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TITLE OF THESIS/*TITRE DE LA THÈSE* SYNTHESIS AND REACTIONS OF 2',3'- ANHYDRO- NUCLEOSIDES (NUCLEOSIDE RIBO AND LYXO EPOXIDES)

UNIVERSITY/*UNIVERSITÉ* University of Alberta

DEGREE FOR WHICH THESIS WAS PRESENTED/*GRADE POUR LEQUEL CETTE THÈSE FUT PRÉSENTÉE* PH. D

YEAR THIS DEGREE CONFERRED/*ANNÉE D'OBTENTION DE CE GRADE* 1975

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THE UNIVERSITY OF ALBERTA

# SYNTHESIS AND REACTIONS OF 2',3'-ANHYDRO-NUCLEOSIDES (NUCLEOSIDE RIBO AND LYXO EPOXIDES)

by

© YVES FOURON

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1975

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled Synthesis and Reactions of 2',3'-Anhydronucleosides (Nucleoside Ribo and Lyxo Epoxides)

submitted by Yves Fouron

in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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Date April 28th 1975

## A B S T R A C T

Reaction of 2',3'-O-methoxyethylideneadenosine with pivalyl chloride in pyridine solution followed by treatment of the crude reaction mixture with methanolic sodium methoxide was found to give good yields of 9-(2,3-anhydro-β-D-ribofuranosyl)adenine (Adenosine ribo-epoxide).

Nucleophilic opening of the epoxide ring of this compound was found to proceed predominantly by attack at the C-3' position by all the nucleophiles studied. This type of reaction gave direct access to a number of important nucleosides from the naturally occurring ribonucleoside. Among these are: 9-β-D-xylofuranosyl-adenine, 3'-deoxyadenosine (the antibiotic cordycepin), and 9-β-D-arabinofuranosyladenine (Ara A), in this case via 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine. This useful lyxo-epoxide was opened with the same nucleophiles as the ribo-epoxide and predominant attack at C-3' was again observed.

Reaction of tubercidin,4-amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine, with α-acetoxyisobutyryl chloride in the presence of sodium iodide gave quantitative yields of an iodo intermediate which was transformed into 4-amino-7-(2,3-anhydro-β-D-ribofuranosyl)-pyrrolo[2,3-d]pyrimidine (tubercidin ribo-epoxide) by mild treatment with base. This compound was a convenient

starting material for the first synthesis of two tubercidin epimers of biological interest, 4-amino-7-(β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine (xylotubercidin) and 4-amino-7-(β-D-arabinofuranosyl)-pyrrolo[2,3-d]pyrimidine (arabinotubercidin), again in the latter case via the corresponding lyxo-epoxide, 4-amino-7-(2,3-anhydro-β-D-lyxofuranosyl)pyrrolo-[2,3-d]pyrimidine.

The usefulness of the Dekker column [Dowex 1-X2 ($OH^-$)] has again been demonstrated by the easy separation of a number of diastereoisomeric compounds in both the adenosine and tubercidin series. Confirmation of structures was readily deduced through the combined use of mass spectrometry and nmr spectroscopy.

## A C K N O W L E D G M E N T S

It is my pleasure at this point to thank those who in a direct or indirect way have helped me through the course of this work:

- Professor Robins for his continuing support and guidance.
- Professor Metzger for setting off the chain of events that resulted in this thesis and for his encouragement.
- Doctor MacCoss for numerous and challenging discussions as well as much helpful advice.
- My parents and parents-in-law for their unfailing support.
- Miss Walia Halim for excellent technical assistance.
- My friends in the laboratory for making my stay with them a pleasant and enriching experience.
- Finally last but not least my wife and children for the happiness which they have given me.

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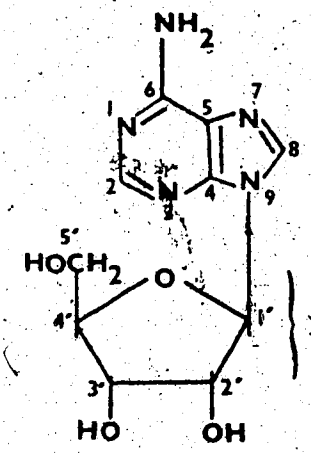
## A. A BRIEF HISTORICAL OUTLINE OF NUCLEOSIDE STRUCTURE AND SYNTHESIS.

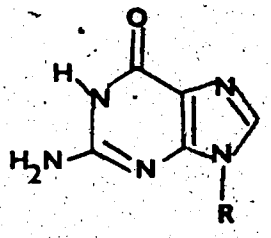
In 1871 Friedrich Miescher (1) published his fundamental investigations which led to the discovery of what we now call "nucleic acids" (2).

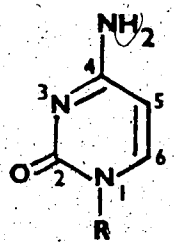
It was Levene and Jacobs (3) who introduced the term nucleoside to describe the purine-carbohydrate derivatives isolated from alkaline hydrolysates of yeast ribonucleic acid. The term is now widely used to include all the compounds of synthetic or natural origin which contain an heterocyclic base linked, through nitrogen or carbon, to the C-1 position of a sugar.

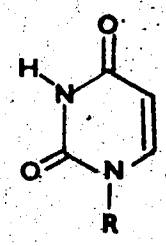
The major nucleosides obtained from ribonucleic acids are the purine derivatives, adenosine (1), guanosine (2), and the ribosyl pyrimidines, cytidine (3) and uridine (4).



R = D-ribose







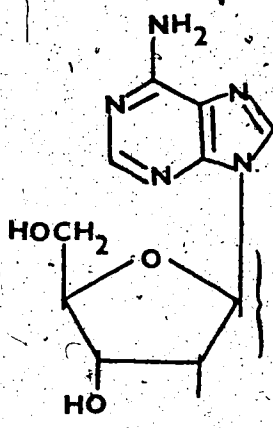
1 Adenosine

2 Guanosine

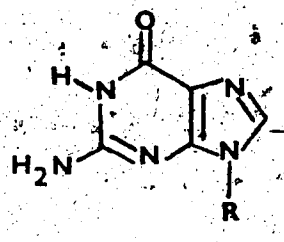
3 Cytidine

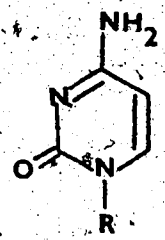
4 Uridine

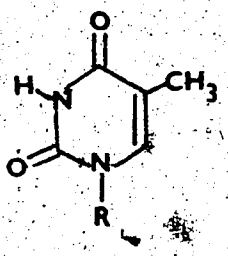
The deoxyribonucleic acids contain 2'-deoxyadenosine (5), 2'-deoxyguanosine (6), 2'-deoxycytidine (7) and thymidine (8).



R = 2-deoxy-D-erythro-pentose (2-deoxy-D-ribose)







5 — 2'-Deoxyadenosine

6 — 2'-Deoxyguanosine

7 — 2-Deoxycytidine

8 — Thymidine

Since the bases of the major ribonucleosides are readily obtained by acidic hydrolysis, they were early identified as adenine, guanine, cytosine, and uracil (4).

The carbohydrate moiety of adenosine (1) and guanosine (2) remained unidentified for many years until, in 1911, Levene and Jacobs crystallized it and characterized it as D-ribose (5). Confirmation of the presence of D-ribose in uridine (4) and cytidine (3) was obtained by Gulland and co-workers in 1947 (6).

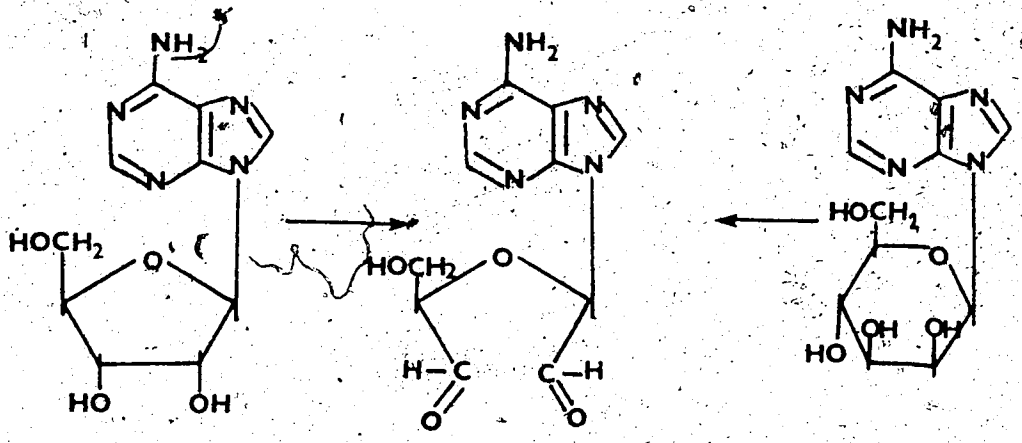
The determination of the sugar moiety of the deoxynucleosides was accomplished by Levene and co-workers (7) when they showed that this sugar showed many of the properties characteristic of 2-deoxy sugars and was iden-

tical with synthetic L-2-deoxyribose except that the specific rotation, while of the same numerical value, was opposite in sign (8). The next step, the size of the ribofuranosyl ring, was elucidated by Levene and Tipson (9). They obtained, by simultaneous methylation and deacetylation of tri-O-acetyladenosine, tri-O-methyl-N-methyladenosine which on acid hydrolysis yielded 6-methylaminopurine and a trimethylribose, identified as 2,3,5-trimethyl-D-ribofuranose by oxidation first to trimethyl-γ-D-ribonolactone and then to meso-dimethoxysuccinic acid.

Two questions remained unsolved: (1) What is the chemical bond and position of attachment of the sugar to the base? (2) What is the configuration at the sugar-base linkage?

The rapid acid hydrolysis of purine nucleosides suggested that the sugar was linked to the base as a ring N-glycosyl derivative rather than through a C-C bond, the amino groups of adenosine (1) and guanosine (2) were excluded since deamination could be performed without loss of the sugar residue. Through ultra-violet absorption spectral studies (10, 11, 12) it was evident that the purine nucleosides are 9-ribosylpurines. Confirmation of the location of the sugar was given by Todd and his co-workers (13) through the synthesis of 9-D-mannopyranosyl adenine (10). By oxidation with periodate,

this compound gave a dialdehyde 9 identical with that obtained from adenosine (1).



1 9 10

Scheme I

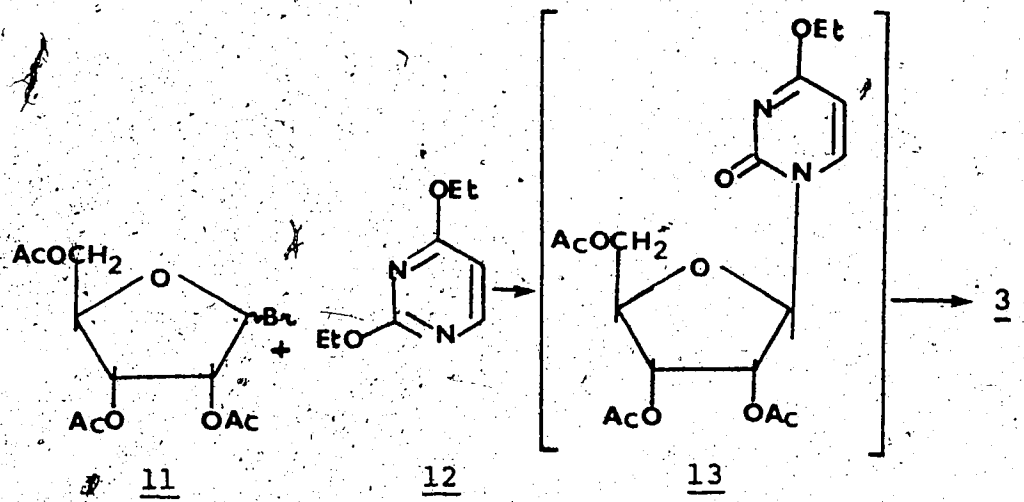
Todd and his co-workers also answered the last question when they demonstrated in 1946 (14) the identity of the aldehyde obtained by periodate oxidation of adenosine (1) with that resulting from similar treatment of 9-β-D-glucopyranosyladenine, the β-configuration of which was indicated by synthesis of the compound from α-acetobromo-D-glucose. The same group established proof of the β-D-configuration when they discovered (15) the formation of 5'-cyclonucleosides derived from cytidine (3) ($O^2 \rightarrow 5'$) and adenosine (1) ($N^3 \rightarrow 5'$).

As in many other fields of chemistry, the period of structure elucidation was followed by a period during which numerous workers devoted their energies to the

development of methods suitable for the synthesis of naturally occurring nucleosides.

Three main classes of methods exist: In the first, the appropriate heterocyclic base is coupled with a reactive form of a presynthesized sugar, commonly a sugar halide. In the second, the heterocyclic base is elaborated from a simple N-glycosyl precursor. In the third, the nucleoside is modified either in the sugar moiety or in the heterocyclic base or in both. All three types of methods have been used with success as will be discussed in terms of some interesting examples. The synthetic work in this area was started by E. Fischer and B. Helferich in 1914 (16). These workers condensed tetra-O-acetyl-α-D-glucopyranosyl bromide with the silver salts of certain purines. This provided a route to 9-β-D-glucopyranosyladenine and 9-β-D-glucopyranosylguanine. It is interesting to note that the same method was used by Todd's group some thirty years later to synthesize adenosine (1) and guanosine (2) using 2,3,5-tri-O-acetyl-D-ribofuranosyl bromide (11) as the sugar component (17) (18).

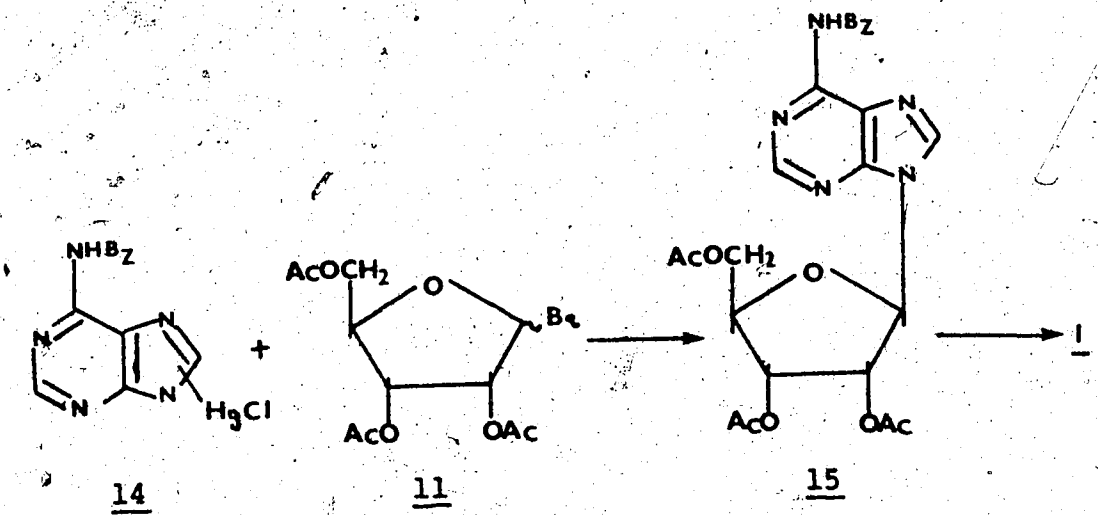
In the pyrimidine series, coupling of tri-O-acetyl-D-ribofuranosyl bromide (11) and 2,4-diethoxy pyrimidine (12) (the Hilbert-Johnson method (19)) led to the synthesis (20) of cytidine (3) and also uridine (4).




11 12 13

Scheme II

Only three years later a significant improvement in technique was introduced by Davoll and Lowy (21). They used the chloromercuri derivatives of purines in place of the silver salts of Fischer and Helferich. Thus, adenosine (1) could be synthesized in fair yield from chloromercuri-6-benzamido purine (14) and 2,3,5-tri-O-acetyl-D-ribofuranosyl bromide (11).




14 11 15

Scheme III

It was shown later (22) that mercuri derivatives of pyrimidines are effective reagents for the preparation of pyrimidine nucleosides.

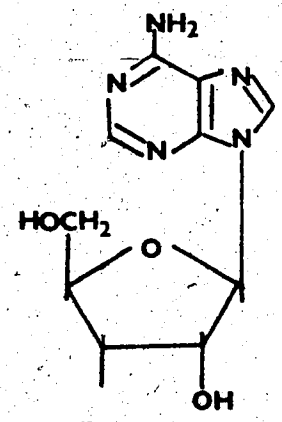
However, it was as recent as 1958 that the first component of deoxynucleic acids, the pyrimidine 2'-deoxyribonucleoside thymidine (8), was synthesized by Shaw and Warrener (23). In 1959, B. R. Baker and his group (24) achieved the synthesis of the first purine 2'-deoxy-nucleoside, 2'-deoxyadenosine (5), using the chloromercuri salt method.

Until 1948 each of the four known classes of nucleic acid was thought to consist of only the four basic nucleoside monomers 1-4. However, in that year, Hotchkiss (25) detected the first modified component of a nucleic acid, 5-methylcytosine, in a sample of calf thymus DNA. Since that time, five modified nucleosides in DNA and over thirty-five modified nucleosides in RNA have been identified. It has also become apparent that it is not possible to estimate how many nucleic acid components actually exist. The discovery of these modified nucleosides opened a wider field to nucleoside chemists. It was the isolation of the first nucleoside antibiotic (defined here as a compound of microbial origin that is able to disrupt the normal functioning of other cells), Cordycepin (16) (26) more than any other single factor, that provided the

impetus for chemical research in the nucleoside area.

Since that discovery, a number of nucleoside antibiotics have been isolated. To cite only a few of particular interest to this work:

- 9-(3-Deoxy-β-D-erythro-pentofuranosyl)adenine (16) (3'-Deoxyadenosine or Cordycepin) (26), (27), (28)
- 9-β-D-Arabinofuranosyladenine (17) (Ara A) (29)
- 9-(3-Amino-3-deoxy-β-D-ribofuranosyl)adenine (18) (30) (31)
- 4-Amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (19) (Tubercidin) (32)
- 7-Amino-3-(β-D-ribofuranosyl)pyrazolo[4,3-d]pyrimidine (20) (Formycin) (33) (34).



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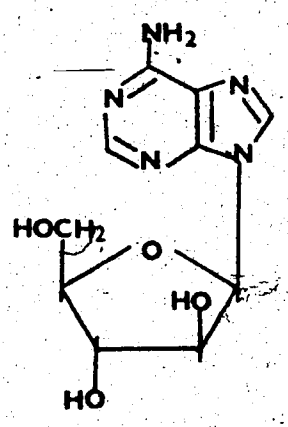

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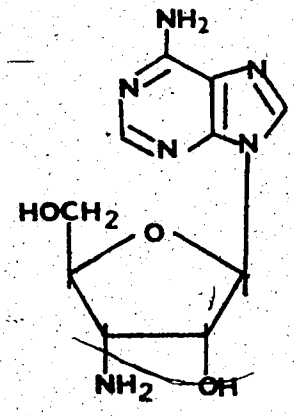

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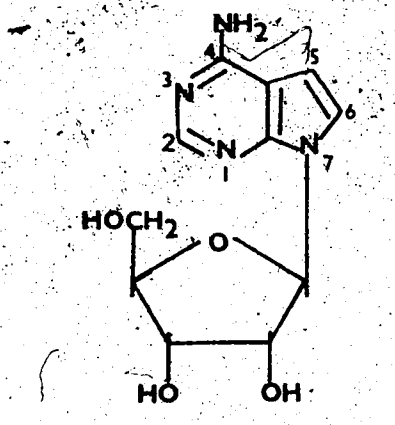

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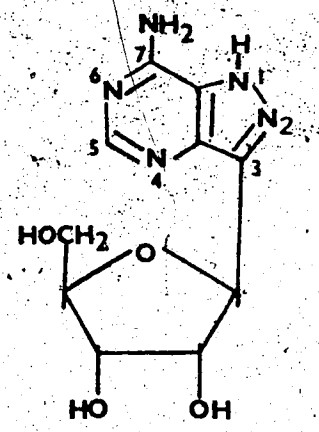

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Nucleoside antibiotics have been studied in a variety of ways including uses as: biochemical tools, models for conformational studies, mass spectroscopy, nuclear magnetic resonance, optical rotatory dispersion and circular dichroism measurements. They have been used in the elucidation of steps involved in the reading of the genetic message at the ribosome, for protein biosynthesis, RNA synthesis, DNA synthesis, and a host of other biological problems. Their close resemblance to the purine nucleosides and nucleotides have made them useful as structural analogs and inhibitors.

Cordycepin (16) has been the object of numerous studies by biochemists. It has been found to be a cytotoxic nucleoside and an RNA synthesis inhibitor, but it does not inhibit DNA synthesis. It is also known to act as a negative feedback inhibitor of purine nucleotide biosynthesis (35).

Ara A (17) on the other hand, inhibits DNA synthesis

in animal cells in culture, bacteria and DNA-viruses. It has significant therapeutic activity against Herpes simplex keratitis in hamsters (36). Ara A was found (36a) to be rapidly deaminated to 9-(β-D-arabinofuranosyl)hypoxanthine. The rate was approximately 20% that of adenosine while 9-β-D-xylofuranosyladenine (23b) was more rapidly deaminated than Ara A.

Tubercidin (19) is a nucleoside analog of adenosine (1) with a modified base. The nitrogen at position 7 of the imidazole ring of adenosine has been replaced by a carbon atom. Tubercidin was first isolated in 1957 (32) from the culture filtrates of Streptomyces tubercidicus, its structure was elucidated in 1960 by Suzuki et al. (37) and confirmed by Tolman et al. (38) by synthesis. It inhibits both DNA and RNA viruses. It is an excellent substrate for adenosine kinase but is not subject to glycosidic bond phosphorolysis. Its triphosphate can replace adenosine triphosphate but interestingly it is not deaminated by adenosine deaminase (39). Very recently (40) tubercidin has been used topically on patients suffering from actinic keratoses with good therapeutic results.

Finally, formycin (20) is one representative of a new class of nucleoside antibiotics called C-nucleosides. This refers to the fact that the C-1 of the D-ribofuranose is joined to the heterocyclic base by a carbon-carbon

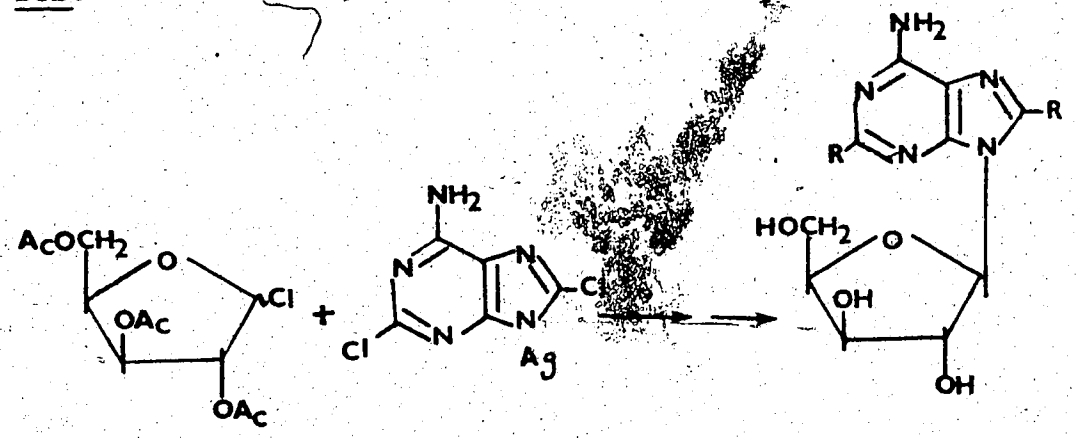
bond. It was originally isolated from the culture filtrates of the actinomycetes Nocardia interforma n. sp. in 1964 (33) and its first total synthesis appeared (41) in 1971. Formycin (20) effectively replaces adenosine (1) in a number of enzymatic reactions. At high concentrations it inhibits DNA synthesis in some cell culture strains but does not inhibit RNA synthesis and only has a slight effect on the inhibition of protein synthesis. It is known to be deaminated readily by adenosine deaminase.

These nucleoside antibiotics and many others have been reviewed in detail by Suhadolnik (42) in 1970.

## B. SYNTHESES OF CERTAIN BIOLOGICALLY IMPORTANT NUCLEOSIDES

Certain syntheses of particular significance to the work described in this dissertation, which involves preparation of adenosine analogs *via* transformation of the nucleoside to a 2',3'-anhydro (epoxide) derivative, will now be discussed. Only brief mention will be made of methods used for pyrimidine transformations.

In 1950 (43), the first of several syntheses of 9-β-D-xylofuranosyladenine (23b) appeared. Treatment of 2,3,5-tri-O-acetyl-D-xylofuranosyl chloride (21) with the silver salt of 2,8-dichloroadenine (22) was followed by deblocking with base. A compound identified as 9-(β-D-xylofuranosyl)-2,8-dichloroadenine (23a) was obtained in 40% yield which was hydrogenolyzed to give 23b.




21 22 23a R = Cl

b R = H

Scheme IV

No conclusive structure proof was given. In 1957, Baker and Hewson (44) described an alternative route. Thus, 23b was prepared in 47% overall yield from α-D-xylofuranose tetrabenzoate, via coupling of the derived 1-bromide and chloromercuri-6-benzamido purine (14). The purity of this valuable intermediate for further nucleoside transformations was again in doubt. For example, paper chromatography showed about 5% of adenine; and the α-anomer could well have been present.

In 1963, Lee et al. (45) reported the synthesis of 23b by the fusion method. This method, originated by Shimadate and co-workers (46), consists of heating a polyacylated sugar and a substituted purine under vacuum in the presence of p-toluenesulfonic acid. In this case, fusion of tetra-O-acetyl-D-xylofuranose with 6-nonanamidopurine gave approximately equal amounts of 23b and its α-anomer.

Finally, in 1971 Ikehara and co-workers (47) also reported the synthesis of 23b by the fusion method. They used 1,2,3,5-tetra-O-acetyl-xylofuranose and $N^6$-benzoyladenine with p-toluenesulfonic acid as catalyst. The crude yield for the condensation was 47%. After deblocking this material with sodium methoxide in methanol, the crystallized material was shown to be a mixture of the α and β isomers. The β isomer 23b, could, according to the authors, be obtained pure in an unspecified yield.

However, the data given are somewhat questionable. It is interesting to note the wide range of reported specific rotations of 23b: $[\alpha]_D^{24}$: -22.5° (C 1.22, $H_2O$) (45), -16.4° (C 1.10, $H_2O$) (47), -30.1° (C 1.2, $H_2O$) (48), -19° (C 1.2, $H_2O$) (43).

Those examples illustrate difficulties encountered during coupling or condensation reactions. It is difficult to separate the α and β anomers simultaneously formed and to obtain either of them in the high state of purity required if the compound is going to be useful in biochemistry. In addition, it has been found that the mercuri salt coupling method can give products which are contaminated with minute amounts of mercuric ions. These toxic trace ions are difficult to remove and may be biologically significant (49).

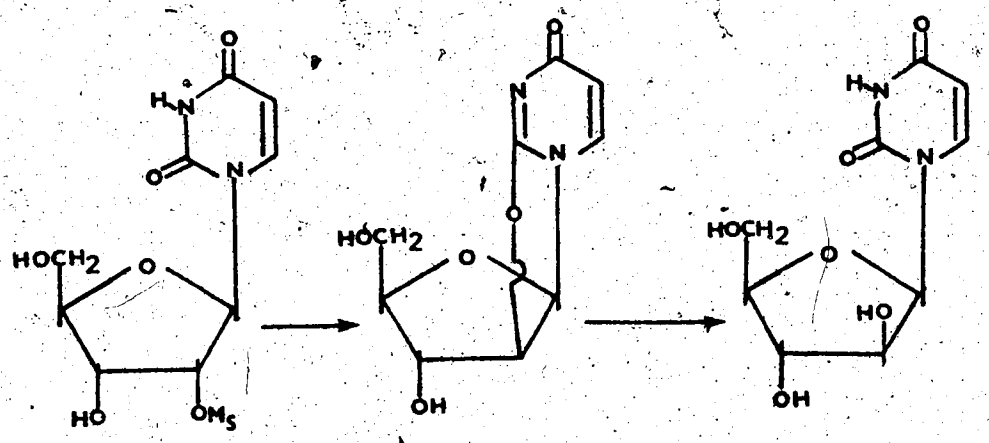
Another problem associated with the condensation methods using metal salts is the stereochemical preference for one of the possible isomers. In 1954 Baker stated what is now known as "Baker's trans rule:"

> Condensation of a heavy metal salt of a purine or pyrimidine with an acylated glycosyl halide will form a nucleoside with a C-1 to C-2 trans configuration in the sugar moiety regardless of the original configuration at C-1 (50).

