation at the anomeric center.— Oxidation of 5-azido-2,3-O-benzylidene-5-deoxy-β-D-ribofuranose (31) [Chart VII, p. 69] proceeded smoothly to give a high yield of the 5-azido-2,3-O-benzylidene-5-deoxy-D-ribohex-1,4-lactone (32). The chromium(VI) oxide—dipyridine complex offered a procedural simplification along with an increase in yield, for synthesis of the lactone 32 over that which had been reported earlier77 using the Sarett procedure. The product obtained had physical constants in agreement with those published.77

3. Oxidation of secondary, exocyclic hydroxyl groups.— The exocyclic secondary alcohols of the α-D-gluco (33) and α-D-ido (35) configuration were oxidized with equal facility to give >90% yields of 3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranos-5-ulose (34). The crystalline products were identical to the ketone 34
CHART VII: Oxidations Using Chromium(VI) Oxide—Dipyridine: Synthesis of

the Lactone 32 and the Methyl Ketone 34
obtained in ~50% yield upon two successive applications of the Sarett procedure to either 33 or 35.

4. Attempted oxidation of isolated, secondary hydroxyl groups.— Both of the endocyclic, secondary alcohols, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (7) and 1,6-anhydro-3,4-O-isopropylidene-β-D-galactopyranose (36) were found to be essentially inert toward the reagent, whereas 1,6-anhydro-2,3-O-isopropylidene-β-D-mannopyranose (37) gave an intractable mixture of products. Thus an attempt to extend the procedure to the oxidation of "isolated," secondary alcoholic groups was unsuccessful. All three compounds, 7, 36 and 37 have been demonstrated to undergo effective oxidation with methyl sulfoxide—acetic anhydride.56

5. Summary.— The chromium(VI) oxide—dipyridine complex as employed in the foregoing examples appears, therefore, to be of probable general application for the oxidation of primary alcohols to aldehydes and the oxidation of secondary, exocyclic hydroxy groups to methyl ketones. The generality of the procedure may in all likelihood be extended to the oxidation of suitably protected hemiacetals to give lactones, following the single example given. The procedure is not effective, however, with "isolated," secondary alcohols.
CHART VIII: Compounds Not Oxidized by the Chromium(VI) Oxide—Dipyridine Reagent
A considerable procedural advantage is offered, in both carrying out the reactions and isolating the products, in comparison with other methods. Both the fire hazard and the problem of solvent removal associated with the Sarett procedure are eliminated and the often-tedious separations associated with the methyl sulfoxide-based reagents are also avoided. The reaction has proven quite useful for the large-scale synthesis of

(204) S. E. Eitelman and D. Horton, unpublished results.

1,2:3,4-di-O-isopropylidene-\(\alpha\)-D-galacto-hexodialdo-1,5-pyranose (27), being preferred over both the lead tetraacetate or methyl sulfoxide—dicyclohexylcarbodiimide


procedure advocated in earlier reports.
IV. EXPERIMENTAL

General Methods.— Evaporations were carried out in vacuo at 40±5°. Melting points were determined with a Thomas-Hoover "Unimelt" apparatus and are uncorrected. G.l.c. was performed with a Beckman GC-5 dual-column instrument with flame-ionization detectors, and helium was used as the carrier gas. Conditions were either A, a 1/8 in x 11 ft column of 10% Carbowax 20M on 60—80 mesh HMDS Chromosorb W, helium flowrate 80 ml. min.⁻¹, column temperature 200°, injector temperature 250°; B, 1/8 in x 6 ft column of 3% SE-30 on 80—100 mesh Chromosorb P, helium flowrate 40 ml. min.⁻¹, column temperature 155°, injector temperature 240°; or C, as in B, with the following modifications: a helium flowrate 65 ml. min.⁻¹, injector temperature 210—220°, and column temperatures as indicated in parentheses for each compound. Retention times (T_R) are given as adjusted values relative to the solvent peak (T_R = 0). For compounds 7 and 10, standard solutions of each were used to calibrate the detector response to allow conversion of peak-area ratios into quantitative ratios: 7 and 10 gave almost identical responses. T.l.c. was performed on 0.25 mm plates of Silica Gel G (Merck) activated at 110°; 10% aqueous
sulfuric acid was employed for detection. Column chromatography was carried out using a 70—325 mesh silica gel (7734, E. Merck). Chromatography solvents, unless otherwise indicated were A, 1:1 ether—chloroform, or B, 1:2 ether—chloroform.

Infrared spectra were routinely measured with a Perkin—Elmer Model 237 spectrophotometer; high-resolution i.r. spectra were measured using a Perkin—Elmer Model 467 grating instrument. Optical rotations were determined with a Perkin—Elmer Model 141 polarimeter by using 1-dm. tubes. O.r.d. spectra were measured using a JASCO Model 5 recording spectropolarimeter. N.m.r. spectra were recorded at 100 MHz with a Varian HA-100 or JEOL MH-100 instrument, using tetramethylsilane as an internal standard and as a lock signal. Chemical shifts are given on the r scale, and couplings recorded are first-order spacings. Mass spectra were measured with an AEI-MS-9 double-focusing, high-resolution mass spectrometer, at an ionizing potential of 70 eV and an accelerating potential of 8 kV. A direct-insertion probe (T 150—250°) was employed for samples. A Du Pont MS-21-490 instrument was employed for mass spectroscopic examination of g.l.c. peaks. Microanalyses were performed by W. N. Rond. X-Ray powder diffraction data give interplanar spacings in Å for CuKα radiation (camera diameter = 114.59 mm). Relative intensities are
estimated visually; m, moderate; s, strong; v, very; w, weak. The three strongest lines are numbered (1 = strongest).

Solvents and reagents were of reagent grade. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride, and pyridine was distilled from barium oxide; both were stored over Linde 4Å molecular sieves prior to use.

Preparation of 1,2:5,6-di-0-isopropylidene-α-D-ribo-hexofuranos-3-ulose hydrate (9).—To a well-stirred solution of 1,2:5,6-di-0-isopropylidene-α-D-glucofuranose \(7,154\) 125 g, 0.48 mole) in 550 ml of alcohol-free chloroform (prepared by passing reagent-grade chloroform through a 3 x 50-cm column of neutral alumina, activity I) contained in a 3-l Morton flask (flask with indented sides), was added water (500 ml), potassium metaperiodate (165 g, 0.72 mole), potassium carbonate (18 g), and 2 g of ruthenium dioxide (50—60% hydrated reagent, Engelhard Industries, Newark, New Jersey, U.S.A.). The mixture was stirred vigorously for 12—15 h at \(\sim 25^\circ\), by which time t.l.c. (1:1 ether—chloroform or 19:1 benzene—methanol) indicated complete disappearance of the starting material 7 \(R_f\) 0.37 and 0.45, respectively). The resultant hydrated ketone (9) was observed as a slower-migrating zone \(R_f\) 0.31 and 0.39 respectively); in some preparations a faster-migrating zone, presumably the parent ketone, was
also observed.* The oxidation was then terminated by adding isopropyl alcohol (50 ml) and stirring the mixture for 10 min. The mixture was then filtered through a pad of Celite, and the filter was washed with two 50-ml portions of chloroform. The organic layer was separated, and the aqueous phase was extracted with three 200-ml portions of dichloromethane. The combined organic extracts were dried (magnesium sulfate) and evaporated to give the hydrated ketone 9 as a yellowish, crystalline solid suitable for use directly in the next step.

Dissolution of the crystalline mass in ~250 ml of warm ether, addition of an equal volume of warm petroleum ether (b.p. 30—60°) and allowing the product to crystallize afforded pure 9; yield 114 g (86%), m.p. 111—112°, \([a]_{D}^{25} +44° \text{ (c 1, ethanol) }, \text{ (lit.} \text{ m.p. 112—114°, } [a]_{D}^{25} +44.5° \text{ in ethanol).} ]
Preparation of 1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-allofuranose (10).— The non-recrystallized product from the preceding preparation was dissolved in 700 ml of 3:7 ethanol—water, and 12 g (1.3 equivs.) of sodium borohydride was added portionwise at \(-25^\circ\), with stirring and cooling to moderate the mildly exothermic reaction. After 1 h the solution was evaporated to \(-500\) ml. Water (200 ml) was added and the solution was again evaporated to \(-500\) ml. The solution was extracted with four 200-ml portions of dichloromethane, and the combined extracts were dried (magnesium sulfate) and evaporated to give crystalline 10; yield 94 g (75% based on 7), suitable for use directly in the next step. Recrystallization from cyclohexane gave analytically pure 10, m.p. 75.5—76\(^\circ\), \([\alpha]_{D}^{25} +37.8^\circ\) (c 1, chloroform), lit.\(^{155}\) m.p. 75—76\(^\circ\), \([\alpha]_{D}^{25} +38^\circ\) in chloroform).

Preparation of \(\beta\)-D-allose (11).— To a stirred suspension of 10 (90 g, 0.35 mole) in water (700 ml) kept at 45 \(\pm\) 5\(^\circ\) was added 150 g of Amberlite IR-120 (H\(^+\)) ion-exchange resin (moist resin, 50 mesh, analytical grade). The mixture was stirred for 3 h, filtered through a pad of Celite, and the resin was washed with two 50-ml portions of water. The filtrate was either lyophilized or evaporated, to give crystalline 11; yield 62 g (99.5%). The product was recrystallized by dissolving it in the minimum
volume of water at 60° and adding two volumes of ethanol. Slow cooling and seeding gave white crystals of chromatographically and analytically pure β-D-allose (11); yield 59 g. From the mother liquors there was obtained, after slow crystallization at -20°, a further 2.55 g of 11; total yield 61.55 g (98.8%); m.p. 141—142° (lit.206 m.p. 141—142°) (an isomorph having m.p. 128° was not encountered, [α]25D -2.5° (2 min) → +14.5° (equil., c 1, water, complex mutarotation observed), (lit.207 [α]D +14.4° in water); Rglucose 1.28 (chromatography on Whatman No. 1 paper; 8:2:1 ethyl acetate—pyridine—water as developing solvent).

The residual syrup (0.45 g) obtained by evaporation of the final mother liquor was (trimethylsilylated with N-(trimethylsilyl)imidazole in dry pyridine ("Tri—Sil Z", Pierce Chemical Co., Rockford, Illinois, U.S.A.). G.l.c. analysis in system B showed three major components, one corresponding to per(trimethylsilylated β-D-allose (retention time 10.2 min) in 75% proportion, and the


other two corresponding to per(trimethylsilylated) a-(and β)-D-glucose (retention times 12.1 + 18.9 min, respectively in ~25% proportion. The amount of D-glucose detected corresponds to 0.15% of 7 and 99.85% of 10 being formed in the borohydride reduction of 9.

Analytical studies on the reduction of the hydrated ketone 9.—A. With lithium aluminum hydride. To a solution of 210 mg (0.76 mmole) of 9 (shown to be free of 7 by g.l.c. in system A) in anhydrous ether (20 ml) was added lithium aluminum hydride (30 mg), and the mixture was heated for 4 h under reflux in an atmosphere of nitrogen. The solution was cooled and the excess reagent was decomposed by adding 10% aqueous ammonium chloride (0.5 ml). The mixture was filtered, the salts were washed with three 5-ml portions of ether, and the filtrate was dried (magnesium sulfate) and evaporated to a syrup that crystallized to a solid mass upon addition of ether; yield 183 mg (93%). A solution of this total crude product in tetrahydrofuran was analyzed by g.l.c. (system A), and three components were observed; the major one (97.3% of the reduced products, T 43.6 min) corresponded to the allo derivative 10, a minor component (2.7 ±0.5% of the reduced products, average of 3 experiments, T 49.1 min) corresponded to the gluco derivative 7, and a rapidly eluted product (~10% of the total products, T 1.9 min) corresponded to
the peak obtained when the unreacted ketone hydrate 9 was processed similarly. Crystallization of the crude product from cyclohexane afforded 170 mg (86%) of pure 10.

B. With sodium bis(2-methoxyethoxy)aluminum hydride. The foregoing procedure (A) was repeated with 102 mg (0.37 mmole) of 9, but with 0.5 ml of a 70% solution (1.79 mmole) of sodium bis(2-methoxyethoxy)aluminum hydride ("Vitride," Eastman Organic Chemicals, Rochester, N. Y., U.S.A.) in benzene as the reductant. The crude product was freed from 2-methoxyethanol by keeping it in vacuo at 5 torr. G.l.c. analysis (system A) of the product (95 mg, 96%) indicated 10 as the near-exclusive product, and the proportion of a component corresponding to the gluco derivative 7 amounted to only 1.4 ± 0.5% (average of three experiments). Crystallization of the product gave pure 10 in high yield.

C. With sodium borohydride. Reduction of 100 mg of 9 by a scaled-down version of the preparative experiment already given, and g.l.c. analysis of the product (system A) showed quantitative reduction of 9 and the near-exclusive formation of the allo derivative 10. Only a trace (<< 0.5%) of the gluco product 7 was detected.
Preparation of 1,2:5,6-di-O-isopropylidene-\(\beta\)-ribo-hexofuranose-3-ulose (8).—A solution of 10 g (36 mmol) of 1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-ribo-hexofuranose-3-ulose hydrate (9) in 450 ml of toluene was heated under reflux for 0.5 h with azeotropic removal of water by distillation of ~50 ml of the solvent. The remaining solvent was evaporated at 40° to give the ketone (8) as a syrup. Drying at 5 Torr for 8 h at 25° gave pure 8, showing negligible absorption in the O-H stretching region (2.88 \(\mu\)m) and a large peak at 5.73 \(\mu\)m (C=O stretch) in the i.r. spectrum; \([\alpha]^{21}_D +101^\circ \text{ (c 1, dry chloroform)}; \) [lit.]\(^{120} [\alpha]_D^{22} +107^\circ \text{ (chloroform)}]. The product was found to be stable for ~3 months when stored over calcium sulfate in a vacuum desiccator, and it was found to be adequately pure for use as a starting material in the following reaction.

3-C-Ethynyl-1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-allofuranose (12).—Following an established procedure\(^{186-188}\) 50 mmol. of ethylmagnesium bromide in dry THF (prepared by diluting 18 ml of a 2.83 M solution of the pre-formed reagent\(^{208}\) in THF to 120 ml) was added to a saturated

solution of acetylene in THF. Dry acetylene was bubbled into the solution for 45 min, at which time a solution of 4.52 g (17.5 mmole) of 1,2:5,6-di-O-isopropylidene-\(\alpha\)-D-ribo-hexofuranos-3-ulose (8) in THF (20 ml) was added dropwise over a period of 20 min, all the time maintaining a rapid flow of acetylene into the well-stirred solution which was kept at room temperature. The resultant cloudy mixture was stirred for 2 h (with passage of acetylene continued), at which time the flask was cooled in an ice bath, and ~70 ml of a saturated solution of ammonium chloride was added slowly with stirring to decompose the Grignard complex. The solution was washed with a saturated ammonium chloride solution (2 x 75 ml), and the separated aqueous phase was extracted with ether (2 x 25 ml). The combined, organic extracts were dried (magnesium sulfate) and evaporated to dryness, yielding 12 as a yellow solid.

A solution of the product in ~15 ml of ether was passed through a short column (2 x 20 cm) of silica gel, and the column was eluted with ~200 ml of ether.* The solid

*Alternatively, when the preparation appeared highly colored and was contaminated (t.l.c.) with larger amounts of impurities, column chromatography was effected on silica gel (~2 g of crude 12 per 100 g silica gel) with 1:1 ether—chloroform as the eluant.
obtained upon evaporation of the solvent was recrystallized from ether (7 ml per g of 12), yielding 4.27 g (86%) of pure 12 in two crops, m.p. 106—107°, [α]_D^{21} +9.5° (c 1.05, chloroform); R_f 0.64 (solvent A); T_R = 2.5 min (150°, system C); λ_{max}^{KBr} 2.85 (OH), 3.08 (C=CH), 3.34 (CH), 4.68 (C=C), 7.25, 8.23, 9.75, 11.37, and 14.02 μm; for n.m.r. data, see Table 1; for mass-spectral data see Table 2; X-ray powder diffraction data: 10.84 s, 7.30 s (3), 5.71 s (2), 5.37 w, 5.11 vw, 4.69 vs (1), 4.54 vw, 4.50 m, 3.94 m, 3.83 vw, 3.66 vw, 3.55 s, 3.48 w, and 3.32 w.


In one preparation, in which 9.5 g (33.5 mmol.) of β and 105 mmol. of ethylmagnesium bromide had been used, the acetylene flow was insufficient to maintain a saturated solution, and 2.34 g of an additional product, identified as 1,2-bis(1,2,5,6-di-O-isopropylidene-α-D-allofuranos-3-yl)acetylene (12) was isolated by column chromatography as described;* m.p. 163.5—164.5°, [α]_D^{21} -6.5° (c 2.31 chloroform); R_f 0.24 (solvent A); λ_{max}^{KBr} 2.91 (OH), 3.36 (CH), 7.26, 8.20, 9.33, and 11.42 μm; for n.m.r. data see Table 1; for mass-spectral data see Table 2; X-ray powder diffraction data: 13.80 m, 11.33 s, 9.50 m, 7.77 w, 6.52 s (3), 5.61 vs (1), 5.31 m, 5.05 m, 4.65 s (2), 4.43 m, 4.27 w, 4.14 w, 4.01 w, and 3.90 w.
Anal. Calc. for C_{26}H_{38}O_{12}: C, 57.56; H, 7.06.
Found: C, 57.34; H, 7.09; Calc. for C_{25}H_{35}O_{12} (M^+ - 15) 527.2128; observed (high-resolution m.s.): m/e 527.2137.
Earlier fractions from the column gave the acetylene 12 (4.9 g); total conversion yield of 8 into 12 + 13, 70%.

3-C-Carboxyl-1,2-O-isopropylidene-α-D-allofuranose-3,5-lactone (15).-- A solution of 284 mg (1 mmole) of 3-C-ethynyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (12) in 20 ml of methanol, was treated with an ozonized stream of oxygen (0.5 l/min) for 30 min at 0°. Excess ozone was displaced by bubbling oxygen into the solution for ten min, and then the solvent was evaporated. The syrupy product was treated with ∼5 mg of p-toluenesulfonic acid in a refluxing mixture (60 ml) of 4:1 benzene—ethanol during a period of 48 h, with gradual removal of a total of 20 ml of distillate. Sodium carbonate (∼50 mg) was added with stirring, and the salts were removed by filtration. Evaporation of the solvents gave a solid, which was applied to a column (0.7 x 20 cm) of silica gel. Elution with 125 ml of chloroform, followed by 125 ml of ether, gave 151 mg (61%) of chromatographically homogeneous 15. An analytical sample was prepared by recrystallization from 1:1 ether—hexane; m.p. 143—144.5°, \([\alpha]_{D}^{21} +34°\) (c 1, chloroform); R_f 0.37 (solvent A); λ_{KBr max} (high resolution) 2.92 (OH), 3.38 (CH), 3.68 (C=O), 7.29,
7.92, 8.36, 8.50, 9.21, 9.67, 11.45, 12.81, and 14.69 μm; for n.m.r. data see Table 1; for mass-spectral data see Table 2; X-ray powder diffraction data: 9.89 vs (1), 8.24 w, 6.51 s, 5.79 w, 5.38 s (2), 4.81 s (3), 5.60 vw, 4.06 w, 3.87 m, 3.71 m, 3.56 m, 3.35 m, 3.25 m, 3.13 w, 2.97 w, and 2.80 m.

**Anal. Calc.** for C_{10}H_{14}O_{7}: C, 48.78; H, 5.73. **Found:** C, 48.61; H, 5.64.

3,6-Di-O-acetyl-3-C-carboxy-1,2-O-isopropylidene-a-D-allofuranose-3\textsuperscript{1},5-lactone (17). — To a solution of 75 mg (0.30 mmole) of 15 in 5 ml of pyridine was added 1 ml of acetic anhydride, and the mixture was stirred overnight. Methanol (~2 ml) was added, and stirring was continued for 2 h, at which time the solvent was evaporated. Evaporation of 3 x 5-ml portions of toluene from the residue gave a crystalline solid, which was recrystallized from hexane containing a little ether to give 88 mg (89%) of pure 17; m.p. 113—113.5°, [α]\textsubscript{D} +6.2° [α]\textsubscript{365} +33.0° (c 1.7, chloroform); Rf 0.72 (solvent A); λ\textsubscript{max} ^KBr (high resolution) 3.34, 3.36, 3.40 (CH\textsubscript{3}), 5.58, 5.73, 5.76 (C=O), 7.31, 7.95, 8.20, 8.50, 9.61, and 11.48 μm; for n.m.r. data see Table 1; mass-spectral data see Table 2; X-ray powder diffraction data: 12.99 vw, 12.02 w, 10.10 w, 8.36 vs (1), 6.69 m, 6.17 m, 6.03 m, 5.82 m, 5.33 s (2), 4.69 s (3), 4.40 s, 4.15 vw, 3.97 w, 3.72 w, and 3.69 w.
Anal. Calc. for C_{14}H_{18}O_{9}: C, 50.91; H, 5.49.

Found: C, 50.79; H, 5.51.

**1,2:5,6-Di-O-isopropylidene-3-C-vinyl-α-D-allofuranose (14).**—A. By Addition of vinylmagnesium chloride to 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (8). A solution of 3 g (11.7 mmol.) of the ketone 8 in THF (~20 ml) was added dropwise, with stirring during 5 min, to a solution of 38 mmol of vinylmagnesium chloride [prepared by diluting 13.5 ml of a 2.84 M solution of the commercial reagent in THF (Ventron Corp., Beverly, Mass., U.S.A.) to ~30 ml with THF]. Stirring was continued under reflux for 3 h, at which time the flask was cooled to 0°, and the excess Grignard reagent was decomposed by addition of ~30 ml of a saturated solution of ammonium chloride. Isolation and processing as described for 12 gave the product 14 as a syrup, which was purified by chromatography on a column (3 x 60 cm) of silica gel with 1:1 ether—chloroform as eluant. Evaporation of the solvents gave a syrupy product, homogeneous by t.l.c., which was crystallized from ~8 ml of ether with slow addition of an equal volume of petroleum ether (b.p. 30—60°) and cooling to -20°; yield 0.96 g (29%); m.p. 66.5—67.5°, [α]_{D}^{21} +27.6° (c 1, chloroform); R_{f} 0.71 (solvent A);
$T_R$ 2.6 min (150°, system C); $\lambda_{\text{KBr} \text{ max}}$ 2.88 (OH), 3.33 (=$CH$), 7.28, 8.22, 9.37, 9.92, 10.71, 11.40, and 11.73 μm; for n.m.r. data see Table 1; mass-spectral data see Table 2; X-ray powder diffraction data: 7.77 vs (1), 5.33 vw, 5.08 s (2), 4.55 m, 4.34 m, 3.82 w, 3.61 m, and 3.48 w.

**Anal. Calc. for C$_{14}$H$_{22}$O$_6$:** C, 58.73; H, 7.74.

**Found:** C, 58.57; H, 7.70.

**B.** By reduction of 3-C-ethynyl-1,2:5,6-di-O-isopropylidene-a-D-allofuranose (12) with lithium aluminum hydride. A solution of 200 mg (0.70 mmole) of 12 in THF was treated with ~50 mg of lithium aluminum hydride, and the mixture was heated under reflux for 8 h, at which time the solution was cooled, and the excess reductant was decomposed by addition of a few drops of 1:1 water—methanol. The salts were filtered, washed with ether, and the organic phase was evaporated to dryness, yielding a semi-solid mass. Crystallization as described in the foregoing section gave 160 mg (79%) of pure 14, identical by m.p., mixed m.p., and [α]$_D$ with the product isolated in part A.

**trans-1,2-Bis(1,2:5,6-di-O-isopropylidene-a-D-allofuranos-3-yl)ethylene** (18).— A solution of 200 mg (0.37 mmol.) of 13 in 30 ml of THF was heated for 5 h under reflux with ~50 mg of lithium aluminum hydride. Addition of a few drops of 1:1 water—methanol, followed by removal of the salts by filtration, drying of the
filtrate (magnesium sulfate), and evaporation of the solvent and drying at 5 torr gave 191 mg (96%) of crystalline and chromatographically homogeneous 18. An analytical sample was prepared by recrystallization from ether; m.p. 253—255°, [α]$_D^{21}$ 0°, [α]$_D^{365}$ -16.2° (c 1, c chloroform); R$_f$ 0.43 (solvent A); λ$_{KBr}^{max}$ 2.86 (OH), 3.35 (=CH), 7.31, 8.20, 8.65, 9.36, 9.79, 9.98, and 11.70 μm; for n.m.r. data see Table 1; mass-spectral data see Table 2; X-ray powder diffraction data: 14.13 m, 11.36 m, 9.16 s (3), 7.13 vw, 6.65 s (2), 5.90 vw, 5.58 vs (1), 5.16 w, 5.07 vw, and 4.80 m.

Anal. Calc. C$_{26}$H$_{40}$O$_{12}$: C, 57.35; H, 7.35. Found: C, 57.15; H, 7.16. Calc. for C$_{25}$H$_{35}$O$_{12}$($\text{M}^+-\text{CH}_3^+$): 527.2128. Found (high resolution m.s.): m/e 527.2137.

3-C-Hydroxymethyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (16).—A. By ozonolysis-reduction of 1,2:5,6-di-O-isopropylidene-3-C-vinyl-α-D-allofuranose (14). A solution of 413 mg (1.44 mmol.) of 14 in dry methanol was treated with an ozonized stream of oxygen (0.5 l/min) for 1 h at -78°, at which time the solution had turned deep blue. Oxygen was bubbled into the solution to dispel the ozone, and 75 mg (an excess) of sodium borohydride was added portionwise at 0° with stirring. After 30 min the solution was carefully neutralized with acetic acid, and the solvent was evaporated. Methanol
(3 \times 5 \text{ ml}) was evaporated from the residue to decompose the borate complex, and the product was partitioned between water and chloroform. The dried (magnesium sulfate) organic layer was evaporated to a thick oil that was applied to a 0.7 \times 20-\text{cm} column of silica gel, which was eluted with solvent A. Unreacted starting material 14 (166 mg) was collected in the early fraction, followed by 182 mg (85\%, with recovered 14) of analytically pure 16; m.p. 62—63°; [\alpha]_D^{22.6} +19.8° (c 1.1, chloroform); R_f 0.24 (solvent A); \lambda_{\text{max}}^{\text{KBr}} 2.88 (OH), 3.32 (CH), 7.27, 7.91, 8.20, 8.58, 9.40, 9.89, 11.44, and 11.86 \mu\text{m}; for n.m.r. data see Table 1; mass-spectral data see Table 2; X-ray powder diffraction data: 13.53 m, 9.06 s (2), 7.48 m, 6.86 vw, 5.78 w, and 5.08 vs (1).

\textit{Anal. Calc. for C}_{13}\text{H}_{22}\text{O}_7: \text{ C, 53.78; H, 7.64.} \\
\text{Found: C, 53.67; H, 7.56.}

\textbf{B. By ozonolysis—reduction of 1,2-bis(1,2:5,6-di-O-isopropylidene-\alpha-D-allofuranosyl-3-yl)ethylene (18).} \\
Under the same conditions as described in A, 18 was ozonized (30 min) and reduced to give directly a crystalline product, which was homogeneous and identical to 16 by t.l.c. Recrystallization was effected by dissolving the product in 5 ml of ether, adding hexane, and boiling until a slight turbidity was noticed. Cooling to -20° gave 72 mg (64\%) of crystals of pure 16, identical in all respects with the compound described under A.
3,3'-O-Carbonyl-3-C-hydroxymethyl-1,2:5,6-di-O-
isopropylidene-D-allofuranose (19).— To a solution of
60 mg (0.21 mmole) of 16 in 3 ml of pyridine cooled in an
ice bath to 0° was added 0.60 ml of a 12% solution of
phosgene in benzene. After stirring for 30 min, the
mixture was poured into 30 ml of ice-water and extracted
with chloroform (3 x 5 ml). Evaporation of the solvent,
followed by evaporation of toluene (3 x 5 ml) from the
residue gave 62 mg of a white solid. Crystallization from
1:1 ether—hexane gave 48 mg (73%) of analytically pure 19
as long needles; m.p. 116—116.5°, [α]_D$^{22}$ +40.2° (c 2,
chloroform); Rf 0.57 (solvent A); λ$^{max}$ 3.40 (CH), 5.42,
5.50 (C=O), 6.31 7.24, 8.19, 9.02, 9.21, 9.80, 11.51, and
13.04 μm; for n.m.r. data see Table 1; mass-spectral data
see Table 2; X-ray powder diffraction data: 12.40 vs (1),
10.87 vw, 9.55 vw, 8.17 m, 7.20 w, 6.37 s (2), 5.82 m,
5.19 w, 4.73 s (3), 4.50 s, 4.19 m, 3.98 m, 3.77 m, and
3.47 w.

Anal. Calc. for C_{14}H_{20}O_{8}: C, 53.16; H, 6.37.
Found: C, 52.80; H, 6.55.

Oxymercuroative hydration of 3-C-ethynyl-1,2:5,6-di-
O-isopropylidene-D-allofuranose (12).— To a solution of
3.8 g (13.4 mmol.) of 12 in 380 ml of ethyl acetate was
added 7.6 g (23.8 mmol.) of mercury(II) acetate. The
resulting solution was stirred for 14 days at ~25°, at
which time t.l.c. (solvent A) showed a single, non-migrating spot, with complete disappearance of starting material 12 (Rf 0.64). The product, apparently a mercury complex, was then decomposed by passage of hydrogen sulfide for 5 min. After being kept for 30 min, the mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness. The resulting syrup was applied to a 2.5 x 50-cm column of silica gel and eluted with solvent A to give, after a void volume of 150 ml, three major components that were collected in 10-ml fractions. Fractions 18—23 gave 1.77 g (38%) of 3-C-acetyl-3-O-acetyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (20) as a viscous, non-distillable syrup, [α]$_D$$_{21}^2$ +75.3° (c 1, chloroform); Rf 0.72 (solvent B); $T_R$ 4.0 min (150°, system C); $\lambda_{max}^{neat}$ 3.33 (CH$_2$), 5.71, 5.82 (C=O), 7.30, 8.08, 9.33, 9.82, 11.45, and 11.88 μm; for n.m.r. data see Table 1; mass-spectral data see Table 2.