For instance, the acetylated D-arabinofuranosyl halides give the α nucleoside anomer upon condensation.

This makes this route inapplicable to the synthesis of β-D-arabinonucleosides (51).

In the pyrimidine series, β-D-arabinofuranoside synthesis was solved by a new route: formation of a $O^2 \rightarrow 2'$-cyclonucleoside, an important class of nucleosides, and subsequent anhydro ring opening by attack at the pyrimidine $C^2$. These $O^2 \rightarrow 2'$-cyclonucleosides form readily when the 2'-O-sulfonate esters which are trans to the base are treated with ammonia or dilute alkali (52). Hydrolysis of $O^2 \rightarrow 2'$-cyclouridine (25) to give 1-β-D-arabinofuranosyluridine (26) is achieved, for instance, by either base or acid, the later being more generally applied in this case.




24 25 26

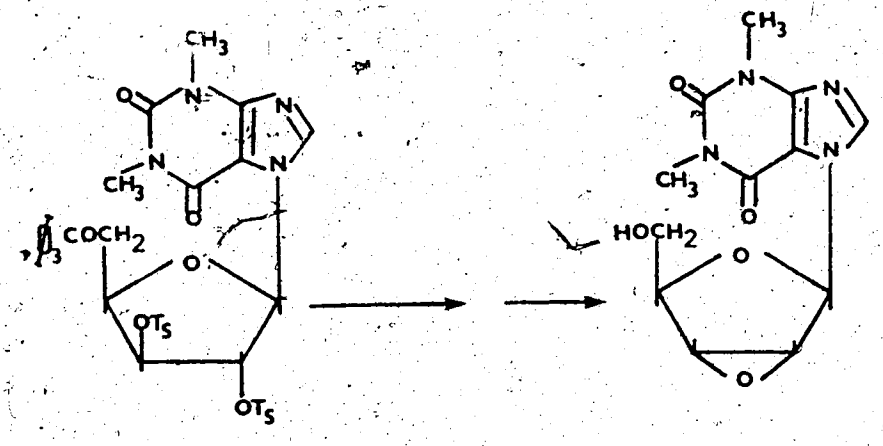
Scheme V

In the purine series, the preparation of certain cis-1'-2'-nucleosides was achieved through intra-

molecular nucleophilic substitution reactions. Very early it was found that direct displacement reactions at functionalized sugar hydroxyl groups, especially the secondary hydroxyls on the ring, are difficult. In 1960 Todd and Ulbricht (53) reported limited success in an $SN_2$ displacement of 3'-O-p-nitrobenzenesulfonyl derivative of adenosine using sodium iodide. They also mention that attempted displacements at the 2'-position failed.

An alternative route using neighboring group transformations provided an answer to this problem. An example of a simple neighboring group reaction is illustrated by the conversion of a trans-1,2-hydroxysulfonate or trans-1,2-di-O-sulfonate to an epoxide. This represents one of the easiest ways of access to an important type of intermediate in nucleoside interconversions.

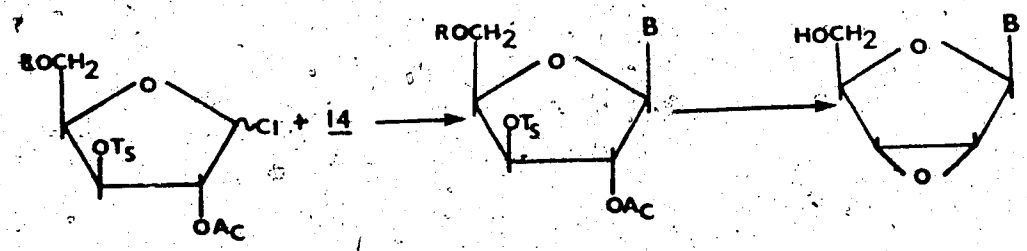
An early example of a nucleoside 2',3'-epoxide was reported by Davoll et al. (54). Treatment of 7-[2,3-di-O-p-(toluenesulfonyl)-5-O-trityl-β-D-xylofuranosyl]-theophylline (27) with sodium methoxide gave the 2',3'-anhydroriboside 28.



27 28

Scheme VI

The anhydroriboside 31 derived from adenosine (1) was first reported by Baker and co-workers (24) in 1959. The last step of this elaborate synthesis was the treatment of the trans acetoxytosylate 30 (obtained by coupling reaction of 29 with chloromercuri 6-benzamido purine (14) with base. The overall yield was 8.9% from 29.



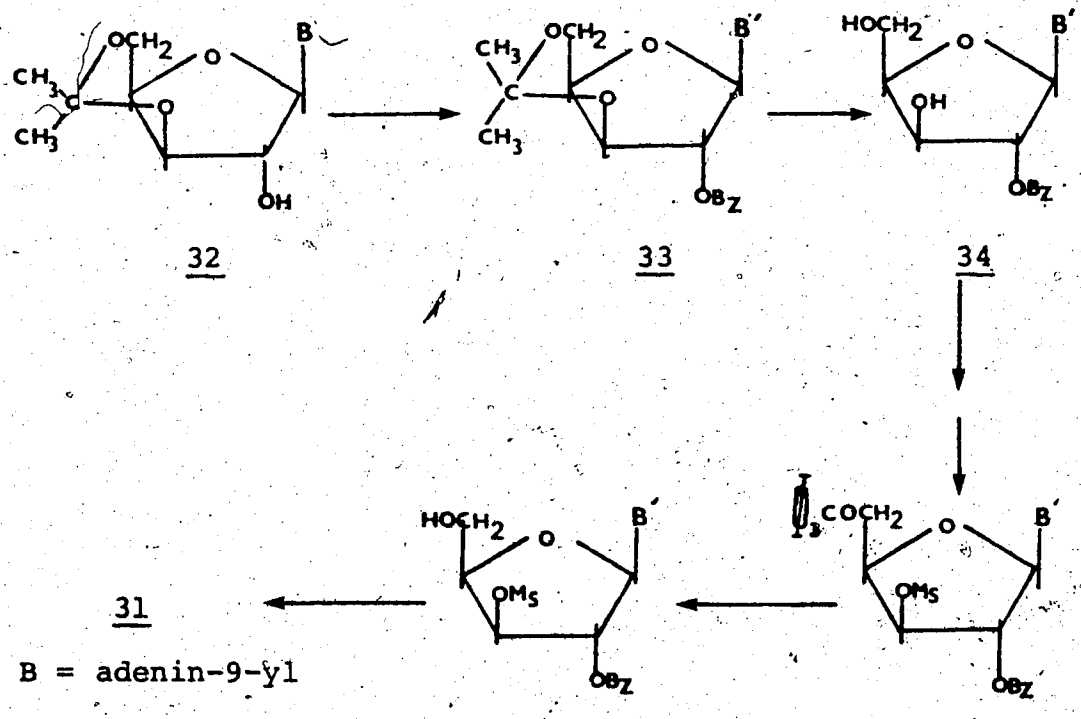
29 30 31

B = adenin-9-yl

$R = CH_3OCO_2$

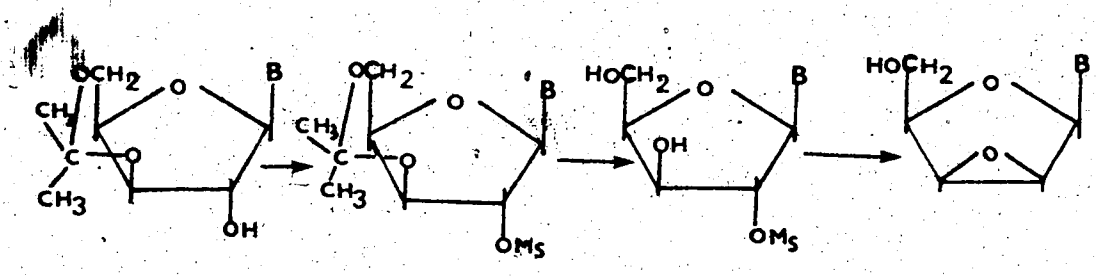
Scheme VII

This synthesis was improved (55) by converting 9-β-D-xylofuranosyladenine (23b) to the 3',5'-O-isopropylidene derivative 32. Reaction of 32 with a large excess of benzoyl chloride in pyridine gave a compound thought to be the tribenzoyl derivative 33. Cleavage of the O-isopropylidene group of 33 gave 34 which was treated with trityl chloride/pyridine. The product of that reaction was treated directly with excess methanesulfonyl chloride to form the mesylate 35. The crude material was detritylated to give 36, which was converted to the anhydro nucleoside 31 with sodium methoxide. The overall yield from 23b was 19%.




Scheme VIII

The epimeric adenine anhydrofuranoside, 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (38), was also prepared by the same group of workers (56) by treatment of 32 with methanesulfonyl chloride to give 37. Removal of the ketal group from 37 was followed by epoxide formation using sodium methoxide to give 38.



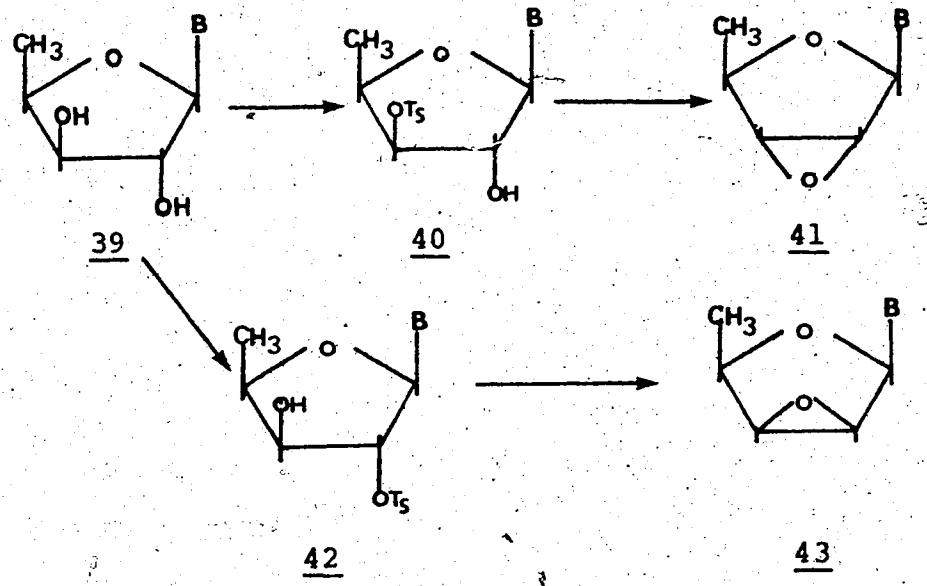
32 37 37a 38

B = adenin-9-yl

Scheme IX

In 1966 the syntheses of two more epoxides in the adenine nucleoside series were reported (57). The preparation of 9-(2,3-anhydro-5-deoxy-β-D-lyxofuranosyl)adenine (43) was attempted starting from 9-(5-deoxy-β-D-xylofuranosyl)adenine (39). Treatment of 39, with a slight excess of p-toluenesulfonyl chloride gave a monotosylate which was readily converted to a crystalline epoxide 41 by treatment with sodium methoxide at reflux. On steric, as well as on electronic, grounds it was reasonable to expect that the crystalline tosylate was 42. It was, however,

shown to be 40. When 39 was treated with 2 moles of sodium hydride followed by a slight molar excess of p-toluenesulfonyl chloride, the desired deoxy-lyxoepoxide 43 was obtained in good yield following treatment by base.

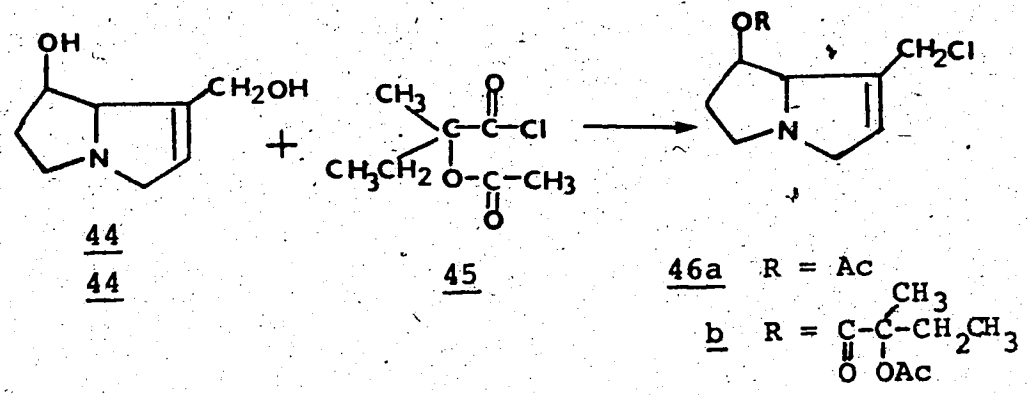



B = adenin-9-yl

Scheme X

More recently Moffatt and co-workers (58) published an alternative route to 9-(2,3-anhydro-β-D-ribo-furanosyl)adenine (31). This route makes use of the "abnormal reaction" of α-acetoxyisobutyryl halides with cis diols. This reaction was discovered by Mattocks (59) during studies on the chemistry of pyrazolidine alkaloids. When the 1,4 diol 44 reacted with 2-acetoxy-2-methyl-

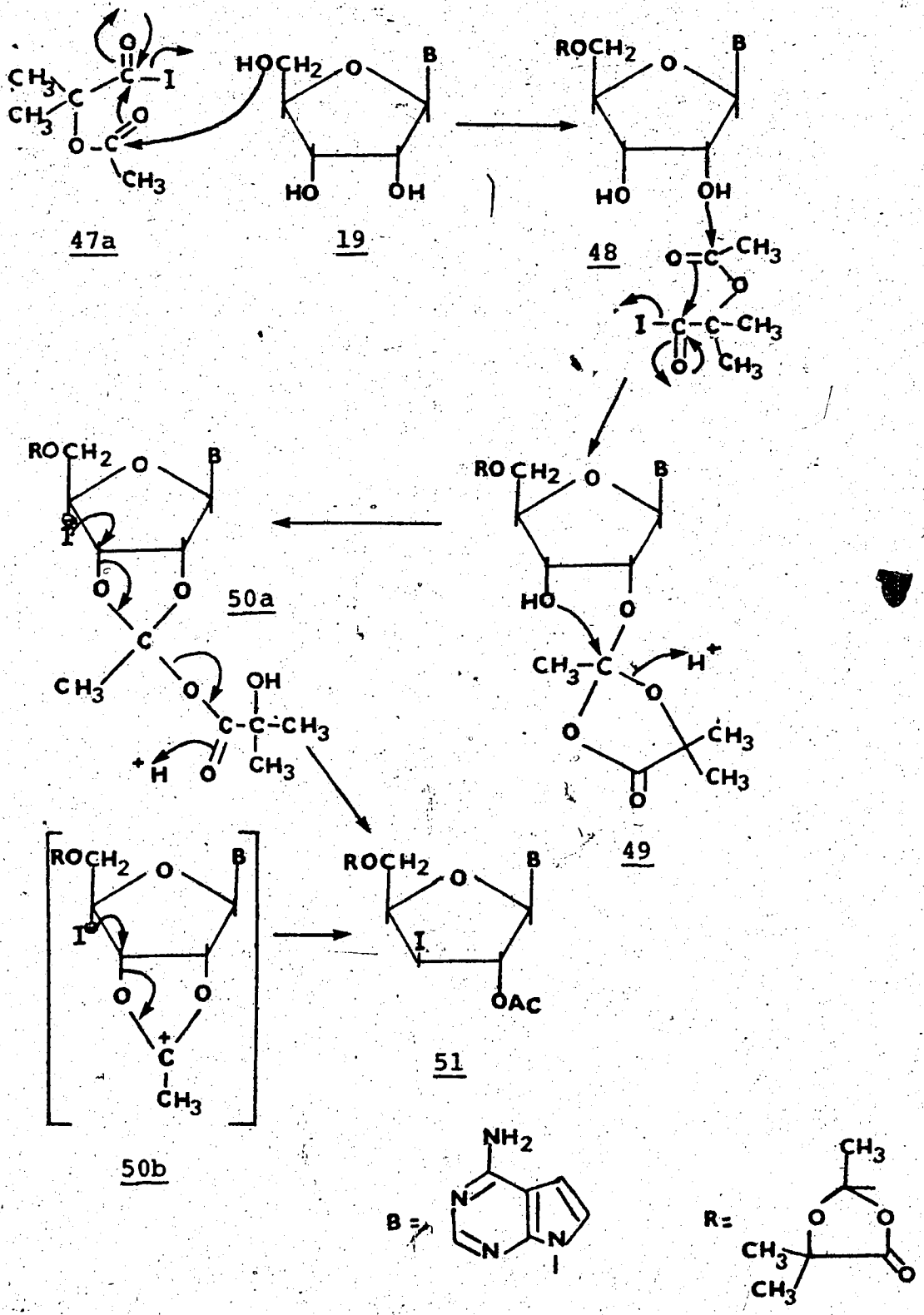
butanoyl chloride (45) the unexpected products of the reaction were the chloroesters 46a and 46b.




Scheme XI

Mattocks also showed that the acetoxyacyl chloride 45 reacts abnormally with 1,2 and 1,3 diols to form chloroacetates.

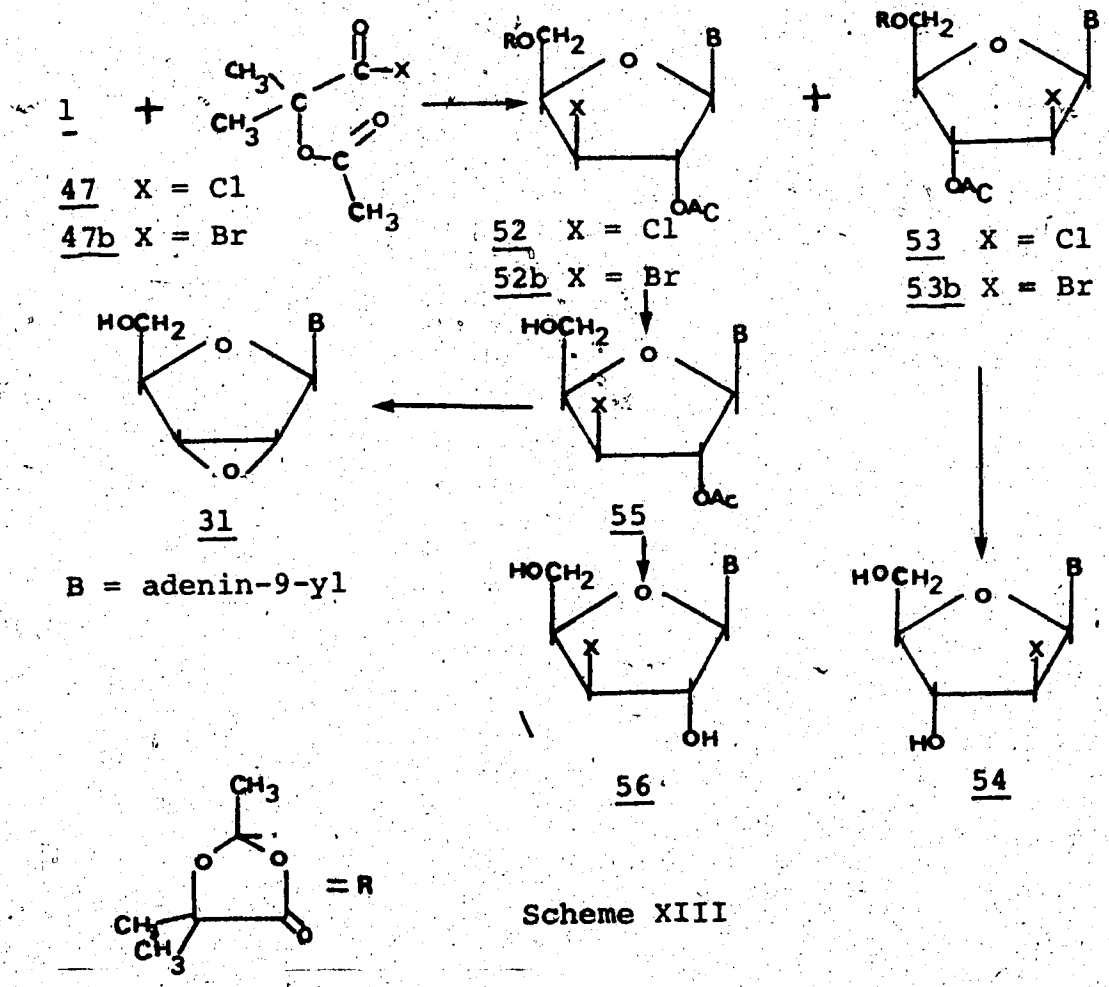
The potential of such a reaction was recognized by Moffatt (59a) and in 1973 Robins and co-workers (60) reported its application to nucleoside antibiotics. They found that treatment of tubercidin (19) with α-acetoxyisobutyryl chloride (47) in the presence of excess sodium iodide in acetonitrile gave an excellent yield of 4-amino-7-(2-O-acetyl-5-O-[2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl]-3-iodo-3-deoxy-β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine (51).



Scheme XII

The proposed mechanism (60) is outlined in scheme XII. The useful intermediate 51 provided easy access to 3'-deoxytubercidin upon hydrogenolysis and saponification. The same reaction was applied to formycin (20) to give 3'-deoxyformycin and 2'-deoxyformycin in an approximate ratio of 3:2.

Moffatt and co-workers (58) have explored the same reaction with adenosine (1). Treatment of 1 with an excess of α-acetoxyisobutyryl chloride (47) in acetonitrile at 80° gave predominantly a mixture of the diastero-isomers 52.

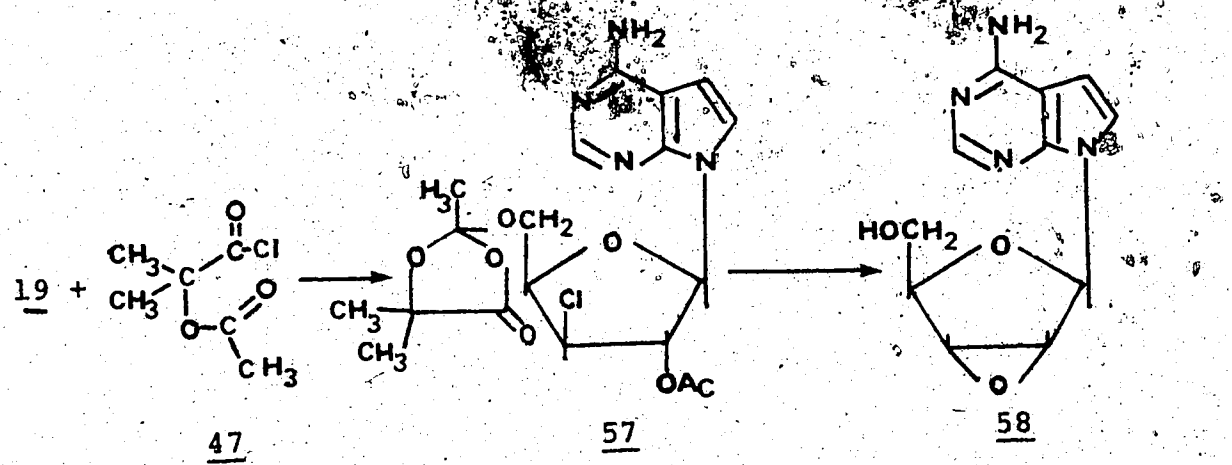



Scheme XIII

Treatment of the crude reaction product with hydrogen chloride rapidly removed the 5'-substituent and led to the isolation of 9-(2-O-acetyl-3-chloro-3-deoxy-β-D-xylofuranosyl)adenine (55) in 60% yield. More prolonged treatment with methanolic hydrochloric acid gave 9-(3-chloro-3-deoxy-β-D-xylofuranosyl)adenine (56). Treatment of the crude reaction product (52) with methanolic sodium methoxide gave the epoxide 31 in 67% yield after an elaborate process which involved two crystallizations, repeated extractions and preparative thin layer chromatography using multi-development. Direct crystallization of the crude reaction product (52) gave a homogenous compound in 20% yield which was shown to be a single diastereoisomer of 52. Treatment of the mother liquors from crystallization of 52 with 10% methanolic ammonium hydroxide permitted the isolation, in 7% yield, of a minor compound identified as 9-(2-chloro-2-deoxy-β-D-arabinofuranosyl)adenine (54). These authors (58) noted a striking difference between the two chloro compounds 54 and 56. Although sodium methoxide at 0° efficiently converts the 3'-chloronucleoside 56 to the epoxide 31, the 2'-chloro-isomer 54 is inert under these conditions. The reaction of the acyl bromide 47b with adenosine (1) was also studied and found to be similar to that of the acyl chloride 47.

The same group (61) have extended their study of

acyl halides 47 and 47b to tubercidin (19), amicetin (20). Reaction of 19 with 47 in acetonitrile at 3[illegible] during 18 hours gave the intermediate 57 in high yield.



47 57 58

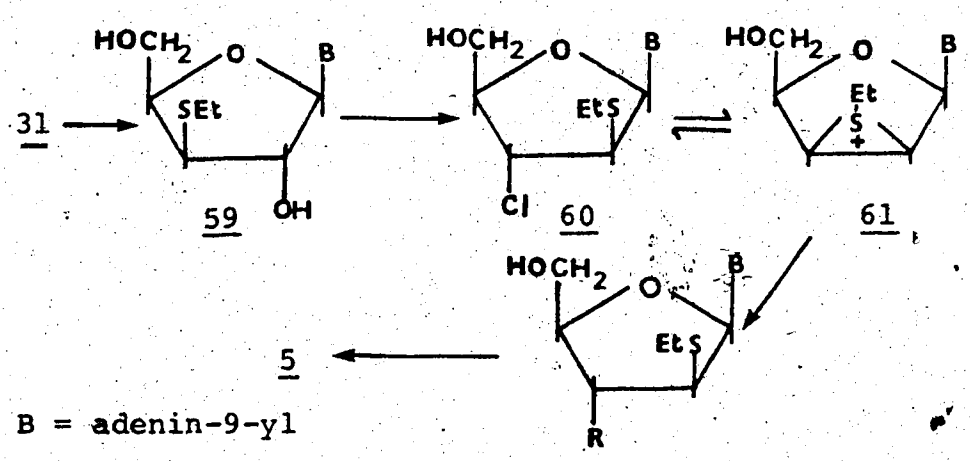
Scheme XIV

In contrast to the reaction with adenosine (1), no 2'-chloro isomer of 57 was detected. The analogous reaction using α-acetoxyisobutyryl bromide (47b) gave identical results. The epoxide 58 was formed in good yield by treatment with sodium methoxide at room temperature and could be obtained pure by preparative thin layer chromatography.

## C. EPOXIDES AS STARTING MATERIALS IN CARBOHYDRATE AND NUCLEOSIDE CHEMISTRY

The synthetic utility of the above nucleoside epoxides has been amply demonstrated. Ring opening of 31 with sodium ethylmercaptide gave 9-[3-deoxy-3-(ethylthio)-β-D-xylofuranosyl]adenine (59) in 66% yield (24), which could be desulfurized (62) to 3'-deoxyadenosine (16) (shown (63), in 1964, to be the antibiotic, cordycepin).

2'-Deoxyadenosine (5) was also prepared (55) starting from 59. Treatment of the latter intermediate with thionyl chloride at room temperature gave 9-[3-chloro-2,3-dideoxy-2-(ethylthio)-β-D-arabinofuranosyl]adenine (60) in high yield, the rearrangement of the ethylthio group occurred presumably via the episulfonium ion 61.