**Anal. Calc. for C$_{16}$H$_{24}$O$_{18}$: C, 55.81; H, 7.02. Found: C, 55.72; H, 6.99.**

Fractions 24—27 gave 0.54 g (14%) of 12, identical with authentic starting material by m.p., i.r., and mass spectrometry. Fractions 28—34 gave 1.27 g (39%) of 1,2-O-isopropylidene-[3-C,5-0,6-O-(methylmethylidyne)]-α-D-allofuranose (21); m.p. 156—157°, [α]$_D$$_{21}^2$ -34.4° (c 0.9, chloroform); Rf 0.44 (solvent A); $T_R$ 1.9 min (150°).
system C); $\lambda_{ \text{max} }^{\text{KBr}}$ 2.88 (OH), 3.33, 3.35 (CH), 7.28, 8.06, 8.61, 9.10, 9.90, 10.68, 11.62, 12.00, and 14.28 μm; for n.m.r. data see Table 1; mass-spectral data see Table 2; X-ray powder diffraction data: 10.13 m, 7.03 s (2), 5.67 w, 5.39 vw, 5.11 m, 4.89 vs (1), 4.70 vw, 4.49 s (3), 4.42 vw, 3.91 vw, 3.68 vw, 3.56 w, and 3.09 w.

**Anal.** Calc. for C$_{11}$H$_{16}$O$_6$: C, 54.09; H, 6.60. Found: C, 54.08; H, 6.34.

Calc. for C$_{11}$H$_{16}$O$_6$: m/e 244.0947. Found (high resolution m.s.): m/e 244.0949.

The net conversion yield from 12, of 20 and 21, taking into account recovered 12 was 91%.

**Attempted oxymercuration of 1,2:5,6-di-0-isopropylidene-3-C-vinyl-α-D-allofuranose (14).—** Following the method of Brown and Geoghegan$^{202}$ solution of 286 mg (1 mmole) of 24 and 319 mg (1 mmole) of mercury(II) acetate in 15 ml of 1:2 THF—water was stirred for 2 days at ~25°. The initial yellow color of the suspension did not change, indicating$^{202}$ lack of a complete reaction. The solution was brought to reflux for 1 h, cooled, and the yellow solution was treated with 1 ml of 3 M sodium hydroxide and 1 ml of a 5 M sodium borohydride. The solution was saturated with sodium chloride, and the THF layer was separated. The aqueous layer was washed with 20 ml of ether, and the combined organic extracts were dried.
(magnesium sulfate) and evaporated to give 260 mg (91%) of starting material 14, as identified by t.l.c. and i.r. spectrum.

Various modifications of the foregoing process (e.g. the use of more concentrated solutions of reactants; varying the time of reaction and the temperature failed to effect the conversion of 14 into 22a and 22b.

Conversion of 3-C-acetyl-3-0-acetyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (20) into 1,2-O-isopropylidene-[3-C,5-0,6-O-(methylmethylidyne)]-α-D-allofuranose (21). — A. Saponification of 20. A 40-mg sample of compound 20, shown by both t.l.c. and g.l.c. to be free from 21, was heated for 1 h under reflux with a 0.1M solution of sodium methoxide in methanol. Glacial acetic acid was added to the point of neutrality (pH ~6.5), and the solvent was evaporated. T.l.c. analysis (solvent A) revealed a single, new zone (Rf 0.83) that migrated somewhat more slowly than 20 (Rf = 0.90). The same mixture, when subjected to a g.l.c.—mass spectrometric analysis (150°, system C) indicated a single zone (TR 3.6 min) that was eluted faster than compound 20 (TR 4.0 min), and which appeared from its mass spectrum to be 3-0-deacetylated 20. Its mass spectrum showed a highest-mass at m/e 287 (16%, M+ = CH3*, C13H19O7+) and a base peak m/e 101 (100%,
C₅H₉O₂⁺), together with intermediate fragments [m/e 259 (8%), 229 (16), 201 (19), 172 (24), 143 (14), 129 (41), 111 (55), 85 (30), 71 (47), and 59 (75)] that could be reasonably assigned to fragmentations of the product derived by 3-O-deacetylation of 20.

When the reaction was conducted at ~25°, no saponification of 20 was detected (t.l.c.) after a reaction time of ~8 h, and the heating procedure used was required to achieve the conversion of 20 into the saponified product.

B. 5,6-Deacetonation of the saponification product of 20 and its conversion into 21. The crude, de-O-acetylated 20 was treated with 3 ml of 80% acetic acid for 12 h at 55 ± 5°. T.l.c. analysis (solvent A) of the product obtained upon evaporation of the acid showed a new product having Rf 0.16 (presumably 5,6-deacetonated, 3-O-deacetylated 20), but little of the anticipated, cyclized product 21 at Rf 0.44. The residue was dissolved in 5 ml of abs. ethanol, and the solution was heated under reflux for 12 h, with periodic removal of a few drops of ethanol—water azeotrope. Analysis of the product by t.l.c. and g.l.c. indicated formation of a substantial proportion (~35%) of the acetal 21; Rf 0.44 (t.l.c.), TR 1.9 min (150°, system C), together with the component having Rf 0.16 (t.l.c.). A g.l.c.—mass-spectrometric analysis of the mixture revealed a component (TR 1.9 min
(150°, system C) whose mass spectrum displayed the following peaks m/e: 244 (2%), 299 (6), 187 (2), 170 (1), 156 (1), 145 (1), 127 (11), 126 (11), 115 (4), 109 (7), 101 (2), 98 (43), 97 (21), 85 (20), 73 (2), 71 (2), 59 (34), and 43 (100)]. This fragmentation pattern is essentially that recorded for 21 (Table 2) and is identical in all respects to the spectrum obtained for authentic 21 when the pure compound was processed similarly.

The foregoing experiment was performed twice and concordant results were obtained.

Epimeric 3-C-(1-hydroxyethyl)-1,2:5,6-di-O-isopropylidene-α-D-allofuranoses (22a and 22b).—A solution of 1.78 g (5.18 mmol.) of 3-C-acetyl-3-O-acetyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (20) in THF was heated for 36 h under reflux with 100 mg of lithium aluminum hydride, with addition of a further 50-mg portion of reductant after 24 h. The solution was cooled, and the excess reagent was decomposed by the addition of a few drops of a saturated solution of ammonium chloride. The salts were filtered and washed with 5 x 20 ml of hot chloroform. The organic extracts were combined and evaporated to give 1.44 g (~95%) of recovered product, shown by t.l.c. to contain two slower-moving components, together with ~5% of non-reduced 20. Chromatography on a column (3 x 60 cm) of silica gel with solvent B gave 250 mg of the faster-moving diol (22b) (Rf 0.45) and
450 mg of its slower-migrating isomer (22a) \( (R_f 0.32) \). Analytical samples of each were prepared by dissolution of a 100-mg portion in 8 ml of ether, with slow addition of hexane and boiling to incipient turbidity, cooling initially at room temperature, and finally at 5° gave 22b as sharp needles, m.p. 119—119.5°, \([\alpha]_D^{25.4} +26.8° (c 1.7, \text{chloroform})\); \( \lambda_{\text{max}}^{\text{KBr}} 2.81 (\text{OH}), 3.33 (\text{CH}), 7.28, 7.88, 8.26, 8.57, 8.88, 9.24, 9.62, 9.90, 11.39, \text{and 11.72 } \mu\text{m} \); for n.m.r. data see Table 1, mass-spectral data see Table 2; X-ray powder diffraction data: 10.51 vs (1), 7.54 m, 6.20 s (2), 5.60 m, 5.32 m, 4.94 vw, 4.53 s (3), 4.13 w, 3.93 vw, 3.74 w, 3.58 vw, 3.38 vw, and 3.27 m.

**Anal. Calc. for C_{14}H_{24}O_7:** C, 55.25; H, 7.95.

**Found:** C, 55.38; H, 7.98.

Recrystallization of 22a gave the product as a fluffy deposit of fine needles, m.p. 97.5—98°, \( [\alpha]_D^{25.4} +14.3° (c 1.1, \text{chloroform}) \); \( \lambda_{\text{max}}^{\text{KBr}} 2.88 (\text{OH}), 3.33 (\text{CH}), 7.36, 8.00, 8.32, 8.67, 9.40, 9.91, 11.44, \text{and 11.69 } \mu\text{m} \); for n.m.r. data see Table 1; mass-spectral data see Table 2; X-ray powder diffraction data: 14.19 w, 9.96 vs (1), 8.03 m, 7.20 s (2), 5.96 w, 5.88 w, 5.40 w, 5.03 s (3), 4.76 vw, 4.59 m, 4.29 vw, 4.27 m, 4.06 vw, 3.72 vw, and 3.60 m.

**Anal. Calc. for C_{14}H_{24}O_7:** C, 55.25; H, 7.95.

**Found:** C, 55.32; H, 7.86.
A mixture of 22a and 22b melted at 87—90°.

Epimeric 3,1\textsuperscript{1}-O-carbonyl 3-C-(1\textsuperscript{1}-hydroxyethyl)-1,2:5,6-di-O-isopropylidene-\alpha-D-allofuranoses (23a and 23b). A. Under anhydrous conditions 2.2 ml of a 12.5% solution of phosgene in benzene was added to a solution of 218 mg (0.72 mmole) of 22a in 10 ml of pyridine cooled to 0°. Stirring was continued for 0.5 h at room temperature, at which time the mixture was poured into ice-water with stirring. The mixture was extracted with 3 x 10 ml of chloroform, and the chloroform extract was dried (magnesium sulfate), evaporated, and toluene (3 x 10 ml) was distilled from the residue. Trituration with ether gave a white mass of needles, and these were recrystallized from 1:1 ether—petroleum ether (b.p. 30—60°) to give 189 mg (80%) of analytically pure 23a; m.p. 153—154°, [\alpha]_{D}^{25.4} +26.4° (c 1.8, chloroform); R\text{f} 0.52 (solvent B);\n\lambda_{\text{max}}^{KBr} 3.35 (CH), 5.54 (C=O), 7.27, 7.44, 7.90, 8.24, 8.74, 9.41, 9.99, 11.52, 11.82, and 13.08 \text{µm}; for n.m.r. data see Table 1; mass-spectral data see Table 2; X-ray powder diffraction data: 9.02 m, 8.41 m, 7.59 m, 6.80 vs (1), 6.26 m, 5.63 vw, 5.27 s (2), 4.84 w, 4.62 s (3), 4.44 vw, 4.18 m, 3.94 m, 3.76 w, 3.52 w, and 3.36 w.

Anal. Calc. for C\textsubscript{15}H\textsubscript{22}O\textsubscript{8}: C, 54.54; H, 6.71.

Found: C, 54.22; H, 6.58.
B. As already described (A), 230 mg (0.76 mmole) of 22b was carbonated by using 2.3 ml of a solution of phosgene. Recrystallization of the product gave 207 mg (83%) of pure 23b; m.p. 205—205.5°, [a]_D^{25.4} +25.4° (c 1.3, chloroform); Rf 0.46 (solvent A); λ_{max}^{KBr} 3.34 (CH), 5.52 (C=O), 7.25, 7.92, 8.22, 8.68, 9.30, 9.90, 11.52, 11.83, 12.94, and 13.30 μm; for n.m.r. data see Table 1; mass-spectral data see Table 2; X-ray powder diffraction data: 8.64 s (3), 7.16 m, 6.46 vs (1), 5.39 m, 5.11 w, 4.84 s (2), 4.34 m, 4.15 vw, 3.99 w, 3.82 w, 3.61 m, and 3.48 w.

Anal. Calc. for C_{15}H_{22}O_{8}: C, 54.54; H, 6.71.

Found: C, 54.45; H, 6.70.

A mixture of 23a and 23b melted at 125—128°.

General oxidation procedure for using the chromium(VI) oxide—dipyridene complex.— Chromium trioxide (12 mole per mole of CrO₃) in sufficient dichloromethane to give a solution ~10% (v/v) of the CrO₃·2C₅H₅N complex. The mixture was stirred with exclusion of moisture for 15—20 min at ~25° to afford a deep-red solution. The alcohol to be oxidized was dissolved in dichloromethane, and the solution was added in one portion, with stirring at ambient temperature, to the solution of oxidant. A tarry deposit of chromium reduction-products formed at once. After stirring for a further 15—20 min at ~25°, the supernatant solution was decanted into a separatory
funnel containing an equal volume of ice-cold, saturated aqueous sodium hydrogen carbonate. The tar was extracted with a little ether, and the extract was added to the contents of the separatory funnel. After thorough agitation at 0°, the organic layer was separated, washed with water, dried (magnesium sulfate), and evaporated to give the crude carbonyl derivative. Toluene was evaporated at ~5 torr several times from the residue to remove traces of pyridine and afford either a syrupy or crystalline residue, which was analyzed by g.l.c. or t.l.c. and distilled or recrystallized to give an analytically pure product. The data given are obtained from experiments all performed at least twice with concordant results.

2,3:4,5-Di-O-isopropylidene-aldehydo-α-D-arabinohexosulos-2,6-pyranose (29).— 2,3:4,5-Di-O-isopropylidene-α-D-fructopyranose^{209} (28, 1.0 g, 3.85 mmol.)


in dichloromethane (5 ml) was oxidized by the foregoing procedure with a solution of chromium trioxide (4.7 g, 47 mmol.) and pyridine (7.4 ml, 94 mmol.) in dichloromethane (115 ml) to afford the aldehyde 29 as a syrup; yield 0.54 g (53%), homogeneous by t.l.c. but migrating at the same rate as 28; retention time 1.76 min
by g.l.c. at 135° (a second peak having ~1% of the area of that for 29 had a retention time of 3.33 min and corresponded to starting alcohol 28). Distillation at 0.04 torr gave analytically pure 29, b.p. 79—80°, [α]D -72° (c 1.2, chloroform); λ max 5.70 (C=O), 7.24 μm (CMe2); for n.m.r. data see Table 3; (relative intensities and probable assignments given in parentheses): 243 (55), 143 (28), 125 (21), 113 (29), 97 (8), 85 (45), 83 (7), 69 (44), 59 (55), and 57 (23).

**Anal. Calc. for C12H18O6: C, 55.80; H, 7.03.**

**Found: C, 55.97; H, 7.11.**

**Alddehyde—aldehydrol equilibrium of compound 29 in 3:7 water—tetrahydrofuran.**— The n.m.r. spectrum of a solution (~10%) of 29 in 3:7 deuterium oxide—tetrahydrofuran was kept for 6.5 h at ~25° to establish equilibrium. The n.m.r. spectrum (internal tetramethylsilane as standard) showed the signal for H-1 of the aldehydo form 29 at 0.70 and a singlet at 5.21 ascribed to H-1 of the aldehydrol form 29a, in approximately relative intensities 1:10.

**2,3:4,5-Di-O-isopropylidene-aldehydo-α-D-arabino-hexosulos-2,6-pyranose(p-nitrophenyl)hydrazone (30).** A solution of the aldehyde 29 (530 mg, 2.06 mmol.) and p-nitrophenylhydrazine (330 mg, 2.16 mmol.) in methanol (10 ml) was boiled for 15 min under reflux, and then evaporated. The residue was dissolved in benzene, and
the solution was washed successively with ice-cold 10% sulfuric acid, aqueous sodium hydrogen carbonate, and water. The dried (magnesium sulfate) solution was evaporated, and the dark-red residue was recrystallized from 4:1 ethanol—benzene to afford orange needles of analytically pure 30; yield 521 mg (65%), m.p. 176—177°, \([\alpha]_D^{25} -121° (c 1, \text{chloroform}); \lambda_{\text{max}}^{\text{KBr}} 3.08 (\text{NH}), 6.25 (\text{C=N}), 6.68 (\text{asym. NO}_2), 7.27 (\text{sym. NO}_2), 11.91, \text{and } 12.34 \text{ m (aryl)}; \) for n.m.r. data, see Table 3; X-ray powder diffraction data: 16.35 vw, 9.84 s (2), 9.73 s, 7.05 w, 5.67 vs (1), 5.27 s (3), 4.96 s, 4.54 s, 4.18 m, 3.94 w, 3.74 m, 3.57 s, and 3.28 m.

Anal. Calc. for C\(_{18}H_{23}N_3O_7\): C, 54.96; H, 5.89; N, 10.68. Found: C, 54.97; H, 5.99; N, 10.46.

Other aldehyde sugar derivatives.— A. Methyl 2,3-0-isopropylidene-\(\beta\)-D-ribo-pentodialdo-1,4-furanoside (25).
Methyl 2,3-0-isopropylidene-\(\beta\)-D-ribofuranoside\(^{210}\) (24).

0.50 g, 2.45 mmol.) was oxidized by the general procedure, and the product was recrystallized from cold 1:1 ether—petroleum ether (b.p. 30—60°) to afford 25 as white needles; yield 0.38 g (75%), m.p. 60—61°, \([\alpha]_D^{22} -220° (c 1, \text{chloroform}) \) [lit.\(^{40}\) m.p. 60—61°, \([\alpha]_D^{22} -214° (c 0.1,}\)
chloroform); homogeneous (>99%) by g.l.c., \( T_R 0.69 \) (relative to \( 24 = 1.00 \)) at 125°; X-ray powder diffraction data: 9.02 s (3), 8.05 s, 6.28 m, 5.52 m, 7.73 vs (1), 4.64 m, 4.29 m, 4.19 s (2), 3.75 w, 3.66 w, 3.38 w, 3.24 w, and 3.13 m.

The \( \beta \)-nitrophenylhydrazone of \( 25 \) had m.p. 149—150° (lit.43 m.p. 151—152°); X-ray powder diffraction data: 10.39 s, 7.82 vs (1), 5.98 m, 5.63 s (2), 5.08 s (3), 4.46 w, 3.76 s, 3.52 m, 3.22 s, 2.83 m.

Repetition of the procedure, with a 20-min period of reaction at \(-25^\circ\) with 6:1, 9:1, and 12:1 molar ratios of oxidant to substrate \( 24 \), followed by g.l.c. analysis of the product for residual starting material, showed that 71, 76, and 99%, respectively, of the starting material \( 24 \) had reacted.

B. 1,2:3,4-Di-O-isopropylidene-\( \alpha \)-D-galacto-hexodialdo-1,5-pyranose (27). Oxidation of 1,2:3,4-di-O-isopropylidene-\( \alpha \)-D-galactopyranose\(^{41} \) (26, 12 g, 46.5 mmol.) gave the aldehyde 27 as a syrup, homogeneous (>99%) by g.l.c., \( T_R 0.69 \) (relative to \( 26 = 1.00 \)); yield 7.4 g (62%). An analytical sample was prepared by short-path distillation; b.p. 105° (0.05 torr), \([\alpha]_D^{22} -111^\circ \) (c 2.3, chloroform) [lit.\(^{41} \) b.p. 104—105° (0.5 torr), \([\alpha]_D^{22} -131^\circ \) (c 0.9, chloroform)]; n.m.r. data identical with those reported.\(^{41} \)
The d-nitrophenylhydrazone had m.p. 213-215°, [α]$_D^{22}$ -102° (c 1, chloroform) [lit. 41 m.p. 214-215°, [α]$_D^{22}$ -84° (c 1, chloroform)]; X-ray powder diffraction data identical with those published. A sample of the original preparation 41 was found to have [α]$_D^{22}$ -102° (c 0.7, chloroform).

Oxidation of 5-azido-2,3-0-benzylidene-5-deoxy-β-D-ribofuranose (31) to 5-azido-2,3-0-benzylidene-5-deoxy-β-D-ribono-1,4-lactone (32). The hemiacetal 31 (0.45 g, 1.71 mmol.) gave the crystalline lactone 32, recrystallized from 1:1 ether—petroleum ether (b.p. 30—60°); yield 0.39 g (88%), m.p. 145—146°, [α]$_D^{22}$ -17° (c 0.7, acetone [lit. 57 m.p. 146—147°, [α]$_D^{22}$ -13° (c 0.7, acetone)]; homogeneous by t.l.c.

Oxidation of secondary alcohol derivatives to ketones.— A. Oxidation of 3-0-benzyl-6-deoxy-1,2-0-isopropylidene-α-D-glucofuranose$^{211}$ (33) and the β-L-ido analog$^{211}$ (35). By the standard oxidation procedure, the α-D-gluco derivative$^{71}$ (33) (1.0 g, 3.40 mmol.) gave 3-0-benzyl-6-deoxy-1,2-0-isopropylidene-α-D-xylo-hexofuranos-5-ulose$^{71}$ (34); yield 0.91 g (91%), homogeneous by t.l.c.; $R_f$ = 0.78 (1:1 dichloromethane—ether).

Recrystallization from 1:1 ether—petroleum ether (b.p. 30—60°); yield 0.39 g (88%), m.p. 145—146°, [α]$_D^{22}$ -17° (c 0.7, acetone [lit. 57 m.p. 146—147°, [α]$_D^{22}$ -13° (c 0.7, acetone]); homogeneous by t.l.c. (211) M. L. Wolfrom and S. Hanessian, J. Org. Chem., 27, 1800 (1962).
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30—60°) gave analytically pure 34; yield 0.78 g (78%), m.p. 56—57°, [α]_D^22 = -88° (c 1, chloroform) [lit. 71 m.p. 55—56°, [α]_D = -89° (c 1.5, chloroform)]; X-ray powder diffraction data: 13.85 m, 10.10 s (2), 8.26 s, 5.74 s, 5.13 vs (1), 4.69 s (3), 4.54 s, 4.35 w, 4.14 w, and 3.97 m.

Repetition of the experiment with the β-D-ido derivative 35 (150 mg, 0.51 mmole) as starting material gave the ketone 34 (131 mg, 87%), identical in all respects with the preceding product.

Behavior of endocyclic secondary alcohol derivatives on treatment with chromium trioxide—pyridine.— Under the standard oxidation conditions, 1,2:5,6-di-0-isopropylidene-α-D-glucofuranose (7) was recovered unchanged in >90% yield. Similarly, treatment of 1,6-anhydro-3,4-0-isopropylidene-β-D-galactopyranose (36) with the CrO_3·2C_5H_5N reagent led to recovery of 93% of the original mass, which was shown by i.r. and t.l.c. to contain only a small proportion of the 2-ketone. 93 Treatment of 1,6-anhydro-2,3-0-isopropylidene-β-D-mannopyranose with the oxidation reagent led to much decomposition of the sugar, affording only a low yield (<20%) of a product judged by i.r. and t.l.c. to be only partially oxidized to the 4-ketone. 56
<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Chemical shifts in τ values (first-order couplings in parentheses)</th>
</tr>
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<tr>
<td></td>
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<td>H-1</td>
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<tr>
<td>3-2-Ethynyl-</td>
<td>CDCl₃</td>
<td>4.34 d</td>
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<tr>
<td>1,2:5,6-di-O-</td>
<td>(J₁,₂ 3.7)</td>
<td>(J₂,₅ 7.1)</td>
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<td>isopropylidene-</td>
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<td>19.5 Hz</td>
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<tr>
<td>α-D-allofuranose</td>
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<td>12 b</td>
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<tr>
<td>Bis(1,2:5,6-</td>
<td>CDCl₃</td>
<td>4.25 d</td>
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<tr>
<td>di-O-</td>
<td>(J₁,₂ 3.4)</td>
<td>(J₂,₅ 8)</td>
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<tr>
<td>isopropylidene-</td>
<td></td>
<td>17.5 Hz)</td>
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<tr>
<td>α-D-allofuranoses-</td>
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<tr>
<td>3-yl)acetylene</td>
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<tr>
<td>Compound Description</td>
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<td>δ</td>
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<tr>
<td>Di-2-iso-propylidene-</td>
<td>CDCl₃</td>
<td>4.27 d</td>
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<td>3-C-vinyl-α-</td>
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<td>α-D-3¹,5-</td>
<td>lactone</td>
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<tr>
<td>3-C-carboxy- (CD₃)₂CO</td>
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<td>4.12 d</td>
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<td>1,2-iso-propylidene-</td>
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<td>(J₂,3 =0)</td>
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<td>α-D-3¹,5-</td>
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<tr>
<td>3-C-hydroxy- C₆D₆</td>
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<td>4.51 d</td>
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<td>methyl-1,2:5,6-</td>
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<td>(J₂,3 = 3.7)</td>
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<td>α-D-3¹,5-</td>
<td>lactone</td>
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TABLE 1, continued

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<tr>
<th>3,6-di-O- (CD&lt;sub&gt;3&lt;/sub&gt;)CO</th>
<th>3.92 d</th>
<th>4.98 d</th>
<th>5.06 d</th>
<th>5.36 m&lt;sup&gt;h&lt;/sup&gt;</th>
<th>5.61 s, 8.37, 8.60</th>
<th>7.84, 7.94</th>
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<tr>
<td>acetyl-1,2-</td>
<td>(J&lt;sub&gt;1,2&lt;/sub&gt; 3.8)</td>
<td>(J&lt;sub&gt;5,6&lt;/sub&gt; 2.0)</td>
<td>(width 5.66 d&lt;sup&gt;2&lt;/sup&gt;)</td>
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<td>(OAc)</td>
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<td>3,5-lactone</td>
<td>(J&lt;sub&gt;5,6&lt;/sub&gt; 6.5)</td>
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<tr>
<td>Bis(1,2:5,6- CDCl&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>4.22 d</td>
<td>5.76 d</td>
<td>5.82 ———— 6.16 m</td>
<td>8.39, 8.56, 7.33 s&lt;sup&gt;d&lt;/sup&gt; (OH),</td>
<td>8.64, 8.67</td>
<td>4.02 s (vinyl)</td>
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<tr>
<td>di-O-</td>
<td>(J&lt;sub&gt;1,2&lt;/sub&gt; 3.6)</td>
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<td>18</td>
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<td>3,5-&lt;sup&gt;1&lt;/sup&gt;-O- C&lt;sub&gt;6&lt;/sub&gt;D&lt;sub&gt;6&lt;/sub&gt;</td>
<td>4.82 d</td>
<td>5.79 d</td>
<td>6.53 d</td>
<td>5.8 m</td>
<td>6.06—</td>
<td>8.49 (6H), 8.76, 8.79</td>
</tr>
<tr>
<td>Carbomyl-3-&lt;sup&gt;1&lt;/sup&gt;-</td>
<td>(J&lt;sub&gt;1,2&lt;/sub&gt; 3.8)</td>
<td>(J&lt;sub&gt;5,6&lt;/sub&gt; 9.1)</td>
<td>6.25 m&lt;sup&gt;h&lt;/sup&gt;</td>
<td>8.76, 8.79</td>
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<tr>
<td>hydroxymethyl-</td>
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<tr>
<td>1,2:5,6-di-O-</td>
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<td>isopropylidene-</td>
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<td>3-yl allo-</td>
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<tr>
<td>furanose 19</td>
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</table>
### TABLE 1, continued

| Compound | 
|----------|-------------------------------------------------|
| 3-0-Acetyl- | **CDCl₃** |
| 3-0-acetyl- isaopropylidene- | 4.17 d | 5.01 d | 5.82 s | 6.26 m | 8.18, 8.52, 7.75 s (3-Ac), 8.67 (6H) 7.82 s (2-Ac) |
| 1,2:5,6-di-0-isoopropylidene- | 6.48 (6H) |
| **α-D-allofuranose 20** | 8.57 (3H) |
| 1,2-0- | **CDCl₃** |
| isoopropylidene-[3-0-5-0, 6-0-(methylmethylidyne)]- | 4.14 d | 5.67 d | 5.85 s | 5.51 t | 6.31 d, 6.37 d | 6.79 d (OH); 8.42 (6H); 8.57 (3H) |
| **α-D-allofuranose 21** | 8.60 (6H) |
| 3-0-(1°- | **CDCl₃** |
| Hydroxyethyl)- | 4.29 d | 5.46 d | 5.70 s | 6.20 m | 8.41, 8.45, 5.90 q, H-3¹ |
| 1,2:5,6-di-0-isoopropylidene- | 8.63 (6H) (J₃,₄ = 7); 6.9 d (OH); 8.83 d, H-3² |
| **α-D-allofuranose 22a** | 6.37 s In | 6.79 d (OH); 8.42 (6H); 8.57 (3H) |
### TABLE 1, continued

<table>
<thead>
<tr>
<th>Compound</th>
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<tbody>
<tr>
<td>3-(\text{O}^1)-CDC(\text{Cl}_3) Hydroxyethyl)-1,2:5,6-di-O-isopropyldene-(\alpha)-(\text{P})-allofuranose 22b</td>
</tr>
<tr>
<td>3,3(^1)-O- CDC(\text{Cl}_3) Carbonyl-3-(\text{C}^{-})(1(^1)-hydroxyethyl)-1,2:5,6-di-O-isopropyldene-(\alpha)-(\text{P})-allofuranose 23a</td>
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<tr>
<td>3,3'-O-</td>
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<tr>
<td>---------</td>
</tr>
<tr>
<td>Carboxyl-3-¢</td>
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<tr>
<td>(1'-hydroxy-ethyl)-1,2:5,6-</td>
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</table>

² Apparent first-order couplings are given in Hz; peak multiplicities: d, doublet; dd, doublet of doublets; s, singlet; q, quartet; t, triplet. ³ For spectrum with Eu(fod)₃ added, see Fig. 1. ⁴ An AB portion of ABX system; calculated couplings are given. ⁵ Exchanges upon addition of D₂O. ⁶ Spectrum at 60 MHz. ⁷ Apparent AₓX pattern. ⁸ AB portion of ABX system that approaches AₓX; outer transitions undetectable. ⁹ Includes H-3',3'β. ¹ A 7-line symmetrical multiplet. ¹¹ C(Me)₂ and 3'-Me resonances not distinguished.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Mass-spectral peaks (relative intensities and probable assignments are given in parentheses)</th>
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<tbody>
<tr>
<td>3-(\text{C-Ethynyl-1,2:5,6-di-})isopropylidene-(\alpha)-D-allofuranose 12</td>
<td>269 (37) ((\text{M}^+)-(\text{CH}_3)), 243 (1) (269-(\text{C}_2\text{H}_5)), 226 (&lt;1)</td>
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<td>((\text{M}^+)-(\text{C}_3\text{H}_5\text{O}_2)), 211 (1) (226-(\text{CH}_3)), 189 (5), 183 (&lt;1)</td>
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<td></td>
<td>((\text{M}^+)-(\text{C}_3\text{H}_5\text{O}_2)), 168 (7) (183-(\text{CH}_3)), 153 (4)</td>
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<td></td>
<td>((\text{M}^+)-(\text{C}<em>6\text{H}</em>{11}\text{O}_3)), 151 (5) ((\text{C}_6\text{H}_7\text{O}_3^+)), 158 (4) (155-(\text{CH}_3)),</td>
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<td>152 (41) ((\text{M}^+)-(\text{C}_6\text{H}_6\text{O}_3)), 123 (8) ((\text{C}_7\text{H}_7\text{O}_2^+)), 113 (5),</td>
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<td>111 (4), 110 (11), 109 (5), 101 (36) ((\text{C}_6\text{H}_6\text{O}_2^+)), 97</td>
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<td>(11) ((\text{C}_6\text{H}_6\text{O}_2^+)), 96 (13), 95 (4), 93 (7), 85 (9)</td>
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<td>((\text{C}_4\text{H}_5\text{O}_2^+)), 73 (4), 72 (19), 71 (6) ((\text{C}_3\text{H}_5\text{O}_2)), 68</td>
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<td>(5), (63) (7), 59 (78) ((\text{C}_2\text{H}_7\text{O}^+)), 43 (100) ((\text{C}_3\text{H}_5\text{O}^+))</td>
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<tr>
<td>1,2-Bis-(1,2:5,6-di-(\text{O-isopropylidene-(\alpha)-D-allofuranos-3-yl}-)acetylene 13</td>
<td>527 (50) ((\text{M}^+)-(\text{CH}_3)), 469 (1) (527-(\text{C}_3\text{H}_5)), 441 (&lt;1)</td>
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<td>((\text{M}^+)-(\text{C}_3\text{H}_5\text{O}_2)), 426 (1) (441-(\text{CH}_3)), 411 (1) (426-(\text{CH}_3)),</td>
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<td>385 (1) (441-(\text{C}_3\text{H}_5)), 366 (1) (426-(\text{CH}_3\text{O}_2)), 365</td>
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<td>(1), 353 (4) (411-(\text{C}_3\text{H}_5)), 352 (3), 339 (2), 337 (2),</td>
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<td>312 (2), 297 (5), 296 (6), 295 (3), 281 (2), 269 (2),</td>
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<td>265 (2), 256 (3), 253 (4), 238 (5), 221 (4), 208 (7),</td>
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<td>193 (7), 182 (10), 166 (10), 137 (10), 131 (29), 101</td>
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<td>(83) ((\text{C}_3\text{H}_5\text{O}_2^+)), 85 (24) ((\text{C}_4\text{H}_5\text{O}_2^+)), 72 (22), 59 (45)</td>
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<td>((\text{C}_3\text{H}_7\text{O}^+)), 43 (100) ((\text{C}_2\text{H}_5\text{O}^+))</td>
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<td>TABLE 2, continued</td>
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<td>1,2:5,6-Di-O-</td>
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<tr>
<td>C-vinyl-α-D-</td>
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<tr>
<td>allofuranose 14</td>
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<tr>
<td>286 (&lt;1) (M⁺), 271 (23) (M⁺—CH₃⁻), 228 (2)</td>
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<td>(M⁺—C₂H₅O), 213 (1) (271—C₃H₇O), 189 (2), 185 (1) (M⁺—C₂H₅O₂⁻), 171 (4), 170 (9) (185—CH₃⁻), 153 (6) (C₃H₇O₃), 127 (1) (C₄H₇O₃), 125 (4) (C₇H₉O₂), 98 (67), 99 (36) (C₃H₅O₂), 95 (10), 85 (9) (101—CH₃—H⁺), 72 (21), 59 (75) (C₃H₇O⁺), 55 (101—C₁H₅O, 43 (100) (C₂H₅O)</td>
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<td>3-α-Carboxy-1,2:5-</td>
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<td>allofuranose-3¹,5-</td>
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<tr>
<td>lactone 15</td>
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<tr>
<td>251 (22) (M⁺—CH₃⁻), 188 (9) (M⁺—C₃H₇O), 171 (28)</td>
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<td>(251—C₃H₅COH), 158 (12), 153 (10) (171—H₂O), 125 (3) (155—CO), 141 (6), 130 (9), 113 (5), 101 (7) (C₃H₇O₂⁺), 100 (30) (C₄H₇O₃⁺), 89 (5), 85 (14) (101—CH₃—H⁺), 72 (12), 59 (90) (C₃H₇O⁺), 43 (100) (C₂H₅O⁺)</td>
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<td>3-α-Hydroxymethyl-</td>
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<td>allofuranose 16</td>
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<td>275 (40) (M⁺—CH₃⁻), 257 (2) (275—H₂O), 233 (1),</td>
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<tr>
<td>217 (10) (275—C₃H₇O), 215 (5) (275—C₂H₄O₂), 201 (2), 199 (2), 189 (5) (M⁺—C₄H₉O₂⁺), 175 (3), 174 (1), 172 (3), 171 (1) (189—H₂O), 159 (4), 158 (1) (189—CH₂OH), 157 (12) (215—C₃H₇O), 143 (10), 139 (15) (C₇H₁₀O₂), 131 (18) (189—C₃H₇O), 129 (4), 126 (4) (157—CH₂OH), 116 (8), 113 (14) (C₃H₅O₂), 101 (72) (C₃H₇O₂⁺), 100 (16) (C₄H₇O₃⁺), 99 (10), 85 (26) (C₄H₇O₂), 72 (22), 59 (79) (C₃H₇O⁺), 57 (10), 43 (100) (C₂H₅O⁺)</td>
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<tr>
<td>Compound Description</td>
<td>Frequencies (MHz)</td>
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<tr>
<td>3,6-di-0-acetyl-3-C-carboxy-1,2-0-isopropylidene-0-D-allofuranose-3',5'-lactone 17</td>
<td>315 (32) H&lt;sup&gt;+&lt;/sup&gt;-CH&lt;sub&gt;3&lt;/sub&gt;·, 288 (3) (H&lt;sup&gt;+&lt;/sup&gt;-C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;), 273 (1) (288-CH&lt;sub&gt;3&lt;/sub&gt;·), 257 (&lt;1) (C&lt;sub&gt;11&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;), 255 (&lt;1) (515-C&lt;sub&gt;8&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;), 241 (1), 231 (1), 214 (14), 196 (8), 171 (12), 153 (21) (171-H&lt;sub&gt;2&lt;/sub&gt;O), 132 (4), 125 (9) (153—CO), 113 (2), 101 (3), 100 (2) (C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;), 85 (5), 71 (3), 59 (8) (C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;), 43 (100) (C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>trans-1,2-Bis-(1,2:5,6-di-0-isopropylidene-0-D-allofuranosyl)ethylene 18</td>
<td>529 (55) H&lt;sup&gt;+&lt;/sup&gt;-CH&lt;sub&gt;3&lt;/sub&gt;·, 428 (1) (529-C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;·), 425 (2), 413 (1) (428-CH&lt;sub&gt;3&lt;/sub&gt;·), 411 (2), 370 (1) (428-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;0), 355 (8) (413-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;0), 353 (2), 357 (5), 312 (11), 298 (15), 256 (6), 240 (12), 211 (7), 197 (10), 182 (7), 168 (24), 131 (18), 101 (65) (C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;·), 100 (95) (C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;), 97 (22), 85 (25) (C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;), 71 (16), 59 (10) (C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;), 43 (100) (C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>3,3'-0-Carbonyl-3-0-hydroxymethyl-1,2:5,6-di-0-isopropylidene-0-D-allofuranose 19</td>
<td>301 (100) H&lt;sup&gt;+&lt;/sup&gt;-CH&lt;sub&gt;3&lt;/sub&gt;·, 288 (11) (H&lt;sup&gt;+&lt;/sup&gt;-28), 269 (10) (301-C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;0), 243 (5) (301-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;0), 241 (4) (301-C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;·), 206 (2) 200 (3) (301-C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;·), 187 (8) (288-C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;·), 183 (20) (241-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;0), 149 (9), 143 (5), 139 (15), 129 (14), 115 (5), 111 (7), 101 (98) (C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;), 97 (6), 85 (11) (C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;), 83 (10), 81 (8), 72 (14), 59 (22) (C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;), 57 (14), 55 (36), 43 (98) (C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>
TABLE 2, continued

<table>
<thead>
<tr>
<th>Structure</th>
<th>Masses (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-O-Acetyl-3-O-acetyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose 20</td>
<td>329 (3) (M⁺—CH₃⁺), 271 (4) (329—C₆H₅O), 243 (3) (M⁺—C₅H₁₀O₂⁺), 228 (1) (243—CH₃⁺), 211 (1)</td>
</tr>
<tr>
<td></td>
<td>(271—CH₃CO₂H), 185 (11) (228—C₆H₅O), 155 (4), 153 (8), 151 (1) (211—CH₃CO₂H), 143 (6), 141 (4), 127 (7), 101 (69) (C₆H₅O₂⁺), 97 (4), 85 (5) (C₄H₄O₂⁺), 71 (7), 59 (12) (C₃H₇O⁺), 43 (100) (C₂H₅O⁺)</td>
</tr>
<tr>
<td></td>
<td>244 (3) (M⁺), 229 (8) (M⁺—CH₃), 187 (2), 186 (&lt;1) (M⁺—C₆H₅O), 170 (1), 156 (&lt;1) (C₇H₆O₄⁺), 145 (1), 144 (&lt;1) (186—C₆H₅O), 127 (8), 126 (8) (114—H₂O), 115 (4), 101 (1), 98 (38), 97 (16), 85 (21) (C₄H₄O₂⁺), 71 (7), 71 (18), 61 (3), 60 (2), 59 (32) (C₃H₇O⁺), 43 (100) (C₂H₅O⁺)</td>
</tr>
<tr>
<td>Epimeric 3-O-(1α-hydroxyethyl)-1,2:5,6-di-O-isopropylidene-α-D-allofuranose 22a and 22b</td>
<td>289 (11) (M⁺—CH₃⁺), 275 (1), 271 (2) (289—H₂O), 259 (2), 231 (6) (289—C₃H₆O), 229 (3) (289—C₄H₄O₂), 217 (2) (275—C₆H₅O), 213 (2) (231—H₂O), 203 (7) (M⁺—C₅H₁₀O₂⁺), 201 (7) (259—C₆H₅O), 189 (4), 187 (4), 185 (2), 171 (7), 169 (3), 157 (5), 153 (10), 144 (10), 131 (15), 127 (15), 115 (16), 113 (12), 101 (75) (C₆H₅O₂⁺), 100 (23) (C₄H₄O₂⁺), 99 (21), 97 (12), 85 (22) (C₄H₄O₂⁺), 83 (13), 73 (14), 72 (20), 71 (40), 69 (14), 59 (76) (C₃H₇O⁺), 57 (18), 55 (26), 43 (100) (C₂H₅O⁺)</td>
</tr>
<tr>
<td>Epimeric 3,1(^1)-●-</td>
<td>315 (8) (\text{M}^+ - \text{CH}_3) (\cdot), 289 (&lt;1), 287 (&lt;1) (315—CO)</td>
</tr>
<tr>
<td>carbonyl-3-●-</td>
<td>285 (&lt;1), 257 (2) (315—C(_3)H(_6)O), 256 (4), 255 (1)</td>
</tr>
<tr>
<td>(1(^1)-hydroxyethyl)-</td>
<td>(315—C(_6)H(_4)O(_2)), 230 (1), 229 (1) (330—C(_3)H(_6)O(_2)(\cdot)),</td>
</tr>
<tr>
<td>1,2:5,6-di-●-</td>
<td>214 (1) (315—C(_5)H(_6)O(_2)(\cdot)), 201 (3) (229—CO), 197 (7)</td>
</tr>
<tr>
<td>isopropylidene-</td>
<td>(257—C(_2)H(_4)O(_2)), 185 (1), 171 (1), 153 (5), 140 (2),</td>
</tr>
<tr>
<td>α-(\beta)-allofuranoses</td>
<td>131 (2), 125 (3) 111 (5), 101 (68) (\text{C}_5\text{H}_3\text{O}_2^+), 100</td>
</tr>
<tr>
<td>23(\alpha) and 23(\beta)</td>
<td>(4) (\text{C}_4\text{H}_4\text{O}_2^+), 85 (6) (\text{C}_4\text{H}_5\text{O}_2^+), 72 (26), 59 (20)</td>
</tr>
<tr>
<td></td>
<td>((\text{C}_3\text{H}_7)^+), 55 (56), 43 (100) (\text{C}_2\text{H}_3)^+</td>
</tr>
</tbody>
</table>
TABLE 3
N.M.R. Spectral Data for Compounds 29 and 30

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Shifts</th>
<th>Multiplicities and Coupling Constants</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>r 0.49 (1H singlet, H-1), 5.36 (doublet of doublets, J&lt;sub&gt;4,5&lt;/sub&gt; 7.6 Hz, J&lt;sub&gt;4&lt;/sub&gt;-H-4), 5.51 (doublet, J&lt;sub&gt;3,4&lt;/sub&gt; 3.5 Hz, H-3), 5.72 (width 15.5 Hz, multiplet, H-5), 5.96, 6.16 (AB of ABX system, J&lt;sub&gt;5&lt;/sub&gt;,&lt;sub&gt;6&lt;/sub&gt; 2.0 Hz, J&lt;sub&gt;5&lt;/sub&gt;,&lt;sub&gt;6&lt;/sub&gt;' 1.0 Hz, J&lt;sub&gt;6&lt;/sub&gt;,&lt;sub&gt;6&lt;/sub&gt;' 1.0 Hz, H-6&lt;sup&gt;+&lt;/sup&gt;, 6&lt;sup&gt;-&lt;/sup&gt;'), 8.44, 8.56, 8.58 and 8.65 (3H singlets, 2 CMe&lt;sub&gt;2&lt;/sub&gt;)</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>r 1.93 (1H singlet, disappears on deuteration, -NH&lt;sub&gt;2&lt;/sub&gt;), 2.04, 3.14 (4H proton AA'&lt;sup&gt;-BB'&lt;/sup&gt; pattern, J&lt;sub&gt;A,B&lt;/sub&gt; 10.0 Hz, aryl protons), 2.83 (1H singlet, H-1), 5.35 (doublet, J&lt;sub&gt;3,4&lt;/sub&gt; 2.4 Hz, H-3), 5.48 (doublet of doublets, J&lt;sub&gt;4,5&lt;/sub&gt; 8.0 Hz, H-4), 5.87 (broad doublet, width 10.5 Hz, H-5), 6.15, 6.37 (AB of ABX system, J&lt;sub&gt;5&lt;/sub&gt;,&lt;sub&gt;6&lt;/sub&gt; 1.8 Hz, J&lt;sub&gt;5&lt;/sub&gt;,&lt;sub&gt;6&lt;/sub&gt;' 0.7 Hz, J&lt;sub&gt;6&lt;/sub&gt;,&lt;sub&gt;6&lt;/sub&gt;' 12.8 Hz, H-6&lt;sup&gt;+&lt;/sup&gt;, 6&lt;sup&gt;-&lt;/sup&gt;'), 8.59, 8.67, 8.76, and 8.82 (3H singlets, 2 CMe&lt;sub&gt;2&lt;/sub&gt;)</td>
<td></td>
</tr>
</tbody>
</table>

a. Measured at 100 MHz in CDCl<sub>3</sub>, using tetramethylsilane as an internal standard and source for a lock signal.
PART TWO:
SYNTHESIS AND MODIFICATION
OF NUCLEOSIDES
I. INTRODUCTION AND HISTORICAL BACKGROUND

A. Historical Perspectives

In a paper published in 1909 entitled "Uber die Hefe-Nucleinsaure,"¹ Levene and Jacobs first proposed the term "nucleoside" as a generic name for the group of compounds containing glycosylic derivatives of purines and pyrimidines that were obtained upon the alkaline hydrolysis of yeast nucleic acid. This work was an outgrowth of the pioneering studies of Miescher² and others³-⁶

who had isolated "nuclein," the material obtained from pus cells upon their treatment with dilute hydrochloric acid and extraction with ether. Recognition of the fact that there were two types of nucleic acids, the one isolable from yeast (RNA) and the one from salmon sperm or thymus tissue (DNA) is attributed to the observations of Kossel and Neuman. The nitrogenous bases, being the mere stable


components chemically, were identified by Kossel, Schulze, Fischer and others, and they had all been synthesized by 1903. It was in 1911 that Levene was able to


identify the sugar moiety of yeast RNA as \( \text{D-ribose} \).


However, it was many years later before the elusive sugar of thymus DNA, 2-deoxy-\( \text{D-erythro}\)-pentose, was identified. The nucleic acid was subjected to a tedious hydrolytic procedure that was carried out in a portion of the intestinal tract of a living dog.\(^{17}\)


The progress of nucleic acid chemistry in the early to middle Nineteenth Century was largely that of the isolation of naturally-occurring nucleosides from various plant and animal sources. In addition to the four nucleosides derived from RNA, adenosine, guanosine, uridine, and cytidine, [Chart I] and their counterparts in the DNA series, 2'-deoxyadenosine, 2'-deoxyguanosine, thymidine, and 2'-deoxycytidine [Chart II], numerous unusual nucleosides were isolated. Among these were a riboside of uric acid, identified in 1922,\(^{18}\) and
CHART I: Nucleosides Derived from Ribonucleic Acid (RNA)
CHART II: Nucleosides Derived From Deoxyribonucleic Acid (DNA)
123

(18) A. R. Davis, E. B. Newton, and S. B. Benedict, 

isoguanosine (2-hydroxyadenosine) isolated in 1932.¹⁹ In


the 1940's some consideration was given to nucleosides 
as potentially useful medicinal agents, both as antibiotics 
and as antitumor drugs. It was early recognized that some 
purine and pyrimidine analogs, 5-bromouracil, 8-azaguanine, 
2,6-diaminopurine, and 6-mercaptopurine, interfere with 
cell growth²⁰,²¹ and possess some degree of antitumor

(20) G. H. Hitchings, E. A. Falco, and M. B. Sherwood, 
Science, 102, 151 (1945).

(21) R. O. Robin, Jr., I. O. Lampen, J. P. English, 
67, 290 (1945).

activity.²²,²³ These findings, together with the ever-

(22) J. H. Burchenal, A. Bendich, G. B. Brown, 
G. B. Elion, G. H. Hitchings, C. P. Rhoads, and C. C. 

(23) D. A. Clarke, F. S. Philips, S. S. Sternberg, 
C. C. Stock, G. B. Elion, and G. H. Hitchings, Cancer 
increasing interest in the role of nucleosides in the structure of nucleic acids and the latter's relation to the fundamental life processes, brought the study of nucleosides into an age of its own. Advances such as the Watson—Crick model for DNA, announced in 1953, gave impetus to the field. During the period 1950-1970 there has been intense activity in all areas of research in the chemistry, biochemistry, and pharmaceutical applications of nucleosides and nucleoside analogs.

Numerous reviews cover the early developments in the chemistry of nucleosides, and to these the reader is directed for a comprehensive account.

B. Synthesis of Nucleosides

In a broader sense, the term "nucleoside" has gradually emerged as an all-encompassing term that includes not only those glycosyl purines and pyrimidines which are constituents of nucleic acids, but all glycosylamines in which the amine is a heterocyclic base. This terminology has become necessary largely because of the interest, developed over the last half-century, and particularly since 1950, in the synthesis and modification of nucleosides.

The earliest synthetic work in the nucleoside field is traceable to the laboratory of Fischer, who, with his student Helferich, reported the synthesis\(^\text{29}\) of a purine nucleoside by condensation of the purine silver salt with an acetylated glycosyl bromide. Deacetylation of the condensation product gave the nucleoside. Much developmental work has been extended in the area of nucleoside synthesis, partially as a complementary method to degradative studies on nucleic acids, and partially to study the effects of unnatural nucleosides on biological systems. Much of the synthetic effort has been directed
in recent years towards the development of nucleosides of value in the chemotherapeutic control of cancer (see Section C).

Numerous reviews\textsuperscript{25,26,30-34} have appeared on the

\begin{itemize}
\end{itemize}

synthesis of nucleosides, and a two-volume compendium\textsuperscript{35} that serves as a laboratory guide has been published.

Nucleoside chemistry may be conveniently divided into three categories, \textit{i.} condensation of suitably protected sugars with activated purines or deivatized pyrimidines; \textit{ii.} modifications of the sugar portion of existing nucleosides; \textit{iii.} modifications on the heterocyclic system. Of these, only \textit{i.}, which is most pertinent...
to the work presented in this dissertation, will be discussed at length.


The classical method of Fischer and Helferich, whereby the "active" salt of a purine is condensed with a suitably protected glycosyl halide has been the general method employed for the synthesis of purine nucleosides. Todd and coworkers, almost thirty years after the Fischer-Helferich work appeared, applied the route for the synthesis of the natural purine nucleosides, including adenosine and guanosine. Low yields were encountered in the coupling reaction. A major advance in the procedure was made by Davoll and Lowy, who substituted the chloromercuiri salt, in place of the more expensive silver salt, and obtained fair yields of nucleosides.


Coworkers further improved the technique so that high (60—80%) yields could be obtained.
Most of the nucleosides obtained by the Fischer—Helferich method and its modifications have been shown to be 9-glycosylpurines, despite a few examples, most notably the first, which was later shown to be a 7-substituted theophylline. Examples of nucleosides that have shown to be 7-glycosyl derivatives are largely limited to the theophyllines, although several N₆-dialkyl adenines give mixtures of 7- and 9-glycosyl nucleosides. Ultraviolet absorption spectroscopy has proven valuable for determining the site of substitution, particularly for the adenine derivatives. The site of glycosylation may have some dependence on the nature of the glycosyl halide.
as well as the purine, although these effects have not been clearly explained.

The anomeric configuration of the nucleoside obtained upon coupling of a per-O-acetylglycosyl halide (of say, D-ribose or D-glucose) with a heavy-metal salt of a purine was observed, from many examples, to be β. These observations have been formulated as the "trans rule."\(^{43,44}\)


The rule\(^ {44}\) states that "condensation 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 at C-1-C-2." Anchemeric assistance of the 2-acyloxy group was invoked to explain\(^ {43,44}\) the stereochemistry observed. Similar observations had earlier been made in the sugar series for the action of silver acetate upon acylated glycosyl halides.\(^ {45}\) In order to achieve a synthesis of an

\(a\)-nucleoside, Khorana employed a non-participating 2,3-\(\text{O}\)-carbonyl glycosyl halide and obtained a 17:3 ratio of \(\alpha:\beta\) anomers.\(^{46}\) A later development, in which titanium tetrachloride was employed to generate the glycosyl halide \textit{in situ}, was shown to give an \(\alpha,\beta\) mixture of nucleosides.\(^{47}\)


This latter method is particularly useful in cases where both anomers are desired, or where the glycosyl halide is difficult to prepare by conventional methods.\(^{48}\)


Numerous attempts to improve the synthesis of purine nucleosides by using other derivatives to activate the purine ring have been reported. Taylor and coworkers describe the use of a titanium salt, which although useful for obtaining simple alkyl purines with substitution exclusively at N-9, gave only a 2% yield of adenosine.\(^{49}\)
Some high yields of nucleosides from substituted purines have been reported\textsuperscript{50,51} using the glycosylation conditions of Helferich and Weis\textsuperscript{52}, which makes use of mercury(II) cyanide in nitromethane.

b. Condensations of glycosyl halides with trimethylsilyl purines. Trimethylsilyl derivatives have been found effective in a number of purine nucleoside syntheses. Two early papers\textsuperscript{53,54} report variable yields of nucleosides from the (trimethylsilyl)purine precursors. However, the procedure using bis(trimethylsilyl)-6-
benzamidopurine was employed to advantage to secure an α-adenine nucleoside analog, otherwise difficulty accessible. The procedure gives rise to both α- and β-anomers and 7-glycosyl derivatives.

c. Fusion methods. A valuable technique for the synthesis of purine nucleosides involves the simple expedient of heating a mixture of the purine, an acylated sugar and an acid catalyst together under diminished pressure in the molten state. The procedure gives excellent yields in numerous instances, and generally gives both anomers of 9-glycosylpurines, a notable exception being theophylline, which gives exclusively the 7-glycosylated product. The need for fusion limits, of course, the procedure to those purines have relatively low melting points, so that a melt can be obtained in the 100—200°
range. In this manner, 2,6-dichloro-, 58 2,6-dibromo-, 59 6-alkyl-, 60 2,6,8-trichloro-, 61 and other 6-substituted purines 62 have been converted into nucleosides. The


Fusions are conducted either in the presence of acid catalysts, 58-60 iodine, 63 or without catalyst. 62, 64 A


(64) T. Sato, ref. 35, Vol. 1, p. 264.

Recent study gives a plausible mechanism for the action of the acid catalyst; an initial acid—purine conjugate is indicated, rather than an attack on the per-O-acylated sugar. 65
d. Fusion of free sugars with nucleoside bases. A synthesis proposed by Schramm and coworkers,\textsuperscript{66} involves the fusion of a free sugar with a nucleoside base in the presence of phenyl polyphosphate. Despite extensive work to improve yields and arrive at optimum conditions\textsuperscript{67-69} for the reaction, the results have proven difficult to reproduce. Low yields of two important nucleosides, 2'-deoxyadenosine,\textsuperscript{70} and the rare cis nucleoside, 9-(\textbeta-\textgamma-}

\textgamma-arabinofuranosyl)adenine,\textsuperscript{71} have nevertheless been prepared by this method.
2. Synthesis of pyrimidine nucleosides:— a. The Hilbert—Johnson procedure. Fischer and Helferich attempted, without success, to extend their classical purine nucleoside synthesis to the pyrimidines.\(^{29,72}\)

Later attempts by others\(^ {73}\) failed to effect a nucleoside synthesis, and the lactam—lactim tautomerism \(-\text{C} = \text{N}-\leftrightarrow-\text{C} = \text{N}-\) was recognized\(^ {74}\) as being responsible for the difficulties in achieving a synthesis of N-1 glycosyl derivatives of pyrimidines. Following these observations, Hilbert and Johnson converted the pyrimidines into the 2,4-dialkoxypyrimidines, and condensed these non-tautomeric compounds with acylated glycosyl halides and obtained the desired coupling to N-1.\(^ {74}\) Dealkylation of the pyrimidine base, followed by O-deacetylation of the
sugar moiety, furnished the nucleoside. The reaction sequence just described has provided a method, with numerous variations, for the preparation of a great many pyrimidine nucleosides which have been adequately reviewed.\(^30,75\) The preponderant anomer is generally \(\beta\) as predicted by the \textit{trans} rule.\(^43-45\)

By far the major advance in the synthesis of pyrimidine nucleosides is the modification of the Hilbert—Johnson method in which 2,4-bis(trimethylsiloxy)pyrimidines\(^76\) are used instead of their 2,4-dialkyl oxy counterparts. The reaction as a whole is easier to carry out, in that the pyrimidines are easily (trimethylsilyl)ated, and the silyl ethers are readily cleaved from the reaction products with water or alcohols. Furthermore, the silylation technique is directly applicable to cytosine,\(^76-78\) which

\begin{itemize}
  \item \(^{75}\) J. Pliml and M. Prystaš, \textit{Adv. Heterocycl. Chem.}, 8, 115 (1967).
  \item \(^{77}\) E. Wittenburg, \textit{Z. Chem.}, 4, 303 (1964).
\end{itemize}
had earlier been prepared by an ammonolysis of the 4-alkyloxy pyrimidine.