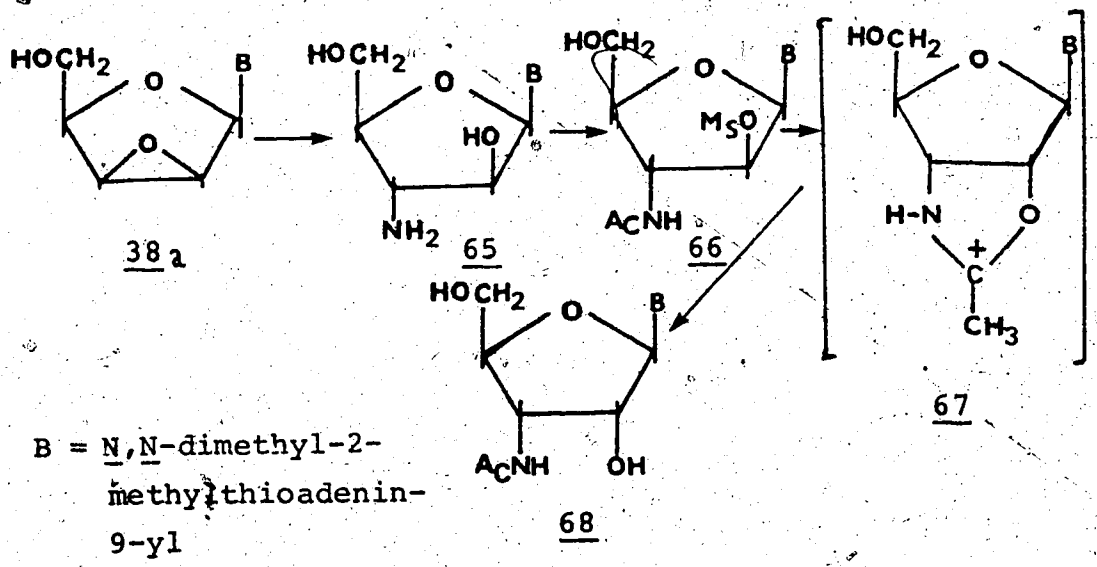

Scheme XV

Treatment of 60 with sodium acetate and subsequent desulfurization of the resulting arabino-S-ethyl product gave 2'-deoxyadenosine (5).

Treatment of 60 with sodium azide gave the 3'-azido derivative 63 which was desulfurized (62) to give 3'-amino-2',3'-dideoxyadenosine. Similarly, treatment (64) of 60 with potassium thiocyanate gave 64 which was desulfurized to give 2',3'-dideoxyadenosine. Baker (65) also used the lyxoepoxide 38 in the first synthesis of 9-β-D-arabinofuranosyladenine (17). Treatment of 38 with sodium benzoate or sodium acetate in 95% aqueous N,N-dimethyl formamide (DMF) effectively displaced the epoxide oxygen in good yield to give a crude product from which the desired arabinoside 17 could be isolated. A number of similar reactions have been carried out on the 5'-deoxy counterparts 41 and 43. For instance, the 5'-deoxy analog of 17, 9-(5-deoxy-β-D-arabinofuranosyl)-adenine was obtained in reasonable yield from a reaction similar to the one just described.

Examples of products possessing trans 2',3' groups have been given thus far as illustrations of the use of nucleoside epoxides. However, epoxides can also be used for the synthesis of compounds with cis 2',3' groups by employing a further neighboring group participation. Baker et al. demonstrated such a sequence (66) in their synthesis of the aminonucleoside 18 from the antibiotic

puromycin. Opening of 38a with ammonia gave 65 which was transformed into the 2'-O-methanesulfonyl compound 66 by a series of steps. Reaction of 66 with sodium acetate occurred by intramolecular attack of the N-acetyl oxygen on the trans sulfonate ester to give the cis 1,2-acetamido alcohol 68 via the rapidly hydrolyzed oxazoline 67.



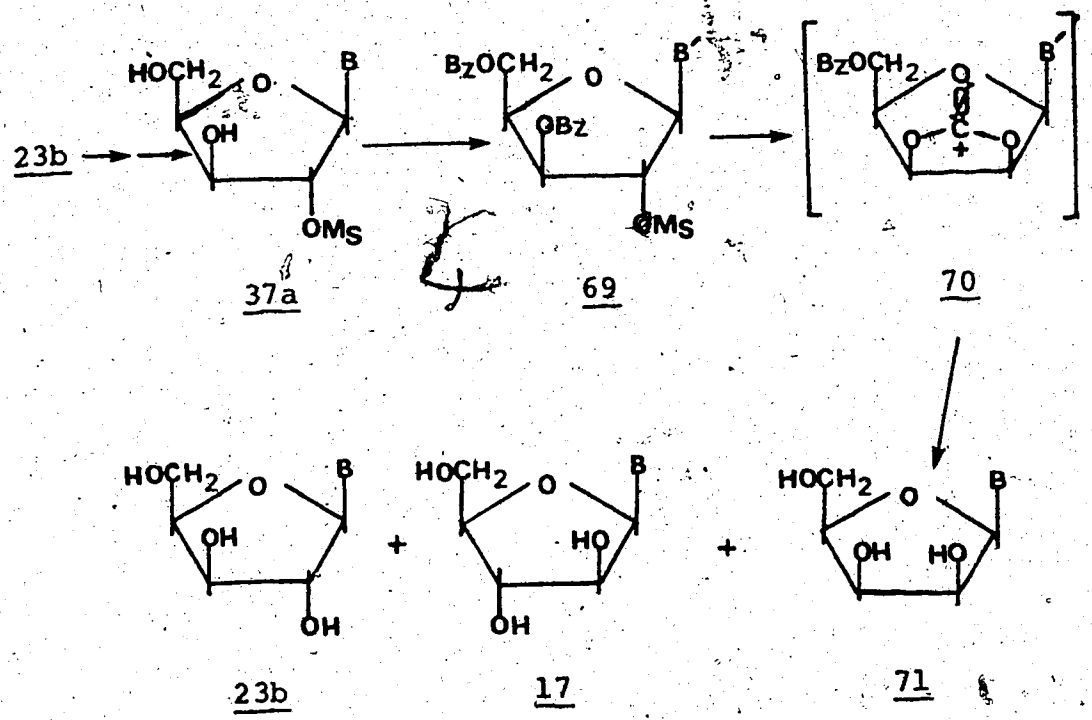

38a 65 66 67 68

B = N,N-dimethyl-2-methylthioadenin-9-yl

Scheme XVI

An example of the conversion of a trans-2',3'-diol to a cis-2',3'-diol was also given by Goodman and co-workers (67). The 2'-O-(methanesulfonyl)nucleoside 37a, obtainable from 9-β-D-xylofuranosyladenine (23b), was benzoylated and then treated with sodium fluoride in N,N-dimethylformamide (DMF). A mixture was obtained which contained mainly the lyxoside 71 as well as some

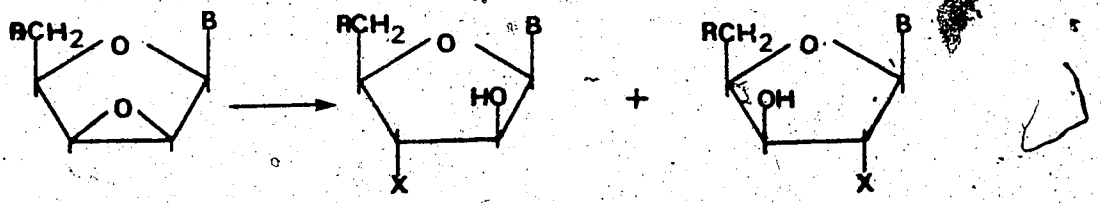
arabinoside 17 and xyloside 23b, presumably via the benzoxonium ion 70.




Scheme XVII

It is important to note that attack of the nucleophile on the epoxide ring occurred mainly at the C-3' position in the syntheses which have been discussed. In an early attempt to obtain 2'-deoxynucleosides, Davoll et al. (54) treated epoxide 28 with ethylmercaptide. Unfortunately, attack occurred almost exclusively at the 3'-position. Further examples of this phenomenon indicated that attack at C-3' by nucleophile is predominant

for the riboepoxide 31, the lyxoepoxide 38, and their 5'-deoxy analogs 41 and 43. In 1967 Goodman and co-workers published (68) a study of this phenomenon in the 5'-deoxy series. They found that when 43 was treated with sodium benzoate in wet N,N-dimethylformamide (DMF) a mixture of 9-(5-deoxy-β-D-xylofuranosyl)adenine (39) and 9-(5-deoxy-β-D-arabinofuranosyl)adenine (72) was obtained in the ratio of 1:2.



38 R = OH
43 R = H

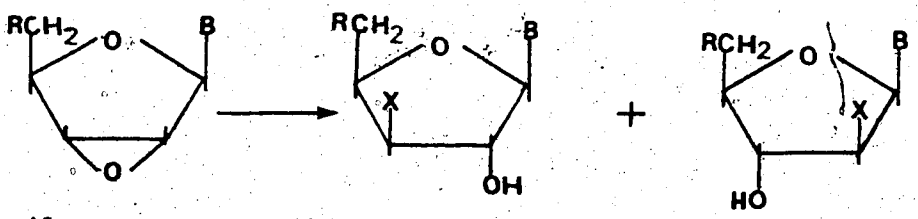
17 X = OH, R = OH
72 X = OH, R = H
73 X = $SCH_2\phi$, R = H
75 X = $N_3$, R = H

39 X = OH, R = H
74 X = $SCH_2\phi$, R = H
76 X = $N_3$, R = H

Scheme XVIII

Treatment of 43 with sodium benzylmercaptide in methanol gave a mixture of the 3'-S-benzylnucleoside 73 and 2'-S-benzylnucleoside 74 in a ratio of almost 1:1. Treatment of 43 with sodium azide in 2-methoxyethanol gave the 3'-azido nucleoside 75 and its 2' isomer 76 in the ratio of 3:1. However, the total yield was only

52%. Treatment of 41 with sodium benzoate gave no isolable product, a result which will be discussed later. On the other hand, treatment of 41 with sodium azide in 2-methoxyethanol gave a mixture of azides shown to be the 3'-azido 77 and the 2'-azido 78 isomers in a ratio of 4:1. Appreciable decomposition of the starting material was once again noticed and the yield was only 19%.



41 R = H  77 X = $N_3$, R = H

79 X = $SCH_2\phi$, R = H  78 X = $N_3$, R = H

B = adenin-9-yl

Scheme XIX

Treatment of 41 with sodium benzylmercaptide in methanol gave a yield of 94% of the 3'-S-benzylnucleoside 79. No traces of the isomeric 2'-S-benzylnucleoside could be detected.

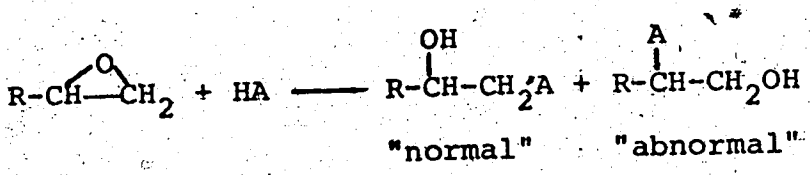
These results were given the following tentative explanation, by the authors (68). First, the difference in position of opening of 43 compared to 41 was ascribed primarily to steric effects. Thus, sodium

benzylmercaptide attacks exclusively at the C-3' position of 41 because the 2'-position is sterically unavailable to this large nucleophile. In contrast, the small azide nucleophile can attack at the C-2' position of 41 although the major site of attack remains C-3'. The lyxoepoxide 43 always gives a mixture of C-3' substitution and C-2' substitution regardless of the nucleophile. To explain the different ratios of opening, the authors postulated that the more powerful the nucleophile is, the less selective it becomes.

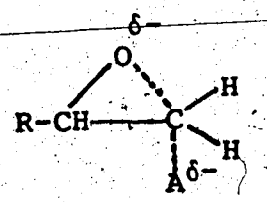
The authors then tried to rationalize the differences in selectivity in attack of nucleophiles on 43 and 38. Sodium benzoate reacted with 38 to give almost exclusive attack at C-3' (65). Attack of sodium benzylmercaptide gave a 5:1 ratio of C-3' to C-2' products. Finally, sodium azide with 38 gave a mixture of 3'-substituted product to 2'-substituted product in the ratio of 15:1. These differences, according to the authors, could be rationalized by postulating that the greater electronegativity of the 5-hydroxyl group in 38 compared to the hydrogen in 43 makes the C-3' more electron deficient relative to C-2' and thus more susceptible to nucleophilic attack.

In 1959 a review article concerning the mechanism of epoxide opening reactions was published by Parker and Isaacs (69). Some of the conclusions of this review

are very interesting in relation to the publications just described and will be summarized here. First, there is very little doubt that the vast majority of ring opening reactions of epoxides take place by ionic mechanisms. The bond which is broken is the highly polar carbon-oxygen bond which would be expected to break ionically and the reactions are generally carried out in polar solvents. When the epoxide is unsymmetrically substituted, two products are clearly possible. All the known examples indicate that under basic or neutral conditions the major product, if not the only isolated one, is the so-called "normal" isomer (corresponding to attack on the least substituted carbon).




This, as well as the stereochemistry of the ring opening, provide strong evidence for an $S_N2$-like attack of a reagent molecule or ion on the epoxide ring carbon atom, involving a transition state of the type:



Such reactions are well known to be sensitive to steric hindrance and, provided the group R has no very marked polar or conjugative effect, the "normal" isomer will be formed for steric reasons.

This would obviously apply to the case of the ribo-epoxides such as 31 or 41 where attack at C-2' is sterically disfavoured, but would not explain the results in the lyxoepoxide series where attack at either side is sterically equivalent.

Clearly, another effect is at work here, the electronic effect. Numerous examples indicate that if an electron withdrawing substituent is present it inhibits reaction at the carbon atom to which it is attached Since, in a bimolecular reaction, the presence of an electron withdrawing substituent facilitates the approach of the nucleophilic reagent but inhibits bond breaking to the leaving group, it seems likely that the reaction by which the epoxides open is a modified $S_N2$ reaction in which bond breaking is more important than bond making. It is reasonable in this case to suppose that the carbon atom under attack carries a fractional positive charge.

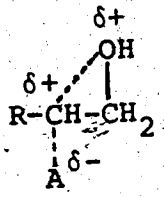
The 2',3'-epoxides of nucleosides are good examples of this situation. In the lyxo series as well as in the ribo series the anomeric carbon (which is attached to one oxygen atom and one nitrogen atom) is much more

electron-attracting than C-4' and consequently attack would be expected to take place at C-3'. In the ribo series, the steric effect and the electronic effect are cumulative and this explains why 2'-attack should be minimal. This is not always evident in the examples reported by Goodman (68). Sodium azide opening of 41 gave a ratio of C-3' to C-2' attack of 4:1. However, the total isolated yield was only 19% (68) and, as Parker and Isaacs point out (69), conclusions must be drawn with caution when low yield reactions or isolations are considered.

In the lyxo series, since the steric effect cannot be of significant importance, the electronic factor must be determining the site of attack and all examples show the major product resulting from attack at C-3' as would be expected. One explanation offered to rationalize the different ratio of opening of 38 and 43 was that the increased electronegativity of the C-5' in 38 would make the C-3' more electron deficient and therefore more prone to attack (68). This explanation seems questionable since it is in direct contradiction to all the known examples reviewed (69).

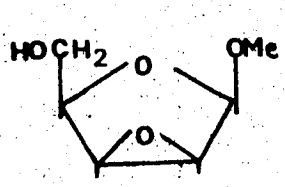
It is well established (69) that under acidic conditions there is a marked tendency towards the formation of "abnormal" products. This, as well as other experimental results, has been rationalized by Parker

and Isaacs by evoking a mechanism of the $SN_2$ type in which the reagent is further away from the seat of attack and the driving force for the reaction is provided more by transfer of electrons from carbon to oxygen than from reagent to carbon. Such a mechanism referred to sometimes as "borderline $SN_2$" must have a transition state of the kind depicted below:

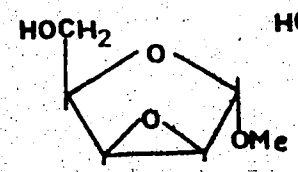



Under acidic conditions (or conditions in which the oxygen is complexed), nucleoside or sugar epoxides would be expected to open even more predominantly at the C-3' (or C-3) position.

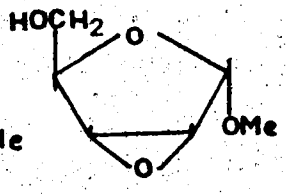
Good models for examination of the importance of the electronic effect versus the steric effect are provided by the following anhydrosugars:



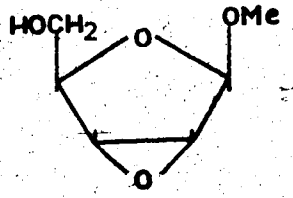

80




81

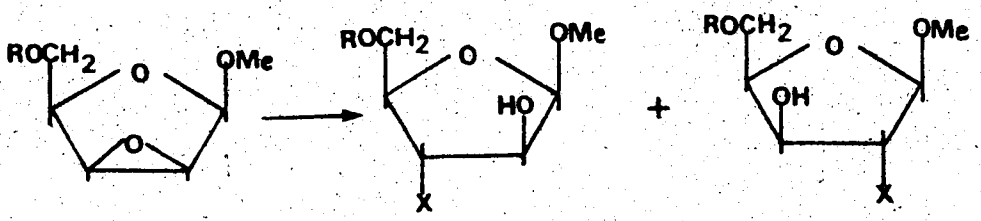



82




83

Methyl 2,3-anhydro-β-D-lyxofuranoside (80) prepared by Baker et al. (70), should have the least steric effect and its opening by sodium benzyl-mercaptide provided the first example (71) of ring opening of a 2,3-anhydrofuranoside which occurs predominantly at C-2.




80 R = H

86 R = Ac

84 X = $SCH_2\phi$, R = H

89 X = SCN, R = H

87 X = Br, R = Ac

85 X = $SCH_2\phi$, R = H

90 X = SCN, R = H

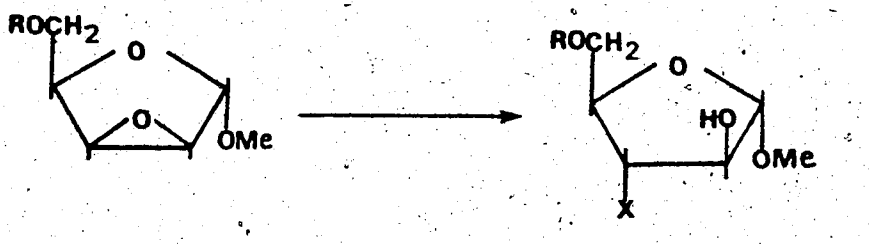
88 X = Br, R = Ac

Scheme XX

The ratio of 85 to 84 was 6:4. A chemical proof of structure for 84 and 85 was obtained by desulfurization with Raney nickel followed by acetylation. The nmr spectra of the products obtained were in agreement with the given assignments. Another example was opening of the epoxide ring of 86 with magnesium bromide. Here also according to the authors (72) the ring opening occurred predominantly at C-2. The structures were tentatively given as 87 and 88 and a 1:2 ratio of 87 to 88 was reported. These cases are exceptional, however, and more often attack at C-3 is predominant.

For instance, when SCN was used as the nucleophile the ratio of 89 to 90 was 7:3 (73).

In the case of methyl 2,3-anhydro-α-D-lyxofuranoside (81) (70), attack at C-3 remains sterically unhindered but attack at C-2 is now adjacent to the cis C-1 substituent. The effect is dramatic. Ring opening with sodium benzylmercaptide gave methyl 3-S-benzyl-3-thio-3-deoxy-α-D-arabinoside (91) exclusively (74).




81 R = H

94 R = Ac

92 R = $\phi CH_2$

91 R = H, X = $SCH_2\phi$

93 R = $\phi CH_2$, X = F

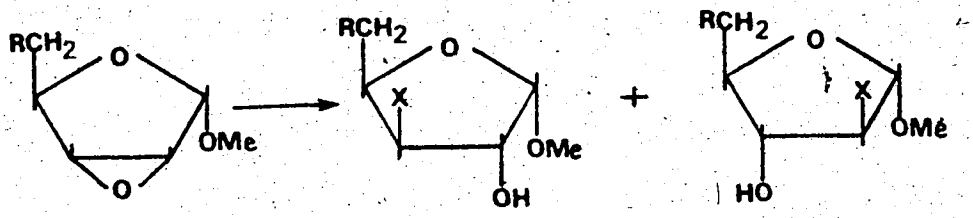
95 R = Ac, X = Br

Scheme XXI

Also when 92 was treated with $KHF_2$ (75) only 93, the product resulting from C-3 attack, was detected in the major components of the reaction mixture. When the 5-O-acetyl derivative 94 was reacted with magnesium bromide only the 3-bromo-3-deoxy-arabinoside 95 was detected (72). That the C-3 opening is the rule was also confirmed when ammonia ($NH_3$) was used as the nucleophile (70) (76). Only one case where significant C-2

attack was noticed has been reported (77). The 5-O-methyl derivative of 81 was treated with sodium methoxide and a 2:1 ratio of C-3 opening to C-2 opening was reportedly formed. It may seem strange that steric hindrance due to the methoxyl group at C-1 would be sufficient to provoke such a change in the direction of ring opening. An alternative, or complementary explanation was suggested by Reist and Holton (78). The lone pairs of the anomeric oxygen atom could create an electronic repulsion of the approaching nucleophile and result in a significant increase of the energy of the transition state for C-2 substitution.

Methyl 2,3-anhydro α-D-ribofuranoside (82), prepared by Schaub et al. (79), contains reversed steric constraints when compared to 81. Attack at C-2 is now free of steric hindrance whereas C-3 attack is hindered by the hydroxymethyl (C-5) substituent. Therefore increased ratios of C-2 to C-3 opening are expected and this is indeed the case. Treatment of the derivative 82a with magnesium bromide afforded a mixture of the xylo 96 to arabino 97 derivatives in a ratio of 2:5 (78).



82 R = OH
82a R = OAc
101 R = OTs
98 R = $OCH_2\phi$
106 R = H

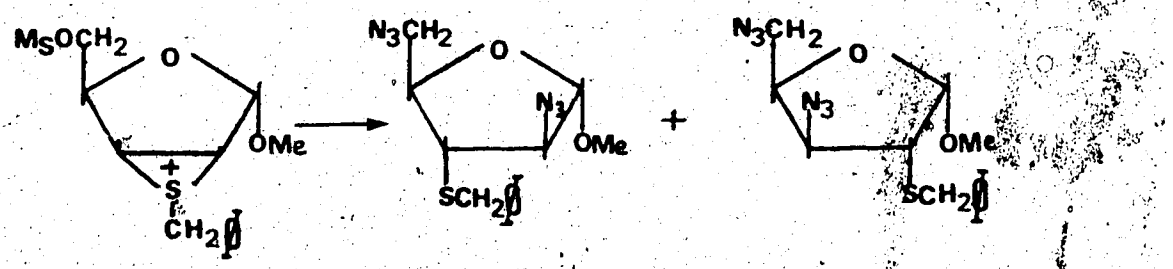
96 R = OAc, X = Br
99 R = $OCH_2\phi$, X = F
104 R = X = H
105 R = OH, X = $NH_2$
107 R = H, X = $NH_2$

97 R = OAc, X = Br
100 R = $OCH_2\phi$, X = F
102 R = X = $SCH_2\phi$
103 R = X = H
108 R = H, X = $NH_2$
109 R = OH, X = $NH_2$

Scheme XXII

It was also found (79) that, with $KHF_2$, 98 gave a 40% yield of the 2-fluoro derivative 100, but only small amounts of the isomeric 3-fluoro product 99 were detected. Even more striking, when sodium methoxide was the nucleophile, attack on 82 was exclusively at C-2 (79a). This result was confirmed recently by Montgomery (79b) who indicated that no chromatographic or pmr evidence for the formation of the 3-O-methyl xylo isomer was found. The 5-O-p-toluenesulfonyl derivative 101 was treated with sodium benzyl-mercaptide, and only the di S-benzyl arabinoside 102 was formed in very good yield (80). Reduction of 101 with lithium aluminium hydride (80) gave a ratio of 103 and 104 of 8:1. In all these cases, the product of C-2 attack is

predominant. However, some early results appeared to contradict this. Baker (81) reported that reaction of ammonium hydroxide with 82 gave methyl-3-amino-3-deoxy-α-D-xylofuranoside (105). Similarly Kuzuhara and Emoto (82) treated methyl-2,3-anhydro-5-deoxy-α-D-ribofuranoside (106) with ammonia and reportedly obtained a single product which they assigned structure 107. They later reinvestigated (83) the structure of their product by chemical degradation and changed their structure assignment to 108. These conflicting results were clarified when Montgomery et al. (84) reinvestigated these reactions. It was found (84) that 82 gave a mixture of 105 and the 2'-isomer 109 in the ratio of 1:1.5 under Baker's condition. Similarly, when 106 was treated with ammonium hydroxide according to the conditions reported by Kuzuhara and Emoto (82), a 1:1 mixture of 107 and 108 was obtained. Interestingly, ring opening of the episulfonium ion 110 with sodium azide gave a 7:3 mixture of the arabinoside 111 and the xyloside 112 (74).




110 111 112

Scheme XXIII

In Methyl 2,3-anhydro-β-D-ribofuranoside (83), (81) the 1-O-methyl and C-5 groups are trans to the oxirane ring. The steric effect of the two groups might be expected to be somewhat comparable. Thus, the direction of cleavage of the epoxide ring would be expected to be controlled primarily by electronic effects. In harmony with this prediction, exclusive or predominant 3-substitution is observed and no exception to this trend has been reported. For instance, the 5-O-benzyl derivative 113 when treated with $KHF_2$ gave only the 3-fluoro derivative 114 (85).


83 R = H

113 R = $CH_2\phi$

115 R = Ac

114 R = $CH_2\phi$, X = F

116 R = Ac, X = Br

117 R = H, X = $SCH_2\phi$

Scheme XXIV

Similarly treatment (78) of 115 with magnesium bromide gave only the 3-bromo compound 116. When 83 was treated with sodium benzylmercaptide (86) mainly one compound was obtained which was shown to be 117. Even with the bulky triphenylmethyl ether group at C-5, ring opening

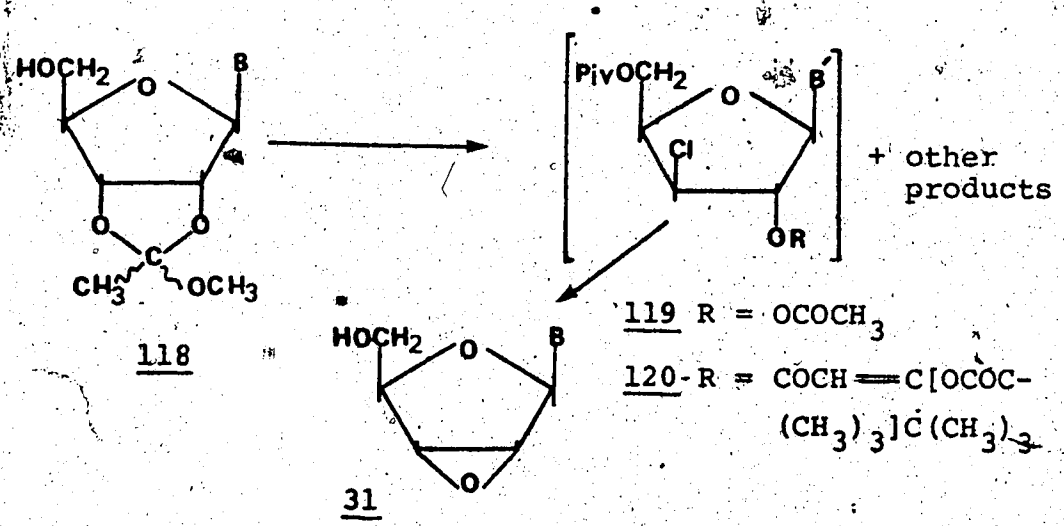
at C-3 with the same nucleophile was observed.