In general, the reaction of the silylated pyrimidines with acylated glycosyl halides is more sluggish than their alkoxy analogs, necessitating the use of higher temperature to effect condensation. To obviate this problem, a procedure that employs silver perchlorate has been developed, whereby the reactions proceed exothermically at or near room temperature. Mercury salts apparently also catalyze the reaction. In nearly all condensations using bis(trimethylsiloxy)pyrimidines anomeric mixtures are obtained, in contrast to the products obtained from classical Hilbert—Johnson method.

b. The mercuri procedure. Following the developments of Davoll and Lowy in purine nucleoside synthesis, Fox and coworkers, using mercury-derivatized pyrimidines, were able to demonstrate a facile route to pyrimidine nucleosides. The procedure is more rapid (0.5 h for


reaction) than the Hilbert—Johnson synthesis (1—5 days for reaction), and is therefore more useful whenever highly unstable glycosyl halides are being used. Whenever comparisons have been made, the products seem to be of the same relative anomeric composition as those from the Hilbert—Johnson procedure; the mercuri process, therefore, follows the trans rule.43-45

A modification of the mercuri procedure in which acylated glycals are coupled with pyrimidines is the basis for a useful synthesis of 2'-deoxynucleosides.34,83 The mercury(II) cyanide—nitromethane procedure has also proven useful in the pyrimidine series,34,84 particularly

where the standard mercuri procedure fails with strongly electronegative groups at C-5.85


C. Biologically Active Nucleosides

1. Biological effects of antimetabolites.— Aside from their presence as components of nucleic acids, a number of nucleosides have been isolated in the free state from living systems, especially certain bacterial organisms. These naturally occurring, free nucleosides are, for the most part, structural analogs of those nucleosides found incorporated into nucleic acids. Many of these compounds have demonstrated antimicrobial activity and cell toxicity, and some are useful as antibiotics. These function as antimetabolites—that is to say, because of their close similarity to the nucleosides found in nucleic acids, these analogs are able to interfere either with cellular enzyme processes or they become incorporated as "fraudulent" links in cellular nucleic acid chains, and thereby modify vital cell processes, including DNA replication, DNA code transcription to RNA, and RNA-directed protein synthesis. An antimetabolite that alters normal enzyme function may do so at several levels. The compound may compete with a substrate for an active site on the enzyme, or it may replace the normal cofactor, if the enzyme utilizes a cofactor in its action. A compound that mimics an end product of a biosynthetic pathway may regulate enzyme action through a feedback mechanism, acting at an allosteric site of an earlier enzyme in the sequence.
The concept of the antimetabolite may be traced to the observation that the synthetic, non-nucleoside antibiotic, sulfanilamide, a structural analog of the natural cofactor, L-aminobenzoic acid, can compete with the latter in the cellular enzyme system and thereby inhibit folate biosynthesis.86


The early observation that a number of purine analogs were effective inhibitors of cell growth20,21 and possessed antitumor activity,22,23 together with the discovery that purines and "unnatural" purine analogs could become incorporated into nucleic acids87,88 prompted an in-depth


survey into the role of nucleosides as antimetabolites. Much synthetic effort has since then been directed towards producing these "fraudulent" nucleosides, and, indeed, a great many synthetic and naturally occurring nucleosides have been evaluated for their biological activities. A composite listing of those nucleosides which have been
assayed for antitumor activity, together with the testing results, have been reported. The nucleoside antibiotics


have been the subject of reviews and a monograph on the subject.

2. Nucleoside antibiotics. — a. Purine nucleoside antibiotics. Puromycin was one of the earlier nucleoside antibiotics discovered in cultures of Streptomyces alboniger and its structure was elucidated as a N-3'


 derivative of N,N-dimethyl-9-(3'-amino-3'-deoxyribofuranosyl)adenine [Chart III]. Its synthesis has

Puromycin

3'-Amino-3'-deoxyadenosine: $R = -H$
Iysylaminoadenosine: $R = O\text{-}C\text{CH(CH}_2)_4\text{NH}_2$
Homocitrullylaminoadenosine: $R = O\text{-CH(CH}_2)_4\text{NHCHNH}_2$

CHART III: Puromycin and Related Antibiotics
been reported,\textsuperscript{95} and its anomeric configuration established.\textsuperscript{96} The activity of the nucleoside depends upon its resemblance to the amino acid-bearing end of transfer RNA and the resulting interference with protein synthesis.\textsuperscript{97,98} The compound shows only limited antitumor activity,\textsuperscript{99} and this effect may well depend upon its demethylation in vivo to the adenosine analog.\textsuperscript{100,101}
which itself has shown anticancer activity. Although puromycin has limited use as a medicinal agent, its usefulness as a probe in biochemical research to elucidate the mechanisms in protein synthesis is unparalleled by any other chemical compound.

A number of nucleoside antibiotics related to puromycin have been discovered in extracts from *Streptomyces* and certain fungi. These include 3'-amino-3'-deoxyadenosine, homocitrullylaminoadenosine, and lysylaminoadenosine [Chart III], and all possess, to various degrees, toxicity towards bacterial cells, viruses, and tumors.

A number of synthetic efforts have been directed towards producing a simple, biologically active puromycin
analog, including carbocyclic\textsuperscript{106} and acyclic\textsuperscript{107} analogs.


The studies carried out on the carbocyclic analog\textsuperscript{106} show that a minimal contribution towards \textit{in vitro} activity comes from either the furanosyl oxygen of the sugar ring or the hydroxymethyl terminus.

Nebularine is a nucleoside antibiotic, \(9-\text{(\textbeta-D-ribofuranosyl})\text{purine}\) [Chart IV], that is inhibitory against a variety of microorganisms.\textsuperscript{92} Its acute toxicity towards mice and rats is noteworthy, since purine is relatively non-toxic.\textsuperscript{108} Its synthesis is best achieved via the fusion process.\textsuperscript{109}


Cordycepin was the first nucleoside antibiotic to be discovered,\textsuperscript{110} and was incorrectly identified as a

CHART IV: Purine Nucleoside Antibiotics
branched-chain sugar derivative. It was later shown


to be 9-(3-deoxy-β-D-erythro-pentofuranosyl)adenine
[Chart IV], as verified by synthesis.112-114


Nucleocidin, a rare fluoro-sugar nucleoside [Chart IV] has shown remarkable toxicity toward trypanosomes in rodents115 and cattle,116 but its narrow margin of safety


has prevented any widespread use. A synthesis has been reported.117

b. Pyrimidine nucleoside antibiotics. Although these are less commonly encountered than their purine counterparts, a few noteworthy examples do exist, such as amicetin,118 gougerotin,119 and the polyoxins92,120


[Chart V]. Aside from their common structural unit being a pyrimidine base (cytosine, for amicetin and gougerotin, and uracil or 5-substituted uracils for the polyoxins), these antibiotics are all either aminoacyl or peptidyl-derivatized compounds. They contain an amino acid moiety (which invariably has a "free" amino function) attached to a nucleoside "carrier." Both gougerotin and amicetin have been shown to interfere with protein biosynthesis in a manner similar to that of puromycin.92 The polyoxins, despite their aminoacyl structure function, interfere in cell-wall biosynthesis by virtue of their structural resemblance to UDP-2-acetamido-2-deoxy-D-glucose.121

CHART V: Pyrimidine Nucleoside Antibiotics
C. C-Glycosyl nucleoside antibiotics. A number non-glycosylamine nucleosides, all of them derivatives of D-ribose, in which the heterocyclic base is attached to the sugar moiety by a C—C linkage, have shown antibiotic activity. These compounds include formycin, oxoformycin, formycin B and showdomycin [Chart VI] and their chemistry and pharmacology have been reviewed. In very recent years, because of their biological importance, these nucleosides have been the target for a number of chemical syntheses. Both formycin B and oxoformycin were synthesized by ingenious cyclization routes. Showdomycin has been synthesized independently in two laboratories.


CHART VI: ζ-Nucleoside Antibiotics
3. Nucleoside antitumor agents.— A great many antimitabolites show some selectivity toward malignant cells and thus function to some degree as antitumor agents; of these, a number are nucleosides. These antimitabolites generally act as antagonists to purine or pyrimidine biosynthesis, and through these effects are able to control the growth and multiplication of cells. Some of the more important nucleosides that have antitumor activity are discussed in the sections that follow. Authoritative reviews have appeared, and to these the reader is directed for a comprehensive account. A most informative article concerned with the relationship between structure and biological activity of nucleosides has been published.


a. Purine-6(1H)-thione ("6-mercaptopurine"). Among the unnatural purine and purine nucleosides that have shown significant, reproducible activity against tumor systems, derivatives of 6-mercaptopurine [Chart VII] are most frequently encountered. 6-Mercaptopurine itself has been shown to interfere with a large number (perhaps as many as twenty) of vital cell processes, and cytotoxicity may depend upon several of these processes acting concertedly.\(^{127}\) It is generally conceded, however, that 6-mercaptopurine, in order to be an effective antitumor agent, must be converted \textit{in vivo} to its nucleotide by reaction with 6-O-phosphono-\textalpha-\textD-ribofuranosyl pyrophosphate.\(^{132,133}\) These contentions are further supported by the fact that 6-mercaptopurine has been shown to be incorporated into cellular nucleic acid.\(^{134-136}\)


The ribonucleoside of 6-mercaptopurine [Chart VII] has shown a higher therapeutic index than 6-mercaptopurine when assayed in vitro. The nucleoside has shown a tendency to be cleaved rapidly in vivo but it has, nevertheless, in a clinical evaluation, been shown to result in longer mean survival times than those observed for patients who were treated with 6-mercaptopurine.

Other 6-mercaptopurine nucleosides, including the D-arabinofuranosyl and D-xylofuranosyl analogs have
been synthesized, and both have shown in vivo activity, but neither have merited clinical trials. Both nucleosides have been shown to be neither cleaved nor phosphorylated to nucleotides in vivo, suggesting that their behavior in vivo might be similar to a number of 9-alkyl-6-mercaptopurines which show activities that are as yet unexplained.

b. 6-Chloropurine. This purine base and its β-D-ribofuranosyl nucleoside [Chart VII] both show in vivo activity against L-1210 leukemia. The nucleoside is far less toxic than the base, but is therapeutically of lesser value since it is rapidly converted to inosine by the action of adenosine deaminase. The metabolic fate of 6-chloropurine and its ribonucleoside is similar to

that of 6-mercaptopurine and its ribonucleoside, \(^{(146,147)}\)


but in all examples, the therapeutic effects have been found less than those\(^{(145)}\) for the 6-mercaptop compounds.

c. 5-Fluorouracil. 5-Fluorouracil [Chart VII] has been shown to achieve its activity as an antimetabolite by inhibiting thymidylate synthetase, the enzyme that converts \(2'\)-deoxyuridylic acid into \(2'\)-deoxythymidylic acid, a nucleotide necessary for DNA synthesis.\(^{(148,149)}\)


The \(2'\)-deoxynucleoside has been shown to be a less toxic and more effective chemotherapeutic agent than 5-fluorouracil, both in mice\(^{(150)}\) and in clinical trials.\(^{(151)}\)


Perhaps, with the new, efficient method that has been
developed for producing 5-fluorouracil nucleosides
directly,\textsuperscript{152} advantage will be taken of the enhanced

\begin{footnotesize}
\end{footnotesize}

therapeutic value of the nucleoside. A non-carbohydrate
nucleoside analog, 1-(tetrahydro-2-furanyl)-5-fluorouracil,
has been reported to possess significantly greater activity
than 5-fluorouracil, but with $1/5-1/6$ of the toxicity;\textsuperscript{153}

\begin{footnotesize}
\end{footnotesize}

a simplified synthesis has been described.\textsuperscript{154}

\begin{footnotesize}
\end{footnotesize}

d. 1-(\textbeta-\textdelta-Arabinofuranosyl)cytosine. Perhaps the
most useful nucleoside antitumor agent is 1-(\textbeta-\textdelta-
arabinofuranosyl)cytosine [Chart VII], which is effective
against a number of human neoplasms and is widely used for
treatment of acute leukemia.\textsuperscript{155} The mechanism of its

\begin{footnotesize}
\textsuperscript{(155)} M. D. Dowling, Jr., I. H. Krakoff, and D. A.
\end{footnotesize}
action has not been fully elucidated, but it does effectively halt the production of 2'-deoxycytidine. \(^{156,157}\)

\(\text{(156) M. Y. Chu and G. A. Fischer, Biochem. Pharmacol., 11, 423 (1962).}\)

\(\text{(157) M. Karon, W. F. Benedict, and N. Rucker, Cancer Res., 32, 2612 (1972).}\)

Phosphorylation in vivo occurs by action of a kinase, \(^{158}\)


and the resulting nucleotide may be responsible for the enzyme inhibition. A serious limitation to the effectiveness of the nucleoside is the fact that it is rapidly deaminated \(^{159}\) to the ineffective uracil analog. A number of 5'-O-acyl derivatives have been prepared in an attempt to inhibit this deamination process. \(^{131}\) A remarkably straightforward synthesis for the compound has been developed that enables it to be synthesized in large quantity. \(^{160}\)

\(\text{(159) L. I. Pizer and S. S. Cohen, J. Biol. Chem., 235, 2387 (1960).}\)

\(\text{(160) D. H. Shannahoff and R. A. Sanchez, J. Org. Chem., 38, 593 (1973) and references cited therein.}\)
CHART VII: Nucleosides and Nucleoside Bases Having Antitumor Activity
Nucleoside antiviral agents.— A number of the nucleosides classed as antibiotics and antitumor agents have shown degrees of antiviral activity. However, at least two nucleosides have demonstrated powerful antiviral properties, and as a result are presently being evaluated for clinical use. Reviews, devoted to a discussion of antiviral agents have appeared.

a. 9-(β-D-Arabinofuranosyl)adenine. This rare cis nucleoside [Chart VIII] has demonstrated limited activity against bacteria and tumors, but its activity as an antiviral agent is of some promise in the treatment of Herpes simplex and Vaccinia viruses. A chemical

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synthesis $^{168}$ that has been adapted to large-scale production $^{169}$ of the nucleoside has been reported. Although cultures of Streptomyces antibioticus provide a principal source of the compound, a newer chemical synthesis has been described $^{170}$. Very recently, it has been shown that 9-$\beta$-$\Delta$-arabinofuranosyladenine is biosynthesized via an epimerization at C-2' of adenosine, quite possibly via either a 2'-keto nucleoside or nucleotide $^{171}$. 

$^{166}$ F. M. Schabel, Chemotherapy, 13, 321 (1968).


$^{169}$ G. Holstein, Pfanstiehl Laboratories, Inc., personal communication.


• 1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide.

A broad-spectrum antiviral appears to be 1-β-D-ribo
ribofuranosyl-1,2,4-triazole-3-carboxamide172 [Chart VIII]


"Virazole"), in that activity against both DNA and RNA
virus types has been demonstrated.173,174 Its mode of

(173) R. W. Sidwell, J. H. Huffmann, G. P. Khare, 
J. T. Witkowski, and R. K. Robins, Science, 177, 705 
(1972).

(174) D. G. Streeter, C. P. Khare, R. W. Sidwell, 
576 (1972).

action may quite possibly be due to the inhibition of the
biosynthesis of guanosine monophosphate at the step 
involving the conversion of IMP to xanthosine
5'-phosphate.175 A number of analogs have been synthesized

(175) D. G. Streeter, J. T. Witkowski, G. P. Khare, 
R. W. Sidwell, R. J. Bauer, R. K. Robins, and L. N. Simon, 

and tested for antiviral activity.176

(176) J. T. Witkowski, R. K. Robins, G. P. Khare and 
CHART VIII: Nucleoside Antiviral Agents

9-(β-D-arabinofuranosyl)adenine

Virazole
II. STATEMENT OF THE PROBLEM

The research is in the area of the synthesis and modification of nucleosides with the aim of producing compounds that are of biochemical and biomedical interest as both antimicrobial agents and antitumor agents.

Specifically, a route to nucleoside 5'-aldehydes, that are of interest as antimicrobial agents and as synthetic intermediates in chain-extension reactions of nucleosides was to be developed by using the photolysis of 5'-azido-5'-deoxy nucleosides (Section III-A). Further modifications at the 3'-position of nucleosides were to include a synthesis of nucleosides having the terminal hydroxymethyl group replaced by the cyclopropyl function (Section III-B). Thirdly, a series of acyclic-sugar nucleosides of 6-mercaptopurine, in which the acyclic-sugar chain is derived from the four pentose sugars, were to be synthesized and evaluated for biological activity. The possible effects of configurational and conformational changes along the acyclic-sugar chain were to be investigated (Section III-C).
III. DISCUSSION AND EXPERIMENTAL RESULTS

A. Synthesis of 5'-Aldehydo Nucleosides
by Photolysis of Azides

1. General Considerations.— Nucleosides having the
terminal hydroxymethyl group replaced by an aldehyde
function ("nucleoside 5'-aldehydes") have been prepared
by the oxidation of suitably protected nucleosides with
the Pfitzner—Moffatt reagent. Numerous 2',3'-O-
substituted ribonucleosides and 3'-O-substituted-2'-
deoxynucleosides have been synthesized by this
method.\(^\text{177,178}\) A report that describes an alternative

\(^\text{177}\) K. E. Pfitzner and J. G. Moffatt, J. Amer.

\(^\text{178}\) J. G. Moffatt, Sulfoxide-Carbodiimide and
Related Reactions in "Oxidation," Vol. 2, ed. by R. L.
Augustine and D. J. Trecker, Marcel Dekker, 1971,
Chapter 1.

oxidation reagent, a ketene-imine (\(\text{Ph}_2\text{C}=\text{C}=\text{N}(-\text{CH}_3)\))
that gives the aldehyde from 2',3'-O-isopropylidene
adenosine in 63% yield, has also appeared.\(^\text{179}\) These

\(^\text{179}\) R. E. Harmon, C. V. Zenerosa, and S. K. Gupta,
compounds are difficult to obtain as homogeneous, crystalline products. An elimination reaction that readily produces 3',4'-unsaturated aldehydes and 4'-epimeric aldehydes by the influence of chromatographic adsorbents precludes purification by adsorption chromatography. Recently, however, N,N-diphenylimidazoline derivatives, that liberate the free aldehydes upon mild acid treatment, have been described as a route to the pure compounds.

These compounds provide versatile intermediates for the synthesis of nucleoside analogs. Condensation of a 2',3'-O-protected 5'-aldehyde nucleoside with the appropriate phosphorane, followed by reduction of the intermediate vinyl phosphonate, has been used to prepare 6'-deoxyhomonucleoside phosphonic acids. However, only a few examples of nucleophilic additions to the 5'-carbonyl group have been reported. Methylmagnesium iodide was found to add slowly, under forcing conditions, to the aldehyde function of crude adenosine-5'-carboxaldehyde to
give a mixture of 5'-C-methyl epimers.\textsuperscript{182} Nitromethane, under alkaline conditions, was found to add to the same aldehyde to give the analogous nitromethyl adducts.\textsuperscript{183}

In the same report, the stabilized Wittig reagent, ethoxycarbonylmethylenetriphenylphosphorane, produced the epimeric ethoxycarbonyl alkenes that were subsequently reduced to the corresponding alkanes. These products were of interest as intermediates in the synthesis of analogs to 5'-deoxyadenosylcobalamin. [See Section B] The reported low yields of the foregoing products, from Grignard reagents in particular, may be attributed, in part, to the use of a crude aldehyde preparation containing a considerable amount of the less reactive, hydrated aldehyde.\textsuperscript{184} A definitive report on related nucleophilic additions to nucleoside-5'-aldehydes is in press.\textsuperscript{184} A novel chain-extension reaction that employed


(184) J. G. Moffatt, personal communication.
the 5'-aldehyde derived from 2',3'-O-cyclohexylidineuridine, was used for the synthesis of the basic skeleton of the polyoxin complex, an important group of antibiotics.185


By making use of the elimination reaction described in the foregoing, a number of antibacterial nucleoside analogs, which are either 3',4'-unsaturated analogs or 4'-epimers of the natural ribonucleosides, have been claimed.186 Also, for biochemical studies, the aldehydes


have been employed for the synthesis of tritium-labeled adenosines.187,188


In order to develop an alternative method for the synthesis of nucleoside 5'-aldehydes, the photolysis of azido nucleoside derivatives was investigated. Azide photolysis, first applied to the synthesis of aldehydo
sugars in this laboratory,\(^{189}\) has found wide applicability


for generation of \(\omega\)-aldehydes in monosaccharide systems,\(^ {190,191}\) where either an unprotected\(^ {191}\) or fully


blocked derivative\(^ {190}\) may be employed. Extension of the

method to polysaccharide systems of both cellulose\(^ {192}\) and


amylose\(^ {193}\) has shown the procedure to be highly efficient.


The successful photolytic conversion of a primary azide

in an aryl glycoside system\(^ {194,195}\) into the corresponding

aldehyde formed the basis for the evaluation in nucleoside systems:

2. Preparation of azido nucleoside derivatives.—
The derivative selected for study in the adenosine series, 5'-azido-5'-deoxy-2',3'-0-isopropylideneadenosine (4) [Chart IX] was prepared from 2',3'-O-isopropylideneadenosine \(^{196}\) (1) in three steps. Conversion of 1 into the crystalline \(\text{N}^6\)-formyl-5'-O-\(\text{P}\)-tolylsulfonyl derivative (2) essentially by the procedure of Jahn \(^{197}\) proceeded practically quantitatively when the acetic formic anhydride used was prepared by a new procedure. \(^{198}\) Displacement of the sulfonate group in 2 by azide proceeded readily to give the crystalline 5'-azide 3 in 89% yield by action of sodium azide in methyl sulfoxide, without significant
CHART IX: Synthesis and Photolysis of 5'-azido-5'-deoxy-2',3'-O-isopropylideneadenosine
interference by commonly encountered side-reactions\(^{197,199}\)


leading to anhydronucleoside salts. Deformylation of \(^3\) by use of sodium methoxide gave the desired, crystalline azido nucleoside \(^4\) in essentially quantitative yield. The intermediates \(^2\), \(^3\), and \(^4\) were characterized in detail by elemental analyses, i.r. and u.v. spectra, and X-ray powder diffraction patterns [see Experimental Section] and by n.m.r. [see Table 1] and mass spectrometry [see Table 2].

In the pyrimidine nucleoside series [Chart X], the \(^{2',3'}\)-benzylidene acetal\(^{200}\) (7) of uridine was \(^{5'}\)-p-


toluenesulfonylated by the general procedure of Levene and Tipson\(^{201}\) to give the crystalline \(^{5'}\)-p-toluenesulfonate


\(^8\) in a yield of 96%. Lithium azide in methyl sulfoxide converted \(^8\) into the \(^{5'}\)-azide (\(^9\)), obtained in 70% yield as a glass. This reagent was more effective\(^{202}\) than sodium
CHART X: Synthesis and Photolysis of 5'-Azido-2',3'-O-benzylidene-5'-deoxyuridine
azide, and interfering reactions were minimized. The three products, 7, 8, and 9, were characterized in detail by the procedures used for the adenosine derivatives 2, 3, and 4 [see Experimental Section and Tables 1 and 2].

3. Photolysis of the azides 4 and 9. -- To effect the desired photolytic conversion of the azide, presumably through formation of an intermediate nitrene (R—CH₂N⁺) that becomes stabilized by hydrogen migration to give an aldimine (R—CH=NH), a solvent (benzene) that is a poor hydrogen donor was used to minimize a possible competing side reaction that would lead to the corresponding primary amine. In view of the known susceptibility of the nucleoside bases to structural modification by short-wavelength radiation, a Corex filter was used to


surround the medium-pressure, mercury-arc lamp used as the light source; this filter excludes most of the radiation of wavelengths shorter than 260 nm. Under these conditions it was found that photolysis of the azides 4 and 9 at room temperature under nitrogen was completed in 0.5—2 h, as evidenced by disappearance of the starting materials (t.l.c.) and the absence from the products of the characteristic i.r. absorption near 4.75 μm for the azide group. The u.v.-absorbing, methanol-soluble, and benzene-insoluble photolysis products were treated immediately with Amberlite IR-120 (H⁺) resin at room temperature, by the general procedure established in earlier work,¹⁸⁹-¹⁹⁵ to hydrolyze the presumed aldimine product from the photolysis step. In each case there was obtained an amorphous product that by t.l.c. showed a principal component migrating as a single spot that gave a positive reducing-sugar test with aniline phthalate, a positive Schiff reaction indicative of the aldehyde group, and u.v. fluorescence behavior characteristic of a nucleoside; these data, and analogy with previous work,¹⁸⁹-¹⁹⁵ indicate that these reducing products were the aldehydes 5 and 10, respectively. Both products by t.l.c. showed the presence
of a minor non-migrating, u.v.-absorbing, non-reducing component; the possibility that the respective 5'-amino-5'-deoxy derivatives were present in these side-products cannot be excluded.

4. Characterization of the products.— The aldehyde derivatives 5 and 10 were not obtained crystalline, and because of the ease with which such aldehydes can form a multitude of possible solvation products, oligomers, and elimination products, they were characterized by direct transformation into stable, readily identified compounds. It has already been shown, in the preparation of 6-aldehydo derivatives by photolysis of 6-azido-6-deoxy derivatives of cellulose, and starch that reduction of the aldehydo derivatives with borodeuteride and determination of the position and extent of deuterium incorporation in the reduced product provides a more convenient and accurate method for determining the aldehyde group than conventional derivatization through hydrazone derivatives. Accordingly, similar reduction procedures were used with the aldehydes 5 and 10. Reduction of the crude aldehyde 5 with borohydride gave 2',3'-O-isopropylideneadenosine (1), isolated crystalline in 54% yield (based on the starting azide 4). Similarly, reduction of the aldehyde 10 gave crystalline 2',3'-O-benzylideneuridine (7) in 58% yield.
based on the azide 9. These yields of reduced products can be regarded as minimum values for the yields of the aldehydes from the azide precursors.

When the reductions were performed with borodeuteride, the corresponding 5'-monodeuterated analogs 6 and 11 of the nondeuterated nucleoside derivatives 1 and 7 were obtained. The position and extent of deuterium incorporation in these products was established by n.m.r. and mass spectrometry. The n.m.r. spectra of the deuterated derivatives 6 and 11 were closely similar to those of the nondeuterated analogs 1 and 7 [for full details see Table 1], but the integrated intensity of two protons for the C-5' protons in 1 and 7 was decreased to one proton for 6 and 11; no replacement of other protons bonded to carbon could be detected by integration. Examination of the fine structure of the spectra was further concordant with replacement of one C-5' proton by deuterium in the products 7 and 11. Thus, the 6-line pattern observed for H-4' in 1 became a 4-line pattern in 6 by loss of one of the H-4', H-5' couplings and its replacement by the much smaller H-D coupling. The anticipated changes were observed in the signals for the C-5' protons, and the signals for H-3', H-2', and H-1' were not affected. Likewise, the multiplet observed for H-4' in compound 7 collapsed to a narrower multiplet in 11 through similar
loss of one H-4', H-5' coupling; again the expected patterns were observed for the C-5' proton resonances, and there was no change in the H-3', H-2', and H-1' signals.

The mass spectra of the deuterated products 6 and 11 each showed a molecular-ion peak one mass-unit higher than the nondeuterated analogs 1 and 7 [for full details of the mass spectra see Table 2]. In addition, a number of key fragmentations, in which the deuterium-labeled intermediate exhibited a peak one m/e unit higher than the nondeuterated analog, served to pinpoint the deuterium label at C-5'. Of particular interest is a key fragmentation involving loss of C-5' as formaldehyde from the nucleoside. In related nucleosides, the following fragmentation has been postulated by use of the

5-OD derivative. This transformation is exhibited in 1 in formation from the molecular ion (m/e 307) by loss of formaldehyde (30 daltons) of the fragment ion m/e 277; in the deuterated derivative 6 the same ion (m/e 277) is formed from the molecular ion (m/e 308), evidently by loss of the deuterium atom in a monodeuterioformaldehyde
(DHC=0, 31 daltons) fragment. In the pyrimidine derivative 7 the principal fragmentation mode leads to an even-electron ion m/e 301 corresponding to loss of formaldehyde and the benzylic hydrogen atom; the parent M - 1 ion is observed at m/e 331. The deuterated analog 11 likewise shows the m/e 301 fragment, but this ion is formed by loss of DHC=0 (31 daltons) from the M - 1 ion (m/e 332).

5. Summary.— The foregoing transformations illustrate the applicability of the azide photolysis procedure\textsuperscript{189-195} as a route for generating aldehyde functionality in the carbohydrate moiety of nucleosides and their derivatives, to provide intermediates useful for chain-extension reactions of various types. The reaction may be a useful alternative to chemical methods of oxidizing the hydroxymethyl group in systems where functional groups sensitive to oxidants are present.
While this work was in progress, a communication describing a photolytic procedure for generating a nucleoside 5'-aldehyde as a synthetic intermediate in the synthesis of the 4'-fluoronucleoside, nucleocidin, appeared.117

B. Synthesis of 9-\{4-C-Cyclopropyl-\(\alpha\)(and \(\beta\))-D-ribo-tetrofuranosyl\}adenine (21)

1. General considerations.— A serious limitation in the effectiveness of adenosine analogs as antimetabolites is their ready degradation by adenosine deaminase to the hypoxanthine nucleoside, which is almost always pharmaceutically inactive. In a comprehensive study210 that involved the evaluation of a number of adenosine analogs, it was shown that modifications at either the 2' or 3' hydroxyl group (or both) altered, but did not eliminate, the deamination reaction. Furthermore, it was definitively established that removal of the 5'-hydroxyl group invariably abolished substrate activity except in those few compounds where either a 5'-amino function or a 3'-hydroxyl group (cis to the adenine moiety) was present, and presumably, could assume at least a partial binding to the active site of the enzyme. Although the 5'-hydroxyl
group is a general requirement for adenosine deaminase activity, its absence by no means limits other activities in vivo.

A number of nucleosides which lack a 5'-hydroxyl function have demonstrated bacterial growth-inhibition. Among these are 9-α-L-threofuranosyladenine, 9-β-D-threofuranosyladenine, and the potent antibiotic Angustmycin A (decoyinine), which also exhibits marked antitumor activity.


The synthesis of purine nucleosides having the 5'-hydroxyl function replaced by hydrogen (5'-deoxy nucleosides)
have been described,\textsuperscript{212-215} and where biological data are available,\textsuperscript{214,215} these have shown a reluctance to undergo N\textsuperscript{6}-deamination to the corresponding hypoxanthine.

Analogs of adenosine having 3-C-alkyl modifications at C-5' are of interest as intermediates in the synthesis of analogs of 5'-deoxyadenosylcobalamin,\textsuperscript{216} a compound that acts as a coenzyme in hydrogen-transfer reactions between adjacent atoms of the substrate,\textsuperscript{217-219} or in reductions of ribonucleotides.\textsuperscript{220}

\begin{itemize}
\item \textsuperscript{217} R. H. Abeles, Enzymes, \textbf{5}, 481 (1971).
\item \textsuperscript{218} H. A. Barker, Enzymes, \textbf{6}, 509 (1972).
\item \textsuperscript{219} T. C. Stadtman, Enzymes, \textbf{6}, 539 (1972).
\item \textsuperscript{220} In these enzymic
\end{itemize}
processes, the coenzyme is a hydrogen carrier, in which both hydrogens at C-5' participate in the process. Any modification at C-5' would have a profound effect on the activity of the coenzyme.

The preparation of adenine nucleosides having the terminal hydroxymethyl group replaced by a small alkyl or cycloalkyl group was therefore of interest. Following the procedures developed by Horton and Tindall for

the synthesis of sugars having a terminal cyclopropyl group, 4-C-cyclopropyl-a,β-D-ribo-tetrofuranose (19) was synthesized [Chart XI] and subsequently converted into the adenine nucleosides 21 as outlined [Chart XII]. The compounds 21 are the D-ribo analogs of the D-xylo nucleosides222 reported earlier.

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CHART XI: Synthesis of 4-α-Cyclopropyl-αβ-ribo-tetofuranose, 18
i. 6-Benzamido-9-chloromercuripurine, 
TiCl$_4$, toluene reflux
ii. NaOCH$_3$—methanol, reflux

CHART XII: Synthesis of $9$-[$4$-$C$-Cyclopropyl-\(\alpha\)and\(\beta\)-\(\beta\)-ribo-tetrafuranosyl]adenine, 21
2. Synthesis of tri-O-acetyl-4-C-cyclopropyl-α,β-
D-ribo-tetrofuranose (19).—1,2:5,6-Di-O-isopropylidene-
α-D-allofuranose was converted into the 3-benzyl ether 12
in nearly quantitative yield by a modification\textsuperscript{221} of the
original procedure.\textsuperscript{223} Partial hydrolysis of 12 in dilute
acetic acid afforded the 5,6-deacetonated compound 13,
which was then treated with triethyl orthoformate
acid to give a mixture of the diastereoisomeric
orthoacetates 14. Pyrolysis of the orthoesters 14 at
\( \sim 200^\circ \) in the presence of triphenylacetic acid, gave,
after a preliminary separation from the acid catalyst,
the alkene, 3-O-benzyl-5,6-dideoxy-1,2-O-isopropylidene-
α-D-ribo-hex-5-enofuranose (15), which was distilled
directly to give \( >95\% \) yields of the pure product.

Conversion of the alkene 15 into 4-C-cyclopropyl-
1,2-O-isopropylidene-α-D-ribo-tetrofuranose (16) proceeded
with some difficulty. The Simmons–Smith procedure,\textsuperscript{224}

\textsuperscript{223} J. S. Brimacombe and O. Ching, \textit{Carbohyd. Res.},
8, 82 (1968).

\textsuperscript{224} H. E. Simmons and R. D. Smith, \textit{J. Amer. Chem.}

which had been employed\textsuperscript{221} for the synthesis of 16, gave
inconsistent results. The particular grade of zinc metal
used for preparation of the zinc—copper couple \(^{225}\) was found to be important. Whereas, various grades of zinc powder gave a zinc—copper couple that led to the desired cyclopropyl derivative \(16\) in only low yields, the use of a coarse (20-Mesh) granular zinc furnished a zinc—copper couple that was active. Heating a solution of the alkene \(15\) in ether under reflux with a ten-fold excess of the zinc—copper couple, gave, after 48 h, a high yield of the cyclopropyl analog \(16\) of sufficient purity for use directly in the synthetic sequence. The product \(16\) of the reaction could be distinguished from the alkenic precursor \(15\) by either t.l.c. or by subtle differences (at 10.74 \(\mu m\)) in their i.r. spectra [see Experimental Section].

Debenzylation of the cyclopropyl derivative \(16\) was effected cleanly in sodium—liquid ammonia to give crystalline 4-C-cyclopropyl-1,2-O-isopropylidene-\(\alpha\)-D-ribo-tetrofuranose \((17)\) in \(>90\%\) yield. The procedure with sodium—liquid ammonia was found effective on a multi-gram scale, whereas the hydrogenation procedure, reported \(^{221}\) to effect the debenzylation of \(16\), at least on small-scale preparations, failed.
The carefully purified, crystalline 17 was deacetonated in water at ~45° with a strongly acidic cation-exchange resin to give 4-C-cyclopropyl-\(\alpha,\beta\)-D-ribo-tetrofuranose (18) as a clear syrup. Subsequent acetylation of the free sugar 18 with hot acetic anhydride—sodium acetate gave the syrupy triacetate 19 as a 2:3 mixture of \(\alpha,\beta\) anomers, as determined by n.m.r. spectroscopy. It was noted that, whenever the crystalline, starting material 17 was carefully purified prior to the deacetonation procedure, the resulting syrupy acetates 19 were sufficiently pure, without column chromatography, for use in the following nucleoside condensation reaction.

3. Synthesis of the nucleosides 21. — a. Condensation procedure. The anomeric mixture of tri-O-acetyl-4-C-cyclopropyl-\(\alpha\)(and \(\beta\))-D-ribo-tetrofuranoses (19) was condensed with 6-benzamido-9-(chloromercuri)purine in the presence of titanium tetrachloride by Baker's general procedure\(^{47,48}\) to give a dark, syrupy product, that by t.l.c. revealed a single, major zone attributable, on the basis of its absorbance of u.v. light and charring with sulfuric acid spray-reagent, to the blocked nucleoside derivatives, 20. No further characterization was made on these intermediates. An anomeric mixture of protected nucleosides 20, as was found in the synthesis of the D-xylo analog,\(^{221}\) is assumed.
b. Saponification of the acyl blocking groups.

Removal of both the \(N^6\)-benzoyl and the O-acetyl protecting groups of 20 was effected by heating, under reflux in 0.1 M sodium methoxide, the crude product from the condensation reaction. The deblocked nucleosides, however, migrated as a single zone on t.l.c., and the two anomers were inseparable in numerous solvent systems. Crystallization from methanol afforded, as the first crop of crystals, a 3.4:1 mixture of \(\beta:\alpha\) anomers of 21, as determined by observing the H-1 signals in the n.m.r. spectrum. The optical rotation for this mixture was negative at the D-line of sodium, and became increasingly negative with decreasing wavelength. [see Experimental Section] The m.p. (212—213\(^\circ\)) was sharp, which is unusual for an anomeric mixture of nucleosides.

A five-fold crystallization from methanol afforded a small sample (~20 mg) that was enriched in one isomer and gave a more negative optical rotation, but essentially the same melting point as the first crop of crystals (3.4:1 of \(\beta:\alpha\)). An analytical-scale, high-pressure liquid chromatographic separation of this mixture on a surface-porosity cation-exchange column (Zipax, DuPont) revealed [Figure 1] that the ratio of anomeric nucleosides had been increased to 9:1 (presumably \(\beta:\alpha\)). Chromatographic separation by conventional methods was shown to
FIGURE 1: High-Pressure Chromatography of the Anomeric Mixture of Nucleosides
be ineffective.


The anomeric α (and β) nucleosides, 21, together with the β-D-xylo analog, were assayed a. for inhibition in bacterial systems; b. for adenosine deaminase activity; c. for antileukemic activity, both in vivo (mouse) and in vitro. The results are summarized in Table 3.

The only activity for compound 21 and the D-xylo analog noted was a marginal inhibition of E. coli and L-1210 cells. However, the slight stimulatory effect noted for 21 in S. faecalis culture indicates either the presence of a contaminating portion of adenine, or release of adenine by hydrolysis in vivo. With these facts in mind, any inhibitory effects in either E. coli or L-1210 culture must be interpreted with caution, as adenine itself is inhibitory in these systems at $5 \times 10^{-6}$ M concentration. Compound 21 and its D-xylo analog both were not substrates for adenosine deaminase, a finding that is in agreement with the general requirements that have been established for binding to adenosine deaminase; no inhibition of enzymic activity was observed. Both compounds were inactive in mouse leukemia screens.

(226) A. Bloch, personal communication.
C. Acyclic-Sugar Nucleosides

1. General Considerations. — a. Biological rationale. The acyclic-sugar nucleoside, l-deoxy-l-S-ethyl-l-[purin-9-y1-6(1H)-thione]-l-thio-aldehydo-D-glucose aldehydrol (22) [Chart XIII] has demonstrated activity against L-1210 lymphoid leukemia in mice [see Table 9], whereas its C-4' epimer, l-deoxy-l-S-ethyl-l-[purin-9-y1-6(1H)-thione]-l-thio-aldehydo-D-galactose aldehydrol (23) [Chart XIII] is inactive in the same screen. In view of the fact that the heterocyclic base, purin-6-(1H)-thione ("6-mercaptopurine"), is by itself a potent antimetabolite and possesses considerable antileukemic activity [see Chapter I, Section C], the findings for 22 and 23 suggest that the stereochemistry of the attached acyclic-sugar chain may play a major role in determining biological activity. The differences in conformational disposition of bulky groups along the acyclic carbon skeleton as has been determined for a great many acyclic-sugar derivatives, (228-231) may have a profound


A plausible hypothesis is that, with the D-gluco configuration of the sugar moiety, as in 22, the perhydroxylated chain might fold in such a manner as to render to molecule isosteric with "normal" furanosyl purines, whereas the D-galacto isomer 23 would remain in an extended, or at least a partially extended, form. Possible conformations for 22 and 23 are shown in Chart XIII. It must be emphasized that these structures are proposed on the basis of results of n.m.r. studies made on related systems. As yet, no detailed n.m.r. analysis has been made on 22 or 23, nor on related model systems, because of the fact that signal separation in the n.m.r. spectra of straight-chain, perhydroxylated systems is poor. No suitable crystal of 22 for X-ray analysis has yet been obtained. A similar rationale has been employed to explain the activity of the non-nucleoside antibiotic chloramphenicol. It has been suggested that the latter might adopt, through hydrogen bonding in solution, a rigid "furanosyl-like" configuration and
CHART XIII: Acyclic-sugar 6-Mercaptopurines
effectively mimic in vivo an aminoacyl aminonucleoside.\(^{232}\)


\[
\begin{align*}
\text{Chloramphenicol}
\end{align*}
\]

Although the effect of acyclic-sugar stereochemistry in determining the biological activity of nucleoside analogs has not been systematically investigated, the role of stereochemistry in relation to biological activity for derivatized acyclic polyols has received some attention. Recognizing that there are fundamental differences between nucleoside analogs, functioning as antimetabolites, and \(\alpha,\omega\)-bifunctional acylating agents derived from acyclic sugars (operating possibly by covalent joining of nucleic acid chains), some important parallels arising from acyclic-chain conformation may nevertheless be drawn.
The alditol derivative, 1,6-bis(2-chloroethylamino)-1,6-dideoxy-D-mannitol, is a potent antitumor agent ("mannitol mustard," "mannomustine"), whereas its D-gluco epimer, 1,6-bis(2-chloroethylamino)-1,6-dideoxy-D-glucitol, is inactive. A similar result has been noted for the 1,6-bis(2-bromoethylamino) analogs. The stereochemical selectivities shown for the D-manno configuration over that for the D-gluco configuration in the foregoing examples by no means excludes the D-glucitol derivatives as active compounds, as 1,6-dibromo-1,6-dideoxy-D-glucitol itself is an antitumor drug of some promise.

Likewise, stereochemistry has been shown to determine activity in vivo for a number of alditol α,ω-dimethane-sulfonates, in which only the 1,4-D-threitol dimethane-
sulfonate\(^{237-239}\) \((n = 2)\) and the 1,6-D-mannitol dimethane-

\[
\text{CH}_3\text{SO}_2\text{OCH}_2(\text{CHOH})_n\text{CH}_2\text{OSO}_2\text{CH}_3
\]

\[n = 2, \text{ threo} \]

\[n = 4, \text{ manno} \]

A number of acyclic-polyol purines have been prepared by glycol cleavage-borohydride reduction of both furanosyl- and pyranosyl-adenines,\(^{242}\) as well as other


determined toward adenosine deaminase. In each study, certain stereochemical requirements, especially at C-1', were found to be necessary for substrate activity.\(^242,243\) Furthermore, it has been demonstrated\(^244\) that periodate-

(244) A. Rich, personal communication.

oxidized, borohydride-reduced adenosine is effectively phosphorylated by suitable kinases, demonstrating that the necessary, isosteric orientation is readily achieved by flexing of the chain. An even simpler, straight-chain analog has shown a remarkable degree of adenosine deaminase activity.\(^245\)


b. Synthesis of acyclic-sugar nucleosides. Acyclic-sugar nucleosides were first synthesized by Wolfrom and coworkers, who prepared a pair of epimeric adenine nucleosides having a D-galactose acyclic-sugar chain.\(^246\)

Syntheses which were later reported for the preparation of acyclic-sugar nucleoside analogs include the nucleoside-bases adenine, thymine, uracil, and cytosine. Modified acyclic sugars, including derivatives of D-glucose, D-galactose, D-glucose, and the pentoses, and 2-amino-2-deoxy-D-glucose have been condensed with a suitably activated nucleoside base. The procedure makes use of the bromination reaction developed by Gauthier as applied by Weygand and Weygand.
coworkers\textsuperscript{256} for the synthesis of per-O-acetyl-l-deoxy-l-

halogenated aldehyde aldose aldehydrols, from the dialkyl dithioacetals. The general procedure is outlined as follows:

\[
RCH(SEt)\textsubscript{2} \xrightarrow{Br\textsubscript{3}} RCH-Br \xrightarrow{ROH} RCH-OR' \xrightarrow{Br\textsubscript{2}} RCH OR' \xrightarrow{Br} Base
\]

\[
\text{Base} \xrightarrow{RCH OR'} \text{Base}
\]

\[
R = -(CHOAc)_{n}CH_{2}OAc, \ n = 3, 4
\]

\[
R' = \text{alkyl}
\]

The 1'-deoxy-1'-S-alkyl nucleosides that are produced by the reaction along Path A are possibly unique in the chemical world, for there is created a novel asymmetric
center that contains a tetrahedrally substituted carbon attached to nitrogen and sulfur, in addition to carbon and hydrogen:

\[ R = -(\text{CHOAc})_n\text{CH}_2\text{OAc, } n = 3,4 \]

\[ \text{R'} = \text{alkyl} \]

By Path B, a sequence of reactions leads to an analogous series of nucleoside analogs having a 1'-O-alkyl group. In either case, the stereochemistry of the reaction that leads to the formation of a new asymmetric center at C-1' has not been determined definitively. Two epimers of acyclic-sugar adenines were isolated in one report, and a number of 1'-epimeric acyclic pentose-sugar cytosines have crystallized separately. An n.m.r. study of the cytosines and uracils has permitted a detailed evaluation of the conformations of the acyclic-sugar chains, and an assignment of the probable stereochemistry at C-1' has been indicated.

c. Objectives. In order to systematically investigate the effect of sugar configuration on the biological activity of nucleosides related to 22 and 23,
a series of the four isomeric, acyclic pentose-sugar nucleosides of 6-mercaptopurine were synthesized [Chart XIV], and their biological activities were investigated. Detailed studies were made by n.m.r. spectroscopy to determine the conformation of the acyclic-sugar chains. A combination of o.r.d. and n.m.r. spectroscopy was employed to assign a probable configuration at C-1'.

2. Synthesis of 2,3,4,5-tetra-O-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-1-S-ethyl-1-thio-aldehydo-D-pentose aldehydrols (27a-d).— a. Preparation of the peracetylated pentose diethyl dithioacetals. The original procedure reported by Fischer\(^{257}\) was found adequate for the preparation of both D-arabinose and D-lyxose diethyl dithioacetals. However, due to their solubilities in aqueous media, the diethyl dithioacetals of both D-ribose and D-xylose were more economically prepared by neutralizing the acidic solution of the crude acetal in a slurry of lead carbonate in methanol, as described by Wolfrom and Anno\(^{258}\) for the preparation of 2-amino-2-

\(^{(257)}\) E. Fischer, *Ber.*, 27, 673 (1894).

CH(SET)₂ \( (CHOAc)_3 \) \( CH_2OAc \) + \( Br_2 \) \( \rightarrow \) \( Br \) \( CH-SEt \) \( (CHOAc)_3 \) \( CH_2OAc \) \( \rightarrow \) 26 \( HgCl \) 25 \( a-d \)  

27 \( a-d \)  

28 \( a-d \)  

29 \( a-d \)  

a. D-ribo  

b. D-arabino  

c. D-xylo  

d. D-lyxo  

CHART XIV: Synthesis of the 1-Deoxy-1-S-ethyl-1-[purin-9-y1-5(1H)-thione]-1-thio-aldehyde-\( D \)-pentose aldehydrols, 29 \( a-d \)
deoxy-\(D\)-glucose diethyl dithioacetal. Silver carbonate, used\(^{258}\) for a final neutralization of the solution, was found unnecessary, as was the use\(^{258}\) of gaseous hydrogen sulfide for the removal of sparingly-soluble lead salts [for details, see Experimental Section]. Acetylation of the crude diethyl dithioacetals was effected in acetic anhydride—pyridine by the method of Wolfrom.\(^{259}\)


\(^{(256)}\) Weygand was employed for the preparation of the 2,3,4,5-tetra-O-acetyl-l-bromo-l-deoxy-l-S-ethyl-l-thio-aldehyde-\(D\)-pentose aldehydes (25a-d). Cyclohexene, originally\(^{256}\) employed for the removal of excess bromine in the reaction mixture, was omitted without consequence, and the undesirable by-products reported\(^{254,260}\) to originate from the alkene were thus avoided. Excess bromine, together with the by-product, ethylsulfenyl bromide, were readily removed by evacuating the syrupy 1-bromo compounds (25a-d) at \(25^\circ/5\) torr. The compounds
25a-d as prepared were suitable directly for use in the nucleoside condensation procedure, if used without undue delay [see Experimental Section].

**c. Condensation of 2,3,4,5-tetra-O-acetyl-1-bromo-1-deoxy-1-S-ethyl-1-thio-aldehydo-D-pentose aldihydrols (25a-d) with 6-Chloro-9-(chloromercuri)purine.** The Davoll—Lowy procedure was employed for condensation of the brominated acyclic-sugar derivatives 25a-d with 6-chloro-9-(chloromercuri)purine. The reactions proceeded to give the protected nucleosides 27a-d in high yields. However, the products were, for each sugar, obtained as exceedingly thick, viscous syrups. These were invariably contaminated with numerous by-products as determined by t.l.c. and high-pressure l.c.; however, by column chromatography, material that was judged ~95% pure (by t.l.c. and l.c.) and adequate for use as a synthetic intermediate could be readily obtained.

Further purification of the syrupy compounds 27a-d was effected by using loose layers of silica gel on glass plates. By this method samples of sufficient purity for the measurement of physical constants were obtained. The n.m.r. spectra of compounds 27a-d revealed no signals attributable to impurities other than traces of chloroform, which was retained from the extraction process. Acceptable mass spectra were recorded for each compound [see Table 4].
Acceptable elemental analyses, however, were difficult to obtain for the syrupy products. Their gummy nature, together with their limited stability towards heat, precluded the preparation of samples of compounds 27a-d that were absolutely free from solvents and otherwise suitable for meaningful elemental analyses. These products repeatedly failed to crystallize from a number of solvents and solvent mixtures. The physical constants for 27a-d are tabulated in Table 4. Although the u.v. spectral data for 6-chloropurines do not generally permit a clear distinction between 7- and 9-isomers, the u.v. data for 27a-d fit that reported for 9-alkyl-6-chloropurines.

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3. N.M.R. spectra for the 2,3,4,5-tetra-O-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-1-S-ethyl-1-thio-aldehydo-D-pentose aldehydrols (27a-d).— The n.m.r. spectra were determined for each compound, 27a-d, in acetone-d6 and the data are recorded in Table 5. The general features expected for such compounds were observed. The purine protons, H-2 and H-8, resonated as low-field singlets near 1.12 and 1.32. The protons associated with the acyclic-sugar chain gave rise to signals in the range
Generally, the resonances for the individual protons were well separated, giving rise to spectra that were first order. In each case, except for the \( \text{D-arabino} \) compound 27b, two distinct sets of resonances were observed, attributable to a C-1' isomeric mixture of compounds, ranging from a 2.5 : 1 ratio for the \( \text{D-lyxo} \) species 27d, to 5.2 : 1 for the \( \text{D-ribo} \) compound 27a. A single isomer was invariably indicated for the \( \text{D-arabino} \) compound 27b, even when the crude reaction mixture was examined by n.m.r. spectroscopy. Other associated resonances were present: 7.72—8.24, a set of singlets for the acetate protons, as well as the quartet (7.34—7.46) and triplet (8.79—8.87) for the methylene and methyl protons, respectively, of the ethylthio group. Detailed, conformational analysis of the acyclic-sugar chains was not carried out on these compounds.

4. Optical rotation data for 2,3,4,5-tetra-\( \text{O} \)-acetyl-1-(6-chloropurin-9-yi)-1-deoxy-1-S-ethyl-1-thio-aldehydo-\( \text{D-pentose aldehydrols} \) (27a-d).— The optical rotations were determined at the sodium D line (589 nm) in chloroform solution and are recorded in Table 4. The \( \text{D-arabino} \) compound 27b gave a rotation large and positive (+81—+85°), whereas the \( \text{D-lyxo} \) compound showed a somewhat smaller, but positive rotation (+39°). For the \( \text{D-ribo} \)
compound 27a, the observed rotation fell slightly below zero (-5.5°), and for the D-xylo compound, the observed rotation was large and negative (-57°). These observed data are significant for indicating the configuration of the preponderant isomer present, as it might be expected, on the basis of the fundamental principles of optical rotation, that the chirality of the asymmetric center attached by a polarized bond to a chromophore would largely determine the optical rotation for the compound as a whole. In other words, the chirality a C-1' would largely determine the rotation for compounds 27a-d, and the other three asymmetric centers at C-2', C-3' and C-4' would contribute little to the overall value of the rotation. These rationalizations have been incorporated into a Generalized Heterocycle Rule\textsuperscript{262} which states that,


for a molecule that contains an aromatic group (or a heterocycle) attached to a carbon chain, that has an oxygenated group at C-1, when viewed as a Fischer projection (with the ring system at the top) the epimer having the oxygenated function on the right will be dextrorotatory, and the epimer having the oxygenated function on the left will be levorotatory. An extension
of the rule to include molecules having sulfur, instead of oxygen as the polar group at C-1, would not be expected to cause any difficulty, as the two elements belong to the VI-A family of elements and are adjacent to one another in the Periodic Table. The rule would predict for 27b, (the preponderant isomer, or only isomer, as determined by n.m.r.) to be the 1-(R) epimer, and the other compounds 27a, 27c, and 27d, to be mixtures of (R) and (S) epimers of varying proportion. The large negative rotation (-57°) for 27c would suggest the preponderance of the 1-(S) epimer.

5. Synthesis of 2,3,4,5-tetra-O-acetyl-1-deoxy-1-S-ethyl-[purin-9-yl-6-(1H)-thione]-1-thio-aldehyde-D-pentose aldehydrols (28a-d).—The compounds 27a-d, as isolated in ~95% purity by column chromatography and shown to be epimeric mixtures for 27a, 27c and 27d, were each treated with thiourea in refluxing ethanol to effect the conversion to their respective 6-mercaptopurine derivatives.263


This method for replacing halogen with sulfur was found superior to other methods, including the use264 of

thioacetamide. The products were isolated crystalline in yields of 50—70%, depending upon the specific starting compound, 27a-d. The products 28a-c were shown by n.m.r. spectroscopy and optical rotation data to be single epimers, while 28d was demonstrated to be a mixture of C-1 epimers [see Sections 6 and 7]. Detailed preparative procedures are described in the Experimental Section.

6. Optical rotatory studies and the chirality at C-1' of the 2,3,4,5-tetra-O-acetyl-l-deoxy-l-S-ethyl-l-[purin-9-yl-6(1H)-thione]-1-thio-aldehydo-D-pentose aldehydeols (28a-d).— The products 28a-d, isolated as described in the Experimental Section, gave the optical rotations ([α]D, as determined at the sodium D-line) shown in Table 6; their o.r.d. spectra were measured, and the results are shown in Figure 2.

As can be seen from the values of [α]D [Table 6], 28a and 28c have values that are respectively large and positive, and large and negative, indicating, by application of the Generalized Heterocycle Rule,262 R and S epimers, respectively, at C-1. Compound 28b is also large and positive, and the ~50°-variation from the positive extremum may possibly be due to contributions of the C-2'—C-4' asymmetric centers. The small positive rotation for the D-lyxo compound 28d most certainly indicates an epimeric mixture.
FIGURE 2: Optical Rotatory Dispersion Spectra for Compounds 28a–d
These interpretations are, however, best demonstrated by the o.r.d. spectra [Figure 2]. Whereas the D-ribo (28a) and D-arabino (28b) compounds show large, positive o.r.d. curves in the 250—400 nm region, the D-xylo (28c) compound, shows an equally large, negative curve. The D-lyxo compound 28d had a very low rotation, because of a relatively large proportion of both epimers. These trends in the o.r.d. spectrum, despite the limited accuracy (~10% at best) of the measurements are due to the strongly-absorbing chromophore (>20,000), are unmistakable and strongly suggest, in conjunction with the n.m.r. evidence for single epimers for 28a-c [see Section 7], that compounds 28a and 28b are indeed the single, 1'- (R) (+) epimers, as opposed to 28c, which is indicated to be a 1'- (S) (-) epimer. The D-lyxo product has all indications of being a 1'- (R,S) mixture.

7. N.M.R. spectra for 28a-d and conformation of the sugar chain.— The n.m.r. spectra for the 2,3,4,5-tetra-O-acetyl-l-deoxy-l-S-ethyl-[purin-9-yl-6-(1H)-thione]-l-thio-aldehydo-D-pentose aldehydrols 28a-d were determined in methyl sulfoxide-d₆ and are shown in Figures 3-6, p. 220. Detailed examination of the spectra furnished considerable information on the conformation of the peracetylated side chains and gave evidence in support of the configurational assignments at the C-1' epimeric center. The n.m.r. data
are listed in Table 7.

In general, the n.m.r. data for the acyclic-sugar nucleoside analogs 28a-c indicated the presence of a single epimer; only in the case of the D-lyxose derivative 28d were two epimers indicated. At lowest field, $r 1.40—1.75$, were observed the signals for H-2 and H-8 of the purine ring. These appeared as singlets in every case; for the epimeric mixture of the D-lyxo compound, there was an apparent overlap of signals, indicating that these signals are probably not sensitive indicators for determining ratios of epimeric compounds per se. The signals for H-1'-H-5',5'a of the acyclic-sugar chain appeared in the region of $r 3.8—6.1$. Generally, good signal separation was obtained, permitting a first-order evaluation of the data. In every case, the acetate-group signals were observed as separated singlets in a region $r 7.8—8.2$. The ethylthio group exhibited the characteristic triplet ($r 8.9—8.95$) for the methyl group and a quartet ($r 7.4—7.5$) for the methylene protons. A broad signal that was exchangeable with deuterium oxide appeared at $r 6.5—6.7$. The abundant evidence that suggests that the 6-mercapto purine exists in solution$^{265—267}$ and in the solid state$^{268}$ as the cyclic

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thioamide (~NH-C=S) tautomer strongly suggests that the broad singlet arises from an exchangeable ~NH proton. 

\[ \text{a: 2,3,4,5-Tetra-O-acetyl-1-deoxy-1-S-ethyl-1-} \]

\[ \text{[purin-9-y1-6-(1H)-thionel-1-thio-aldehydo-D-arabinose} \]

\[ \text{aldehydrol (28b). The signal for H-1' appears as a wide doublet at } \tau 4.25. \] 

The large value of \( J \) (9.0 Hz) indicates that H-1' and H-2' are essentially antiparallel, whereas \( J_{2',3'} \) (2.4 Hz) and \( J_{3',4'} \) (7.5 Hz) indicate respectively a gauche disposition between H-2' and H-3' and an antiparallel relationship between H-3' and H-4'. These values are in agreement with a fully-extended, planar, zig-zag chain that includes carbon atoms C-1'—C-5', O—5' and the sulfur atom of the ethylthio group. An argument can be made that the ethylthio group, itself in a fully extended form, favors the C-1'—C-2' antiparallel disposition through the maintenance of favorable 1,3-H-H interactions with H-1'. Thus the n.m.r. data indicate a fully extended, chain structure from the CH\(_3\)-group of the ethylthio function to O—5' function of the sugar chain. This conformation supports the 1-(R) configuration at
C-1' assigned from optical rotatory evidence, with the assumption that the steric requirements for a sulfur group are larger than that for a trigonally-substituted nitrogen. A structure, based on the foregoing arguments, is shown as follows.

![Chemical structure](image)

1-\((R)-\beta\)-arabino, compound 28b

No signals attributable to a second isomer were observed.

b. 2,3,4,5-Tetra-O-acetyl-1-deoxy-1-S-ethyl-1-[purin-9-yl-6-(1H)-thionel-1-thio-aldehydo-\(\beta\)-ribose aldehydrol (28a). The signal for H-1' appears as a narrow doublet (\(J_{1',2'}\), 4.0 Hz) at \(r3.92\), indicating a gauche arrangement for H-1'—H-2'. The signals for H-2' and H-3' appear respectively as a doublet of doublets
(J_{2',3'}, 6.0 Hz) and a triplet (J_{3',4'}, 6.0 Hz). The data do not accord with an extended-chain arrangement for the sugar portion. From the moderately large values of J_{2',3'} and J_{3',4'}, it may be concluded that the major conformer present in solution is the one whose rotameric states would place H-2', H-3' and H-4' in a series of antiparallel positions. At equilibrium the major contributor would be the "sickle" structure shown immediately below.