Very clearly the problem of explaining the nucleophilic opening ratios for all the epoxide series reported is extremely complex. In the anhydro sugar series where the greater number of examples is to be found, the problem is further complicated by technical difficulties such as separation and crystallization. In the purine anhydronucleoside series, the data at hand is insufficient to draw meaningful conclusions. For instance, in the purine ribo epoxide series, only a very limited number of successful epoxide opening reactions have been reported. Even in evaluating the reported examples, conclusions are sometimes tenuous for two reasons. The reported yields are sometimes low. The presence of the minor isomer is often ignored if the major product is obtained directly, for instance by crystallization. The work described in this dissertation, in addition to making new nucleoside structures available for previously mentioned studies, provides more examples of epoxide ring opening, especially in the ribo series. The systematic use of a reliable, sensitive, and accurate method of detection of the possible isomers, the useful Dekker Column (Dowex 1-X2 ($OH^-$) resin with selective anion exchange using aqueous alcohol as eluant) (87) has permitted the generation of precise yield-ratio data.

# D I S C U S S I O N

## A. FORMATION OF ADENOSINE EPOXIDES AND SELECTED SYNTHETIC TRANSFORMATIONS.

The syntheses described in this section derived from a reaction which has been developed by Robins and co-workers. It was found (88) that when 2',3'-O-methoxyethylideneadenosine (118), prepared in near quantitative yield by a modification of the procedure reported by Reese (89, 90), was treated with excess pivalic acid chloride in refluxing pyridine a mixture composed primarily of 6-N-pivalamido-9-(3-chloro-3-deoxy-2-O-acetyl-5-O-pivalyl-β-D-xylofuranosyl)purine (119) and 6-N-pivalamido-9-(3-chloro-3-deoxy-5-O-pivalyl 2-O-[4,4-dimethyl-3-pivaloxypent-2-enoyl]-β-D-xylo-furanosyl)purine (120) was obtained in high yield.




118

119 R = $OCOCH_3$

120 R = $COCH{=}C[OCOC(CH_3)_3]C(CH_3)_3$

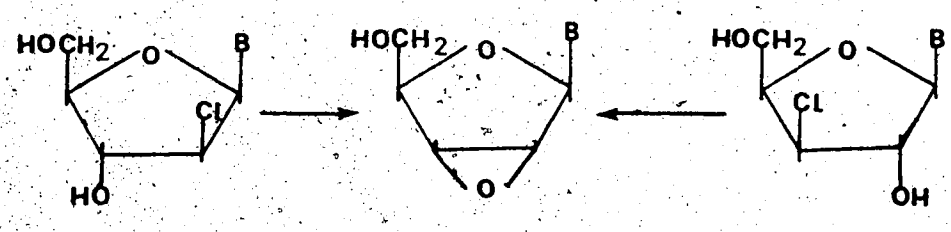
31

B = adenin-9-yl

B' = $N^6$-Pivalyl-adenin-9-yl

Scheme XXV

Treatment of the crude mixture with methanolic sodium methoxide at room temperature gave 9-(2,3-anhydro-β-D-ribofuranosyl)adenine (31). It was shown (91) that 31, obtained by column chromatography on silica gel, was contaminated with small amounts of 9-(2-chloro-2-deoxy-β-D-arabinofuranosyl)adenine (54). It seemed strange, at first, that if the 2'-chloro arabino isomers of 119 and 120 were formed in the reaction mixture they would not be deblocked to 54 and subsequently converted to the epoxide 31.




54 31 56

B = adenin-9-yl

Scheme XXVI

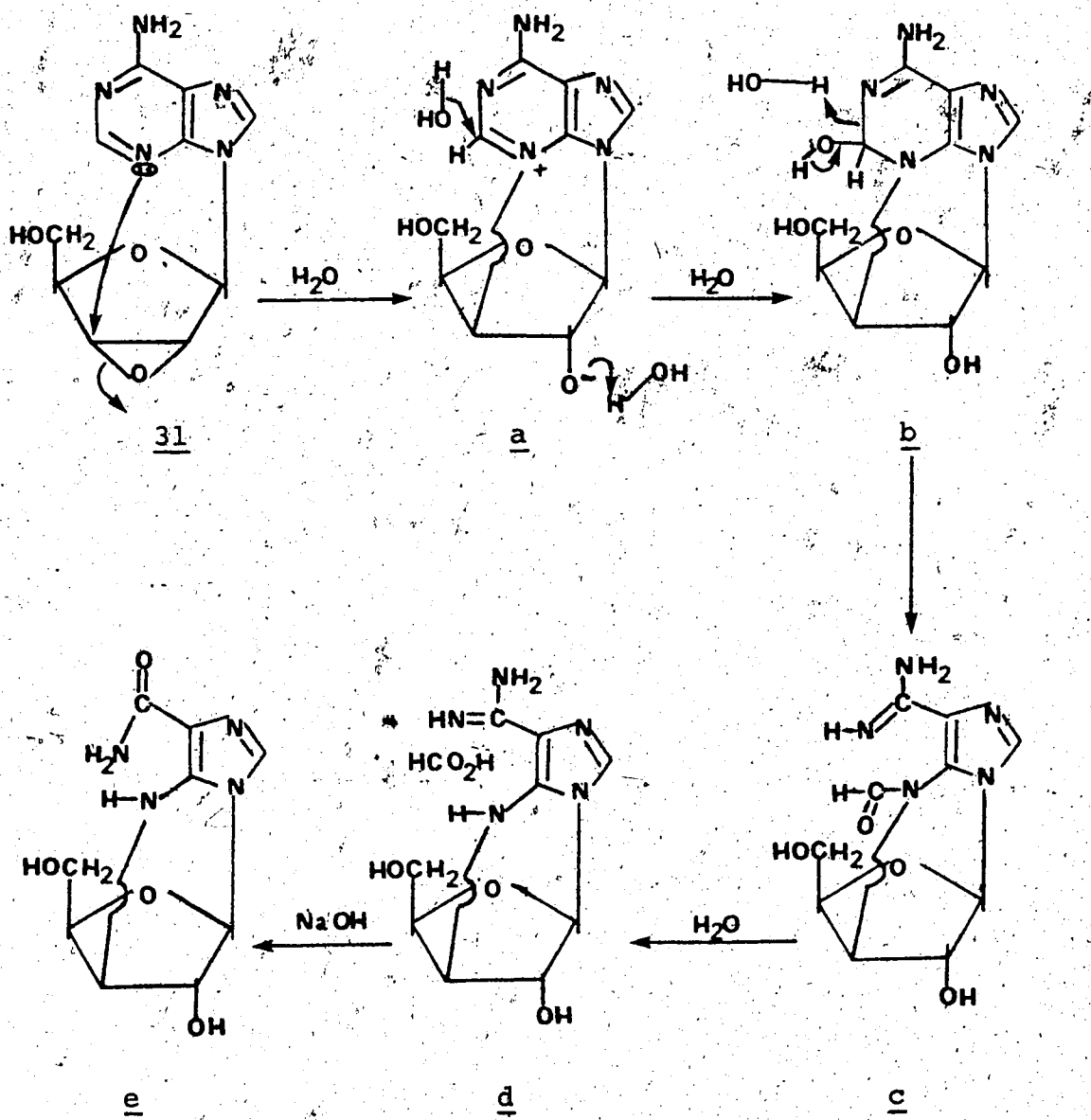
In order to verify this point, the crude reaction mixture was treated with methanolic ammonia and the chloro isomers 54 and 56 were isolated pure in a ratio of approximately 12 to 1. When 56 was treated with sodium methoxide (2%) in MeOH at room temperature the epoxide 31 was formed quantitatively within a few hours. On the other hand 54, under the same conditions, gave 31

very slowly. After a week traces of 54 were still detectable by thin layer chromatography. This observation has been corroborated by Moffatt and co-workers (58) who observed the same reluctance of 54 to undergo cyclization. This shows that intramolecular nucleophilic displacement at the C-2' position is difficult, compared to the same reaction at the C-3', a fact that correlates well with the known difficulty (53) of performing intermolecular nucleophilic displacements at the C-2' of adenosine derivatives. However, 31 could be separated from 54 using rapid column chromatography on Dowex 1-X2 ($OH^-$) and was obtained pure in 63% overall yield from 1. An alternative procedure, more convenient for larger scale reactions, was also developed which involves selective precipitation of 31 (see Experimental Section).

Epoxide 31, which has been prepared from adenosine (1) by a recently reported different procedure (58), had properties generally consistent with recorded values (24, 55, 58). Its melting-decomposition range depends on the rate of heating and its $^1H$ nmr spectrum has $J_{1'-2'}$ and $J_{3'-4'} \cong 0$ (58). An interesting point concerning 31 per se is its optical activity. Baker and co-workers reported $[\alpha]_D^{26}$ -18.3° (c 0.6, 20% aqueous pyridine) for a solid which had "several spots as contaminants" (55). They recorded $[\alpha]_D^{26}$ -17.5° (c 0.4,

20% aqueous pyridine) and $[\alpha]_D^{26}$ -35.2° (c 0.33, $H_2O$) for an analytical sample [see footnote 11 in ref (55)]. Moffat and co-workers (58) report $[\alpha]_D^{23}$ -21.8° (c 0.2, $H_2O$) and quoted the $[\alpha]_D$ -18.3° value, with no concentration nor solvent specified, from ref (55). A carefully purified and dried sample of 31, which had no observable impurities when applied heavily to a tlc plate, had $[\alpha]_D^{24}$ -35.4° (c 0.22, $H_2O$) and -20.4° (c 0.4, 20% aqueous pyridine) in close agreement with Baker's values (55). It was noted (91) that 31 was slowly decomposing upon standing in $H_2O$ and that the normal ultra-violet absorption at 260 nm was decreasing with concomitant appearance of a new peak with a maximum at ∿293 nm. This decomposition was greatly accelerated by heating. This may be correlated with the observation of Goodman and co-workers (57, 68) who noted the formation of water soluble products in reactions of adenine nucleosides involving 2',3'-ribo-epoxides (57, 68) and episulfonium (92) intermediates. They postulated $N^3 \rightarrow 3'$-cyclonucleoside structures analogous to a on the basis of salt like properties and a bathochromic shift to 293 nm in the uv absorption maximum.

It should be noted, however, that the shift observed in going from the nucleoside (∿260 nm) to the postulated $N^3 \rightarrow 3'$-cyclonucleoside a (57, 68, 92) (∿293 nm) is 33 nm, whereas a shift of about 12 nm to 272 nm is ordinarily




Scheme XXVI-I

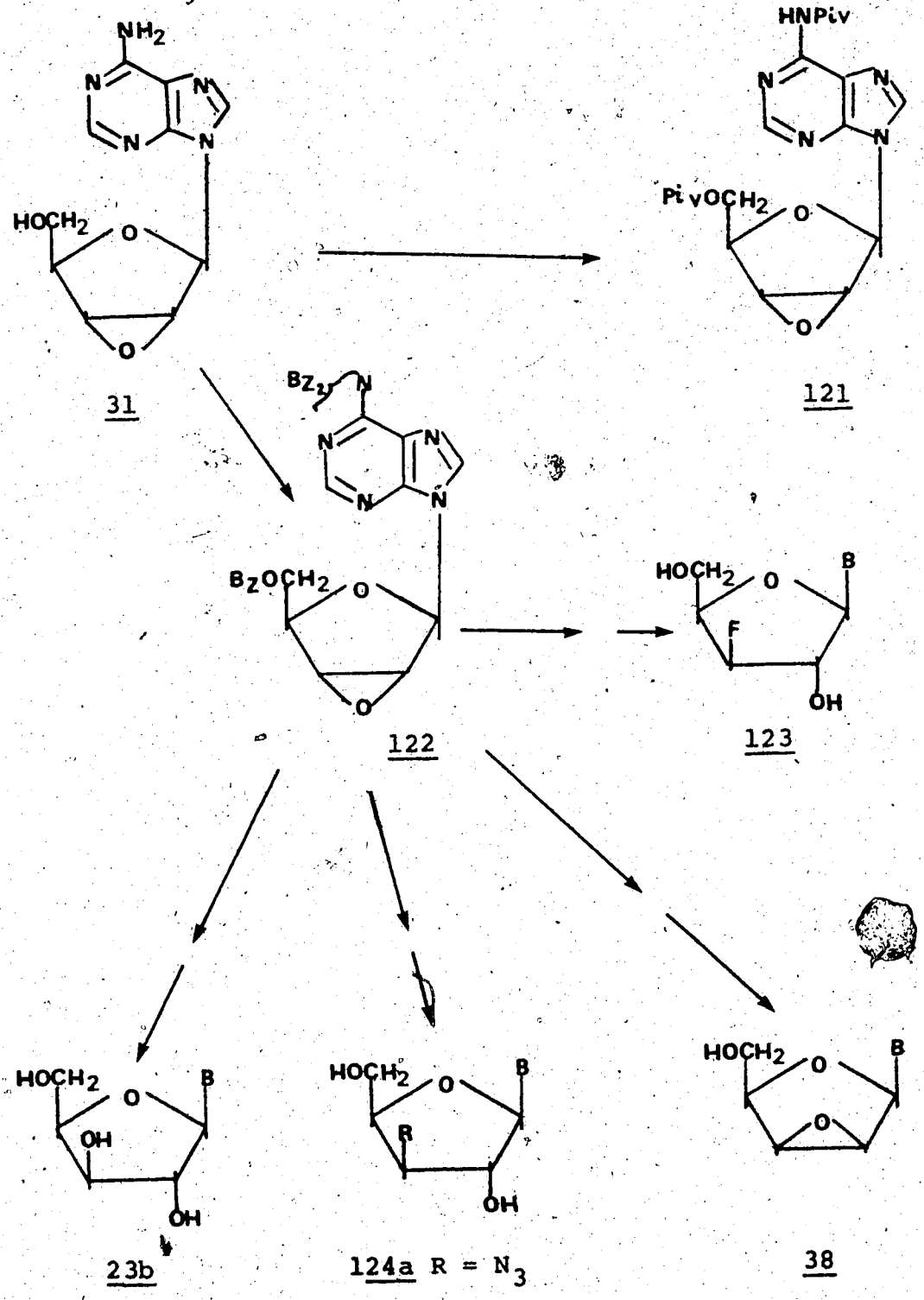
found with known $N^3 \rightarrow 5'$-cyclonucleosides (15). The uv maxima of the postulated $N^3 \rightarrow 3'$-cyclonucleosides at ~293 nm is in reasonable agreement (92a) with that of a $N^3 \rightarrow 5'$-cyclonucleoside in the puromycin aminonucleoside series (288 nm). However, the 6-N,N-dimethylamino-purine nucleoside precursor in that case (92a) had its uv maximum at 275 nm, which again corresponds to a 13-nm shift. Uv absorption in the 280-290 nm range has been reported for 5-aminoimidazole-4-carboxamidine (92b).

That the same phenomenom was taking place in this case was indicated by the isolation of d, a highly dextrorotatory product with uv maximum 293 nm, (and e obtained by treatment of d with base) and its complete characterization including a single crystal x-ray analysis (91). The formation of d can be rationalized as follows (Scheme XXVII). Initial attack on the C-3 of the epoxide ring by the unshared electron pair of $N^3$ with concomitant proton abstraction by the oxygen anion would lead to a. Attack of water on the positively polarized C-2 of the $N^3 \rightarrow 3'$-cyclonucleoside a would give the covalently hydrated species b which would give the $N^5$-formyl derivative c by ring opening. Hydrolysis of the latter c would lead to d. Treatment of d with hot aqueous sodium hydroxide would hydrolyze the amidine function to give e.

Attempts to open the epoxide ring of 31 with sodium

benzoate in wet DMF gave poor yields of the desired compound, 23b, because of preponderant formation of d (57). Owing to the instability observed with 31, adenine ring-acetylated derivatives were prepared. Jahn (93) has reported that such N-acylated adenosine 5'-tosylates were effective substrates for nucleophilic displacement reactions whereas the unprotected nucleoside readily forms $N^3$→5'-cyclonucleoside under those conditions. Treatment of 31 with pivalic acid chloride in pyridine at room temperature gave 6-N-pivalamido-9-(5-O-pivalyl-2,3-anhydro-β-D-ribofuranosyl)purine (121) in essentially quantitative yield. Benzoylation similarly afforded an N,N,$O^5$-tribenzoyl derivative, 122. Bis-N-benzoylation has usually been assigned, $N^1$,$N^6$-dibenzoyl structures (94) after the suggestion of Khorana (94a); however, the $N^1$,$N^6$-dibenzoyl isomer was postulated recently (95).

Treatment of either 121 or 122 with tetraethylammonium fluoride in dry acetonitrile at reflux for an extended period effected epoxide ring opening by fluoride. After deblocking and purification on a Dekker column (87), 9-(3-fluoro-3-deoxy-β-D-xylofuranosyl)adenine (123) was obtained in over 60% yield. Physical properties of 123 were generally in agreement with values reported (85) for a sample prepared by coupling of 2,5-di-O-benzoyl-3-fluoro-3-deoxy-α,β-D-xylofuranosyl bromide and 6-benzamidopurine mercury salt (14). No 2'-fluoro




31 121 122 123 23b 124a 38

124a R = $N_3$

124b R = $NH_2$ B = adenin-9-yl

Scheme XXVIII

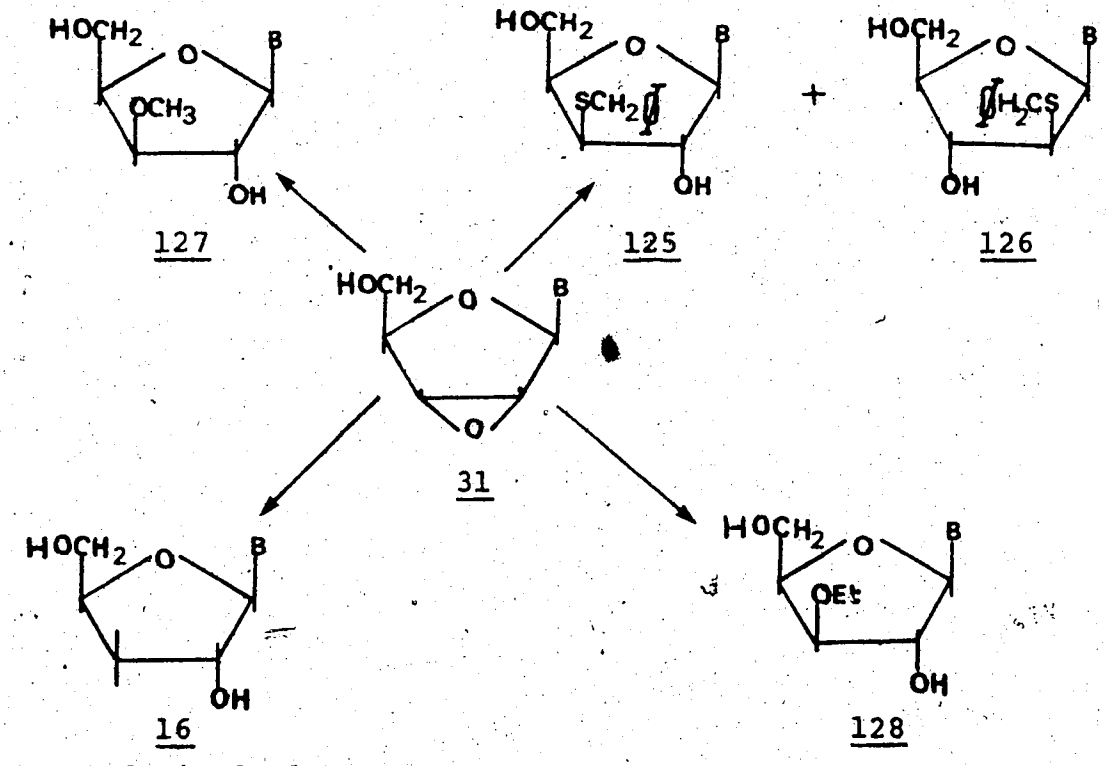
isomer (79) was observed in our sequence of 122 → 123, although a small amount of 9-β-D-xylofuranosyladenine (23b) was formed.

Sodium benzoate in hot DMF containing some water (65) converted 122 into a presumed mixture of mono and di-N-benzoylated 9-(3,5-di-O-benzoyl-β-D-xylofuranosyl)-adenine intermediates which were deblocked to give excellent yields of 9-β-D-xylofuranosyladenine (23b) after Dowex 1-X2 ($OH^-$) chromatography using MeOH:$H_2O$ as eluant. Further elution using higher concentrations of MeOH gave a small quantity of 9-β-D-arabinofuranosyl-adenine (17). Acid hydrolysis of 23b and paper chromatography (96) of the sugar versus the four aldopentoses showed only xylose present (91). The arabino product 17 was shown to be free from the isomeric 23b by paper chromatography and electrophoresis. Over a number of runs the ratio of 23b to 17 varied between 10:1 and 20:1. The separation of these two compounds using Dowex 1-X2 ($OH^-$) presented no difficulty. It has been reported (67) that the two isomers 23b and 17 could only be separated incompletely using the same type of column. To verify this point two artificial mixtures of 23b and 17 with relative concentrations of 11:1 and 1:11 were prepared and chromatographed using identical columns. In both cases the separation was clean and complete as shown by the uv absorption

profiles and the quantitative recovery. Previously recorded physical constants for 23b are rather ill defined (43, 44, 45, 47, 48). The $^1$H nmr spectrum was in agreement with reported values (47, 97). The mass spectrum (see Table 1) agreed with the tabulation of McCloskey and co-workers (98). The melting point, ~ 185° with decomposition, is dependent on how it is heated and previous values (43, 44, 45, 47, 48) differ. The $[\alpha]_D^{25}$ -67° (c 1.14, $H_2O$) of 23b is significantly more strongly levorotatory than recorded for other preparations (43, 47, 48). All of those, however, involved coupling procedures and anomer contamination was possible. This sequence of reactions represents the direct transformation of a naturally occurring ribonucleoside to its xylo epimer.

Treatment of 122 with sodium azide in hot DMF (99) followed by deblocking gave high yields of 9-(3-azido-3-deoxy-β-D-xylofuranosyl)adenine (124a). A trace of presumed 2'-azido isomer was separated by column chromatography (87) and its structure was suggested by mass spectroscopy. This reaction could be performed on the unprotected epoxide 31 with identical results. Catalytic hydrogenation of 124a to give 9-(3-amino-3-deoxy-β-D-xylofuranosyl)adenine (124b) proceeded smoothly. This product is seen to be the 3' epimer of $N^6$-bis(desmethyl)-puromycin aminonucleoside.

It was noted by Goodman and co-workers (71, 68) that, among the nucleophiles studied, sodium benzylmercaptide was giving the more C-2' attack (C-2 for the anhydro sugar) on 80 and 43 although for 41 no trace of the 2'-isomer was found. Treatment of 31 with sodium benzyl mercaptide (synthesized *in situ*) in refluxing methanol gave almost quantitative yields of 9-(3-S-benzyl-3-deoxy-β-D-xylofuranosyl)adenine (125). A trace of the 2'-isomer, 9-(2-S-benzyl-2-deoxy-β-D-arabinofuranosyl)adenine (126) was separated by column chromatography and its structure established by mass spectroscopy (see table 1) and nmr ($H_1$, at δ 6.5 p.p.m., see nmr section). The ratio of 125 to 126 was approximately 12:1.




B = adenin-9-yl

Scheme XXIX

In order to assess the utility of 31 as a starting material for the synthesis of 2' or 3'-deoxy nucleosides the reaction of 31 with sodium borohydride was investigated. Reaction of 122 with large excess of sodium borohydride in MeOH proceeded slowly at room temperature to give 9-(3-O-methyl-β-D-xylofuranosyl)adenine (127) after deblocking. Alternatively, heating 31 in MeOH at reflux with sodium borohydride proceeded to give good yields (77%) of 127 without apparent cyclonucleoside formation. An analogous reaction has been reported very recently (100) in the steroid series. No 2'-isomer was detected by chromatography, the only by-product being 3'-deoxyadenosine (16) formed in 8% yield. Interestingly, heating a methanolic sodium methoxide solution of 31 at reflux gives but a trace of product migrating (t.l.c.) with 127 plus material not moving from the origin. Inhibitory biological activity of 9-β-D-xylofuranosyladenine (23b) has been reported (48, 101, 102) and the investigation of O-methyl ethers of biochemically important nucleosides is of current interest (103).

Treatment of 31 with excess sodium borohydride in 98% EtOH at reflux gave fair yields of 3'-deoxyadenosine (16). Anion exchange chromatography revealed some cyclonucleoside formation and the presence of 9-(3-O-ethyl-3-deoxy-β-D-xylofuranosyl)adenine (128). This

sequence of reactions provides an easy access to the well studied antibiotic cordycepin (16) utilizing adenosine (1) as a starting material. Interestingly, when small amounts of sodium borohydride in 98% ethanol were used instead of the usual large excess, the reaction of 31 gave 128 in 70% yield. Very little cyclonucleoside or 3'-deoxyadenosine (16) were detected.

Treatment of the crude product from reaction of 122 with sodium benzoate-DMF with methanesulfonyl chloride in cold pyridine gave a monomesylate, which was converted to 9-(2,3-anhydro-β-D-lyxofuranosyl)-adenine (38) by methanolic sodium methoxide. Direct access to this useful (56, 104) lyxo-epoxide from adenosine (1) is thus provided. However, large scale preparation of 38 by this route suffered from some drawbacks. Extended reaction times for the opening of the epoxide ring of 122 with benzoate resulted in partial loss of the sugar benzoyl groups. This was presumably due to hydrolysis in the slightly alkaline moist medium at 100°. This phenomenom has been observed by Baker and co-workers (65) during work on the opening of the lyxoepoxide 38 with the same reagent under similar conditions. This loss of the 3'-O-benzoyl group resulted presumably in the formation of small quantities of a 2,3'-di-mesylate in the mesylation step which, upon treatment with methanolic sodium methoxide,

regenerated some of the starting ribo-epoxide 31 (54). Separation of 31 and the lyxo isomer 38 is difficult by silica gel chromatography and was impossible by the usual Dowex 1-X2 ($OH^-$) procedure. An alternative route to 38 was devised by Baker and co-workers (56), starting from 9-β-D-xylofuranosyl adenine (23b) (see scheme IX). Their procedure was adapted as follows. The deblocked xylo product 23b was transformed into 9-(3,5-O-isopropylidene-β-D-xylofuranosyl)adenine (32) in quantitative yield using 2,2-dimethoxypropane in acetone with p-toluenesulfonic acid as a catalyst. (The original procedure (56) called for ethanesulfonic acid in acetone). The isopropylidene derivative 32 crystallized readily from 95% ethanol (in an ether containing desiccator) as a 1:1 solvate with ethanol as evidenced by its nmr spectrum and elemental analysis. Heating these crystals at 110° for a week under high vacuum resulted in only partial removal of the crystallization solvent. The same problem was encountered by other investigators (105). It is interesting to note that the nmr spectrum (DMSO-$d_6$) of 32 showed the anomeric proton as a singlet whereas it is a doublet ($J_{1'-2'}$ = 2 Hz) in the parent compound 23b. Mesylation of the C-2' hydroxyl group of 32 to give 37 was realized using methanesulfonyl chloride in pyridine at room temperature, the reaction being quantitative within minutes as in-

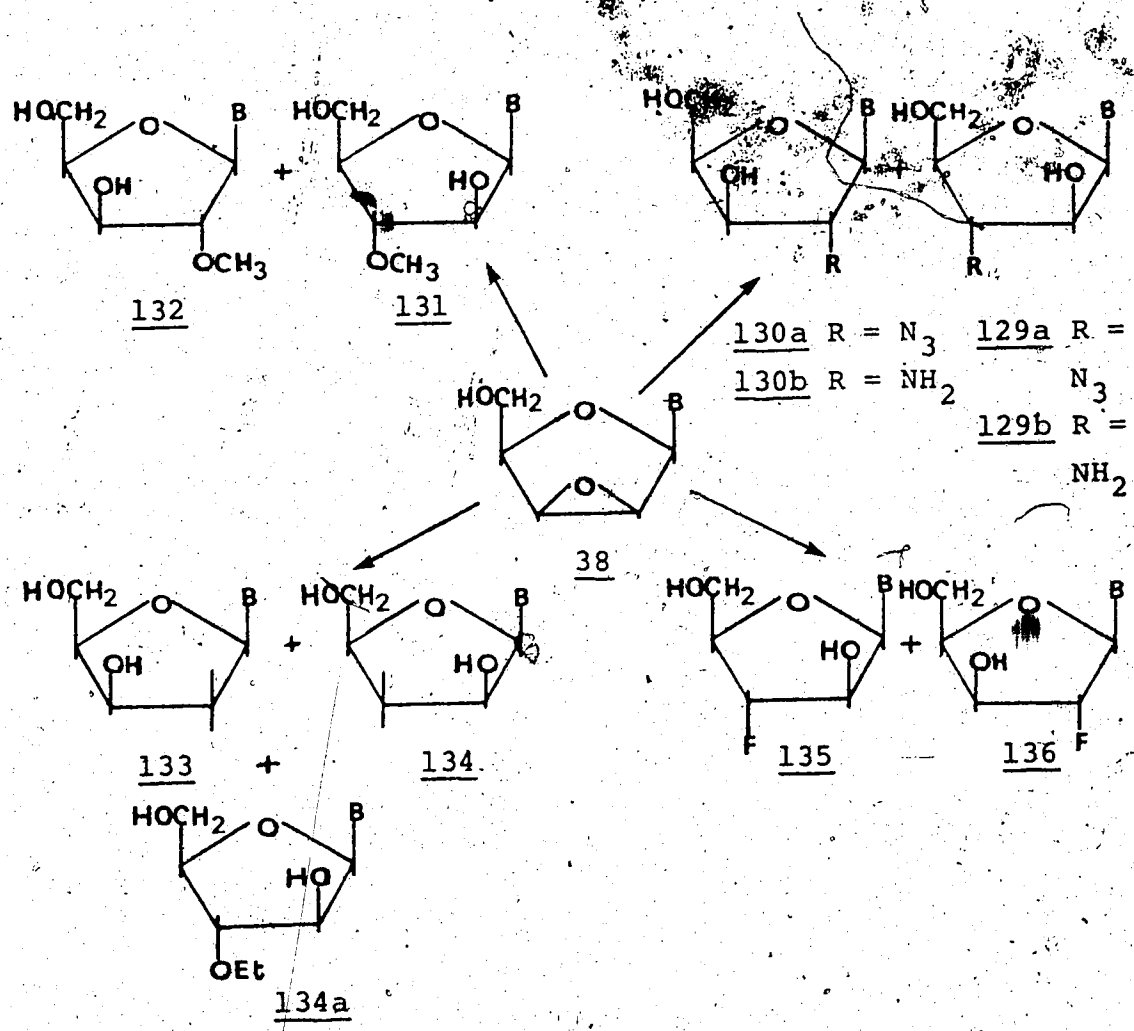
dicated by tlc. Removal of the isopropylidene group, to give 9-[2-O-(methanesulfonyl)-β-D-xylofuranosyl)-adenine (37a), was reportedly effected with some difficulty (56) using 90% acetic acid at 100° for 5 hr. Use of 90% trifluoroacetic acid (106) gave quantitative removal of the ketal ring at room temperature within minutes. Finally ring closure to 38 was realized by treatment of 37a with sodium methoxide in methanol (2%) at room tempefature. A point of interest is the ease of cyclization from 37a to 38 where the leaving group at the C-2' position is the mesyl group (in the xylo configuration) whereas cyclization from 54 to 31, where the leaving group is chlorine, occurred very slowly. The lyxo-epoxide 38 was obtained as a pure white solid after Dowex 1-X2 ($OH^-$) chromatography (57), no purification of intermediates was necessary when this final chromatography step was included in the procedure.