[Diagram of the sickle structure]

1-[(R)-D-ribo, compound 28a

Major Conformer

To a limited extent a second conformation, shown in the following figure, would be expected to contribute, as evidenced by the J values obtained for 28a in solution.
No signals attributable to a second C-1' epimer were evident.

c. 2,3,4,5-Tetra-O-acetyl-1-deoxy-1-S-ethyl-1-
[purin-9-yl-6-(1H)-thione]-1-thio-aldehydo-D-xylose
aldehydrol (28c). The H-1' signal appeared as wide doublet
(J_1',2', 7.0 Hz) at 4.32, whereas the H-2' and H-3' signals
appeared respectively at 4.17 (J_2',3', 4.1 Hz, doublet of
doublets) and 4.90 (J_3',4', 5.7 Hz, doublet of doublets).
An antiparallel disposition is indicated for H-1'—H-2',
although the somewhat lower value for J_1',2' would indicate
some distortion between H-1' and H-2', or a contribution
from other rotamers having a gauche relationship. The
small J_2',3' (4.3 Hz), together with a moderately large
J_3',4' value (5.7 Hz) indicates that the major conformational
contributor is the "sickle" structure shown immediately below.
Undoubtedly, as indicated by the somewhat perturbed $J$-values for the H-2—H-3 and H-3—H-4 couplings, a substantial contribution to the state at equilibrium is made by the conformer shown below, with the base in an extended position (left) or the ethylthio group fully extended (right).
These data do clearly support a sickle conformation for $28c$, and indicate the $1$-($S$)-configuration, which places the bulky ethylthio group in an extended position that favors the antiparallel disposition of $H-1'$ and $H-2'$.

From its n.m.r. spectrum, $28c$ is determined to be a single, C-1 epimer; no signals from a second epimer were evident.

$\text{d': 2},3',4',5\text{-Tetra-0-acetyl-1-deoxy-1-S-ethyl-1-}$

\[\text{[purin-9-yl-6-(1H)-thione]-1-thio-aldehydo-D-lyxose} \]

\text{aldehydrol (28d). Examination of the n.m.r. spectrum for}

\text{compound 28d revealed two sets of resonances, indicating}

\text{an epimeric mixture of compounds in a ratio of 1:4.}

\text{Signal overlap, however, prevented any reliable measure-
ment of $J_{2'3'}$ or $J_{3'4'}$ for the major isomer, thus}

\text{precluding any definitive conformational assignment or}

\text{assignment of configuration at C-1. However, for the}

\text{minor isomer, sufficient signal separation was achieved}

\text{to assign $J_{1'2'}$ (4.0 Hz), $J_{2'3'}$ (8.7 Hz) and $J_{3'4'}$}

\text{($\sim$3 Hz). These data indicate a planar, zig-zag}

\text{conformation, which is free from unfavorable 1,3-
interactions. The disposition of the ethylthio group}

\text{appears, from the examination of a molecular model, to}

\text{favor an extended conformation for a 1'-(S) configuration.}

\text{The structure described is pictured below. The}

\text{particular C-1--C-2 rotamer has H-1 and H-2 gauche-disposed;}

\text{the form having maximum staggering of groups along C-1--}
FIGURE 3: Partial N.M.R. Spectrum (DMSO-d$_6$) of 2,3,4,5-Tetra-O-acetyl-1-deoxy-1-$\text{S}$-ethyl-1-
[purin-9-yl-6(1H)-thione]-1-thio-aldehyde-$D$-ribose aldehydrol, 28a
FIGURE 4: Partial N.M.R. Spectrum (DMSO-d$_6$) of 2,3,4,5-Tetra-O-acetyl-1-deoxy-1-$\beta$-ethyl-1-$\beta$-[purin-9-yl-6(1H)-thione]-1-thio-aldehydo-$\alpha$-arabinose aldehydrol, 28b
FIGURE 5: Partial N.M.R. Spectrum (DMSO-d$_6$) of 2,3,4,5-Tetra-O-acetyl-1-deoxy-1-S-ethyl-1-
[purin-9-yl-6(1H)-thione]-1-thio-aldehydo-$D$-xylose aldehydrol, 28c
FIGURE 6: Partial N.M.R. Spectrum (DMSO-$d_6$) of 2,3,4,5-Tetra-$O$-acetyl-1-deoxy-1-$S$-ethyl-1-
[purin-9-yl-6(1H)-thione]-1-thio-aldehyde-$D$-lyxose aldehydrol, 28d
C-2 would generate a 1,3-interaction between OAc-3 and 1-SEt.

![](image)

1-(S)-D-lyxo (minor epimer), compound 28d

8. 1-Deoxy-1-S-ethyl-[purin-9-y]-6-(1H)-thione]-1-thio-aldehyde-D-pentose aldehydrols 29a-d. — Deacetylation of compounds 28a-d was carried out to give the free hydroxy nucleoside analogs 29a-d. Conventional methods that employ either sodium methoxide or methanolic ammonia were found to be unsatisfactory for the deacetylation reaction, and caused much decomposition of the products. Experimentation led to the use of a modified n-butylamine—tetrahydrofuran—methanol system that gave satisfactory yields of deacetylated products 29a-d. The protected nucleosides (compounds 28a-d) of which 28a- were shown to be single, epimeric products, were each heated under reflux in the
reagent mixture, until t.l.c. analysis indicated a satisfactory, although incomplete, deacetylation to give 29a-d. At this point, the products were isolated, with a sacrifice in yield due to incomplete deacetylation, by the methods outlined [see Experimental Section], freed, with some difficulty, from acetylated contaminants, and crystallized to give analytically pure 29a-d. This method was found advantageous to the one in which the deacetylation process was carried to completion, and in all cases gave products which lent themselves more readily to purification.

9. The chirality at C-1' for 1-deoxy-1-S-ethyl-1-[purin-9-yl-6-(1H)-thione]-1-thio-aldehydrols 29a-d. -- For each of the analytically pure compounds 29a-d, the optical rotation ([α]D) was determined and its n.m.r. spectrum recorded. As would be expected for compounds 29a-c, whose precursor acetates 28a-c were shown to be single epimers, single epimers were indicated on the basis of their optical rotatory data and n.m.r. spectra. The values for [α]D were large and positive for 29a and 29b (+85.8° and +59.7°, respectively), whereas 29c showed a large, negative value (-84.5°), indicating, as expected, that no change in chirality at C-1 had occurred during the deacetylation procedure.*
*One such epimerization has been suggested to explain two epimeric acyclic D-galacto derivatives of adenine that were obtained from a seemingly homogeneous, blocked nucleoside precursor.

For the D-lyxo compound 29d, whose precursor 28d was an apparent 3:1 mixture of 1-(R) and 1-(S) epimers, a further fractional separation was achieved by crystallization. Compound 29d showed a large, positive rotation (+53.4°); examination of the n.m.r. spectrum showed only one set of resonances [see Table 8], on a singly recrystallized sample. The mother liquors of the reaction appeared to be a complex, intractable mixture of products.

N.M.R. analysis of 1-deoxy-l-S-ethyl-l-[purin-9-yl-6-(1H)-thione]-l-thio-aldehydo-D-ribose aldehydrol (29a).— The n.m.r. spectrum of 29a [see Table 8] revealed, in contrast to the spectra obtained for compounds 29b-d, considerable detail and fine structure, with good signal separation for the acyclic-sugar proton resonances. The H-1' signal appeared as a narrow doublet (r3.23; J_1'2', 2.1 Hz), and H-2' and H-3' each resonated as separate doublets of doublets at r5.04 (J_2'3', 8.0 Hz) and 6.12 (J_3'4', 4.8 Hz), respectively. The H-4' signal appeared as an apparent triplet (r5.54). These data indicate a gauche disposition for H-1' and H-2', followed by a largely antiparallel arrangement between H-2' and H-3'.
intermediate-sized coupling between H-3' and H-4' would indicate a conformation whose rotamers show substantial contribution from a gauche-disposed H-3—H-4 conformation. One conformation that would accord with the n.m.r. data for 29a in solution is shown immediately below:

1-Deoxy-1-S-ethyl-1(R)-[purin-9-yl-6-(1H)-thionyl]-1-thio-aldehydo-D-ribose aldehydrol (29a),
Major Conformer.

The data ($J_{2',3'}$, 8.0 Hz and $J_{3',4'}$, 4.8 Hz) indicate that a second conformer which amounts to perhaps 30—50% of the equilibrium mixture is the other conformer depicted below:
1-Deoxy-1-S-ethyl-\((R)\)-[purin-9-yl-6-(1H)-thione]-1-thio-aldehydo-D-ribose aldehydrol (29a), Minor Conformer

11. Biological evaluation for the 1-deoxy-1-S-ethyl-[purin-9-yl-6-(1H)-thione]-1-thio-aldehydo-D-pentose aldehydrols (29a-d) and their tetraacetates 28a-d. The derivatives 28a-d and 29a-d were assayed for their activity in vitro against selected bacterial systems and against cultures of L-1210 lymphoid leukemia cells. The results are listed in Table 9, together with data for the active acyclic-sugar D-gluco analog 22 and the inactive D-galacto epimer 23. As may be noted, the D-ribo analog 29a is active in inhibiting the growth for both \textit{E. coli} K-12 and \textit{S. faecalis} at molar concentrations 20—80 times lower.
than the least active compound in the series 29a-d. Furthermore, the molar concentration required for 50% inhibition is in the range (10^{-5} - 10^{-6} \text{ M}) that is considered "moderate" when compared with known antitumor compounds, including 6-mercaptopurine.\(^{269}\) When compared with the

\begin{center}
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(269) A. Bloch, personal communication.
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\textbf{in vivo} active \(\text{\textalpha}\text{-gluco}\) precursor 22, the results indicate that the \(\text{\textbeta}\text{-ribo}\) analog 29a is a significantly more effective inhibitor, and in particular, shows moderate activity in the L-1210 cell culture; in the latter test, compound 22 failed to show any activity, although it was highly active (T/C 147) when assayed \textit{in vivo} in L-1210 leukemoid mice. These results suggest that the \(\text{\textbeta}\text{-ribo}\) analog 29a may well prove active in animal screens, but \textit{in vivo} data are not yet available. The data from the \textit{S. faecalis} culture studies have been demonstrated to closely reflect the activity of antimetabolites in mammalian systems (especially in \textit{de novo} synthesis of purines and quite possibly in purine interconversions).\(^{270}\)

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This assay has been widely employed as a useful indicator for potential activity \textit{in vivo}. 
The mode of action for 22 and 29a in biochemical systems remains unresolved. Whether these compounds act merely as carriers for the known, active 6-mercaptopurine, or whether these compounds successfully mimic natural nucleosides, become phosphorylated, and are incorporated into the nucleic acid chain remains to be determined.

The former possibility, that 22 and 29a act as carriers for 6-mercaptopurine, would require hydrolysis of the non-glycosylic C-1'—N bond. Such a process would most likely have to occur spontaneously in vivo, and there is no indication to suggest that 29a-d have a tendency to auto hydrolyze at near neutral pH. Furthermore, the observed fact that the D-glucos isomer 22 shows high in vivo antitumor activity (T/C 147 in the L-1210 lymphoid leukemia screen) whereas the D-galacto analog 23 is inactive in this screen supports the hypothesis that the sugar chain and its precise stereochemistry play an active role in the metabolic utilization of these compounds.

For the D-ribo compound 29a, a possible stereochemical arrangement that would be isosteric with normal nucleosides is shown as follows:
The above conformation could possibly form on the enzyme surface and account for the biological activity of 29a.
IV. EXPERIMENTAL

General Methods.— For a description of general procedures, see Part One, Chapter IV, p. 73.

Preparation of N^6-formyl-2',3'-O-isopropylidene-5'-O-p-tolylsulfonyladenosine (2).— 2',3'-O-Isopropylidene-adenosine (1, 9.80 g, 32 mmol.) was p-toluenesulfonylated, and the crude product immediately suspended in 100 ml of acid-free acetic-formic anhydride. The mixture was stirred overnight at ~25°, evaporated below 30°, and the residue was triturated with methanol to give the crude, crystalline product; this procedure is essentially that of Jahn. One recrystallization from 1:1 methanol—ethyl acetate gave pure 2; yield 10.20 g (98% based on 1), m.p. 160—163° (dec.) [lit.197 m.p. 165°, sinters], Rf 0.75 (5:5:1 chloroform—acetone—cyclohexane); \( \lambda_{KBr}^{\text{max}} 2.91 \) (NH), 5.78, 5.82 (C=O), 6.15, 6.20, 6.80, 7.35, 8.15, 8.45, 9.22, 10.31, 11.44, 12.32, and 12.90 \( \mu \text{m} \); X-ray powder diffraction data: 11.62 \( \text{vw} \), 8.50 vs (1), 7.60 \( \text{vw} \), 6.68 \( \text{w} \), 5.72 vs (2), 5.29 \( \text{w} \), 4.96 s (3), 4.63 m, 4.38 s, 4.11 s, 3.79 \( \text{vw} \), 3.55 \( \text{w} \), 3.41 m, 3.20 s.

Anal. Calc. for $C_{21}H_{23}N_5O_7$: C, 51.53; H, 4.74; N, 14.31; S, 6.54. Found: C, 51.62; H, 5.07; N, 14.45; S, 6.84.

5'-Azido-5'-deoxy-N$^6$-formyl-2',3'-O-isopropylidene-adenosine (3). A solution of 12.0 g (22.9 mmol.) of N$^6$-formyl-2',3'-O-isopropylidene-5'-O-p-tolysulfonyl-adenosine and 6.5 g (100 mmol.) of sodium azide in 100 ml of anhydrous methyl sulfoxide was heated for 30 min on a steam bath with exclusion of moisture. The resulting yellow solution was poured into water and extracted with four, 100-ml portions of chloroform. The combined extracts were washed twice with water, dried (magnesium sulfate) and evaporated to a syrup that crystallized upon trituration with ether. Recrystallization from ethanol afforded pure 3; yield 7.40 g (89%), m.p. 104—106°, $[\alpha]_{D}^{25}$ -28.2° (c 1, chloroform); $R_{F}$ 0.70 (5:5:1 chloroform—acetone—cyclohexane, detection by u.v. light); $\lambda_{\text{EtOH}}^{\text{max}}$ 257.3 (ε13,400), 272.8 (18,200) and 282.7 nm (12,300); $\lambda_{\text{KBr}}^{\text{max}}$ 3.21, 3.41 (CH), 4.75 (N$_3$), 5.84 (C=O), 6.15 (NH bend), 6.28, 8.14, 8.28, 9.10, 9.30, 9.48, 11.40, 11.78, and 12.47 μm; for n.m.r. and mass-spectral data see Tables 1 and 2; X-ray powder diffraction data: 10.18 w, 7.49 s, 6.55 m, 5.27 s (3), 4.98 vs (1), 4.18 s, 4.15 vs (2), 3.63 w, 3.48 vw, 3.35 w.

Anal. Calc. for $C_{14}H_{16}N_8O_4$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.87; H, 4.62; N, 31.00.
5'-Azido-5'-deoxy-2',3'-O-isopropylideneadenosine (4).—To a suspension of 1.00 g (2.79 mmol.) of the foregoing N^6-formyl derivative 3, in 20 ml of abs. methanol was added 1 ml of 0.10 M methanolic sodium methoxide. The mixture was stirred for 15 min at ~25°, and the resultant clear solution was stirred for a further 10 min with 1 g of Amberlite IR-120 (H+) resin. The mixture was filtered, the resin was washed with methanol, and the filtrate was evaporated to a syrup. Crystallization from 9:1 ethyl acetate—petroleum ether (b.p. 30—60°) gave needles of the pure azide 4; yield 0.91 g (98%), m.p. 137—138.5°, [α]_D^{25} +16.4° (c 1, chloroform); R_F 0.48 (13:1 ethyl acetate—methanol); λ_{EtOH, max} 258.2 nm (ε15,400); λ_{KBr, max} 2.93, 2.90 (NH₂), 3.16, 3.44 (CH), 4.76 (N₃), 5.98 (NH bend), 6.25, 6.84, 7.08, 7.29, 7.33, 7.55, 9.26, 11.31, and 12.54 μm; for n.m.r. and mass-spectral data see Tables 1 and 2; X-ray powder diffraction data: 10.77 s, 7.23 s, 6.24 s, 5.78 w, 5.24 vs (3), 4.79 vs (1), 4.41 vw, 4.04 vs (2), 3.83 s, 3.56 m, 3.39 vw, 3.24 w, 3.09 m, 2.97 m, and 2.74 w.

Anal. Calc. for C_{13}H_{16}N₆O₃: C, 46.98; H, 4.82; N, 33.73. Found: C, 47.17; H, 4.86; N, 33.86.

Photolysis of 5'-azido-5'-deoxy-2',3'-O-isopropylideneadenosine (4) to generate the aldehyde 5.—A solution of 450 mg (13.6 mmol.) of the azide 4 in 180 ml of dry benzene was purged with dry nitrogen for 20 min
and then photolyzed under nitrogen at 15—20°. The photolysis product, a finely divided precipitate, was periodically washed from the quartz immersion tube with methanol and collected separately. Irradiation was continued until t.l.c. (13:1 ethyl acetate—methanol, detection by u.v. light) showed that the azide 4 (RF 0.47) was absent (~2.5 h), at which time there was observed a major product having RF 0.22 and a minor, nonmigrating component. The combined benzene suspension and methanol washings were evaporated at 30°, and the resultant, light tan powder was suspended in 50 ml of acetone. Methanol (~10 ml) was added to cause dissolution of most of the product, followed by 1 g of Amberlite IR-120 (H+) resin and 5 ml of water. The mixture was stirred for 18 h at 25°, filtered, and the filtrate was evaporated to give 450 mg of a light tan, amorphous powder. This product was soluble in methanol and ethanol and showed by t.l.c. a principal component (RF 0.2 in 13:1 ethyl acetate—methanol; 0.75 in 6:1 chloroform—methanol) that was indicated to be the aldehyde 5, since it was u.v.-absorbing and gave positive reactions with Schiff reagent and with aniline phthalate; a side-product that did not migrate in either solvent system was u.v.-absorbing but did not show reducing behavior.
Reduction of the aldehyde 5.— a. With borohydride to give 2',3'-O-isopropylideneadenosine (1). To a solution of 200 mg of the crude aldehyde 5 from the preceding experiment 40 ml of 95% ethanol at 5—10° was added portionwise 35 mg of sodium borohydride over a period of 15 min. The mixture was stirred for an additional 30 min, and then the pH was adjusted to 7.0 by dropwise addition of 50% aqueous acetic acid. The solution was evaporated, and the residue was extracted with four, 5-ml portions of ethyl acetate. The combined extracts were evaporated, and the product was purified chromatographically on a 0.5 x 25 cm column of silica gel with 6:1 chloroform—methanol as eluant to give pure 2',3'-O-isopropylidene-adenosine (1); yield 112 mg (54%, based on the azide 4 photolyzed), m.p. 220—221°, undepressed on admixture with authentic 1; X-ray powder diffraction data 13.38 m, 10.52 s, 8.94 m, 6.83 vs (2), 5.64 s, 5.06 vw (3), 4.49 s, 4.21 vs (1), 3.74 m, 3.30 s; identical with authentic 1 by X-ray diffraction data, by i.r. spectrum, and by t.l.c. in 3 solvent systems.

b. With borodeuteride to give 2',3'-O-isopropylidene-adenosine-5'-d (6). The preceding experiment was repeated, but with use of sodium borodeuteride as the reducing agent. The product 6 was obtained in comparable yield and was indistinguishable from 1 by mixed m.p., by X-ray
diffraction pattern, and by t.l.c., but its n.m.r. and mass spectra [see Tables 1 and 2 and Discussion Section] indicated that one atom of deuterium had become incorporated at C-5' in the product.

*2',3'-O-Benzylidene-5'-O-p-tolylsulfonyluridine* (8).— To a solution of 10.3 g (31 mmol.) of *2',3'-O-benzylideneuridine*^200^ (7) in 100 ml of dry pyridine at 0° was added 6.5 g (34 mmol.) of freshly distilled *p*-toluenesulfonyl chloride, and the mixture was stirred for 18 h at 5—10°. The solution was evaporated at 30°, and two 20-ml portions of toluene were evaporated from the residue to give 8 as a glass that was dried at 25° and 0.1 torr; yield 13.6 g (96%). The product was crystallized from 6:1 ethanol—ethyl acetate to give white crystals of 8, m.p. 198—200°, [α]^25_D -0.6° (c 1, chloroform); \(\lambda_{max}^{EtOH}\) 257.7 nm (ε10,700); \(\lambda_{max}^{KBr}\) 3.10, 3.24, 3.41 (CH), 5.81, 5.92 (C=O), 7.39, 8.50 (sulfonate), 9.20, 9.40, 10.32, 12.28, 13.18, and 14.41 μm; for n.m.r. and mass-spectral data see Tables 1 and 2; X-ray powder diffraction data:

10.03 vs (1), 8.75 vw, 7.93 vw, 6.58 w, 6.08 m, 5.61 vs (3), 4.86 vs (2), 4.34 w, 4.16 m, 3.95 s, 3.69 s, 3.51 w, 3.15 m, 3.07 vw, 2.94 vw, 2.75 w.

*Anal.* Calc. for C\(_{23}\)H\(_{22}\)N\(_2\)O\(_8\): C, 56.79; H, 4.52; N, 5.76; S, 6.58. Found: C, 56.50; H, 4.59; N, 5.84; S, 6.50.
5'-Azido-2',3'-O-benzylidene-5'-deoxyuridine (9).-- A solution of 13 g (27 mmol.) of the sulfonate 8 and 7.1 g (5 molar equivalents) of lithium azide in 80 ml of anhydrous methyl sulfoxide was heated under nitrogen for 2.5 h on a steam bath. The resulting, yellow solution was poured into 600 ml of water and extracted with four 80-ml portions of chloroform. The combined extracts were washed twice with water, dried (magnesium sulfate), and evaporated to give 9 as a class, Rf 0.53 (25:25:6 chloroform—acetone—cyclohexane, detection by u.v. light). The product was freed from traces of slower-moving impurities on a 5 x 40 cm column of silica gel by elution with 340 ml of the t.l.c. solvent mixture; yield of chromatographically homogeneous, glassy 9, 7.23 g (70%); [α]D26 +6.5° (c 1.3, chloroform); λ<sub>EtOH max</sub> 258.0 nm (ε 10,200); λ<sub>KBr max</sub> 2.91 (NH), 3.16, 3.30, 3.42 (CH), 4.75 (N₃), 5.86—5.89 (broad, C=O), 6.82, 7.22, 7.84, 9.11, 9.15, 9.32, 13.12, and 14.32 μm; for n.m.r. and mass-spectral data see Tables 1 and 2.


Photolysis of 5'-azido-2',3'-O-benzylidene-5'-deoxyuridine (9) to generate the aldehyde 10.-- By the general procedure used for the azide 4, a solution of 250 mg (7.0 mmol.) of compound 9 in 180 ml of dry benzene was photolyzed under nitrogen at 15—20° to yield, after
irradiation for 45 min and subsequent treatment with acidic ion-exchange resin, the aldehyde 10 as an off-white powder; yield 221 mg, $R_f$ 0.35 (5:5:1 chloroform-acetone-cyclohexane) positive to u.v. light, aniline phthalate, and Schiff reagent. A minor, nonreducing, u.v. absorbing side-product, which did not migrate on t.l.c., was also present.

Reduction of the aldehyde 10.— a. With borohydride to give 2',3'-O-benzylideneuridine (7). A solution of 200 mg of the aldehyde 10 in 50 ml of ethanol was reduced with sodium borohydride by the same procedure used for the adenosine derivative (5). After purification of the product on a column of silica gel with 13:1 ethyl acetate-methanol as eluant there was obtained the pure uridine derivative 7; yield 122 mg (64%), m.p. 187–188°; X-ray powder diffraction data: 10.00 m, 6.84 s (3), 5.89 vs (2), 4.94 s, 4.45 s, 4.09 vs (1), 3.92 m, 3.76 m, 3.44 s, 3.11 w, 3.01 vw, 2.91 m, 2.80 w. The product was identical with an authentic sample of 7 by mixed m.p., i.r. and n.m.r. spectra, X-ray powder diffraction pattern, and t.l.c. in 3 solvent systems.

b. With borodeuteride to give 2',3'-O-benzylidene-uridine-5'-d (11). Reduction of 200 mg of the aldehyde 10 by the foregoing procedure, but with use of 35 mg of sodium borodeuteride as the reductant, gave the 5'-deuterated
derivative 11 in comparable yield. The product was indistinguishable from 7 by mixed m.p., by X-ray diffraction pattern, and by t.l.c., but its n.m.r. and mass spectra [see Tables 1 and 2 and Discussion Section] indicated that one atom of deuterium had become incorporated at C-5' in the product.

Preparation of 3-O-benzyl-1,2-O-isopropylidene-α-D-allofuranose (12).— Following the improved procedure of Horton and Tindall, 70 g (0.319 mole) of 1,2:5,6-di-O-isopropylidene-α-D-allofuranose was converted into its 3-benzyl ether 12 to give directly 95.5 g (98%) of the crystalline product; m.p. 66—66.5°, [α]₂²₀ +102° (c 1, chloroform; [lit. 66—66.5°; [α]₂²₀ +106° (c 1, chloroform)].

Preparation of 3-O-benzyl-1,2-O-isopropylidene-α-D-allofuranose (13).— By a scaled-up version of the reported procedure, 30 g (85 mmol.) of compound 12 was deacetonated to give 25.4 g (96%) of syrupy 13; Rₚ 0.2 (3:1 chloroform—ether); identical with an authentic sample of 13 by i.r. spectrum and [α]₂²₀.

Preparation of a diastereoisomeric mixture of 3-O-benzyl-5,6-O-(ethoxymethylene)-1,2-O-isopropylidene-α-D-allofuranose (14).— The syrupy product (25.4 g, 82 mmol.) from the foregoing procedure was treated with 25 ml (22.5 g, 150 mmol.) of triethyl orthoformate and 3 ml of glacial
acetic acid, and the mixture was heated for 6 h under reflux. Evaporation of the excess reagents at 45°/5 torr followed by drying in vacuo, gave 24.4 g (100%) of a semi-solid deposit that by t.l.c. showed two spots at $R_F$ 0.80 (major) and $R_F$ 0.95 (minor (3:1 chloroform--ether), indistinguishable from those of an authentic sample of 14. The product was identical with authentic 14 by i.r. spectroscopy.

**Preparation of 3-O-benzyl-5,6-dideoxy-1,2-O-isopropylidene-$\alpha$-$\delta$-ribo-hex-5-enofuranose (15).**—Following the procedure of Horton and Tindall, 24.4 g (66.7 mmol.) of the diastereoisomeric mixture of orthoesters 14 was heated with 1 g triphenylacetic acid for 6 h at 190 ± 10° in a Wood's-metal bath. After separation of the acid catalyst, distillation of the residue in vacuo (b.p. 116—118/0.02 torr) gave 17.61 g (96%) of a clear oil that was identical by i.r. and [a]$_D$ with the reported product.

**Preparation of 3-O-benzyl-4-C-cyclopropyl-1,2-O-isopropylidene-$\alpha$-$\delta$-ribo-tetrofuranose (16).**—By a procedure, scaled-up from the one reported, 17.6 g (63.7 mmol.) of alkene 15 and 40 g (an excess) of diiodomethane were dissolved in 50 ml of anhydrous ether and heated at reflux, with protection from atmospheric moisture, with 75 g (x 10 excess) of a zinc—copper
couple [prepared from 20-mesh granular zinc (J. T. Baker reagent grade, lot no. 34062) according to the method of LeGoff\textsuperscript{225}]. The mixture was stirred vigorously, and after 48 h, as judged by t.l.c., the starting material 15 (R\textsubscript{F} 0.42, 3:1 chloroform—ether) had largely disappeared, and was replaced by a slower-migrating zone (R\textsubscript{F} 0.35), attributed to the cyclopropyl compound 16. Isolation according to the reported\textsuperscript{221} method gave 18.4 g (97\%) of 16, judged to be >95\% pure by t.l.c. and i.r. spectrum;*

*The two could be identified by i.r., in that the alkene alone showed a weak absorption at 10.74 \( \mu\)m; the other absorptions for both 15 and 16 were indistinguishable.

\([\alpha]_{D}^{23} +80.5^\circ (c 1, \text{ethanol}) \) [lit.\textsuperscript{221} \([\alpha]_{D}^{22} -81^\circ (c 1, \text{ethanol}))]. The product 16 was used directly in the next step.

Preparation of 4-C-cyclopropyl-1,2-O-isopropylidene-\( \alpha \)-D-ribo-tetrofuranose (17).— Compound 16 (18.4 g, 92 mmol.) from the foregoing procedure was O-debenzylated in the manner reported,\textsuperscript{221} by the addition of 10 g of sodium (435 mmol.) portionwise over a period of 1.5 h to a stirred solution (all-glass stirrer) of 16 in 750 ml of anhydrous ammonia containing 50 ml of THF. After stirring for an additional 1.25 h, the excess reagents were decomposed by the addition of ~10 g of solid ammonium
chloride, and the product 17 was isolated as described, and recrystallized from 60 ml of 1:5 ether—petroleum ether to give 10.1 g (93%) of 17, that was homogeneous by t.l.c. (Rf 0.68, 3:1 chloroform—ether); m.p. 86—87° [lit. m.p. 84—87°]; i.r. spectrum identical to that of an authentic sample.

The hydrogenation procedure reported for the O-debenzylation of 16 was found unsatisfactory for the large-scale preparation of 17.