It has been reported (56) that opening of the epoxide ring of 38 with sodium benzoate in wet DMF gives 9-β-D-arabinofuranosyladenine (17) in 54% yield with only traces of the isomeric xylo compound 23b. When 38 was treated with sodium benzoate in wet DMF (4% $H_2O$) at 100° for 5 hr and the crude reaction mixture placed on a Dowex 1-X2 ($OH^-$) column, two products were obtained: 9-β-D-arabinofuranosyladenine (17), shown free of 23b by tlc, paper chromatography and electrophoresis, in a

yield of 81% and the isomeric 23b, shown pure by the same methods, in a yield of 6.5%. The arabinoside 17 had properties consistent with recorded values (56). Its melting point 265-266° was higher than the reported values (56, 107) and its $[\alpha]_D^{25}$ -12° (c 0.1, pyridine) more levorotatory than reported (107). This route via the lyxoepoxide 38 provides access to this important antibiotic (108) from the naturally occurring ribo-nucleoside adenosine (1).

Martinez et al. have reported (104) the reaction of 38 with sodium azide in 2-methoxyethanol and found that the ratio of the 3'-azido arabino derivative 129a to the 2'-azido xylo derivative 130a was 15:1. Reduction with palladium on charcoal gave the corresponding amino derivatives 129b and 130b.

In an analogous fashion 38 was opened with sodium azide in DMF to give 129a in 68% yield and traces of the 2'-isomer 130a. Reduction of 129a to the corresponding 129b proceeded smoothly.




Scheme XXX

Treatment of 38 with sodium borohydride in methanol at reflux gave excellent yields of the expected 9-(3-O-methyl-β-D-arabinofuranosyl)adenine (131). Column chromatography (87) permitted the separation of 9-(2-O-methyl-β-D-xylofuranosyl)adenine (132), easily identified by its mass spectrum, (see table 1 and mass spectrum discussion) and its nmr spectrum. The ratio of 131 and 132 was approximately 8 to 1. Interestingly,

the other by-product p[illegible]t in trace amounts was identified as 9-(2-deoxy-β-D-threo-pentofuranosyl)adenine (133).

When 38 was treated with sodium borohydride in ethanol at reflux the major product, obtained in 65% yield, was identified as 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine (134). It was possible to separate the 2'-isomer 133 as well as a trace of 9-(3-O-ethyl-β-D-arabinofuranosyl)adenine (134a) by Dowex chromatography. The ratio of 134 to 133 was 13 to 1.

Here, as seen for the ribo-epoxide 31, there is competition between two types of nucleophiles: the hydride ion and the anion derived from the solvent. In the case of the lyxo-epoxide 38 the greater steric ease of attack at C-2' gives positional isomers also. The two deoxy isomers 133 and 134 have been synthesized by Goodman and co-workers (92) by an indirect route from the lyxo-epoxide 38. Opening of 38 with sodium benzyl-mercaptide gave two isomeric S-benzyl derivatives which were desulfurized with hydrogen and a nickel sponge (Raney nickel) catalyst to give 134 and 133 in yields of 46% and 10% respectively.

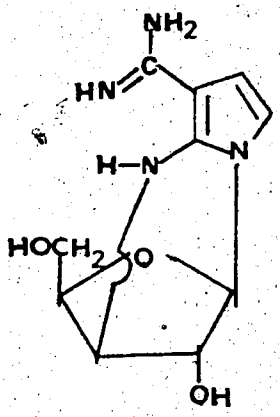
Reaction of 38 with $KHF_2$ in ethylene glycol was reported (109) to give only 9-(3-fluoro-3-deoxy-β-D-arabinofuranosyl)adenine (135) and it was of interest to investigate the behavior of 38 when treated with

tetraethylammonium fluoride in acetonitrile at reflux. Thin layer chromatography (t.l.c.) indicated disappearance of the starting material and appearance of two new products of almost identical $R_F$ values. The two products were partially separated by silica gel chromatography and shown, by mass spectrometry, to be the isomeric 135 and 136. The first compound eluted from the column (136) was obtained pure and its structure confirmed by $^1H$ n.m.r.

## B. SYNTHESIS AND TRANSFORMATION OF TUBERCIDIN EPOXIDES INTO EPIMERIC ANTIBIOTIC STRUCTURES.

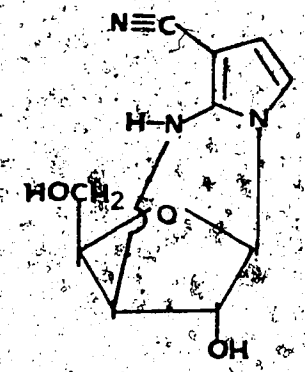
The application of the reactions described above for the adenosine (1) series to the tubercidin (19) series was of considerable interest. Many of the adenosine analogs mentioned have appreciable biological activity and biochemical investigation of the corresponding tubercidin derivatives would be significant by analogy. As well, the previously noted resistance of tubercidin to enzymatic deamination removes this potential route of biological inactivation. Another point to be noted is that whereas an alternative method of synthesis (coupling procedure) exists for the adenosine analogs, this is not the case for the tubercidin derivatives which are not practically amenable to base-sugar (or fraudulent sugar) coupling procedures (110). Although the pivalylchloride-pyridine reaction with 2',3'-O-methoxyethylidenetubercidin is successful (88), the sodium methoxide treatment required for obtaining the corresponding epoxide, 4-amino-7-(2,3-anhydro-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (58) (2,3-anhydrotubercidin), appeared to cause extensive decomposition. Treatment of tubercidin (19) with α-acetoxyisobutyryl chloride (47) at room temperature in the presence of excess sodium iodide (60) gave quantitative yields of the intermediate 51 (Scheme XII). Deblocking with

methanolic ammonia at room temperature gave concomitant epoxide formation. It is interesting to note that epoxide formation from the 3'-chloro analog 57 (or the 3'-bromo) was reported to be very slow under similar conditions (61). Rapid chromatography of this reaction mixture over silica gel gave the desired 58 in good yields. Rapid crystallization of this product from ethanol (in a desiccator containing ether) gave the analytical sample of 58. Its melting range was fairly small 170-173° and its $^1H$ nmr spectrum had $J_{1'-2'}$ and $J_{3'-4'} \simeq 0$ (61). However, it is extremely susceptible to decomposition on standing, either dry or in solution. Decomposition of 58 in solution could be followed by thin layer chromatography (t.l.c.) very easily. Evaporation of such a solution of 58 and drying of the residue under vacuum gave a solid whose mass spectrum contained a peak at m/e 238 (formula $C_{10}H_{14}N_4O_3$ by accurate mass measurement) and another peak at m/e 221 (formula $C_{10}H_{11}N_3O_3$ by accurate mass measurement). By analogy with the adenosine case (Scheme XXVII) these two compounds could be visualized as I and Ii.



$C_{10}H_{14}N_4O_3$

I

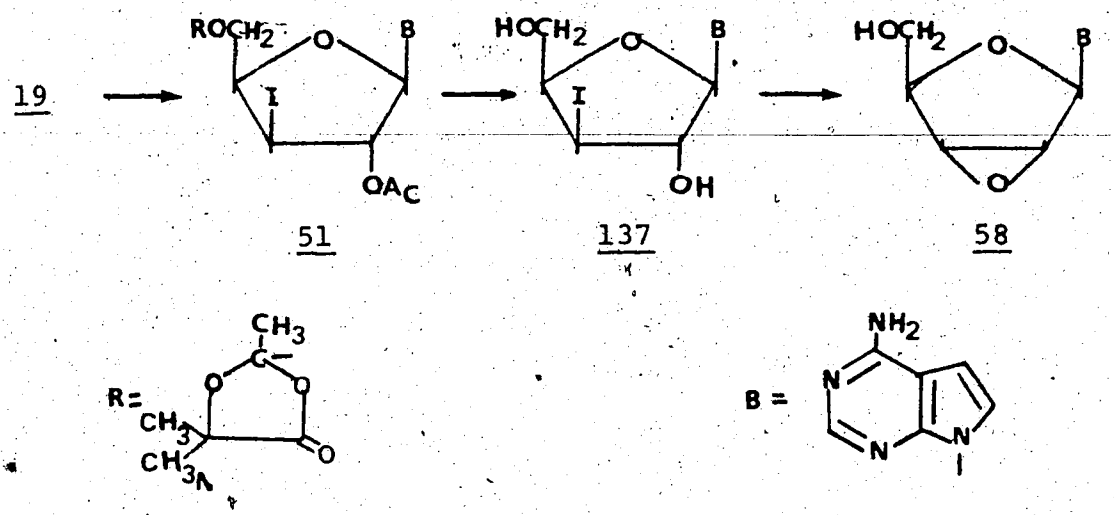


$C_{10}H_{11}N_3O_3$

Ii

It is interesting to note that, although the peak at m/e 221 does not exist in the mass spectrum of pure 58, it was present in the reported (61) mass spectrum of 58 and attributed to the loss of HCN from the parent ion. It seems rather strange that this unique fragmentation takes place for 58 whereas in all reported cases (98) the loss of HCN always arises from the B+H ion (see mass spectrum discussion). An alternative explanation for the presence of this peak at m/e 221 in the reported mass spectrum is suggested by the above results: 58 could have been partially decomposed to I which in turn could give rise to Ii.

By deblocking 51 with methanolic ammonia at -20° it was possible to prevent epoxide formation and 4-amino-7-[-3-iodo-3-deoxy-β-D-xylofuranosyl]pyrrolo-[2,3-d]pyrimidine (137) was isolated in good yield.

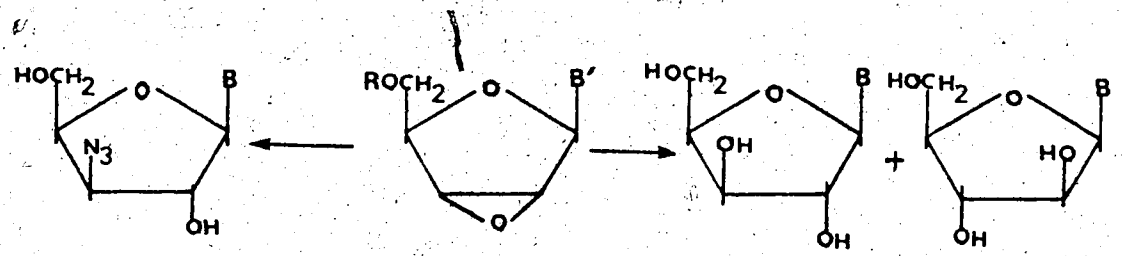


Scheme XXXI

Although the adenine ribo-epoxide 31, like 58, was subject to decomposition via cyclonucleoside formation, it could be used directly as a starting material for a number of reactions including reactions with sodium borohydride in alcohols. However, when 58 was reacted with sodium borohydride in methanol only poor yields of 4-amino-7-(3-O-methyl-β-D-xylo-furanosyl)pyrrolo[2,3-d]pyrimidine (138) were obtained. Similarly reactions of 58 with sodium borohydride in 98% ethanol gave 4-amino-7-(3-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine (139) in but 17% yield.

Treatment of 58 with benzoyl chloride in pyridine at room temperature gave an N,N,O$^{5'}$-tribenzoyl derivative, 140. This readily crystallizable compound was completely stable at room temperature. Sodium benzoate

in hot DMF containing some water converted 140 into a mixture of intermediates. Deblocking with methanolic sodium methoxide at room temperature gave a crude product which gave two well separated products (Dowex 1-X2 ($OH^-$) chromatography) identified as: 4-amino-7-(β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine (xylotubercidin) (141), in 69% yield and a small amount of 4-amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-d]pyrimidine (arabinotubercidin) (142).




143 140 141 142

B = 4-Amino-7-pyrrolo[2,3-d]pyrimidin-7-yl

B'= N,N-dibenzoyl-4-amino-7-pyrrolo[2,3-d]pyrimidin-7-yl

R = COφ

Scheme XXXII

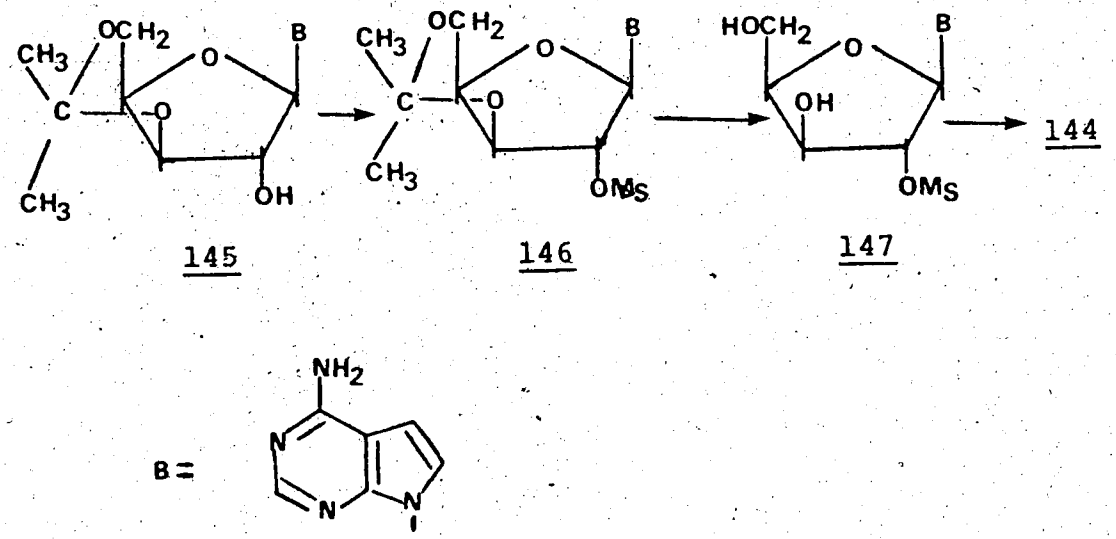
The latter was identified by comparison, using thin layer chromatography (t.l.c.), paper chromatography, electrophoresis, mass spectrometry, and $^1H$ n.m.r. spectroscopy, with an authentic sample of arabinotubercidin (142). In a number of these reactions, the ratio of 141 to 142 was between 20:1 and 10:1. This surprising result constitutes the first reported nucleophilic displacement at the C-2' of tubercidin (19). It is in-

tempting to note that the ratio of xyloadenosine (23b) to arabinoadenosine (17) was not markedly different. Formation of 141 and 142 in this reaction was accompanied by appreciable cyclonucleoside formation as indicated by a u.v. absorption at ∿ 305 nm. Xylotubercidin (141) has a melting point of 223-224° and its $[\alpha]_D^{24}$ -135° (c 0.5, DMF) is strongly levorotatory as expected. Its $^1$H nmr ($H_1$ at δ 5.94, $J_{1',2'}$ ∿ 2 Hz) and mass spectra (see table 1) were similar to those of xyloadenosine (23b). This close resemblance between tubercidin and adenosine analogs was found to be general.

Treatment of 140 with sodium azide in hot DMF (99), followed by deblocking gave fair yields of 4-amino-7-(3-azido-3-deoxy-β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine (143). No 2'-isomer was detected by column chromatography.

The lyxo-epoxide of tubercidin, 4-amino-7-(2,3-anhydro-β-D-lyxofuranosyl)pyrrolo[2,3-d]pyrimidine (144) was obtained by the route (Scheme IXa) used for the corresponding adenine lyxo-epoxide (38). Treatment of 141 with 2,2-dimethoxypropane in acetone in the presence of p-toluenesulfonic acid gave quantitative yields of the isopropylidene derivative 145. This crystalline compound showed the same tendency as 32 to retain solvent molecules. Its $^1$H nmr spectrum contained a singlet for the anomeric proton peak analogously to that of 32.

Mesylation of the 2'-hydroxyl to give 146 was effected at room temperature by reaction with methanesulfonyl chloride in pyridine. Removal of the isopropylidene group to give 147, occurred at room temperature in trifluoroacetic acid (106). The lyxo-epoxide 144 was obtained by ring closure with methanolic sodium methoxide and purified by Dowex-1X2 ($OH^-$) column chromatography. The relatively mild conditions used in this reaction sequence are particularly suitable for this sensitive antibiotic series.




Scheme IXa

Treatment of 144 with sodium benzoate in hot DMF containing some water effected the opening of the epoxide ring in good yield. Column chromatography (87) on Dowex 1-X2 ($OH^-$) gave two well separated compounds: arabinotuber-

cidin (142) and a small amount of xylotubercidin (141). The approximate ratio of 142 to 141 was 1.7:1. Arabinotubercidin (142) had a melting point of 125°-126° and its $[\alpha]_D^{24}$ = +6.9° (c 0.50, DMF) was significantly more dextroratory than that of arabinoadenosine (17). Its $^1$H n.m.r. ($H_1$, at δ 6.42, $J_{1',2'}$ = 4 Hz) and mass spectra are again closely similar to those of arabinoadenosine (17). This sequence of reactions illustrated the transformation of the naturally occurring ribo tubercidin (19) into its xylo and arabino isomers.

As noted earlier, the tubercidin compounds synthesized in this work present close analogies in structures (as evidenced for instance by their nmr and mass spectra) with their adenosine analogs. It is not unreasonable to expect interesting biological properties for xylotubercidin (141) and arabinotubercidin (142) in view of the biological activity of xyloadenosine (23b) and arabinoadenosine (17). Also, a serious limiting factor with 23b and 17, namely biological inactivation via enzymatic deamination, should not prevail for 141 and 142 since it is known that tubercidin (19) is not a substrate for adenosine deaminase (39).

It is clear that the epoxides 31, 38, 58 and 144 are convenient starting materials for the introduction of new functionality at the C-3' and C-2' positions.

It was interesting to briefly explore the introduction of new functionality at the 5'-position of the sugar moiety.

Treatment of 31 with p-toluenesulfonyl chloride in cold pyridine gave high yields of 9-[5-O-p-(toluenesulfonyl)-2,3-anhydro-β-D-ribofuranosyl]adenine (148). Unfortunately this material was unstable in solution (see nmr discussion) due to $N^3 \rightarrow 5'$ cyclonucleoside formation -- an interesting result in view of the reported (111) inertness of the 5'-O-p-toluenesulfonyl derivative of the lyxo-epoxide 38.

In conclusion, it can be said that the present work provides convenient access to members of an important class of nucleosides, the nucleoside epoxides. These compound are versatile starting material for further modification of the carbohydrate moiety.

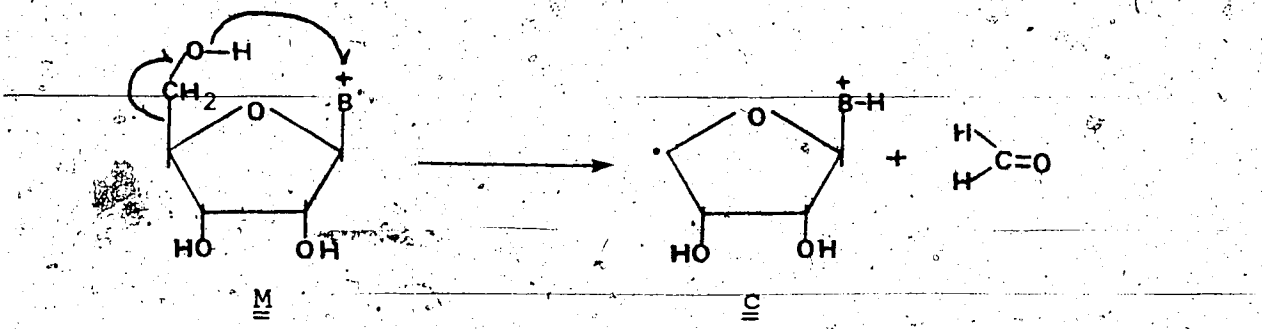
Certain analogs of biological interest have been prepared in the adenosine series as well as certain tubercidin analogs of significant potential biochemical utility. Additional work in this series should provide routes to various other interesting compounds.

## C. MASS SPECTRAL AND NMR OBSERVATIONS.

In 1970 McCloskey and co-workers (98) published a detailed study dealing with the mass spectrometry of adenosine analogs. This study provided an assessment of the structures and mechanisms of formation of the principal fragment ions in nucleosides and structural analog mass spectra. The compounds studied were structural variants of a single base adenine. The synthesis of a number of adenosine analogs, as well as similar ana[illegible]tubercidin (19), is described in this dissertati[illegible]efore, in the light of these new examples, it is interesting to summarize some of the more important conclusions reached in this publication (98).

The more structurally significant ions consist of the purine base, here adenine, (or of the 4-amino-pyrrolo[2,3-d]pyrimidine base in the tubercidin derivatives), plus various portions of the sugar skeleton. With a few exceptions, the sugar fragment per se (ion s) plays a minor role in the fragmentation of adenosine analogs. Loss of hydroxyl radical from the molecular ion M to yield the minor ion a is observed in most spectra; however, a specific hydroxyl group does not appear to be involved and therefore this ion is of no structurally diagnostic value. Elimination of formaldehyde (30 mass units) occurs by proton transfer from

the 5'-hydroxyl group to the base with concomitant loss of C-5' ($H_2CO$) to provide ion c, which is an important structural indicator of the 5' position. This ion c is usually very easily detected, whatever its relative intensity, since it occurs in the high mass region of the spectrum which is usually unobscured by other fragmentations. The proposed dominant route for ion c is depicted below:

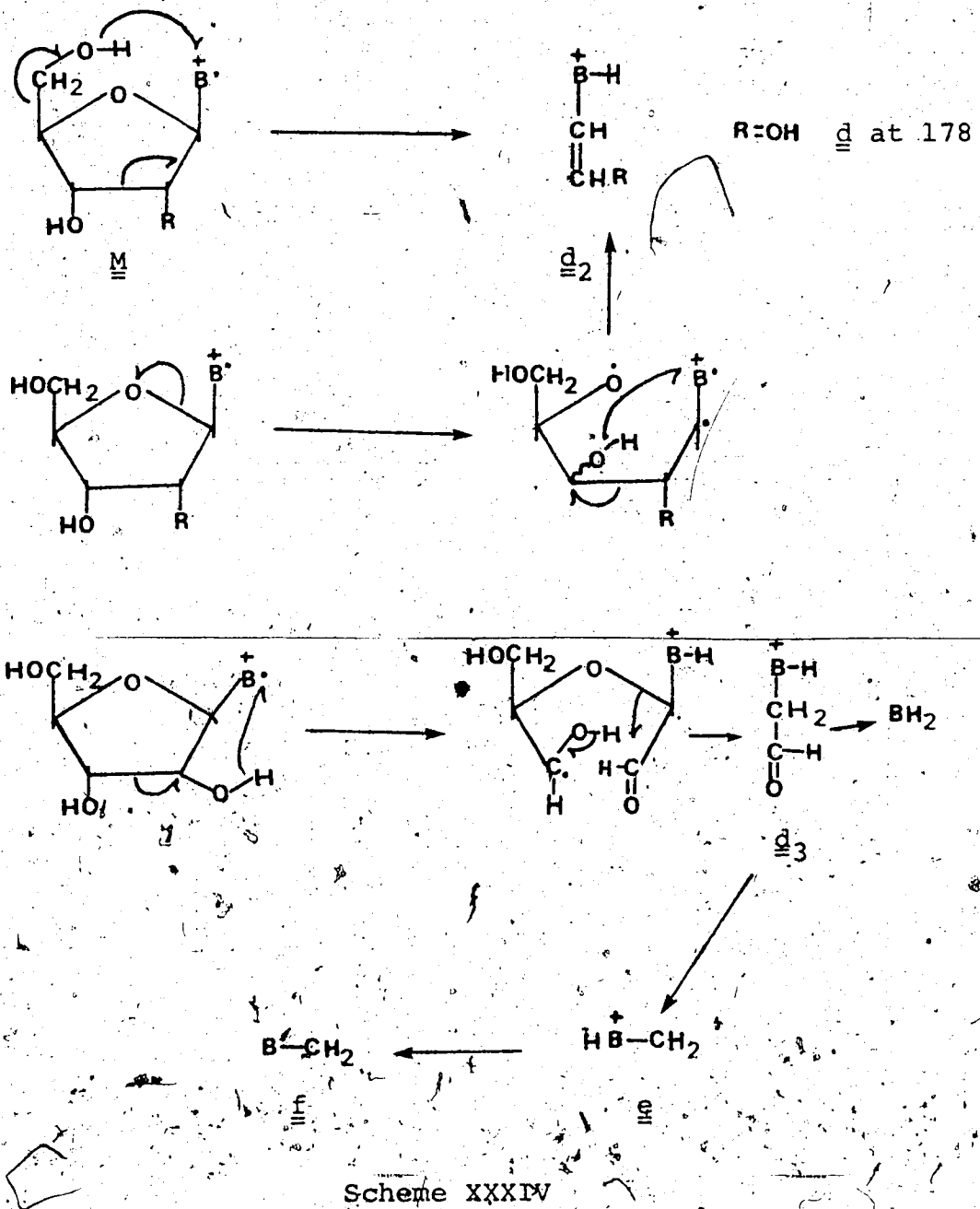



Scheme XXXIII

From table (1) it is clear that ion c is not present in the spectra of 32, 145, 37, 146, 148, 121, 122, and 140 which do not possess the free 5'-hydroxymethyl group. This ion is also noticibly absent in the spectra of a few other compounds: 56, 137, 124a, 129a, 143, 37a, 147. These compounds apparently lose a sugar substituent (in most cases at C-3' or in two examples, 37a and 147 at C-2') before ion c is formed. Loss of the C-5'

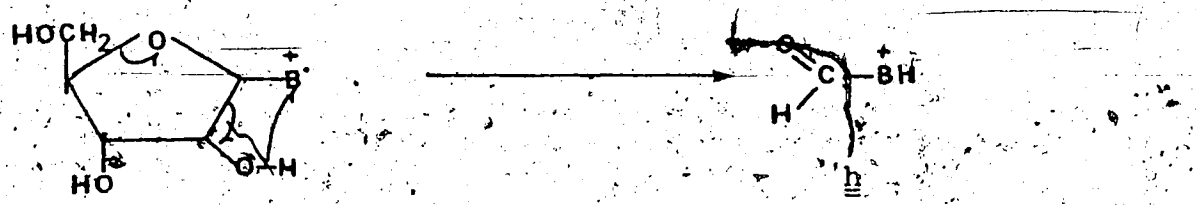
moiety (M-$CH_2OH$) by simple cleavage to give an ion with the 4'-radical center stabilized by the ribose ring oxygen occurs as a minor but general process.