Preparation of 4-C-cyclopropyl-α,β-D-ribo-tetrofuranose (18).— The procedure is essentially that reported by Tindall. A solution of 7.0 g (35 mmol.) of the pure, crystalline product 17 from the foregoing procedure in 80 ml of water was stirred with 15 g of Amberlite IR-120 (H+) resin (20—50 mesh, analytical grade) for 3 h at 45 ± 5°. The resin was filtered off, and the water was evaporated to give, upon drying in vacuo at 40°, 5.18 g (93%) of a light-yellow syrup; \([a]_{D}^{22} +32°\) (c 1.5, water, equilibrium) [lit. \([a]_{D}^{22} +33.4°\) (c 2, water)].
Preparation of tri-O-acetyl-4-C-cyclopropyl-\(\alpha\) (and \(\beta\))-\(\text{D}\)-ribo-tetrofuranose (19).— A mixture of 5.18 g (32.4 mmol.) of product 18 and 1.5 g of anhydrous sodium acetate in 50 ml of acetic anhydride was heated over an open flame with a vigorous effervescence set in (\(-1\) min). The cooled solution was poured slowly into 600 ml of an ice-cold, saturated solution of sodium hydrogen carbonate, and after decomposition of the acid anhydride was complete (\(-1\) h), the aqueous solution was extracted with three, 10-ml portions of dichloromethane. The combined organic extracts were washed with aqueous sodium hydrogen carbonate solution (4 x 50 ml), water (50 ml), dried (magnesium sulfate) and evaporated to give, upon drying in vacuo at 40°, 3.32 g (82%) of syrupy 19, \(R_F\) 0.53 and 0.55 (1:9 methanol—benzene); identical by i.r. and n.m.r. spectroscopy, with an authentic sample.\(^{273}\)

(273) Ref. 272, p. 115.

Acetylation of 18 with acetic anhydride—pyridine for 8 h at 25° was apparently incomplete and gave a mixture of products, as indicated by t.l.c.

\[9-\{4-C-\text{cyclopropyl-\(\alpha\)}(and \(\beta\))-\(\text{D}\)-ribo-tetrofuranosyl\}\]-adenine (21).— A stirred mixture of 2.0 g (7.0 mmol.) of 19, 3.65 g (7.7 mmol.) 6-benzamido-9-(chloromercuri)purine,\(^{35}\) 3 g of Celite, and 175 ml of
1,2-dichloroethane was heated under reflux, and 50 ml of the solvent was removed by distillation. The mixture was cooled to ~45°, and 0.8 ml (7.1 mmol.) of freshly-distilled titanium tetrachloride was added dropwise with stirring. The mixture was again brought to reflux, and heating was continued for 4.0 h, at which time t.l.c. (9:1 benzene—methanol) indicated both the formation of a zone (R_f 0.26), that was detectable by both u.v. (254 nm) light and sulfuric acid spray-reagent, and the disappearance of the starting material 19 (R_f = 0.57). To the cooled solution was added 50 ml of an aqueous saturated solution of sodium hydrogen carbonate, and after stirring for 0.5 h, the mixture was filtered through Celite, and the filter was washed with three 50-ml portions of hot chloroform. Evaporation of the filtrate gave a dark brown syrup that was dissolved in 25 ml of chloroform and washed with two 50-ml portions of a 30% aqueous solution of potassium iodide and a 50-ml portion of water. Evaporation of the dried (magnesium sulfate) chloroform extract gave a syrup that was dried in vacuo at 40° to give 2.30 g of a dark-brown, amorphous solid. Examination of the product by t.l.c. in several solvent systems showed a major, elongated zone, indicating an inseparable mixture of protected nucleosides 20.
The dried glass from the foregoing condensation reaction was suspended in 50 ml of 0.1 M sodium methoxide and heated under reflux for 1.25 h, at which time t.l.c. indicated disappearance of a faster-migrating zone ($R_F$ 0.71, 6:1 chloroform—methanol), with the formation of a slower-migrating zone ($R_F$ 0.42). The cooled solution was neutralized with 1.0 g (5 meq.) of Amberlite IR-120 (H+) resin (dry resin). The resin was filtered off, and the filtrate was evaporated to yield a dark syrup. Extraction of the product with 50 ml of hot (60°) water, followed by decolorization with Norit, gave, upon evaporation of the water and drying of the resultant syrup in vacuo at 50°, 1.56 g (73%) of a light-yellow syrup that was homogenous by t.l.c. ($R_F$ 0.42, 6:1 chloroform—methanol). A single crystallization from methanol gave 0.86 g of a white, crystalline product that by n.m.r. spectroscopy was judged to be a 3.4:1 mixture of $\beta$:$\alpha$ anomers of 21; m.p. 212—213°, $[\alpha]_D^{28}$ -12.7°, $[\alpha]_D^{365}$ -63.6° (c 1, ethanol); $\lambda_{\text{max}}^{\text{EtOH}}$ 260.0 nm ($1.48 \times 10^4$); $\lambda_{\text{max}}^{\text{PHL}}$ 259.5 nm ($1.45 \times 10^4$), $\lambda_{\text{max}}^{\text{PHL2}}$ 260.2 nm ($1.48 \times 10^4$); $\lambda_{\text{max}}^{\text{KBr}}$ 3.0 (OH, NH), 3.18, 3.45 (CH), 6.0, 6.08, 6.20, 6.78, 8.00, 8.88, 9.55, 11.05, 12.10, 12.51, and 13.80 μm; n.m.r. data see Table 3.

A 150-mg portion of the product, that was shown by n.m.r. to be a 3.4:1 mixture of \( \beta: \alpha \) anomers, was fractionally recrystallized by five successive crystallizations to give 26 mg of a product that showed little change in m.p.; 
\[ \alpha \]_{D}^{23} -22^\circ \ (c 1, \text{ethanol}).

High-pressure liquid chromatographic analysis of the foregoing product on a 0.2 x 50 cm column of SCX-Zipax [a surface-porosity, cation-exchange resin (DuPont)] with 0.025 M sodium nitrate buffer at 1.5 ml/min (1200 p.s.i.), showed (254 nm u.v. detection) two separate peaks at 1.25 min and 2.6 min, in 9:1 proportion, respectively. The compounds, were distinguished from adenine by a separate experiment, in which three components eluted when adenine was added to the mixture.

**Preparation of diethyl dithioacetals.**

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**a. \( \delta \)-Ribose diethyl dithioacetal.** Following the method of Wolfrom and Anno, three 10-g portions of \( \delta \)-ribose were each treated with 10 ml of conc. hydrochloric acid, cooled to 0–5°, and 10 ml of ethanethiol was added slowly, with stirring and cooling until the mixture became homogeneous. After a further 20 min at room temperature, the contents of the three flasks were poured into a slurry of 150 g of lead carbonate in 200 ml of methanol. Filtration through a Celite pad, followed by evaporation of the solvent, afforded a light-yellow syrup that was crystallized from
methanol (with filtration of a small amount of lead salts) to give directly 42.5 g (82%) of pure product; m.p. 83—84° [lit.\(^{274}\) 83.5—84°].


d. **D-Lyxose diethyl dithioacetal.** As under b, 10 g of D-lyxose was converted into its diethyl dithioacetal; yield 15.3 g (86%); m.p. 102—104° [lit.\(^{277}\) 103—104°].

Preparation of acetylated diethyl dithioacetals.— By the method of Wolfrom, each of the diethyl dithioacetals described in the foregoing section was acetylated in acetic anhydride—pyridine to give crystalline products, in 80—90% yields, whose physical constants were essentially in agreement with those reported for the tetraacetates of \( \text{D-ribose} \), \( \text{D-arabinose} \), \( \text{D-xylose} \) and \( \text{D-lyxose} \).


diethyl dithioacetals, respectively.

Bromination of the tetra-O-acetyl-\( \text{D-} \)-pentose diethyl dithioacetals.— A solution of 10—20 mmol. of the appropriate tetra-O-acetyl-\( \text{D-} \)-pentose diethyl dithioacetal in 40—60 ml of anhydrous ether was cooled in an ice bath to 0—5°, and 1.0 equivalent of anhydrous bromine was added dropwise from a syringe to the stirred solution over a period of 15 min. After an additional 20 min at 0—5°, the ether was evaporated in vacuo, and the resultant syrup was evacuated at 40°/5 torr for 10 min. The syrupy residue 25a—d, if used within 1 h* was suitable for the

*The bromination product from tetra-O-acetyl-\( \text{D-} \)-xylose diethyl dithioacetal was found to be very unstable and was used within 15 min of preparation.
nucleoside condensation procedure described in the next section.

Condensation of 6-chloro-9-chloromercupurine (26) with the 2,3,4,5-tetra-O-acetyl-1-bromo-1-deoxy-1-S-ethyl-1-thio-aldehyde-2-pentose aldehydrols (25a-d).— A well-stirred suspension of 4.68 g (12.0 mmol.) of 6-chloro-9-chloromercupurine\(^{280}\) (26), 1.5 g of Celite and 0.5 g of cadmium carbonate in 100 ml of toluene was heated to boiling and ~20 ml of the solvent was distilled with the aid of a distillation—reflux head.\(^{281}\) After cooling the mixture to ~45°, a solution of the crude, brominated sugar 25a-d [prepared by brominating, according to the foregoing procedure, 5.09 g (12 mmol.) of the appropriate acetylated thioacetal 24a-d with 0.85 ml of bromine] in ~15 ml of dry toluene was added with stirring, and the mixture was again brought to reflux, and ~20 ml of solvent was distilled off. Heating under reflux was continued for 3.5—4.0 h at which time t.l.c. (9:1 benzene—methanol) indicated the formation of a single major zone [see Table


4 for $R_F$-values] that absorbed u.v. light and charred upon heating after treatment with sulfuric acid spray-reagent. A number of faster- and slower-migrating zones were invariably present.

The hot suspension was filtered through a Celite pad, and the filter was washed with warm chloroform. The organic extract was washed with 3 x 100 ml of a 30% aqueous solution of potassium iodide, followed by 100 ml of water. The dried (magnesium sulfate) extract was evaporated to dryness to give a yellow to brown syrup that by t.l.c. was generally shown to contain several components, together with a major zone, attributed to the protected nucleoside 27α-δ.

The crude syrup, after a period drying in vacuo at ~25°, was applied to a 4 x 60-cm column of silica gel, which was eluted successively with 200 ml of chloroform followed by 1:99 methanol—chloroform. Elution was continued, and the progress of the separation was followed by absorption of u.v. light at 254 nm, 20-ml fractions being taken. The fractions that eluted in a single, large band were combined, and the solvent was evaporated to give a light-yellow syrup, judged to be 95% pure when examined by t.l.c. or high-pressure l.c. [see Table 4 for $R_F$-values]. These products were suitable directly for conversion to the 6-mercaptopurine analogs
described in the following section.

Further purification (for n.m.r., mass spectrometry, and elemental analysis) was effected using 20 x 20 x 2-mm loose layers of silica gel (no. 7734, Merck) and eluting with 9:1 benzene—methanol. The 6-chloropurine derivatives 27a-d migrated as a single, broad zone (Rᶠ 0.25—0.4), which was scraped off and eluted with chloroform to give, upon evaporation of the solvent, a very viscous, light-yellow syrup. Elemental analyses for most samples were highly inaccurate because of the chloroform (verified by n.m.r.) that was retained in the samples after drying at 40°/0.1 torr. The products slowly decomposed at higher temperatures; attempted molecular distillation of the products under ultra-high vacuum failed.

Physical constants for compounds 27a-d are summarized in Table 4; n.m.r. data are provided in Table 5.

2,3,4,5-Tetra-O-acetyl-l-deoxy-l-S-ethyl-[purin-9-
yl-6(1H)-thione]-l-thio-aldehydo-D-ribose aldehydrol

(28a).—A solution of 1.94 g (3.75 mmol.) of 2,3,4,5-
tetra-O-acetyl-l-(chloropurin-9-yl)-l-deoxy-l-S-ethyl-l-
thio-aldehydo-D-ribose aldehydrol (27a), dissolved in 50 ml of hot abs. ethanol, was heated under reflux with 330 mg (1.15 molar excess) of thiourea for 3 h, at which time t.l.c. (3:1 ethyl acetate—chloroform) indicated disappearance of any starting material ($R_F$ 0.6) and the appearance of a zone at $R_F$ 0.4. The hot deep-yellow solution was decolorized with bone charcoal, filtered, and the product was allowed to crystallize; yield 0.96 g of white crystals; m.p. 203—205°, $[\alpha]_D^{+22}$ $+183^\circ$ (c 0.5, chloroform). The mother liquors were evaporated to dryness, and the remaining protected nucleoside was extracted from the residue 3 x 30 ml of hot ethyl acetate. Evaporation gave 0.81 g of a syrup that was shown by t.l.c. to contain some thiourea ($R_F$ 0.2, u.v. absorbing, non-charring); crystallization of the foregoing from 6 ml of abs. ethanol gave 0.57 g of a product identical to the first crop of crystals by m.p. and $[\alpha]_D$. The combined products were recrystallized from 12 ml of ethanol to give 1.41 g (72.6%) of analytically pure 28a; m.p. 205—206° (clear melt); $[\alpha]_D^{+184.5}$ (c 0.4, chloroform); o.r.d. [see Figure 2] $[M]_{500}^{-1120}$, $[M]_{400}^{+1770}$, $[M]_{328}^{+7240}$, $[M]_{300}^{+3300}$, $[M]_{260}^{+2100}$; $\lambda_{\text{EtOH}}^{\text{max}}$ 325.0 (log $\epsilon$ 4.38), 227.3 nm (3.98); $\lambda_{\text{KBr}}^{\text{max}}$ 3.31 (CH), 5.69 (C=0), 6.24, 8.24 (CO), 9.61 (CO), and 10.38 μm; for n.m.r. data, see Table 7; X-ray powder diffraction data: 9.76 s (2), 7.93 vs (1), 6.23 w, 5.43 m, 4.91 w, 4.46 m, 4.09 m, and 3.47 w.
Anal. Calc. for $\text{C}_{26}\text{H}_{26}\text{N}_{4}\text{O}_{8}\text{S}_{2}$: C, 46.68; H, 5.09; N, 10.88, S, 12.46. Found: C, 46.65; H, 5.02; N, 10.59; S, 12.56.

The dark, syrupy residues from the recrystallizations were not further examined.

Examination of the n.m.r. spectrum [see Table 7] revealed that compound 28a was a single epimer. The gross spectral features (especially the signals for H-2, H-8, H-1, SET and OAc) were those of an apparently homogeneous compound [see Discussion Section].

2,3,4,5-Tetra-O-acetyl-1-deoxy-1-S-ethyl-1-[purin-9-yl-6(1-H)-thione]-1-thio-aldehydo-D-arabinose aldehydrol (28b).—A solution of 2.0 g (3.88 mmol.) of 2,3,4,5-tetra-O-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-1-S-ethyl-1-thio-aldehydo-D-arabinose aldehydrol (27b) in 40 ml of abs. ethanol was heated under reflux with 350 mg (1.18 molar excess) of thiourea for 3.5 h, at which time t.l.c. (3:1 ethyl acetate—chloroform) indicated a new product having $R_F$ 0.35, with disappearance of starting material ($R_F$ 0.7). Cooling the solution gave directly 1.21 g (60.5%) of a white, crystalline product; m.p. 198° (dec.), with softening at 178°; $[\alpha]_{D}^{22} +128^\circ$ ($c$ 1.1, chloroform). Slow recrystallization from a minimum of ethanol gave an analytically pure 28b as long, clear needles; m.p. 206—208° (with softening at 179—180° and re-solidification
to melt at 206—208 °; determined in a bath preheated to 155 °, with a gradual rise in temperature of ~1 ° per min for the 180—208 ° range); \([\alpha]^{22}_{D} +131 ° (c 1, \text{chloroform});\)
m.o.r.d. [see Figure 2] \([M]_{500} +216 °, [M]_{400} +986 °, [M]_{320} +5130 °, [M]_{300} +4040 °, [M]_{250} +8240 °; \lambda^{\text{EtOH}}_{\text{max}} 324.9 \text{ (log} \epsilon 4.39), 227.0 \text{ nm} \text{ (3.99);} \lambda^{KBr}_{\text{max}} 3.31 \text{ (CH), 5.70 (C=O), 6.24, 8.25 (C-O), 9.6 (CO), and 10.4 \mu m; for n.m.r. data, see Table 7, X-ray powder diffraction data: 12.99 w, 10.13 w, 8.62 s (2), 7.61 vs (1), 6.75 s (3), 6.19 w, 5.72 m, 5.64 m, 5.17 vw, 4.96 s, 4.65 m, 4.34 w and 4.15 vw.\)

**Anal. Calc. for C_{20}H_{26}N_{4}O_{8}S_{2}:** C, 46.68; H, 5.09; N, 10.88; S, 12.46. Found: C, 47.00; H, 5.28; N, 11.04; S, 12.60.

The n.m.r. spectrum [see Table 7] indicated that 28b consisted of a single epimer, as evidenced by the sharpness of the signals for H-2, H-8, H-1', SET and OAc. The residue from the recrystallizations contained much tarry material and was not further examined.

2,3,4,5-Tetra-O-acetyl-1-deoxy-l-S-ethyl-l-[purin-9-y1-6(1-H)-thione]-1-thio-aldehyde-D-xylose aldehydrol (28c).— A solution of 5.18 g (10 mmol.) of 2,3,4,5-tetra-O-acetyl-1-(6-chloropurin-9-y1)-1-deoxy-1-S-ethyl-1-thio-aldehyde-D-xylose aldehydrol (27c) and 0.85 g (1.12 molar excess) of thiourea in 100 ml of abs. ethanol was heated under reflux for 3.0 h, at which time t.l.c. (3:1 ethyl
acetate—chloroform) indicated the disappearance of the starting material ($R_F$ 0.7) with formation of a new zone ($R_F$ 0.58). Crystals formed upon cooling; these were collected in two crops to give 2.31 g of an off-white, crystalline product. The residue, obtained upon evaporation of the ethanol, was extracted with $2 \times 10$ ml of hot ethyl acetate, and the solution was evaporated to dryness to give a syrup. Crystallization of the latter from 8 ml of ethanol afforded an additional 0.14 g of product. The combined products were dissolved in 30 ml of hot ethanol, decolorized and crystallized, to give 2.26 g (44%) of pure 28c; m.p. 177–179° (clear melt); $[\alpha]_{D}^{22}$ $-179^\circ$ (c 1.3, chloroform); o.r.d. [see Figure 2] $[M]_{400}$ $-414^\circ$, $[M]_{350}$ $[M]_{310}$ $-5960^\circ$, $[M]_{280}$ $-5100^\circ$; $\lambda_{\text{EtOH}}^{\text{max}}$ 325.0 (log ε 4.42), 226.8 nm (3.99); $\lambda_{\text{KBr}}^{\text{max}}$ 3.31 (CH), 5.69 (C=O), 6.25, 8.26 (CO), 9.62 (CO), and 10.4 μm; for n.m.r. data, see Table 7; X-ray powder diffraction data: 10.84 m, 9.35 vs (1), 7.84 m, 6.62 w, 6.36 w, 5.84 s (3), 5.02 w, 4.75 m, 4.31 m, 3.66 s (2) and 3.48 w.

Anal. Calc. for $C_{20}H_{26}N_{4}O_{8}S_{2}$: C, 46.68; H, 5.09; N, 10.88; S, 12.46. Found: C, 46.39; H, 5.26; N, 10.97; S, 12.51.

The n.m.r. spectrum [see Table 7] indicated a single epimer for 28c.
2,3,4,5-Tetra-O-acetyl-1-deoxy-1-S-ethyl-1-[purin-9-y1-6(1-H)-thione]-1-thio-aldehydo-D-lyxose aldehydrol
(28d). A solution of 4.02 g (7.8 mmol.) of 2,3,4,5-tetra-O-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-1-S-ethyl-1-thio-aldehydo-D-lyxose aldehydrol (27d) and 650 mg (1.1 molar excess) of thiourea in 110 ml of abs. ethanol was heated under reflux for 3.25 h, at which time t.l.c. (3:1 ethyl acetate—chloroform) indicated disappearance of 27d, with formation of a zone at Rf 0.40. The warm solution was decolorized with bone charcoal, and the crystals that formed upon cooling were filtered off; yield 2.09 g; m.p. 190—194°; [α]D23 +42° (c 1, chloroform). Recrystallization from 12 ml of ethanol gave 1.96 g (49%) of pure 28d in two crops dried at 100°/0.1 torr for 1 h; m.p. 194—197° (dec.); [α]D22 +47.2° (c 1, chloroform); o.r.d. [see Figure 2]; [M]400 0°, [M]330 +261°, [M]310 +101°, [M]260 -12°; λmax EtOH 325.1 (log ε 4.37); 227.1 nm (3.98); λmax KBr 3.30 (CH), 5.68 (C=O), 6.23, 8.26 (CO), 9.63 (CO) and 10.37 m; for n.m.r. data see Table 7; X-ray powder diffraction data: 9.82 s (2); 7.50 vs (1), 6.30 m; 5.71 w, 5.04 m, 4.86 w, 4.49 w, 4.18 w, 3.98 s (3), 3.77 s, 3.44 m, 3.11 m and 2.90 w.

Anal. Calc. for C20H26N4O8S2: C, 46.68; H, 5.09; N, 10.88; S, 12.46. Found: C, 46.39; H, 5.01; N, 10.59; S, 12.53.
The n.m.r. spectrum [see Table 7] for 28d revealed two distinct sets of resonances that were assignable to two epimers in an apparent ratio of 3:1, based on the signals for H-1'.

1-Deoxy-1-S-ethyl-1-[purin-9-yl-6(1-H)-thione]-1-thio-aldehyde-D-ribose aldehydrol (29a).— A solution of 300 mg (0.58 mmole) of 2,3,4,5-tetra-O-acetyl-1-deoxy-1-S-ethyl-1-[purin-9-yl-6(1-H)-thione]-1-thio-aldehyde-D-ribose aldehydrol (28a) in 15 ml of 1:1 methanol-tetrahydrofuran to which 0.3 ml of n-butylamine had been added, was heated under reflux in an atmosphere of nitrogen for 11 h, at which time t.l.c. (3:1 ethyl acetate—chloroform) indicated only a trace of starting material 28a (Rf 0.4). The solvents were removed in vacuo, and the glassy product was extracted with 3 x 5 ml of boiling chloroform, and the final extract was filtered to give 170 mg (49%) of a grey solid that by i.r. spectroscopy showed negligible absorption at 5.78 µm (acetate carbonyl). Paper chromatography showed a major spot at Rf 0.36; weak zone (~1%) (Rf 0.75) was observed and shown to be the precursor 28a. Two crystallizations from 95% ethanol gave 110 mg of analytically pure 29a; m.p. 178—180° (clear melt); [α]D +85.8° (c 0.9, pyridine); λmax 323.9 (log ε 4.33), 227.5 nm (3.70); λmax 324.9 (log ε 4.40), 226.0 nm (3.72); λmax 318.2 (log ε 4.30), 234.9 nm (3.95);
\[ \lambda_{\text{max}} \] for KBr: 2.90 (OH), 3.39 (CH), 6.23, 7.10, 8.44, 9.26, 9.61, 10.21 and 11.39 m; for n.m.r. data, see Table 8; X-ray powder diffraction data: 13.96 m, 9.93 m, 7.51 m, 6.89 w, 5.95 vw, 5.55 m, 5.02 vs (1), 4.53 w, 4.31 w, 4.02 m, 3.59 s (2) and 3.39 m.

**Anal. Calc.** for C\(_{12}\)H\(_{16}\)N\(_4\)O\(_4\)S\(_2\): C, 41.62; H, 5.24; N, 16.18; S, 18.51. **Found:** C, 41.12; H, 5.34; N, 15.97; S, 18.84.

1-Deoxy-l-S-ethyl-l-[purin-9-yl-6(1-H)-thione]-1-thio-aldehydo-D-arabinose aldehydeol (29b).— A solution of 550 mg (1.07 mmol.) of 2,3,4,5-tetra-O-acetyl-1-deoxy-l-S-ethyl-l-[purin-9-yl-6(1-H)-thione]-1-thio-aldehydo-D-arabinose aldehydrol (28b) in 25 ml of 1:1 methanol—tetrahydrofuran, containing 1.0 ml of n-butylamine, was heated for 8 h under reflux, at which time t.l.c. (3:1 ethyl acetate—chloroform) showed a minor amount of starting material 28b (\(R_F\) 0.35). The solution was evaporated to dryness, and the solid residue was dried overnight at 25\(^\circ\)/0.5 torr. The residue was dissolved in 30 ml of boiling ethanol, decolorized, evaporated to ~18 ml volume, and slowly crystallized to give 254 mg (69%) of 29b that showed only a trace of acetate precursor 28b as evidenced by i.r. spectroscopy and paper chromatography (\(R_F\) 0.29). An analytical sample was prepared by a two-fold recrystallization from a minimal amount of hot
ethanol to give 130 mg of a white, crystalline solid, m.p. 194–195.5° (dec.); \([\alpha]_D^{+59.7}\) (c 1.6, pyridine); 
\[\lambda_{\text{max}}^\text{H}_2\text{O} 323.9 \text{ (log } \epsilon 4.32), 227.4 \text{ nm (3.71)}; \lambda_{\text{max}}^{\text{PH}1} 324.7 \text{ (log } \epsilon 4.31), 226.1 \text{ nm (3.70)}; \lambda_{\text{max}}^{\text{PH}12} 318.0 \text{ (log } \epsilon 4.30), 234.9 \text{ nm (3.98)}; \lambda_{\text{max}}^{\text{KBr}} 2.91 \text{ (OH), 3.38 (CH), 7.11, 7.49, 8.40, 9.19, 9.67, 10.41, 11.34 and 12.62 } \mu\text{m}; \text{ for n.m.r. data see Table 8; X-ray powder diffraction data: 10.24 vs (1), 5.49 m, 4.80 s (2), 4.70 m, 3.68 m and 3.36 w.}

Anal. Calc. for C_{12}H_{18}N_{4}O_{4}S_{2}: C, 41.62; H, 5.24; N, 16.18; S, 18.51. Found: C, 41.79; H, 5.38; N, 15.99; S, 18.30.

Attempted deacetylation of 28b with ammonia-saturated methanol at 0° resulted in an apparent decomposition of the compound.

1-Deoxy-1-S-ethyl-1-[purin-9-yl-6(1-H)-thione]-1-thio-aldehydo-D-xylose aldehydrol (29c).—A solution of 400 mg (0.78 mmole) of 2,3,4,5-tetra-O-acetyl-1-deoxy-1-S-ethyl-1-[purin-9-yl-6(1-H)-thione]-1-thio-aldehydo-D-xylose aldehydrol (28c) in 40 ml of 1:1 methanol—tetrahydrofuran, to which 1 ml of n-butylamine had been added, was heated under reflux in a nitrogen atmosphere for 4 h; at which time t.l.c. (3:1 ethyl acetate—chloroform) indicated that almost all the starting material (R_f 0.6) had been converted into the non-migrating deacetylated product. The solvent was removed
in vacuo, and the solid residue was dissolved in ~10 ml of boiling 95% ethanol with aid of a few drops of water. Cooling slowly to room temperature, and finally to 5° for 12 h, gave a gelatinous precipitate that was filtered with suction (fritted-glass funnel) to give a solid. Extraction of the solids with 3 x 5 ml of hot ethyl acetate gave, upon filtration, a brittle, light tan product that showed minimal carbonyl absorption (5.69 μm) in its infrared spectrum. Paper chromatography indicated a major zone (R_p 0.38), and only a faint spot (R_p 0.82) for the acetate 28c; yield, 207 mg (77%). An analytically pure sample was prepared by dissolving the product in a minimum of hot 95% ethanol and slowly cooling to room temperature to produce a gelatinous precipitate. Further cooling at 5° gave white crystals upon trituration; m.p. 167—168° (clear melt); [α]_D\text{22} -84.5° (c 1; water); \(\lambda_{\text{max}}^\text{H_2O} 323.9\) (log ε 4.32); 227.6 nm (3.71); \(\lambda_{\text{max}}^\text{pH1} 324.8\) (log ε 4.31); 226.0 nm (3.71); \(\lambda_{\text{max}}^\text{pH2} 318.0\) (log ε 4.29), 234.6 nm (3.91); \(\lambda_{\text{max}}^\text{KBr} 2.90\) (OH), 3.39 (CH), 6.24, 7.10, 8.43, 9.26, 9.61, 10.20 and 11.40 μm; for n.m.r. data see Table 8; X-ray powder diffraction data: 10.46 m, 9.02 m, 7.81 s (2), 6.15 vw, 5.61 m, 5.18 s (3), 4.38 w, 3.91 vs (1), 3.62 m and 3.39 w.