Of major structural significance is ion d, which occurs at a mass value equal to the mass of the base (B) plus 44 mass units in the case of adenosine (1). When the base is adenine, d is at 178 mass units (177 for the tubercidin derivatives). Since ion d contains carbon atoms 1' and 2' plus a rearranged hydroxyl hydrogen on the base, it shifts according to the mass of the C-2' substituent. In 136, d appears at m/e 180, in 54 at m/e 196, in 132 at m/e 192, in 133 at m/e 162. This ion permits quick identification of isomers obtained by nucleophilic opening of the epoxide ring. Attack at C-3' will give a compound possessing ion d at m/e 178, whereas the C-2' isomer will have no peak at m/e 178 but possibly an ion d at a different m/e value. The experimental data collected by McCloskey show that more than a single mechanism exists for the general transition M→d. The three proposed mechanisms are depicted below:




Scheme XXXIV

McCloskey preferred $\underline{d}_3$ for the structure of this ion since it is better suited than $\underline{d}_2$ for further decomposition to either $\underline{e}$ or $\underline{B}$ + $2\underline{H}$. Since a free 2'-hydroxyl is required for the postulated route $\underline{M} \rightarrow \underline{d}_3$, compounds without a 2'-hydroxyl were thought to proceed through $\underline{d}_2$ from which creation of ion $\underline{f}$ is difficult to envisage. However 31, 38, 58, 144, 132, 37a, 147 which do not have a labile hydrogen at the 2'-position were found to give a significant ion $\underline{f}$. A characteristic and abundant ion occurs 30 mass units higher than the mass of the base ($\underline{B}$), which contains the base, C-1' and the sugar ether oxygen. The utility of this ion $\underline{h}$ resides in reflecting structural changes at C-1'. Based on the reduced abundance of this ion for compounds unable to provide a 2'-hydroxyl hydrogen, the following mechanism was proposed:




Scheme XXXV

This is of interest since 31, 38, 58, 144, 132, 37a, and 147 which don't have a labile hydrogen at the 2'-position give very intense ions $\underline{h}$. Two more minor but

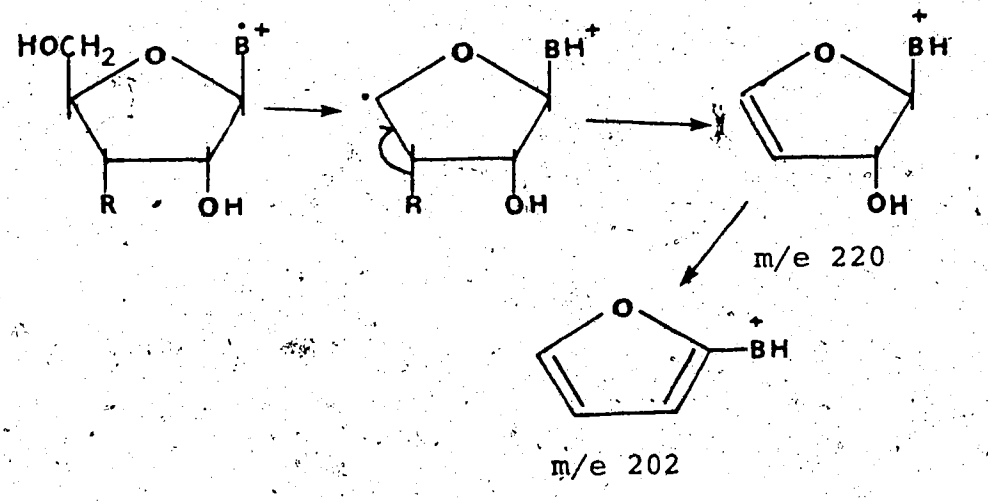
characteristic peaks which occur widely in nucleoside mass spectra are ion i, which consists of the base plus 60 mass units of the sugar, and ion j, which is observed 56 mass units higher than the base fragment.

McCloskey and co-workers also showed that mass spectrometry was particularly useful for the differentiation of O-methyl nucleosides and in particular for the identification of 2'-O-methyl derivatives. As expected, certain ions (B+H, B+2H, c, f, h) are found at the same values for 2'-O-methyl and 3'-O-methyladenosine. However, unambiguous location of the methoxyl on C-2' was established by comparison of ions d and h. Since h occurs at m/e 164 indicating no additional substitution at C-1', the shift of ion d from m/e 178 in 3'-O-methyl derivatives (see for example compound 127 in table 1) to m/e 192 (see compound 132 in same table) confirms methyl substitution in the C-2' grouping. Ion d further loses the O-2'-methyl group to provide ion v, m/e 177 (see 132 in table 1). Ion h was found by McCloskey to be reduced in abundance in the spectrum of 2'-O-methyladenosine compared with that of 3'-O-methyladenosine, a result which was interpreted as in accordance with the preferential involvement of the 2'-O-hydrogen in formation of that ion, as previously discussed. It is interesting to note that in 132 ion h was the base (100% R.I.)

ion. McCloskey also found an intense peak at m/e 146 (ion w), attributed to the sugar fragment less one hydrogen, characteristic to all 2'-O-methylated nucleosides. This intense (42.5 of % R.I.) peak was indeed found in 132 thus confirming unambiguously the position of the methyl group.

Perhaps the most generally characteristic ions in nucleoside mass spectra are those representing the base (deprotonated parent heterocycle) B, B+H, and B+2H. The m/e values for these fragments represent the base portion of the nucleoside and their identification can therefore be extremely important in the structure determination of unknown molecules. There is no evidence for a general fragmentation path leading to B or B+H. The B+2H ion can come from at least two sources: from ion $d_2$ and from ion h. Interestingly the ratio of B+H to B+2H was found (112) to be constant over a 50° range of temperature during sample vaporization. It would thus seem possible to use this ratio as a characteristic of a particular compound. On inspection of table I it is seen how different this ratio is for the diastereoisomeric pairs 23b and 17, and for 141 and 142. It could reasonably be expected that changes in the orientation of the sugar hydroxyl groups (or other groups) would lead to variation in the intensity of a given ion. This was shown to be the

case and although such variations between isomers exist, McCloskey was only moderately successful in his attempt to correlate intensity variation with a particular stereochemical change. A ubiquitous fragment ion of compounds possessing a labile C-3' group such as 56, 137, 124a, 129a, 127, 131, 128 appears at m/e 220 (219 for tubercidin analogs). The mechanism proposed by McCloskey (112) is as depicted:




Scheme XXXVI

Further elimination of water from m/e 220 produces the aromatic secondary product furan, m/e 202. This ion at m/e 220 is of diagnostic value when studying the mass spectrum of compounds resulting from the opening of nucleoside epoxides since its presence is additional proof that substitution has occurred at C-3'. The first

loss from the parent ion was 31 mass units (rather than 30) and the peak at m/e 219 was bigger than that at m/e 220 in certain of the compounds possessing a C-3' group (especially pronounced in the case of a hydroxyl group) in the xylo configuration (for example 23b, 141, 123, 136, 133).

In conclusion, mass spectrometry is an extremely valuable tool for the identification of adenosine analogs such as those prepared in this dissertation. This very sensitive determination requires only microgram amounts of product. A simple inspection of the mass spectrum permits one to discover if the compound is modified on the base, at the C-2', C-3' or C-5' position of the sugar, or any combination of these. With further model compounds and experience, one can recognize a particular configurational isomer in these series with reasonable degree of certainty upon careful examination of its mass spectrum.

TABLE 1

Characteristic Mass Spectral Ions[a]

| Compound[b] | T | M | c | d | h | f | B+H | B+2H |
|---|---|---|---|---|---|---|---|---|
| (31) | 190° | 249(4.5) | 219(4.5) | none | 164(100) | 148(7.5) | 135(85) | 136(48) |
| (38) | 190° | 249(5) | 219(6) | none | 164(100 | 148(10) | 135(45) | 136(45) |
| (58) | 190° | 248(11.5) | 218(2) | none | 163(50) | 147(6.5) | 134(100) | 135(21) |
| (144) | 140° | 248(43) | 218(55) | none | 163(97) | 147(23) | 134(100) | 135(49) |
| (23b) | 170° | 267(6) | 237(3) | 178(36) | 164( | (12) | 135(100) | 136(95) |
| (141) | 170° | 266(3) | 236(1) | 177(45) | 163(66) | 147(19.5) | 134(100) | 135(61) |
| (17) | 215° | 267(3) | 237(3) | 178(21) | 164(100) | 148(9) | 135(81) | 136(54) |
| (142) | 200° | 266(7) | 236(1) | 177(10.5) | 163(60) | 147(8) | 134(100) | 135(32) |
| (123) | 155° | 269(4) | 239(5) | 178(6) | 164(80) | 148(6) | 135(100) | 136(62) |
| (135) | 195° | 269(8.5) | 239(6) | 178(37.5) | 164(100) | 148(8.5) | 135(92) | 136(46) |
| (136) | 185° | 269(10) | 239(5) | 180(90) | 164(55) | none | 135(100) | 136(35) |
| (56) | 190° | 285(4) | none | 178(1.5) | 164(60) | 148(5) | 135(100) | 136(50) |
| (54) | 190° | 285(5) | 255(6.5) | 196(10) | 164(48.5) | 148(3) | 135(100) | 136(97) |

TABLE 1 (continued)

Characteristic Mass Spectral Ions[a]

| Compound[b] | T | M | c | d | h | f | B+H | B+2H |
|---|---|---|---|---|---|---|---|---|
| (137) | 180° | 376(4) | none | none | 163(68) | 147(4) | 134(100) | 135(28) |
| (124a) | 205° | 292(2.5) | none | 178(9) | 164(52) | 148(21.5) | 135(100) | 136(59.5) |
| (129a) | 200° | 292(1) | none | 178(8.5) | 164(21.5) | 148(18.5) | 135(100) | 136(53) |
| (143) | 190° | 291(4.5) | none | 177(55) | 163(29.5) | 147(16.5) | 134(100) | 135(27) |
| (124b) | 210° | 266(1.5) | 236(4.5) | 178(15) | 164(15) | 148(7.5) | 135(50) | 136(100) |
| (129b) | 190° | 266(1) | 236(1) | 178(12.5) | 164(25) | 148(10.5) | 135(33) | 136(100) |
| (127) | 200° | 281(5) | 251(5) | 178(9) | 164(100) | 148(15) | 135(85) | 136(60) |
| (131) | 200° | 281(4) | 251(5.5) | 178(23.5) | 164(100) | 148(21) | 135(97) | 136(89) |
| (138) | 165° | 280(5) | 250(1.5) | 177(4) | 163(67) | 147(10.5) | 134(100) | 135(33) |
| (132) | 210° | 281(3) | 251(2) | 192(39) | 164(100) | 148(16) | 135(76) | 136(100) |
| (128) | 180° | 295(2) | 265(2) | 178(12) | 164(100) | 148(15) | 135(93) | 136(81) |
| (134a) | 180° | 295(1) | none | 178(16.5) | 164(100) | 148(9.5) | 135(57.3) | 136(54.5) |
| (16) | 215° | [illegible](4) | 221(4) | 178(14) | 164(60) | 148(11) | 135(100) | 136(45) |

TABLE 1 (continued)

Characteristic Mass Spectral Ions[a]

| Compound[b] | T | M | c | d | h | f | B+H | B+2H |
|---|---|---|---|---|---|---|---|---|
| (134) | 185° | 251(7.5) | 221(7.5) | 178(15) | 164(97) | 148(9) | 135(100) | 136(51.5) |
| (139) | 150° | 250(10) | 220(1.5) | 177(4) | 163(32) | 147(4) | 134(100) | 135(22) |
| (133) | 200° | 251(8.5) | 221(4) | 162(58.5) | 164(8.5) | 148(2) | 135(100) | 136(41.5) |
| (32) | 190° | 307(4) | none | 178(11.5) | 164(100) | 148(4) | 135(54) | 136(54) |
| (145) | 185° | 306(8.5) | none | 177(5.5) | 163(70) | 147(3) | 134(100) | 135(32) |
| (37) | 200° | 385(4) | none | 178(8) | 164(100) | 148(8) | 135(46) | 136(54) |
| (146) | 180° | 384(5.5) | none | none | 163(95) | 147(9) | 134(100) | 135(32) |
| (37a) | 200° | 345(19) | none | 178(4.5) | 164(100) | 148(12) | 135(85.5) | 136(47.5) |
| (147) | 200° | 344(2.5) | none | none | 163(93) | 147(18) | 134(100) | 135(44.5) |
| (125) | 220° | 373(1.5) | none | 178(10.5) | 164(90) | 148(10.5) | 135(26) | 136(100) |
| (126) | 200° | 373(0.5) | none | none | 164(11) | 148(2.5) | 135(100) | 136(60) |

TABLE 1 (continued)

Characteristic Mass Spectral Ions[a]

| Compound[b] | T | Other Ions |
|---|---|---|
| (31) | 190° | 202 (2, c-17), 190 (4.5, i) |
| (38) | 190° | 218 (3, M-17), 202 (1, c-17), 190 (3, i) |
| (58) | 190° | 217 (3, M-31), 201 (0.5, c-17), 189 (3, i) |
| (144) | 140° | 231 (1.5, M-17), 217 (8.5, M-31), 201 (5.5, c-17), 189 (8.5, i) |
| (148) | 255° | 403 (M, very small), 231 (100, M-$CH_3(Ph)SO_3H$), 172 (20, $CH_3(Ph)SO_3H$), 155 (41, $CH_3(Ph)SO_2$), 136 (10, B+2H), 135 (100, B+H) |
| (122) | 210° | 561 (25, M), 456 [100, M-CO(Ph)], 440 [30, M-OCO(Ph)], 219 (30, s) |
| (140) | 200° | 560 (68, M), 455 [100, M-CO(Ph)], 439 [23, M-OCO(Ph)], 218 (40, s) |
| (121) | 175° | 417 (4, M), 332 [16, M-$COC(CH_3)_3$], 316 [4, M-$OCOC(CH_3)_3$], 220 (16), 199 (28, s) |
| (23b) | 170° | 236 (2, M-31), 220 (3, c-17), 219 [4, M-(31+17)], 207 (1.5), 202 (2), 194 (6, i), 190 (1.5, i) |

TABLE 1 (continued)

Characteristic Mass Spectral Ions[a]

| Compound[b] | T | Other Ions |
|---|---|---|
| (141) | 170° | 235 (1, M-31), 219 (1, c-17), 218 [3, M-(31+17)], 206 (1), 201 (1), 193 (2, i), 189 (2, j) |
| (17) | 215° | 250 (1.5, M-17), 220 (1, c-17), 202 [1, c-(17+18)], 194 (3, i), 190 (1, j) |
| (142) | 200° | 193 (1, i), 190 (0.5, j) |
| (123) | 155° | 219 (5, c-20) |
| (135) | 195° | 252 (1.5, M-17) |
| (136) | 185° | 252 (4, M-17), 221 [12.5, M-(31+17)] |
| (56) | 190° | 250 [15.5, M-35(Cl)], 220 [21, M-(30+35)], 202 (2.5), 190 (2.5, j) |
| (54) | 190° | 268 (1, M-17), 250 (6.5, M-35), 202 (3), 190 (10, j) |
| (137) | 180° | 249 [2, M-127(I)], 248 (4, M-128), 219 [12, M-(30+127)] |
| (124a) | 205° | 264 [0.5, M-28($N_2$)], 250 [7, M-42($N_3$)], 220 (26, c-42), 192 (7), 177 (19) |
| (129a) | 200° | 250 (1.5, M-42), 220 (4, c-42), 194 (5, i), 190 (2, j), 177 (12) |
| (143) | 190° | 263 [1, M-28($N_2$)], 249 [2, M-42($N_3$)], 219 (6.5, c-42) |

TABLE 1 (continued)

Characteristic Mass Spectral Ions[a]

| Compound[b] | T | Other Ions |
|---|---|---|
| (124b) | 210° | 220 [3, C-16($NH_2$)], 194 (32, i) |
| (129b) | 190° | 194 (43, i) |
| (127) | 200° | 250 (3, M-31), 220 (7.5, C-31), 194 (3, i) |
| (131) | 200° | 266 (6.5, M-15), 220 (5.5, C-31), 194 (3, i) |
| (138) | 165° | 249 (1.5, M-31), 219 (21.5, C-31) |
| (132) | 210° | 250 (0.5, M-31), 233 [5, M-(31+17)], 190 (2, j), 177 (6, v), 146 (42.5, w) |
| (128) | 180° | 266 [M-29($C_2H_5$)], 251 [9.5, M-44($OC_2H_5$)], 234 [4, M-(44+17)], 220 (8, C-45), 194 (3, i) |
| (134a) | 180° | 266 (5.5, M-29), 251 (10, M-44), 220 (4, C-45), 194 (3.5, i) |
| (16) | 215° | 202 (4, C-18) |
| (134) | 185° | 234 (2.5, M-17), 202 (6, C-18) |
| (133) | 200° | 234 (3, M-17), 203 [8.5, M-(17+31)], 190 (8.5, j) |
| (32) | 190° | 292 (4, M-15), 220 (3), 194 (4, i) |

TABLE 1 (continued)

Characteristic Mass Spectral Ions[a]

| Compound[b] | T | Other Ions |
|---|---|---|
| (145) | 185° | 291 (4, M-15), 219 (1), 193 (2, i) |
| (37) | 200° | 370 (7.5, M-15), 327 [2, M-58($CH_3COCH_3$)], 248 (11.5), 232 (11.5), 218 (4), 202 (19) |
| (146) | 180° | 369 (3.5, M-15), 247 (5.5), 231 (7), 217 (2), 201 (10.5) |
| (37a) | 200° | 248 (5.5), 219 (5.5), 202 (4.5), 190 (4.5, i) |
| (147) | 200° | 248 (27), 217 (7), 201 (6), 189 (9, i) |
| (125) | 220° | 282 [37, M-91($CH_2Ph$)], 251 (21), 234 (10.5), 220 (52.5), 202 (10.5) |
| (126) | 200° | 282 [19, M-91($CH_2Ph$)] |

[a] Ions named by letters as in ref. 98.

[b] Compounds:

(31) 9-(2,3-Anhydro-β-D-ribofuranosyl)adenine

(38) 9-(2,3-Anhydro-β-D-lyxofuranosyl)adenine

[b] Compounds: (continued)

(58) 4-Amino-7-(2,3-anhydro-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine

(144) 4-Amino-7-(2,3-anhydro-β-D-lyxofuranosyl)pyrrolo[2,3-d]pyrimidine

(23b) 9-β-D-Xylofuranosyladenine

(141) 4-Amino-7-β-D-xylofuranosylpyrrolo[2,3-d]pyrimidine

(17) 9-β-D-Arabinofuranosyladenine

(142) 4-Amino-7-β-D-arabinofuranosylpyrrolo[2,3-d]pyrimidine

(123) 9-(3-Fluoro-3-deoxy-β-D-xylofuranosyl)adenine

(135) 9-(3-Fluoro-3-deoxy-β-D-arabinofuranosyl)adenine

(136) 9-(2-Fluoro-2-deoxy-β-D-xylofuranosyl)adenine

(56) 9-(3-Chloro-3-deoxy-β-D-xylofuranosyl)adenine

(54) 9-(2-Chloro-2-deoxy-β-D-arabinofuranosyl)adenine

(137) 4-Amino-7-(3-iodo-3-deoxy-β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine

(124a) 9-(3-Azido-3-deoxy-β-D-xylofuranosyl)adenine

(129a) 9-(3-Azido-3-deoxy-β-D-arabinofuranosyl)adenine

(143) 4-Amino-7-(3-azido-3-deoxy-β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine

(124b) 9-(3-Amino-3-deoxy-β-D-xylofuranosyl)adenine

[b] Compounds: (continued)

(129b) 9-(3-Amino-3-deoxy-β-D-arabinofuranosyl)adenine

(127) 9-(3-O-Methyl-β-D-xylofuranosyl)adenine

(131) 9-(3-O-Methyl-β-D-arabinofuranosyl)adenine

(138) 4-Amino-7-(3-O-methyl-β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine

(132) 9-(2-O-Methyl-β-D-xylofuranosyl)adenine

(128) 9-(3-O-Ethyl-β-D-xylofuranosyl)adenine

(134a) 9-(3-O-Ethyl-β-D-arabinofuranosyl)adenine

(16) 9-(3-Deoxy-β-D-erythro-pentofuranosyl)adenine

(134) 9-(3-Deoxy-β-D-threo-pentofuranosyl)adenine

(139) 4-Amino-7-(3-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine

(133) 9-(2-Deoxy-β-D-threo-pentofuranosyl)adenine

(32) 9-(3,5-O-Isopropylidene-β-D-xylofuranosyl)adenine

(145) 4-Amino-7-(3,5-O-isopropylidene-β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine

(37) 9-(3,5-O-Isopropylidene-2-O-methanesulfonyl-β-D-xylofuranosyl)adenine

(146) 4-Amino-7-(3,5-O-isopropylidene-2-O-methanesulfonyl-β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine

[b] Compounds: (continued)

(37a) 9-(2-O-Methanesulfonyl-β-D-xylofuranosyl)adenine

(147) 4-Amino-7-(2-O-methanesulfonyl-β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine

(125) 9-(3-S-Benzyl-3-thio-3-deoxy-β-D-xylofuranosyl)adenine

(126) 9-(2-S-Benzyl-2-thio-2-deoxy-β-D-arabinofuranosyl)adenine

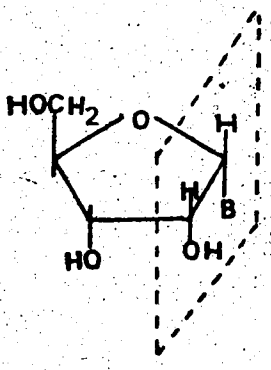
(148) 9-(2,3-Anhydro-5-O-p-toluenesulfonyl-β-D-ribofuranosyl)adenine

(122) N,N-Dibenzoyl-9-(5-O-benzoyl-2,3-anhydro-β-D-ribofuranosyl)adenine

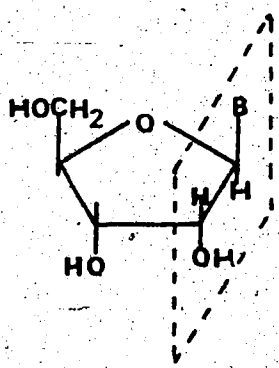
(140) N,N-Dibenzoyl-4-amino-7-(5-O-benzoyl-2,3-anhydro-β-D-ribofuranosyl)pyrrolo-[2,3-d]pyrimidine

(121) 6-N-Pivalamido-9-(5-O-pivalyl-2,3-anhydro-β-D-ribofuranosyl)purine

Nmr spectroscopy has been widely used in nucleoside chemistry and in particular as a tool in the determination of anomeric configuration (113, 114, 115). It has been determined (116, 117) that for furanoid derivatives, the dihedral angle between neighboring, or vicinal, cis hydrogen atoms as with i and neighboring trans hydrogen atoms as with ii may vary between 0-45° and 75°-165° respectively.

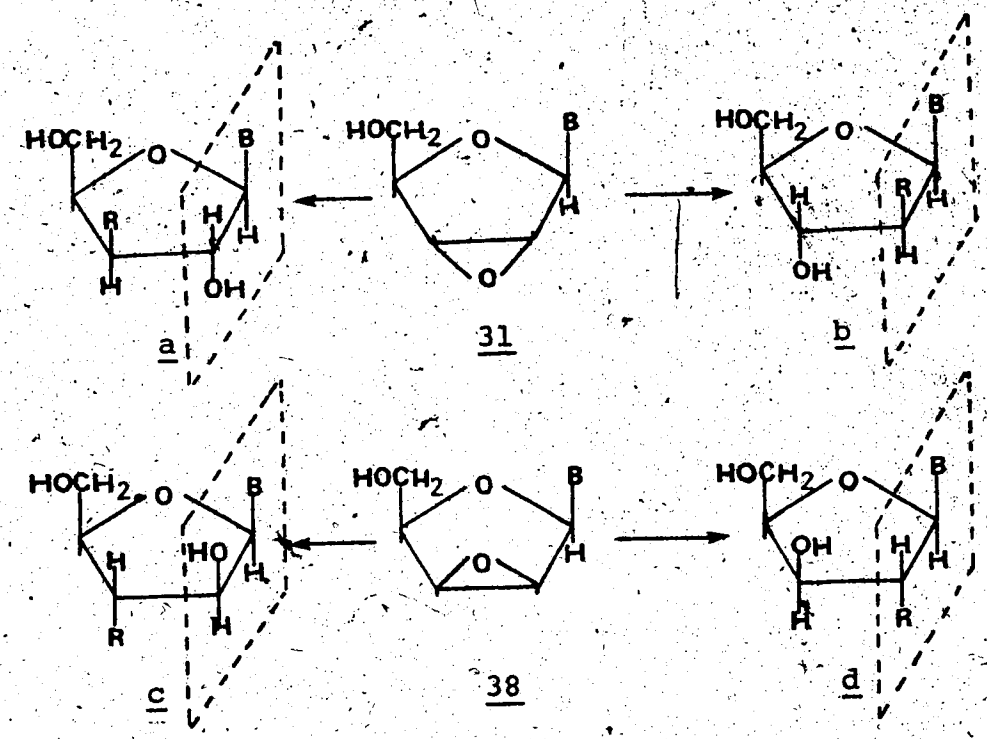



i ≡ α-D




ii ≡ β-D

Using the Karplus equation (118) it has been predicted that the observed coupling constants ($J_{1-2}$) will be in the approximate range of 3.5-8.0 Hz for the α-D (i) case and 0.0-8.0 for the β-D (ii) case. This situation encountered vis a vis the C1'-C2' protons in the α-D and the β-D case is similar to what is found in the products resulting from the opening of the epoxides 31 and 38 with nucleophilic reagents (see scheme XXXVII).




B = adenin-9-yl

Scheme XXXVII

The α-D (cis) situation is obviously analogous to case b and c and the β-D (trans) situation to a and d. Recent studies (113, 115) have established that the trans assignment should be applied with certainty only when the coupling constant ($J_{1',2'}$) is ≤ 1 Hz. In order to obtain a coupling constant that conforms to the foregoing requirement the formation of isopropylidene derivatives is a well known procedure. For example the coupling constant ($J_{1',2'}$) observed for adenosine (1) is ∿6 Hz, and formation of its 2',3'-O-isopropylidene derivative diminishes this coupling

constant to ∿2.5 Hz, which is indicative of the β-D-configuration. However, because the value is greater than 1 Hz, the assignment of the configuration as β-D is not unequivocal. In this regard the case of 9-β-D-xyloadenosine (23b) is very interesting. Its coupling constant for the anomeric proton is 2.0 Hz (91) which is indicative of a trans nucleoside. However, formation of the 3',5'-O-isopropylidene ring (see below) results in a singlet for the anomeric proton peak, thus establishing the β-anomer and giving further proof of the xylo configuration for 23b.

Even more useful is the observation (119, 120-124) that the peak assigned to the anomeric proton of a C1'-C2' trans nucleoside such as a or d appears at higher field (usually $\Delta\delta$ ∿0.5 ppm) than the corresponding peak of a cis nucleoside. This is clearly illustrated in table 2 which shows the position of the anomeric proton and the coupling constant $J_{1'-2'}$ for pairs of xylo and arabino isomers. As expected the coupling constant is usually bigger for the arabino isomer than for the xylo isomer; but this is not always the case.

TABLE 2

Chemical Shift for the Anomeric Proton of Selected Nucleosides

| | $H_{1'}$ (δ in ppm) | Δδ | $J_{1'-2'}$ (Hz) |
|---|---|---|---|
| 9-β-D-Xylofuranosyladenine (23b) | 5.85 | | 2 |
| | | 0.40 | |
| 9-β-D-Arabinofuranosyladenine (17) | 6.25 | | 4 |
| 9-(3-O-Methyl-β-D-xylofuranosyl)adenine (127) | 5.90 | | 2.7 |
| | | 0.31 | |
| 9-(3-O-Methyl-β-D-arabinofuranosyl)adenine (131) | 6.21 | | 4.5 |
| 9-(3-Azido-3-deoxy-β-D-xylofuranosyl)adenine (124a) | 5.85 | | 6 |
| | | 0.31 | |
| 9-(3-Azido-3-deoxy-β-D-arabinofuranosyl)adenine (129a) | 6.22 | | 5 |
| 9-(3-Amino-3-deoxy-β-D-xylofuranosyl)adenine (124b) | 5.60-5.74 | | 6 |
| | | $0.50 \leqslant \Delta\delta \leqslant 0.64$ | |
| 9-(3-Amino-3-deoxy-β-D-arabinofuranosyl)adenine (129b) | 6.22 | | 5.5 |

TABLE 2 (continued)

Chemical Shift for the Anomeric Proton of Selected Nucleosides

| | $H_{1'}$ (δ in ppm) | Δδ | $J_{1'-2'}$ (Hz) |
|---|---|---|---|
| 4-Amino-7-β-D-xylofuranosylpyrrolo[2,3-d]-pyrimidine (141) | 5.94 | | 2 |
| | | 0.48 | |
| 4-Amino-7-β-D-arabinofuranosylpyrrolo[2,3-d]-pyrimidine (142) | 6.42 | | 4 |
| 9-(3-O-Ethyl-β-D-xylofuranosyl)adenine (128) | 5.93 | | 2.25 |
| | | 0.29 | |
| 9-(3-O-Ethyl-β-D-arabinofuranosyl)adenine (134a) | 6.22 | | 5 |
| 9-(3-Deoxy-β-D-erythro-pentofuranosyl)adenine (16) | 5.89 | | 2.5 |
| | | 0.38 | |
| 9-(3-Deoxy-β-D-threo-pentofuranosyl)adenine (134) | 6.17 | | 5 |

It is interesting to note that the "rule" seems also to hold for the pair of tubercidin analogs 141 and 142.

The use of nmr in conjunction with mass spectrometry was also of great value in establishing rigourously the structures of the intermediates in the reaction sequence starting with 9-β-D-xylofuranosyladenine (23b) and proceeding to the lyxo-epoxide 38 via 32, 37 and 37a (see scheme IX). As mentioned above, reduction in the coupling constant of the anomeric proton accompanied the disappearance of the peaks corresponding to the C-3' and C-5' hydroxyl groups clearly indicating the formation of an isopropylidene ring in 32. The appearance of two singlets in the methyl absorption region confirmed this structural feature. Formation of the 2'-O-mesyl derivative 37 was clearly indicated by its n.m.r. spectrum.

TABLE 3

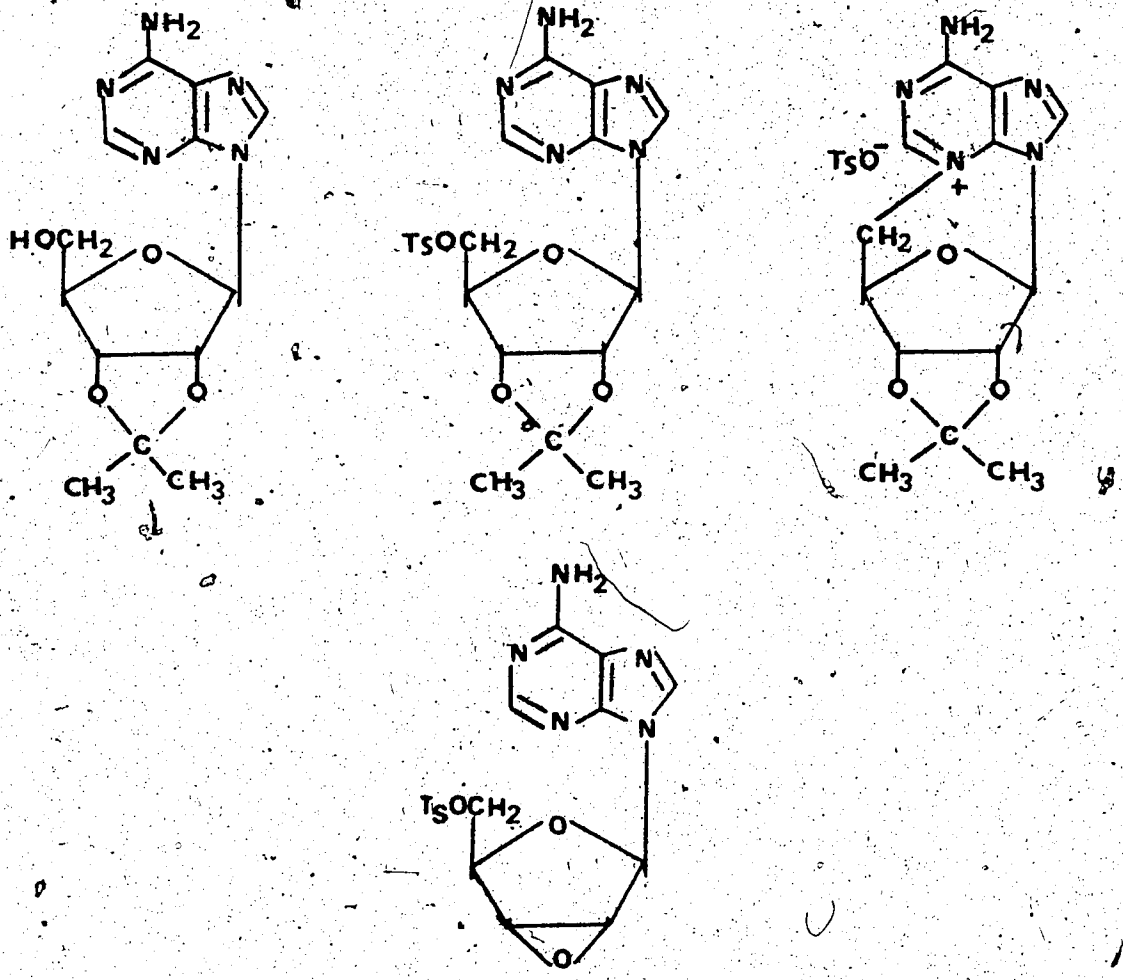
Nmr Evidence of a Reaction Sequence

| | 23b ($J_{1',2'}$=2 Hz) | 32 ($J_{1',2'}$=0) | 37 ($J_{1',2'}$=0) | 37a ($J_{1',2'}$=2.5) |
|---|---|---|---|---|
| $H_{1'}$ | 5.85 | 5.97 | 6.35 | 6.24 |
| $H_{2'}$ | 4.35 | 3.8-4.3 | 5.27 | 5.39 |
| $H_{3'}$ | 4.15 | | 4.71 | 4.46 |
| $H_{4'}$ | | | 4.10-4.30 | 4.19 |
| $H_{5',5''}$ | ~3.7 | | | 3.77 |

As can be seen from Table 3, the greatest downfield shift (0.87 ppm) was observed for the $H_2$, proton of 37 as expected with an estimated downfield shift (∿0.4) almost equal for the $H_1$, and $H_3$, protons. In addition, the appearance of a new singlet (3 protons) and disappearance of the C-2' hydroxyl were supplementary proofs for the proposed structure, 37. Finally, removal of the isopropylidene ring, to give 37a, was indicated by the appearance of a coupling between the anomeric and the H-2' protons, loss of the two singlets corresponding to the methyl groups and the presence of a two hydroxyl absorption peak. Once again it can be seen that the maximum deshielding ($\Delta\delta$ ∿1.0 ppm), for the various protons of 37a compared to those of 23b, was for $H_2$, as expected.

Another example of the use of nmr for structure elucidation was provided by 9-(5-O-p-toluenesulfonyl-2,3-anhydro-β-D-ribofuranosyl)adenine (148). It is known (125) that in the nmr spectrum of 2',3'-O-isopropylidene adenosine (DMSO-$d_6$) and in the spectrum of its 5'-O-p-tolylsulfonyl derivative, in $CDCl_3$, the singlet peaks corresponding to the C-2 and C-8 protons appear essentially at the same place, respectively, $\delta$ 7.9 and 8.25 ppm. However, the spectrum of the same compound in DMSO-$d_6$ shows very significant changes which indicate that $N_3$→C-5' anhydronucleoside formation

has occurred.



148

Scheme XXXIV

The peaks assigned to the protons on C-2 and C-8 are now observed at 8.66 and 8.78, a significant shift downfield. The peak at 6.47 corresponding to the exocyclic amino group is also replaced by a very broad doublet at 9.48. The peak corresponding to the

anomeric proton was also found to be shifted downfield. A parallel behavior is exhibited by 148. In the spectrum (DMSO-$d_6$) of the ribo-epoxide 31, the anomeric proton appears at 6.22 and the C-2 and C-8 protons, respectively, at 8.18 and 8.35. The spectrum of 148 in $CDCl_3$ (containing the minimal amount of DMSO-$d_6$ necessary for solubility) showed these three peaks at 6.20, 8.02 and 8.18 respectively. However, in the spectrum of 148 in DMSO-$d_6$, the anomeric proton peak shifted to 6.55 and the C-2 and C-8 proton peaks to 8.5 and 8.75, respectively. This clearly shows the easy formation of the $N_3 \rightarrow C$-5' cyclonucleoside, a result corroborated by the observation of a bathochromic shift (12 nm) in the uv spectrum.

Thus, nmr spectroscopy has proved to be useful in structure elucidation especially when associated with mass spectrometry. Whereas the latter gives clear-cut information on the position of any particular group, nmr provides the complementary information (i.e. the configuration at this position). Nmr also clearly indicates, as did mass spectrometry, the close resemblance of the adenosine and tubercidin analogs.

# EXPERIMENTAL

## A. GENERAL PROCEDURES

Melting points were determined on a Reichert microstage apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on Varian HA-100 and Bruker 90 spectrometers with TMS ($^{1}H$ spectra) or $CCl_3F$ ($^{19}F$ spectra) as references. Ultraviolet (uv) spectra were recorded on a Cary 15 spectrophotometer. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter using a 10 cm, 1 ml microcell. Mass spectra were determined by the mass spectroscopy laboratory of this department on AEI MS-2 or MS-9 instruments at 70 eV using a direct probe for sample introduction. Elemental analyses were determined by the microanalytical laboratory of this department or by Schwarzkopf Microanalytical Laboratory, Woodside, New York. Thin layer chromatography was performed on Eastman Chromatogram sheets (silica gel No. 13181, indicator No. 6060) in the solvent system indicated. Developed chromatograms were evaluated under uv (2537 Å) light. Evaporations were carried out using a Büchler rotating evaporator with a Dry Ice cooled Dewar condenser under aspirator or oil pump vacuum, at 40° or less. Hydrogenations were effected using a Paar shaking apparatus at room temperature, under the specified hydro-

gen pressure with Matheson, Coleman and Bell 5 or 10% palladium on carbon as catalyst.

Silica gel column chromatography was performed on J. T. Baker No. 3405 silica gel. Pyridine was refluxed over and then distilled from calcium hydride, then treated with chlorosulfonic acid and distilled over potassium hydroxide. Finally it was distilled, and stored over Linde 4A molecular sieves (dried at 200°). Sodium iodide was dried in the presence of phosphorus pentoxide at room temperature under high vacuum. Pivalyl chloride was distilled before use.

Diffusion crystallization, adapted from reference number 126, was effected using EtOH or MeOH as the dissolving solvent and ether or pentane as the diffusing solvent. A concentrated solution of the nucleoside in the first mentioned solvents contained in a beaker was placed in a desiccator containing a large volume of the second solvent in which the material is insoluble. Crystallization was allowed to proceed at room temperature and then the crystals were collected by filtration using water aspirator vacuum.

Electrophoresis was performed on a Savant flat-plate apparatus (HV-3000A) using Whatman number 1 paper.

Descending chromatography was effected using Whatman number 1 paper in the following solvent system (127):

Ammonium acetate, 1 M, containing ethylenediaminetetra-acetic acid disodium salt, 0.01 M, adjusted to pH 9 with ammonium hydroxide and saturated with sodium tetra-borate. 60 ml of the above solution was mixed with 140 ml of 90% EtOH. The mixture was allowed to stand for 1 hr. The slight precipitate which formed during this time was removed by filtration before use.

Other solvents used were of reagent purity and were distilled before use.

TABLE 4

Paper Chromatography[a]

| Compounds | $R_{Arabino-furanosyladenine}$[b] |
|---|---|
| Adenosine (1) | 0.86 |
| 9-β-D-Arabinofuranosyladenine (17) | 1 |
| 9-β-D-Xylofuranosyladenine (23b) | 0.86 |

| | $R_{Arabino-tubercidin}$[b] |
|---|---|
| Tubercidin (19) | 0.67 |
| 4-Amino-7-(β-D-arabinofuranosyl)-pyrrolo[2,3-d]pyrimidine (Arabinotubercidin) (142) | 1 |
| 4-Amino-7-(β-D-xylofuranosyl)-pyrrolo[2,3-d]pyrimidine (141) | 0.90 |

[a] See general procedures.

[b] $R_{Reference} = R_{F(Compound)} \div R_{F(Reference)}$ determined on the same sheet of chromatography paper.

TABLE 5

Electrophoretic Mobilities[a] with Borate Complexing

| Compounds | Distance Migrated Toward Anode in mm |
|---|---|
| Adenosine (1) | 80 |
| 9-β-D-Arabinofuranosyladenine (17) | 0 |
| 9-β-D-Xylofuranosyladenine (23b) | 75 |
| Tubercidin (19) | 97 |
| 4-Amino-7-(β-D-arabinofuranosyl)-pyrrolo[2,3-d]pyrimidine (142) | 32 |
| 4-Amino-7-(β-D-xylofuranosyl)-pyrrolo[2,3-d]pyrimidine (141) | 85 |

[a] Whatman No. 1 paper. 0.1 M sodium borate pH = 9; 1.5 KV (27 V/cm) 30-35 mA; 90 min.

B. SYNTHESES

9-(2,3-Anhydro-β-D-ribofuranosyl)adenine (31) (24) (55) (58) Method A.

To a solution of 2.9 g (0.009 mole) of 2',3'-O-methoxyethylideneadenosine (118) in 60 ml of dry pyridine, was added 12 ml (0.1 mole) of pivalic acid chloride dropwise with stirring and exclusion of moisture. The solution was then slowly (1 hr) heated to reflux and refluxed for 1 hr. The resulting yellow solution was allowed to cool to room temperature and 20 ml of MeOH was added dropwise with stirring. This solution was evaporated until precipitation of solid began. Dry $Et_2O$ (100 ml) was added and the mixture filtered. The filtrate was washed with 2 x 100 ml of 10% $NaHCO_3$ solution, 2 x 100 ml of $H_2O$, dried over $Na_2SO_4$, filtered, and evaporated to give a yellow solid foam.

This material (composed primarily of 119 and 120) was dissolved in 300 ml of MeOH and 3.2 g (0.059 mole) of $NaOCH_3$ was added. The resulting solution was stirred for 17 hours at room temperature, neutralized with $HOAc:H_2O$ (1:9), and evaporated to give a yellow powder. Residual pyridine was removed by codistillation with 3 x 60 ml of dry toluene. The product mixture was partitioned between $Et_2O:H_2O$ (50:20 ml) and the aqueous

layer was applied to a column (4 x 40 cm, 500 ml) of Dowex 1-X2 ($OH^-$) resin packed in MeOH:$H_2O$ (3:7). The column was rapidly developed with the same solvent mixture and the appropriate fractions containing pure 31 were combined and evaporated to give 1.42 g (63%) of solid 31 after drying.

This material had mp ∿180° decomposition (when rapidly heated); $[\alpha]_D^{24}$ -35.4° (c 0.22, $H_2O$); uv ($H_2O$) max 258 nm (ε 14,900), min 225 (2,200); (0.1 N HCl) max 255 nm (ε 14,600), min 228 (3,400); (0.1 N NaOH) max 258 nm (ε 15,000), min 228 (ε 4,000); pKa ≅ 3.55; nmr (DMSO-$d_6$) δ 3.58 (m, 2, $H_{5',5''}$), 4.2 ("t", $J_{4'-5',5''} \cong 5$ Hz, 1, $H_{4'}$), 4.25 (d, $J_{3'-2'} = 2.5$ Hz, 1, $H_{3'}$), 4.45 (d, $J_{2'-3'} = 2.5$ Hz, 1, $H_{2'}$), 5.1 ("t", 1, 5'-OH), 6.22 (s, 1, $H_{1'}$), 7.26 (s, 2, 6-$NH_2$), 8.18 (s, 1, $H_2$), 8.35 (s, 1, $H_8$); mass spectrum (190°) m/e (R.I., ion) 249 (4.5, M), 219 (4.5, c), 202 (2, c-17), 190 (4.5, i), 164 (100, h), 148 (7.5, f), 136 (48, B+2H), 135 (84, B+H). [Reported (24) mp 200-203° dec.; $[\alpha]_D^{25}$ -3 (c 0.6, 20% aqueous pyridine). (55) $[\alpha]_D^{26}$ -17.5° (c 0.4, 20% aqueous pyridine), $[\alpha]_D^{26}$ -36.5° (c 0.33, $H_2O$). (58) $[\alpha]_D^{23}$ -21.8° (c 0.2, $H_2O$)].

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.43; H, 4.62; N, 28.05.

9-(2,3-Anhydro-β-D-ribofuranosyl)adenine (31).

Method B.

To a solution of 29 g (0.09 mole) of 2',3'-O-methoxyethylideneadenosine (118) in 600 ml of dry pyridine, was added 120 ml (1 mole) of pivalic acid chloride dropwise with stirring and exclusion of moisture. The solution was then slowly (1 hr) heated to reflux and refluxed for 1 hr. The resulting yellow solution was allowed to cool to room temperature and 200 ml of MeOH was added dropwise with stirring. This pale yellow solution was then concentrated in vacuo until most of the liquid was evaporated. The thick pale yellow paste was washed with 5 x 400 ml of dry ether and the mixture was filtered. The ether filtrate was evaporated and residual pyridine was removed by coevaporation with toluene (3 x 50 ml) to give a pale yellow foam. This foam was dissolved in 1000 ml of MeOH and sodium metal pieces (washed in ether and dried) were added until moistened pHydron paper indicated a pH ≅ 8-9. The solution was then stirred at room temperature over a period of 7 days while protected from moisture. The volume was reduced to 200 ml and the resulting pale yellow precipitate was collected by filtration. This powder was stirred under ether (500 ml) and the mixture was filtered. The dry weight of this chromatographically pure epoxide was 12.5 g (56%).

9-(3-Chloro-3-deoxy-β-D-xylofuranosyl)adenine (56) and 9-(2-Chloro-2-deoxy-β-D-arabinofuranosyl)adenine (54) (58).

The procedure given for the preparation of 31 was followed to the end of the first paragraph. The pale yellow foam (2 g) was dissolved in 100 ml of MeOH presaturated with ammonia at -5° and allowed to stand at 0° for 24 hr. The ammonia was evaporated at 0° and to the solution was added 20 g of silica. The mixture was evaporated to dryness and the impregnated powder was added to a column (4.3 x 80 cm, 400 g) of silica gel. The products were eluted with $CHCl_3$-MeOH (95:5). The first product to be eluted was 56, slightly contaminated, in the first fractions, with small amounts of 31. Evaporation of the pure fractions gave 0.4 g of 56 as a white powder. A sample for analysis was recrystallized from 95% EtOH (ether, desiccator) and had mp 195-196°; $[\alpha]_D^{24}$ -32° (c 0.14, MeOH); uv (0.1 N HCl) max 255 nm (ε 14,500), min 228 (3,400); uv ($H_2O$) max 258 nm (ε 14,700), min 225 (3,150); uv (0.1 N NaOH) max 258 nm (ε 14,700), min 225 (2,150) nmr (DMSO-$d_6$) δ 3.75 (m, 2, $H_{5',5''}$), 4.50 (br s, 2, $H_{4'}$, $H_{3'}$), 4.80 (br d, 1, $H_{2'}$) 5.30 ("t", 1, 5'-OH), 5.90 (d, $J_{1',2'}$ = 4 Hz, 1, $H_{1'}$), 6.35 (br s, 1, 2'-OH), 7.32 (br s, 2, 6-$NH_2$), 8.16, 8.24 (s, s; 1, 1; $H_2$, $H_8$); mass spectrum (190°) m/e (R.I., ion) 285

(4%, M), 250 (15.5, M-35), 220 [21, M-(30+35)], 202 (2.5, 220-18), 190 (2.5, i), 178 (1.5, d), 164 (60, h), 148 (5, f), 136 (50, B+2H), 135 (100, B+H). [Reported (58) mp 194-196°; $[\alpha]_D^{23}$ -31.6° (c 0.14, MeOH)].

Anal. Calcd for $C_{10}H_{12}ClN_5O_3$: C, 42.03; H, 4.23; N, 24.51; Cl, 12.41. Found: C, 41.94; H, 4.48; N, 24.39; Cl, 12.44.

Further development of the above column with the same solvent system gave fractions containing both isomers followed by fractions which were evaporated to give 0.027 g of pure 54. A sample for analysis was recrystallized from 95% EtOH (ether, desiccator) and had mp 243-245°; $[\alpha]_D^{24}$ -8° (c 0.25, DMSO); uv (0.1 N HCl) max 255 nm (ε 13,400), min 225 (2,850); uv ($H_2O$) max 258 nm (ε 13,800), min 225 (1,750); uv (0.1 N NaOH) max 258 nm (ε 13,800), min 228 (2,350). Nmr (DMSO-$d_6$). δ 3.74 (m, 3, $H_{5',5''}$, $H_{4'}$), 4.5 (m, 1, $H_{3'}$), 5.20 (t, $J_{5'\text{-OH-}5,5''}$ = 5 Hz, 1, 5'-OH), 6.02 (d, $J_{3'\text{-OH-}3'}$ ≈ 5.5 Hz, 1, 2'-OH), 6.48 (d, $J_{1'-2'}$ = 6.5 Hz, 1, $H_{1'}$), 7.30 (br s, 2, 6-$NH_2$), 8.14, 8.34 (s, s, 1; $H_2$, $H_8$); mass spectrum (190°) m/e (R.I., ion) 285 (5, M), 268 (1, M-17), 255 (6.5, c), 250 (6.5, M-35), 202 (3, M-(35+18)), 190 (10, f), 196 (10, d), 164 (48.5, h), 148 (3, f), 136 (97, B+2H), 135 (100, B+H). [Reported (58) mp 245-247° $[\alpha]_D^{23}$ -10.5° (c 0.25, DMSO).

Anal. Calcd for $C_{10}H_{12}ClN_5O_3$: C, 42.03; H, 4.23;

N, 24.51; Cl, 12.41. Found: C, 42.26; H, 4.45; N, 24.29; Cl, 12.25.

6-N-Pivalamido-9-(5-O-pivalyl-2,3-anhydro-β-D-ribofuranosyl)purine (121).

To a suspension of 0.13 g (0.0005 mole) of 31 in 5 ml of dry pyridine was added 0.5 ml (0.004 mole) of freshly distilled pivalic acid chloride and the resulting clear solution was stirred for 28 hr at room temperature. Ice chips were added and the solution was poured slowly with stirring into 150 ml of ice and water. This mixture was extracted with 2 x 150 ml of $CHCl_3$ and the combined organic phase was washed with 2 x 100 ml of 10% aqueous $NaHCO_3$ solution, 2 x 100 ml of $H_2O$, and dried over $Na_2SO_4$. Drying agent was removed by filtration and the filtrate was evaporated to give 0.21 g (100%) of a pale yellow powder. A more rapidly migrating (tlc) contaminant was readily removed by recrystallization from 95% EtOH to give 0.19 g (92%) of 121; mp 176-179° dec.; uv (MeOH) max 270 nm (ε 18,500) min 230 (3,800); nmr (DMSO-$d_6$) δ 1.0 [s, 9, 5'-OCOC-$(CH_3)_3$], 1.28 [s, 9, 6-NHCOC$(CH_3)_3$], 4.0-4.4 (m, 4, $H_{4'}$, $H_{5',5''}$, $H_{3'}$), 4.58 (d, $J_{2'-3'}$ = 2.5 Hz, 1, $H_{2'}$), 6.36 (s, 1, $OH_{1'}$), 8.60, 8.71 (s, s; 1, 1; $H_2$, $H_8$), 10.16 (s, 1, 6 NH-Piv); mass spectrum (175°) m/e (% R.I., ion) 417 (4, M), 332 (16, M-COC$[CH_3]_3$), 316 [4, M-OCOC$(CH_3)_3$], 220 (16, B+2H), 199 (28, sugar).

Anal. Calcd for $C_{20}H_{27}N_5O_5$: C, 57.53; H, 6.52; N, 16.77. Found: C, 57.35; H, 6.45; N, 16.58.

N,N-Dibenzoyl-9-(5-O-benzoyl-2,3-anhydro-β-D-ribofuranosyl)adenine (122).

To a suspension of 1.46 g (0.0059 mole) of 31 in 36 ml of dry pyridine was added 3.6 ml (0.031 mole) of freshly distilled benzoyl chloride and the resulting clear solution was stirred for 6 hr at room temperature. Ice chips were added and the solution was poured slowly into 1000 ml of ice and water with vigorous stirring. The resulting white precipitate was filtered, washed with 1000 ml of cold water, and dried (finally in vacuo at 78°) to give 2.7 g (82%) of 122. Recrystallization of 0.2 g of this product from 16 ml of EtOH gave 0.15 g of pure 122; mp 167-168°; uv (MeOH) max 273; 230 nm (ε 22,600; 35,000) "shoulder" 250 nm (ε 27,800); nmr (DMSO-$d_6$) δ 4.45 (br s, 2, $H_{5',5''}$), 4.6 (m, 2, $H_{3'}$, $H_{4'}$), 4.7 (d, $J_{2',3'} \cong 3$ Hz, 1, $H_{2'}$), 6.42 (s, 1, $H_{1'}$), 7.3-7.8 (m, 15 aromatic), 8.72, 8.78 (s, s; 1, 1; $H_2$, $H_8$); mass spectrum (210°) m/e (% R.I., ion) 561 (25, M), 456 (100, M-$COC_6H_5$), 440 (37, M-$OCOC_6H_5$), 219 (30, sugar).

Anal. Calcd for $C_{31}H_{23}N_5O_6$: C, 66.30; H, 4.13; N, 12.47. Found: C, 66.08; H, 3.85; N, 12.25.

9-(3-fluoro-3-deoxy-β-D-xylofuranosyl)adenine (123) (85).