**Anal.** Calc. for C_{12}H_{18}N_{4}O_{4}S_{2}: C, 41.62; H, 5.24; N, 16.18; S, 18.51. Found: C, 41.32; H, 5.35; N, 16.27; S, 18.29.
1-Deoxy-l-S-ethyl-l-[purin-9-yl-6(1H)-thione]-l-thio-aldehydo-D-lyxose aldehydrol 29d.— A solution of 300 mg (0.58 mmole) of 2,3,4,5-tetra-O-acetyl-1-deoxy-l-S-ethyl-l-[purin-9-yl-6(1H)-thione]-l-thio-aldehydo-D-lyxose aldehydrol (28d) in 40 ml of 1:1 methanol—tetrahydrofuran containing 1 ml of n-butylamine was heated under reflux in an atmosphere of nitrogen for 6.5 h, at which time t.l.c. analysis (3:1 ethyl acetate—chloroform) indicated ~90% deacetylation of the starting material (RF 0.4). The solvent was removed in vacuo, and 2 x 25 ml of ethanol was evaporated from the brown residue. The residue was extracted with 2 x 20 ml of hot chloroform, resulting in the formation of a gum. Crystallization and decolorization was effected from 9:1 2-propanol—methanol to give 176 mg (88%) of an off-white product that showed minimal carbonyl absorption in the i.r. spectrum (5.68 μm) and was judged to be >95% pure by paper chromatography (RF 0.42). An analytical sample was prepared by dissolving the foregoing product in 6 ml of boiling methanol with the aid of 11 drops of water. Slow cooling gave white crystals that were collected after cooling to ~25°; m.p. 192—194° (dec.), [α]$_{D}^{24}$ +53.4° (c 0.9, pyridine); λ$_{H_2O}^{max}$ 324.0 (log ε 4.35), 227.8 nm (3.72); λ$_{PH1}^{max}$ 324.9 (log ε 4.31), 226.0 nm (3.71); λ$_{PH12}^{max}$ 317.9 (log ε 4.30), 234.7 nm (3.93); λ$_{KBr}^{max}$ 2.89 (OH), 3.31 (CH), 5.69 (C=O), 6.23, 6.38, 5.52,
7.26, 7.58, 8.45 (CO), 8.25 (CO), 9.65, 10.44 and 11.50 \( \mu \text{m} \);
for n.m.r. data see Table 8; X-ray powder diffraction
data: 8.42 s (2), 7.33 w, 4.95 w, 5.15 w, 4.72 m, 4.28 m
and 3.66 vs (1).

Anal. Calc. for \( \text{C}_{12}\text{H}_{18}\text{N}_{4}\text{O}_{4}\text{S}_{2} \):
C, 41.62; H, 5.24; N, 16.18; S, 18.51. Found: C, 42.04; H, 5.56; N, 16.25;
S, 18.23.
**TABLE 1**

N.M.R. Spectral Data for Compounds 1—4, 6—9, and 11

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Chemical shifts&lt;sup&gt;a&lt;/sup&gt; (r)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td>H-1'</td>
<td>H-2'</td>
</tr>
<tr>
<td>2',3'-O-Isopropylideneadenosine (1)</td>
<td>(CD&lt;sub&gt;3&lt;/sub&gt;)SO</td>
<td>3.78 s (J&lt;sub&gt;1',2' 3&lt;/sub&gt;)</td>
<td>4.59 dd (J&lt;sub&gt;2',3' 6&lt;/sub&gt;)</td>
</tr>
<tr>
<td>2',3'-O-Isopropylideneadenosine-5'-d (6)</td>
<td>(CD&lt;sub&gt;3&lt;/sub&gt;)SO</td>
<td>3.78 d (J&lt;sub&gt;1',2' 3&lt;/sub&gt;)</td>
<td>4.59 dd (J&lt;sub&gt;2',3' 6&lt;/sub&gt;)</td>
</tr>
<tr>
<td>2',3'-O-Benzylideneuridine&lt;sup&gt;a&lt;/sup&gt; (7)</td>
<td>(CD&lt;sub&gt;3&lt;/sub&gt;)SO</td>
<td>4.01 m (width ~1 Hz)</td>
<td>4.85--5.20 m&lt;sup&gt;—&lt;/sup&gt;</td>
</tr>
<tr>
<td>2',3'-O-Benzylideneuridine-5'-d&lt;sup&gt;α&lt;/sup&gt; (11)</td>
<td>(CD&lt;sub&gt;3&lt;/sub&gt;)SO</td>
<td>4.01 m (width ~1 Hz)</td>
<td>4.85--5.20 m&lt;sup&gt;—&lt;/sup&gt;</td>
</tr>
<tr>
<td>N&lt;sup&gt;α&lt;/sup&gt;-Formyl-2',3'-O-isopropylidene-5'-O-p-tolylsulfonyl adenosine (2)</td>
<td>(CD&lt;sub&gt;3&lt;/sub&gt;)SO</td>
<td>3.69 d (J&lt;sub&gt;1',2' 3&lt;/sub&gt;)</td>
<td>4.60 dd (J&lt;sub&gt;2',3' 6&lt;/sub&gt;)</td>
</tr>
<tr>
<td>Compound</td>
<td>CDCl₃</td>
<td>(J₁,₂ 2.5)</td>
<td>(J₂,₃ 6.0)</td>
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</tr>
<tr>
<td>5'-Azido-5'-deoxy-N°-formyl-2',3'-O-isopropylideneadenosine (3)³</td>
<td>CDCl₃</td>
<td>3.84d</td>
<td>4.51dd</td>
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<tr>
<td>5'-Azido-5'-deoxy-2',3'-O-isopropylideneadenosine (3)³</td>
<td>CDCl₃</td>
<td>3.87d</td>
<td>4.47dd</td>
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<td>2',3'-O-Benzylidene-5'-O-p-tolyl-sulfonyluridine (8)⁶</td>
<td>(CD₂)₂SO</td>
<td>4.18d</td>
<td>—4.8-5.2m—</td>
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<tr>
<td>5'-Azido-2',3'-O-benzylidene-5'-deoxyuridine² (9)</td>
<td>(CD₂)₂CO</td>
<td>4.68d</td>
<td>—5.25-5.80m—</td>
</tr>
</tbody>
</table>

*Measured at 60 MHz, unless otherwise noted. Peak multiplicities: d, doublet; dd, doublet of doublets; m, multiplet; q, quartet; s, singlet; ss, sextet. First-order couplings are given in Hz. *A small proportion of D₂O was present in the (CD₂)₂SO and (CD₂)₂CO; spectra in CDCl₃ were measured before and after addition of D₂O. *Apparent doublet; satellite peaks of anticipated ABX system not observed. *Integrated intensity 1 proton. *A 4:6 mixture of diastereoisomers differing in configuration at the benzyl carbon atom, leading to doubling of the H-6 and PhCH signals [compare N. Baggett, A. B. Foster, J. M. Webber, D. Lipkin, and B. E. Phillips, Chem. Ind. (London), (1965) 136]. *Observed in dry solvent; disappears on deuteration. *Collapses to singlet when D₂O is added to the dry solvent. *As², but in 7:3 proportion. *Measured at 100 MHz.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Mass-spectral peaks (relative intensities and probable assignments given in parentheses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2',3'-O-Isopropylideneadenosine (I)</td>
<td>307 (0.9) M*, 292 (5) (M - CH₂)<em>, 277 (4) (M - H₂CO)</em>, 262 (2) (M - 45)<em>, 249 (3) (M - CH₂COCH₂)</em>, 232 (1) (M - CH₃ - CH₂COCH₂)<em>, 220 (1), 219 (6), 218 (29) (C₆H₅N₄O₂)</em>, 204 (6), 202 (4), 190 (3), 178 (2) (base - CH₃CH₂OH), 173 (2) (sugar moiety)<em>, 165 (4), 164 (34) (base - CH≡OH), 136 (27) (base, 2H)</em>, 133 (100) (base, H)<em>, 134 (5) (base)</em>, 129 (2), 118 (4), 114 (3), 113 (3), 108 (15), 85 (5), 59 (30) (CH₃-CH(OH)CH₃)</td>
</tr>
<tr>
<td>2',3'-O-Isopropylideneadenosine-5'-d (6)</td>
<td>308 (0.8) M*, 293 (4) (M - CH₂)<em>, 277 (4) (M - HDCO)</em>, 262 (2) (M - 46)<em>, 250 (3) (M - CH₂COCH₂)</em>, 233 (1) (M - 15 - CH₂COH)<em>, 219 (8), 218 (40) (C₆H₅N₄O₂)</em>, 204 (7), 202 (4), 178 (2) (base - CH₃CH₂OH), 174 (2) (sugar moiety)<em>, 164 (25) (base - CH≡OH), 136 (30) (base, 2H)</em>, 135 (100) (base, H)<em>, 134 (4) (base)</em>, 129 (1), 119 (3), 116 (3), 115 (1.5), 108 (17), 85 (6), 59 (29) [CH₃-CH(OH)CH₃]</td>
</tr>
<tr>
<td>2',3'-O-Benzylideneuridine (7)</td>
<td>332 (3) M*, 331 (2) (M - 1)<em>, 301 (1) (M - 1 - H₂CO)</em>, 255 (1) (M - C₆H₅)<em>, 221 (9) (sugar moiety)</em>, 220 (6), 219 (3), 193 (3), 192 (2), 180 (3), 179 (4), 175 (8), 167 (4), 165 (10), 141 (3) (base - CH≡OH), 137 (9), 114 (23) (C₆H₅N₄O₂H)<em>, 113 (28) (C₆H₅N₄O₂)</em>, 112 (26) (C₆H₅N₄O₂)<em>, 107 (27), 106 (29) (C₆H₅CHO)</em>, 105 (100) (C₆H₅CO)<em>, 99 (15), 98 (12) (C₆H₅NO)</em>, 91 (18), 79 (23), 77 (31) (C₆H₅)<em>, 69 (90) (C₆H₅NO)</em>, 68 (47), 57 (24) (C₆H₅O)*, 51 (19)</td>
</tr>
<tr>
<td>2',3'-O-Benzylideneuridine-5'-d (13)</td>
<td>333 (3) M*, 332 (2) (M - 1)<em>, 301 (1) (M - 1 - HDCO)</em>, 256 (1) (M - C₆H₅)<em>, 222 (9) (sugar moiety)</em>, 221 (7), 220 (4), 206 (3), 193 (4), 193 (2), 180 (2), 178 (3), 176 (8), 175 (2), 167 (3), 143 (8), 141 (4) (base - CH≡OH), 137 (8), 115 (16) (C₆H₅N₄O₂D)<em>, 114 (4) (C₆H₅N₂O₂D)</em>, 113 (30) (C₆H₅N₂O₂)<em>, 112 (29) (C₆H₅N₂O₂)</em>, 106 (7) (C₆H₅CHO)<em>, 105 (100) (C₆H₅CO)</em>, 91 (11) (C₆H₅)<em>, 79 (14), 77 (68) (C₆H₅)</em>, 69 (64) (C₆H₅NO)<em>, 68 (10), 57 (17) (C₆H₅O)</em>, 51 (24)</td>
</tr>
<tr>
<td>Compound Descriptions</td>
<td>Masses and Peak Assignments</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td><em><em>5'-Azido-5'-deoxy-N</em>-formyl-2',3'-O-isopropylideneadenosine (3)</em>*</td>
<td>560 (0.5) M⁺, 345 (2.5) (M - CH₃)⁺, 333 (18) (M - CH₂CHO)⁺, 304 (9) (M - CH₂N₂)⁺, 302 (3) (M - CH₂COCH₂)⁺, 274 (0.9), 246 (54), 232 (1), 218 (40) (C₆H₆N₂O₃)⁺, 204 (54), 178 (15) (base-CH₃CH⁺OH), 164 (100) (N*-formyl-base, H)⁺, 136 (96) (base, 2H)⁺, 135 (98) (base, H)⁺, 112 (33), 108 (39), 70 (62), 43 (95) (CH₂CO)⁺</td>
</tr>
<tr>
<td><strong>5'-Azido-5'-deoxy-2',3'-O-isopropylideneadenosine (4)</strong></td>
<td>332 (0.4) M⁺, 317 (3) (M - CH₃)⁺, 304 (9) (M - N₂)⁺, 288 (3), 277 (8), 274 (1) (M - CH₂COCH₂), 262 (10), 246 (6), 128 (97) (C₆H₆N₂O₃)⁺, 202 (32), 200 (11), 190 (9), 176 (22), 164 (23) (base-CH₂⁺OH), 148 (8), 136 (100) (base, 2H)⁺, 135 (82) (base, H)⁺, 118 (27), 85 (26), 70 (16), 59 (24), 43 (33) (CH₂CO)⁺</td>
</tr>
<tr>
<td><strong>2',3'-O-Benzylidene-5'-O-p-tolylsulfon furylidine (8)</strong></td>
<td>486 (1) M⁺, 485 (0.3) (M - 1)⁺, 409 (0.5) (M - C₆H₅)⁺, 396 (0.4), 375 (10) (C₆H₅O⁺), 350 (2), 314 (7), 313 (11), 301 (0.3) (C₆H₅O₂⁺), 281 (0.3), 269 (0.6), 244 (2), 241 (1), 239 (5), 209 (2), 195 (3), 193 (8), 172 (54) (C₆H₅O₃)⁺, 157 (6) (base-CH₂CH⁺OH), 148 (8), 136 (100) (base, 2H)⁺, 135 (82) (base, H)⁺, 118 (27), 85 (26), 70 (16), 59 (24), 43 (33) (CH₂CO)⁺</td>
</tr>
<tr>
<td><strong>5'-Azido-2',3'-O-benzytidene-5'-deoxyuridine (9)</strong></td>
<td>357 (&lt;1) M⁺, 356 (0.5) (M - 1)⁺, 329 (0.9) (M - N₂)⁺, 279 (0.4), 235 (0.2), 218 (0.4), 140 (0.6), 122 (1), 112 (5) (base, H)⁺, 106 (96) (C₆H₅CHO)⁺, 105 (19) (C₆H₅CO)⁺, 96 (5), 78 (13), 77 (100) (C₆H₅)⁺</td>
</tr>
</tbody>
</table>
### TABLE 3

Biological Testing Data for 9-[[4-\(\_\)-Cyclopropyl-\(\_\)(and\(\_\))]-D-ribo-
tetrofuranosyl] adenine 21

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molar Concentration for 50% Inhibition After Growth of S. faecalis E. coli K12 L-1210&lt;sup&gt;b&lt;/sup&gt;</th>
<th>T/C&lt;sup&gt;a&lt;/sup&gt; (dose)</th>
<th>Adenosine Deaminase</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>21 stim.&lt;sup&gt;c&lt;/sup&gt; 7 x 10&lt;sup&gt;-6&lt;/sup&gt; 4 x 10&lt;sup&gt;-5&lt;/sup&gt; 98(100 mg/kilo) not a substrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-D-xylo analog&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10&lt;sup&gt;-3&lt;/sup&gt; 8 x 10&lt;sup&gt;-4&lt;/sup&gt; 3 x 10&lt;sup&gt;-5&lt;/sup&gt; 98(100 mg/kilo) not a substrate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Mouse LE screen, Drug Research and Development Branch, NCI, NIH.
b. Cell culture.
c. See ref. 226.
d. See ref. 222.
## TABLE 4

**PHYSICAL CONSTANTS FOR 2,3,4,5-TETRA-O-ACETYL-1-(6-CHLOROPURIN-9-YL)-
1-DEOXY-1-3-ETHYL-1-THIO-ALDEHYDO-D-PENTOSE ALDEHYDROLS, \( \text{II}_a-\text{g} \)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>Epimer Ratio</th>
<th>([\alpha]_D^{22} )</th>
<th>(R, d)</th>
<th>Elemental Anal., ( \text{EtOH max} )</th>
<th>( \lambda_{\text{phill max}} )</th>
<th>( \lambda_{\text{phill2}} )</th>
<th>Mass Spectroscopic Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3,4,5-Tetra-Q-acetyl 92%</td>
<td>5.2:1</td>
<td>-5.34°</td>
<td>0.34</td>
<td>N, 10.28</td>
<td>263.8</td>
<td>258.2</td>
<td>254.0</td>
<td>517(1), 396(4), (log ( \epsilon )) (log ( \epsilon )) (log ( \epsilon )) ( \text{II}_a )</td>
</tr>
<tr>
<td>1-(6-chloropurin-9-yl)</td>
<td></td>
<td>(q 0.7)</td>
<td></td>
<td></td>
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<tr>
<td>1-deoxy-1-3-ethyl-1-thio-aldehydo-D-ribose aldehydrol ( \text{II}_a )</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,3,4,5-Tetra-Q-acetyl 92%</td>
<td>1°</td>
<td>+81.2°</td>
<td>0.35</td>
<td>C, 46.23</td>
<td>263.7</td>
<td>258.0</td>
<td>254.0</td>
<td>517(1), 336(29), (log ( \epsilon )) (log ( \epsilon )) (log ( \epsilon )) ( \text{II}_b )</td>
</tr>
<tr>
<td>1-(6-chloropurin-9-yl)</td>
<td></td>
<td>(q 2.0)</td>
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<tr>
<td>1-deoxy-1-3-ethyl-1-thio-aldehydo-D-arabinose aldehydrol ( \text{II}_b )</td>
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<td></td>
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<tr>
<td>2,3,4,5-Tetra-Q-acetyl 92%</td>
<td>4.8:1</td>
<td>-57.4°</td>
<td>0.45</td>
<td>C, 46.22</td>
<td>263.8</td>
<td>258.3</td>
<td>264.1</td>
<td>517(1), 336(21), (log ( \epsilon )) (log ( \epsilon )) (log ( \epsilon )) ( \text{II}_c )</td>
</tr>
<tr>
<td>1-(6-chloropurin-9-yl)</td>
<td></td>
<td>(q 0.8)</td>
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<td></td>
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<tr>
<td>1-deoxy-1-3-ethyl-1-thio-aldehydo-D-xylene aldehydrol ( \text{II}_c )</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>2,3,4,5-Tetra-Q-acetyl 98%</td>
<td>2.5:1</td>
<td>+38.9°</td>
<td>0.10</td>
<td>1</td>
<td>263.6</td>
<td>258.2</td>
<td>264.0</td>
<td>517(1), 336(26), (log ( \epsilon )) (log ( \epsilon )) (log ( \epsilon )) ( \text{II}_d )</td>
</tr>
<tr>
<td>1-(6-chloropurin-9-yl)</td>
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<td>(q 1.2)</td>
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<tr>
<td>1-deoxy-1-3-ethyl-1-thio-aldehydo-D-lyxose aldehydrol ( \text{II}_d )</td>
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</tbody>
</table>

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a. Products judged >95% pure by t.l.c.; dried 10 h in vacuo at 40°. b. As revealed by n.m.r.; for full details, see Table 5. c. Chloroform solvent. d. 9:1 benzene-methanol; detection by short-wave-length u.v. absorption and sulfuric acid spray. e. Calculated for C\(_{22}\)H\(_{22}\)Cl\(_3\)N\(_2\)O\(_6\); C, 46.46%; H, 4.87%; Cl, 6.85%; N, 10.83%; S, 6.20%. f. pHi in 0.1 \( \text{HCl} \); pH12 0.01 \( \text{NaOH} \). g. Other m/z values were consistent with structure; relative intensities in parentheses. h. A single isomer was observed. i. Not determined.
<table>
<thead>
<tr>
<th>Compounds</th>
<th>Chemical Shifts (τ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1'</td>
<td>H-2'</td>
</tr>
<tr>
<td>2,3',4',5'-Tetra-O-acetyl-1-(6-chloropurin-9-yl)-1-deoxy-1-S-ethyl-1-thio-aldehydo-D-ribose aldehydrol 27a</td>
<td>3.88 d</td>
</tr>
<tr>
<td>epimer b</td>
<td>(J_2', 3' = 7.0)</td>
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<tr>
<td></td>
<td>J_4', 5', 3.9;</td>
</tr>
<tr>
<td>epimer b</td>
<td>3.58 d</td>
</tr>
<tr>
<td></td>
<td>(J_2', 4' = 4.1)</td>
</tr>
<tr>
<td></td>
<td>J_4', 5', 6.8;</td>
</tr>
<tr>
<td>Compound</td>
<td>δ (ppm)</td>
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<tr>
<td>--------------------------------</td>
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</tr>
<tr>
<td>2,3,4,5-Tetra-O-acetyl-</td>
<td>3.95 a</td>
</tr>
<tr>
<td>1-(6-chloropurin-9-yl)-</td>
<td></td>
</tr>
<tr>
<td>1-deoxy-1-O-ethyl-</td>
<td></td>
</tr>
<tr>
<td>1-deoxy-1-O-ethyl-</td>
<td></td>
</tr>
<tr>
<td>thio-aldehyde-D-</td>
<td></td>
</tr>
<tr>
<td>arabinose aldehyde</td>
<td></td>
</tr>
<tr>
<td>27b</td>
<td></td>
</tr>
<tr>
<td>2,3,4,5-Tetra-O-acetyl-</td>
<td></td>
</tr>
<tr>
<td>1-(6-chloropurin-9-yl)-</td>
<td></td>
</tr>
<tr>
<td>1-deoxy-1-O-ethyl-</td>
<td></td>
</tr>
<tr>
<td>1-deoxy-1-O-ethyl-</td>
<td></td>
</tr>
<tr>
<td>thio-aldehyde-D-xylose</td>
<td></td>
</tr>
<tr>
<td>aldehyde d 27c</td>
<td></td>
</tr>
<tr>
<td>epimer a b²</td>
<td>3.73 d</td>
</tr>
<tr>
<td>(J₁, J₂, J₃)</td>
<td>(J₂, J₃, J₄)</td>
</tr>
<tr>
<td>epimer b d²</td>
<td>3.73 d</td>
</tr>
<tr>
<td>(J₁, J₂, J₃)</td>
<td>(J₂, J₃, J₄)</td>
</tr>
</tbody>
</table>

271
2,3,4,5-Tetra-O-acetyl-
1-(6-chloropurin-9-yl)-
1-deoxy-1-ethyl-1-thio-
aldehydo-D-lyxose

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>epimer a&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.94 d</td>
<td>4.50 dd</td>
<td>4.32 dd</td>
<td>4.64 m</td>
<td>5.70, 6.06&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>(J&lt;sub&gt;2&lt;/sub&gt;,&lt;sub&gt;3&lt;/sub&gt;, 2.8)</td>
<td>(J&lt;sub&gt;2&lt;/sub&gt;,&lt;sub&gt;3&lt;/sub&gt;, 9.3)</td>
<td>(J&lt;sub&gt;3&lt;/sub&gt;,&lt;sub&gt;4&lt;/sub&gt;, 3.0)</td>
<td>(width, J&lt;sub&gt;5&lt;/sub&gt;,&lt;sub&gt;5&lt;/sub&gt;'&lt;sub&gt;a&lt;/sub&gt;, 11.7)</td>
<td>1.32 s</td>
<td>7.97, 8.86 t</td>
</tr>
<tr>
<td>epimer b&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.70 d</td>
<td>4.18 dd</td>
<td>5.14 dd</td>
<td>——</td>
<td>1.15 s</td>
</tr>
<tr>
<td>(J&lt;sub&gt;2&lt;/sub&gt;,&lt;sub&gt;3&lt;/sub&gt;, 3)</td>
<td>(J&lt;sub&gt;2&lt;/sub&gt;,&lt;sub&gt;3&lt;/sub&gt;, 9.2)</td>
<td>(J&lt;sub&gt;3&lt;/sub&gt;,&lt;sub&gt;4&lt;/sub&gt;, 3.0)</td>
<td>——</td>
<td>——</td>
<td>7.92, 8.87 t</td>
</tr>
</tbody>
</table>

<sup>a</sup> Measured at 100 MHz in (CD<sub>3</sub>)<sub>2</sub>CO with tetramethylsilane as an internal standard; couplings (Hz) and chemical shifts (τ) are apparent first-order values.  
<sup>b</sup> Major isomer in mixture.  
<sup>c</sup> AB portion of an ABX system.  
<sup>d</sup> Minor isomer in mixture.
<table>
<thead>
<tr>
<th>Compound</th>
<th>([\alpha]_D^a)</th>
<th>Configuration Indicated at C-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>28a</td>
<td>+184.5°</td>
<td>R</td>
</tr>
<tr>
<td>28b</td>
<td>+131.0°</td>
<td>R</td>
</tr>
<tr>
<td>28c</td>
<td>-178.5°</td>
<td>S</td>
</tr>
<tr>
<td>28d</td>
<td>+47.2°</td>
<td>R, S</td>
</tr>
</tbody>
</table>

a. Chloroform solvent, \(t = 22^\circ\).
TABLE 7

N.M.R. SPECTRAL DATA* FOR 2,3,4,5- TETRA-0-ACETYL-1-DEOXY-1-5-ETHYL-1-[PURIN-9-YL-6(1-H)-THIONE]-1-THIO-ALDEHYDO-D-PENTOSE ALDEHYDROS, 28a–d

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Shifts (γ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H-1'</td>
</tr>
<tr>
<td>2,3,4,5-Tetra-</td>
<td>3.92 d</td>
</tr>
<tr>
<td>0-acetyl-1-</td>
<td>(J2',2, 4.0)</td>
</tr>
<tr>
<td>deoxy-1-5-</td>
<td>(J3',5' 6.0)</td>
</tr>
<tr>
<td>ethyl-1-</td>
<td>[purin-9-y1-6(1-H)-thione]-1-thio-</td>
</tr>
<tr>
<td>0-acetyl-1-</td>
<td>(J2',2, 9.0)</td>
</tr>
<tr>
<td>deoxy-1-5-</td>
<td>(J3',5' 7.5)</td>
</tr>
<tr>
<td>ethyl-1-[purin-9-y1-6(1-H)-thione]-1-thio-</td>
<td>aldehydo-D-</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical Shifts</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>2,3,4,5-Tetra-O-acetyl-</td>
<td>4.32 d</td>
</tr>
<tr>
<td>deoxy-1-S-ethyl-1-[purin-9-y1-6(1-H)-thione]-1-thio-aldehydo-D-xylose</td>
<td></td>
</tr>
<tr>
<td>aldehydrol</td>
<td>20C</td>
</tr>
</tbody>
</table>
2,3,4,5-Tetra-
9-acetyl-1-
deoxy-1-\(\text{S}\)-
ethyl-1-[purin-9-yl-6(1H)-
thione]-1-thio-
aldo-sugars

<table>
<thead>
<tr>
<th>Epimer</th>
<th>4.18 d</th>
<th>4.56 m</th>
<th>4.75 s</th>
<th>5.80, 6.12&lt;sup&gt;b&lt;/sup&gt;</th>
<th>1.58 s, 7.82, 6.69 s</th>
<th>7.51 q,&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>((J_2, J_3), 2.8)</td>
<td>(width) ((J_4, J_5), 4.8)</td>
<td>1.73 s, 7.98, 8.95 t</td>
<td>8.04</td>
<td>8.06 s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.82 d&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4.04 m</td>
<td>4.28 s</td>
<td>5.40, 5.81&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.35 s, 7.78, 2.27 s</td>
<td>7.52 q,&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>((J_2, J_3), 2.1)</td>
<td>(width 18, (J_4, J_5), -5)</td>
<td>1.38 s, 7.92, 8.92 t</td>
<td>8.02</td>
<td>8.04 s</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epimer</th>
<th>4.00 d</th>
<th>4.38 dd</th>
<th>5.22 dd</th>
<th>4.75 m</th>
<th>1.56 s</th>
<th>7.83, 6.69 s</th>
<th>7.51 q,&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>((J_1, J_2), 2.1)</td>
<td>((J_2, J_3), 8.7)</td>
<td>((J_3, J_4), -5)</td>
<td>(width 12)</td>
<td>1.73 s, 7.91, 8.95 t</td>
<td>7.99 s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.60 d&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4.75 m</td>
<td>1.14 s</td>
<td>7.82, 2.27 s</td>
<td>7.53 q,&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>((J_1, J_2), 3.1)</td>
<td>(width 12)</td>
<td>1.20 s, 7.94, 8.92 t</td>
<td>8.16</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Measured at 100 MHz in DMSO-\(d_6\), with tetramethylsilane as an internal standard; all values for chemical shifts (\(\delta\)) and coupling constants (\(J\)) are apparent first-order; \(J\)-values and line widths are given in Hz. <sup>b</sup> AB-portion of an ABX pattern.

<sup>c</sup> Exchanges upon addition of deuterium oxide. <sup>d</sup> Major epimer. <sup>e</sup> Measured in C\(_2\)D\(_5\)N solvent. <sup>f</sup> Minor epimer.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Shifts ((\tau))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H-1'</td>
</tr>
<tr>
<td>d-ribo</td>
<td>3.23 d</td>
</tr>
<tr>
<td>(29a)</td>
<td>(J1,2, 2.1)</td>
</tr>
<tr>
<td>d-xylo</td>
<td>3.44 d</td>
</tr>
<tr>
<td>(29b)</td>
<td>(J1,2, 6.4)</td>
</tr>
<tr>
<td>d-arabino</td>
<td>3.55 d</td>
</tr>
<tr>
<td>(29c)</td>
<td>(J1,2, 4.0)</td>
</tr>
<tr>
<td>d-lyxo</td>
<td>3.19 d</td>
</tr>
<tr>
<td>(29d)</td>
<td>(J1,2, 2.0)</td>
</tr>
</tbody>
</table>

* Measured at 100 MHz, using CDCl3 as solvent and tetramethylsilane as an internal standard; the samples were perdeuterated by multiple exchanges in deuterium oxide, followed by lyophilization to dryness.
### TABLE 9

**IN VITRO BIOLOGICAL ASSAYS FOR COMPOUNDS**

22, 23, 28a–d and 29a–d

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molar Concentration for 50% Inhibition after Growth of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. Coli K12</td>
</tr>
<tr>
<td>22c</td>
<td>4 x 10^-5</td>
</tr>
<tr>
<td>22d</td>
<td>10^-3</td>
</tr>
<tr>
<td>23</td>
<td></td>
</tr>
<tr>
<td>28a</td>
<td>8 x 10^-5</td>
</tr>
<tr>
<td>28b</td>
<td>8 x 10^-4</td>
</tr>
<tr>
<td>28c</td>
<td>2 x 10^-4</td>
</tr>
<tr>
<td>28d</td>
<td>1 x 10^-4</td>
</tr>
</tbody>
</table>

- a. Values checked in duplicate, except for 28a–d, which are results from a single assay.
- b. Cell culture.
- c. T/C = 147, L-1210 leukemia in mice; dose, 400 mg per kilo.
- d. T/C = 98–100, L-1210 leukemia in mice; dose 100–400 mg per kilo.