To a solution of 0.28 g (0.0005 mole) of 122 in 25 ml of dry freshly distilled $CH_3CN$ was added 0.45 g (0.003 mole) of dried tetraethylammonium fluoride. The yellow solution was heated at reflux for 5 days while protected from moisture by a "Drierite" drying tube. Evaporation of this solution gave a gum which was dissolved in 100 ml of MeOH, 1.0 g (0.019 mole) of sodium methoxide was added, and the solution was stirred for 15 hr at room temperature. This mixture was neutralized with HOAc:$H_2O$ (1:9) and evaporated. The resulting residue was partitioned between 20 ml of $Et_2O$ and 10 ml of $H_2O$. The aqueous phase was applied to a column (2.2 x 17 cm) of Dowex 1-X2 ($OH^-$) resin packed in MeOH-$H_2O$ (3:7) and elution was begun with the same solvent mixture. A small quantity (27 mg) of material indistinguishable from 9-β-D-xylofuranosyl-adenine (23b) by nmr and mass spectroscopy was obtained and after changing to MeOH-$H_2O$ (6:4), the desired product, 123, was eluted. Evaporation of appropriate fractions and crystallization of the residue from 95% EtOH gave 0.085 g (63%) of 123: mp 212-214°, $[\alpha]_D^{24}$ -30.4° (c 0.64, DMF); uv (0.1 N HCl) max 256 nm (ε 14,100) min 228 (4,300); ($H_2O$) max 256 nm (ε 14,100) min 223 (2,800); (0.1 N NaOH) max 258 nm (ε 14,300),

min 228 (4,000); $^1$H nmr (DMSO-$d_6$) δ 3.85 ("d", 2, $H_{5',5''}$), 4.36 (d of sextets, $J_{4'-3'-F}$ = 28 Hz, $J_{4'-5',5''} \cong$ 5.5 Hz, $J_{4'-3'} \cong$ 2.5 Hz, 1, $H_{4'}$), 4.78 (d of t, $J_{2'-3'-F}$ = 16 Hz, $J_{2'-3'} = J_{2'-1'} \cong$ 2.3 Hz, 1, $H_{2'}$), 5.1 ("t", $J_{5'-OH-5',5''} \cong$ 6 Hz, 1, 5'-OH), 5.13 (d of "t", $J_{3'-3'-F(gem)}$ = 54, $J_{3'-2'} \cong$ 2.3, $J_{3'-4} \cong$ 2.5 Hz, 1, $H_{3'}$), 6.04 (d, $J_{1'-2'}$ = 2.3 Hz, 1, $H_{1'}$), 6.25 (br s, 1, 2'-OH), 7.36 (s, 2, 6-$NH_2$) 8.14, 8.22 (s, s; 1,1; $H_2$, $H_8$); $^{19}$F nmr (DMSO-$d_6$; ppm upfield from $CCl_3F$ external) δ 200.8 ["octet" (d of d of d), $J_{3'-F'-3'(gem)}$ = 55, $J_{3'-F-4'}$ = 28.5, $J_{3'-F-2'}$ = 15.5 Hz, 1, $F_{3'}$); mass spectrum (155°) m/e (R.I., ion) 269 (4, M), 239 (5, c), 219 (5, c-20), 178 (6, d), 164 (80, h), 148 (6, f), 136 (67, B+2H), 135 (100, B+H). [Reported (85) mp 218-220°; $[\alpha]_D^{23}$ -40.1° (c 0.5, $H_2O$)].

Anal Calcd for $C_{10}H_{12}FN_5O_3$: C, 44.61; H, 4.45; F, 7.06; N, 26.01. Found: C, 44.68; H, 4.52, F, 7.03; N, 26.20.

9-β-D-Xylofuranosyladenine (23b) (44) (45) (47):

To a solution of 0.56 g (0.001 mole) of 122 in 50 ml of DMF containing 2 ml of water was added 0.3 g (0.002 mole) of sodium benzoate. This mixture was heated at 100° for 22 hr with stirring and then evaporated in vacuo. The resulting gum was partitioned between 100 ml of $CHCl_3$ and 50 ml of $H_2O$. The aqueous phase was extracted with 2 x 50 ml of $CHCl_3$

and the combined organic phase was washed with 2 x 100 ml of $H_2O$, dried over $Na_2SO_4$, filtered, and evaporated to give a pale yellow foam.

This foam was dissolved in 100 ml of MeOH and 1 g (0.019 mole) of NaOMe was added. The solution was stirred for 16 hr at room temperature, neutralized with HOAc:$H_2O$ (1:9), and evaporated. The residue was partitioned between 20 ml of $H_2O$ and 50 ml of $Et_2O$ and the aqueous phase was applied to a column (2.2 x 20 cm) of Dowex 1-X2 ($OH^-$) resin packed in MeOH-$H_2O$ (3:7). Elution with the same solvent mixture and evaporation of the appropriate fractions gave 0.23 g (85%) of 23b, which could be crystallized from 95% EtOH to give 0.21 g of 23b: mp 185-187° dec; $[\alpha]_D^{25}$ -67° (c, 1.14, $H_2O$); uv (0.1 N HCl) max 255 nm (ε 15,000), min 228 (4,000); uv ($H_2O$) max 258 nm (ε 15,100) min 225 (2,400); uv (0.1 N NaOH) max 258 nm (ε 15,700), min 225 (3,600); nmr (DMSO-$d_6$) δ 3.7 (m, 2, $H_{5',5''}$), 4.15 (m, 2, $H_{3'}$, $H_{4'}$), 4.35 (m, 1, $H_{2'}$), 4.72 (t, $J_{5'\text{-OH-}5',5''}$ = 6 Hz, 1, 5'-OH), 5.78 (br s, 1, 3'-OH), 5.83 (br s, 1, 2'-OH), 5.85 [d, $J_{1'-2'}$ = 2 Hz (by $D_2O$ exchange), 1, $H_{1'}$], 7.3 (s, 2, 6-$NH_2$), 8.15, 8.30 (s, s; 1, 1; $H_2$, $H_8$); mass spectrum (170°) m/e (R.I., ion) 267 (6, M), 237 (3, c), 220 (5, c-17), 194 (6, i), 178 (36, d), 164 (65, h), 148 (12, f), 136 (95, B+2H), 135 (100, B+H).

[Reported (44) mp 125-140, (47) mp 225-230°, $[\alpha]_D^{24}$ -16.4° (c 1.1, $H_2O$); (45) $[\alpha]_D^{24}$ -22.5 (c 1.22, $H_2O$)].

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.20. Found: C, 44.95; H, 4.96; N, 26.33.

Further elution with MeOH-$H_2O$ (1:1) gave 0.024 g of 17. This product had essentially identical mobility to a sample of authentic 17 by thin-layer chromatography, paper chromatography and electrophoresis. The nmr spectrum (DMSO-$d_6$) of the product obtained from similar experimental batches was identical with that of 17 ($H_1'$ at 6.25, $J_{1'-2'}$ = 4 Hz). See table 4 and 5.

Anion exchange column chromatographic resolution of synthetic mixtures of 9-β-D-xylofuranosyladenine (23b) and 9-β-D-arabinofuranosyladenine (17).

A mixture of 0.8 mg of 9-β-D-arabinofuranosyladenine (17) and 11 mg of 9-β-D-xylofuranosyladenine (23b) was dissolved in 1 ml of $H_2O$. This solution was applied to a column (0.8 x 20 cm) of Dowex 1-X2 ($OH^-$) resin. Elution was commenced with $H_2O$ (200 ml) and then successive 10% increments (100 ml per increment) of MeOH were used. At 40% aqueous MeOH 11 mg (uv estimation) of 9-β-D-xylofuranosyladenine (23b) was eluted. The 9-β-D-arabinofuranosyladenine (17) (0.8 mg uv estimation) was eluted with 50% aqueous MeOH. The products were identified and shown to be

pure by thin layer chromatography and mass spectrometry.

A mixture of 0.8 mg of 23b and 11 mg of 17 was also completely resolved on an identical column using the above procedure.

9-(3-Azido-3-deoxy-β-D-xylofuranosyl)adenine (124a)

To a solution of 1.11 g (0.002 mole) of 122 in 100 ml of dry distilled DMF was added 1 g (0.015 mole) of sodium azide. The mixture was heated for 10 hr at 100° with stirring and then evaporated in vacuo. The resulting pale yellow gum was partitioned between 100 ml of $CHCl_3$ and 50 ml of $H_2O$ and the aqueous layer was extracted with 2 x 25 ml of $CHCl_3$. The combined organic phase was washed with 2 x 50 ml of $H_2O$, dried over $Na_2SO_4$, filtered and evaporated to give a pale yellow solid foam. This material was dissolved in 100 ml of MeOH and stirred for 12 hr at room temperature with 1 g (0.019 mole) of NaOMe. The solution was neutralized with HOAc-$H_2O$ (1:9) and evaporated. The residue was partitioned between 50 ml of $Et_2O$ and 20 ml of $H_2O$ and the aqueous layer was evaporated to dryness. The residue was crystallized from $H_2O$ to give 0.54 g (92%) of a pale yellow solid. This material was recrystallized from EtOH to give 0.49 (83%) of 124a: mp 177-178°; $[\alpha]_D^{24}$ -128°

(c 0.94, MeOH); uv ($H_2O$) max 260 nm (ε 15,100) min 232 (3,000); nmr (DMSO-$d_6$) δ 3.65 (br s, 2, $H_{5',5''}$), 4.32 (m, 2, $H_{3'}$, $H_{4'}$), 4.8 ("t", $J_{2'-1'}$ = 6 Hz, $J_{2'-3'}$ ≅ 6 Hz, 1, $H_{2'}$), 5.4 (br s, 1, 5'-OH), 5.85 (d, $J_{1'-2'}$ = 6 Hz, 1, $H_{1'}$), 6.25 (br s, 1, 2'-OH), 7.35 (s, 2, 6-$NH_2$), 8.18, 8.30 (s, s; 1,1; $H_2$, $H_8$); mass spectrum (205°) m/e (R.I., intensity) 292 (2.5, M), 264 [.5, M-28($N_2$)], 250 [7, M-42($N_3$)], 220 [26, c-42($N_3$)], 178 (9, d), 164 (52, h), 148 (21.5, f), 136 (59.5, B+2H), 135 (100, B+H).

Anal. Calcd for $C_{10}H_{12}N_8O_3$: C, 41.09; H, 4.14; N, 38.34. Found: C, 41.35; H, 4.27; N, 38.54.

9-(3-Amino-3-deoxy-β-D-xylofuranosyl)adenine (124b)

A solution of 0.37 g (0.0013 mole) of 124a in 100 ml of 95% EtOH was hydrogenated at 45 psi (gauge pressure) for 48 hr at ambient temperature over 0.19 g of 5% Pd/C catalyst. The mixture was filtered, the filter cake was washed with 20 ml of hot EtOH, and the combined filtrate was evaporated to give a white solid which was recrystallized from 95% EtOH to give 0.27 g (81%) of 124b: mp 250-251°; $[\alpha]_D^{24}$ -30.1° (c 0.5, $H_2O$); uv (0.1 N HCl) max 255 nm (ε 14,500), min 225 (2,500); uv ($H_2O$) max 258 nm (ε 14,300), min 225 (2,000); uv (0.1 N NaOH) max 258 nm (ε 14,000), min

228 (3,000); nmr (DMSO-$d_6$) δ 1.1 (t, J = 7 Hz, 3, $CH_3CH_2OH$), 1.8 (br s, 2, 3'-$NH_2$), 3.3-3.5 (m, 2, $H_3$, and OH), 3.5 (q, J = 7 Hz, 2, $CH_3CH_2OH$), 3.7 (m, 2, $H_{5',5''}$), 4.16 (m, 1, $H_{4'}$), 4.39 ("t", $J_{2'-1'} \cong J_{2'-3'} \cong$ 6 Hz, 1, $H_{2'}$), 5.6-5.74 (br d, $J_{1'-2'} \cong$ 6 Hz, 2, $H_1$, and OH), 7.3 (br s, 2, 6-$NH_2$), 8.16 (s, 1, $H_2$), 8.48 (s, 1, $H_8$). Mass spectrum (210°) m/e (% R.I., ion) 266 (1.5, M) 236 (4.5, c), 220 (3, c-16), 194 (32, i), 178 (15, d), 164 (15, h), 148 (7.5, f), 136 (100, B+2H), 135 (50, B+H).

Anal. Calcd for $C_{10}H_{14}N_6O_3 \cdot C_2H_5OH$: C, 46.13; H, 6.45; N, 26.91. Found: C, 45.93; H, 6.32; N, 27.00.

9-(2-S-Benzyl-2-thio-2-deoxy-β-D-arabinofuranosyl)-adenine (126) and 9-(3-S-Benzyl-3-thio-3-deoxy-β-D-xylofuranosyl)adenine (125)

To a solution of 0.78 g (0.015 mole) of sodium methoxide in 40 ml of MeOH under nitrogen was added 2 ml (0.0174 mole) of benzyl mercaptan. To this solution was added 0.7 g (0.0028 mole) of 31 and the mixture was refluxed for 18 hr under nitrogen. The solution was evaporated in vacuo, the residue dissolved in 100 ml of MeOH, and this solution neutralized with acetic acid-$H_2O$ (1:9). The solution was evaporated to dryness and the white residue was dissolved in 30 ml of $H_2O$ and applied to a Dowex 1-X2 ($OH^-$) (2.3 x

35 cm) column. The column was washed with $H_2O$ (.4 ℓ). Elution with MeOH:$H_2O$ (4:6) afforded 0.075 g (7%) of 126. This product was recrystallized from EtOH-Benzene and gave 0.060 g of pure 126 mp 196-198°; $[\alpha]_D^{24}$ -155° (c 0.55, DMF); uv (MeOH) max 268 nm (ε 16,000), min (4,900); nmr (DMSO-$d_6$) δ 3.6 (m, 1, $H_{2'}$), 3.65 (s, 2, $-S-CH_2$), 3.75 ("d", 2, $H_{5',5''}$), 4.3 (m, 1, $H_{4'}$), 5.16 (s, 1, 5'-OH), 5.8 (s, 1, 3'-OH), 6.5 (d, $J_{1'-2'}$ = 6 Hz, 1, $H_{1'}$), 7.0-7.4 (m, 7, aromatic, 6-$NH_2$), 8.2, 8.30 (s, s; 1, 1; $H_2$, $H_8$); mass spectrum (Calcd for $C_{17}H_{19}N_5O_3S$: 373.1209; Found: m/e 373.1216) (200°) m/e (R.I., ion) 373 (0.5, M), 282 (19, M-$CH_2\phi$), 164 (11, h), 148 (2.5, f), 136 (60, B+2H), 135 (100, B+H).

Further elution with MeOH:$H_2O$ (4:6) gave 0.90 g (85%) of 125. Recrystallization of 0.1 g of this product from MeOH (ether, desiccator) gave 0.085 g of pure 125: mp 182-183°; $[\alpha]_D^{24}$ -152° (c 0.50, DMF); uv (MeOH) λ max 268 nm (ε 15,000), min 230 (4,800); nmr (DMSO-$d_6$) δ 3.5 ("t", $J_{3'-2'} \cong J_{3'-4'}$ = 8 Hz, 1, $H_{3'}$), 3.65 (br s, 2, $H_{5',5''}$), 3.94 (s, 2, $S-CH_2$), 4.25 (m, 1, $H_{4'}$), 4.75 (br s, 1, $H_{2'}$), 5.6 ("t", $J_{5'-OH-5'}$ = 5 Hz, 1, 5'-OH), 5.8 (d, $J_{1'-2'}$ = 6 Hz, 1, $H_{1'}$), 6.0 (d, $J_{2'-OH-2'}$ = 6 Hz, 1, 2'-OH), 7.3-7.55 (m, 7, aromatic, 6-$NH_2$), 8.2 (s, 1, $H_2$), 8.40 (s, 1, $H_8$); mass spectrum (220°) m/e (R.I., ion) 373 (1.5, M), 282 (37, M-$CH_2\phi$), 220 (52.5), 202 (10.5), 178 (10.5, d),

164 (90, h), 148 (10.5, f), 136 (100, B+2H), 135 (26, B+H).

Anal. Calcd for $C_{17}H_{19}N_5O_3S$: C, 54.67; H, 5.13; N, 18.75; S, 8.58. Found: C, 54.11; H, 5.16; N, 18.42; S, 8.32.

9-(3-O-Methyl-β-D-xylofuranosyl)adenine (127)

To a suspension of 0.25 g (0.001 mole) of 31 in 50 ml of MeOH was added 1.15 g (0.03 mole) of $NaBH_4$. The mixture was heated for 12 hr at reflux with three further additions of 0.25 g portions of $NaBH_4$ after heating for 1, 4 and 6 hr. The solution was evaporated and the white residue was dissolved in 30 ml of $H_2O$. This solution was continuously extracted with 100 ml of $CH_2Cl_2$ for 24 hr and the organic phase was evaporated to give 0.28 g (~100%) of white product. This material was purified by column chromatography on Dowex 1-X2 ($OH^-$) using MeOH-$H_2O$ (3:7) as the elution solvent mixture. Evaporation of the appropriately pooled fractions and recrystallization of the residue from MeOH gave 0.24 g (85%) of 127: mp 167-168°; $[\alpha]_D^{24}$ -60.5° (c 0.3, MeOH); uv (0.1 N HCl) max 258 nm (ε 14,100), min 230 (3,000); ($H_2O$) max 258 nm (ε 14,200), min 225 (2,500); (0.1 N NaOH) max 259 nm (ε 14,400), min 225 (3,700); nmr (DMSO-$d_6$) δ 3.3 (s, 3, 3'-O-$CH_3$), 3.72 (br s, 2, $H_{5',5''}$), 3.80 (m, 1, $H_{3'}$), 4.28 (m, 1, $H_{4'}$), 4.56 ("t",

$J_{2'-3'}$ = 2.5 Hz, $J_{2'-1'}$ = 2.7 Hz, 1, $H_{2'}$), 4.86 (br s, 1, 5'-OH), 5.90 (br d, $J_{1'-2'}$ = 2.7 Hz, 2, $H_{1'}$, 2'-OH), 7.26 (s, 1, 6-$NH_2$), 8.12, 8.18 (s, s; 1, 1; $H_2$, $H_8$). Mass spectrum (200°) m/e (% R.I., ion) 281 (5, M), 251 (5, c), 250 (3, M-31), 220 (7.5, c-31), 194 (3, i), 178 (9, d), 164 (100, h), 148 (15, f), 136 (60, B+2H), 134 (85, B+H).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.37; N, 24.90. Found: C, 46.98; H, 5.66; N, 24.70

The same reaction was repeated on 1g of 31. The use of a Dowex 1-X2 ($OH^-$) column (3 x 68 cm) permitted the isolation of 78.5 mg (8%) of 3'-deoxyadenosine (16) from the (1:9) MeOH:$H_2O$ fraction and 860 mg (77%) of the title compound 127 from the (3:7) MeOH:$H_2O$ fraction.

9-(3-Deoxy-β-D-erythro-pentofuranosyl)adenine-[cordycepin; 3'-deoxyadenosine] (16) (58).

To a suspension of 0.25 g (0.001 mole) of 31 in 120 ml of EtOH (98%) was added 1.4 g (0.0037 mole) of $NaBH_4$. The mixture was heated for 12 hr at reflux. The solution was evaporated and the white residue was dissolved in 20 ml of $H_2O$ and applied to a column (2.5 x 60 cm) of Dowex 1-X2 ($OH^-$) resin. The product was eluted using MeOH-$H_2O$ (3:7). Evaporation of the eluate and recrystallization of the

residue from 95% EtOH (ether, desiccator) gave 0.140 g (56%) of 16 as white crystals: mp 229-230°; $[\alpha]_D$ -45.5° (c 0.66, $H_2O$); uv (0.1 N HCl) max 258 nm (ε 14,800) min 228 (2,800); ($H_2O$) max 258 nm (ε 15,200) min 225 (3,500); (0.1 N NaOH) max 258 nm (ε 15,100) min 228 (4,150); nmr (DMSO-$d_6$) δ 1.95 ("octet", $J_{3"-3'} \cong 13$, $J_{3"-4'} = 6$, $J_{3"-2'} = 3$ Hz, 1, $H_{3"}$), 2.28 ("septet", $J_{3'-3"} \cong 13$, $J_{3'-4'} \cong 8$, $J_{3'-2'} = 6$ Hz, 1, $H_{3'}$), 3.64 (m, 2, $H_{5'}$, $H_{5"}$), 4.35 (m, 1, $H_{4'}$), 4.60 (m, 1, $H_{2'}$), 5.19 ("t", $J_{OH-5',5"} \cong 5.5$ Hz, 1, 5'-OH), 5.70 (d, $J_{OH-2'} = 4$ Hz, 1, 2'-OH), 5.89 (d, $J_{1'-2'} = 2.5$ Hz, 1, $H_{1'}$), 7.28 (s, 2, 6-$NH_2$), 8.18 (s, 1, $H_2$), 8.38 (s, 1, $H_8$). Mass spectrum (215°) m/e (% R.I., ion) 251 (4, M), 221 (4, c), 202 (4, c-18), 178 (14, d), 164 (60, h), 148 (11, f), 136 (45, B+2H), 135 (100, B+H). [Reported (58) mp 225-226°; $[\alpha]_D^{23}$ -45.8° (c 0.6, $H_2O$)].

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.21, N, 27.87. Found: C, 47.68; H, 5.35; N, 27.66.

Further elution with MeOH-$H_2O$ (6:4) gave 0.005 g of a product identical to a sample of authentic 9-(3-O-ethyl-β-D-xylofuranosyl)adenine (128) by thin layer chromatography and mass spectrometry.

9-(3-O-Ethyl-β-D-xylofuranosyl)adenine (128)

To a suspension of 0.125 g (0.0005 mole) of 31

in 50 ml of absolute EtOH was added 0.050 g (0.0013 mole) of $NaBH_4$. The mixture was heated 19 hr at reflux. The solution was evaporated and the white residue was dissolved in 120 ml of MeOH. The solution was neutralized with glacial HOAc and evaporated to dryness. The residue was dissolved in 20 ml of $H_2O$ and this solution was applied to a column (2.2 x 30 cm) of Dowex 1-X2 ($OH^-$) packed in $H_2O$. The product was eluted with MeOH-$H_2O$ (3:7) and evaporation of appropriate fractions gave 0.1 g (68.5%) of 128. This product was recrystallized from 10 ml of 95% EtOH (ether, desiccator) to give 0.095 g of 128 as white needles: mp 175-176°; $[\alpha]_D^{24}$ -86.5 (c 0.59, DMF), uv (0.1 N HCl) max 255 nm (ε 13,650), min 230 (3,500); uv ($H_2O$) max 258 nm (ε 14,000), min 230 (3,500); uv (0.1 N NaOH) max 258 nm (ε 14,000), min 230 (4,050); nmr (DMSO-$d_6$) δ 1.10 (t, J ≈ 7 Hz, 3, $OCH_2\underline{CH_3}$), 3.54 (q, J = 7 Hz, 2, $O\underline{CH_2}CH_3$), 3.7 (br s, 2, $H_{5',5''}$), 3.91 ("q", 1, $H_{3'}$), 4.27 ("q", 1, $H_{4'}$), 4.53 (br s, 1, $H_{2'}$), 4.81 (br s, 1, 5'-OH), 5.93 (d, $J_{1'-2'}$ = 2.25 Hz, 2, $H_{1''}$, 2'-OH), 8.16 and 8.18 (s, s; 1, 1; $H_2$ and $H_8$); mass spectrum (180°) (% R.I., ion) 295 (2, M), 266 (2, M-$CH_2CH_3$), 265 (2, c), 251 (9.5, M-44), 234 [4, M-(44+17)], 220 (8, c-45), 194 (3, i), 178 (12, d), 164

(100, h), 148 (15, f), 136 (81, B+2H), 135 (93, B+H).

Anal. Calcd for $C_{12}H_{17}O_4N_5$: C, 48.80; H, 5.80, N, 23.72. Found: C, 48.66; H, 6.07; N, 23.46

9-(2,3-Anhydro-β-D-lyxofuranosyl)adenine (38) (56) (128). Method A.

The procedure given above for the preparation of 23b was followed to the end of the first paragraph. The resulting pale yellow solid foam was dissolved in 50 ml of dry, freshly distilled pyridine and cooled to 0°. Freshly distilled methanesulfonyl chloride (0.1 ml, 0.0013 mole) was added and the solution was stirred for 3 days at 0°. Ice chips were added and the solution was poured into 100 ml of ice water. The mixture was extracted with 150 ml of $CHCl_3$. The organic phase was washed with 100 ml of 10% aqueous $NaHCO_3$ solution, 100 ml of $H_2O$, dried over $Na_2SO_4$, filtered, and evaporated. The resulting residue was dissolved in 70 ml of MeOH and the solution was stirred with 0.4 g (0.0075 mole) of NaOMe for 16 hr at room temperature. This solution was neutralized with HOAc-$H_2O$ (1:9) and 2.3 g of neutral silica gel was added. The mixture was evaporated to dryness and the impregnated powder was added to a column (2 x 28 cm, 47 g) of silica gel. The column was washed with EtOAc and the wash was discarded. The product was eluted using

EtOAc-MeOH (8:2) and evaporation of appropriate fractions gave a yellow powder, which was crystallized from a mixture of 95% EtOH and n-pentane to give 0.126 g (50%) of 38: mp 208-210° dec; $[\alpha]_D^{25}$ -17.5° (c 0.19, $H_2O$); uv (0.1 N HCl) max 258 nm (ε 14,700), min 228 (2,600); uv ($H_2O$) max 258 nm (ε 14,800), min 225 (2,000); uv (0.1 N NaOH) max 258 nm (ε 14,600), min 225 (2,500); nmr (DMSO-$d_6$) δ 3.6 (m, 2, $H_{5',5''}$), 4.14 (m, 2, $H_{3'}$, $H_{4'}$), 4.25 (d, $J_{2',3'} \cong 3$ Hz, 1, $H_{2'}$), 5.0 (br s, 1, 5'-OH), 6.26 (s, 1, $H_{1'}$), 7.32 (s, 2, 6-$NH_2$), 8.18, 8.22 (s, s; 1, 1; $H_2$, $H_8$); mass spectrum (190°) m/e (R.I., ion) 249 (5, M), 219 (6, c), 202 (1, c-17), 190 (3, j), 164 (100, h), 148 (10, f), 136 (45, B+2H), 135 (45, B+H). [Reported (128) mp 210-211°; $[\alpha]_D^{22}$ -14° (c, 1, $H_2O$)].

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 47.95; H, 4.76; N, 28.19.

9-(3,5-O-Isopropylidene-β-D-xylofuranosyl)-adenine (32) (44), (45), (55), (105).

To a stirred solution of freshly distilled acetone (20 ml) containing 2.8 g of p-toluenesulfonic acid and 5 ml (0.02 mole) of 2,2-dimethoxypropane, 1 g (0.0037 mole) of 23b was added. The flask was stoppered and stirred for 12 hr. The brown solution was poured, with stirring into 50 ml of saturated

aqueous sodium bicarbonate solution. After a few minutes the solution was extracted with 20 ml of ether. The ether layer was discarded and the aqueous layer, now colorless, was extracted with 8 x 50 ml of $CHCl_3$ and the combined organic phase was dried over $Na_2SO_4$. Drying agent was removed by filtration and the filtrate was evaporated to give 1.1 g (100%) of 32 as a white powder. The product was recrystallized from 95% EtOH (ether, desiccator) to give 1.3 g (100%) of 32, as long white needles: mp 214-215°; $[\alpha]_D^{24}$ = -95.5 (c 1.05, DMF); uv (0.1 N HCl) max 255 nm (ε 13,800), min 225 (3,350); uv ($H_2O$) max 258 nm (ε 13,600), min 223 (2,550); uv (0.1 N NaOH) max 258 nm (ε 14,300) min 225 (3,450). Nmr (DMSO-$d_6$) δ 1.0 (t, J = 7 Hz, 3, $CH_3$-$CH_2OH$), 1.18; 1.36 (s, s, 3, 3; $C(CH_3)_2$), 3.35 (m, 3, $CH_3CH_2OH$+OH), 3.8-4.3 (m, 5, $H_2$', $H_3$', $H_4$'; $H_5$',$_5$"), 5.92 (s, 1, $H_1$'), 6.06 (d, 1, 2'-OH), 7.16 (s, 2, 6-$NH_2$), 8.14 (s, 1, $H_2$), 8.28 (s, 1, $H_8$); mass spectrum (190°) (% R.I., ion) 307 (4, M), 292 (4, M-15), 220 (3), 194 (4, i), 178 (11.5, d), 164 (100, h), 148 (4, f), 136 (54, B+2H), 135 (54, B+H). [Reported (44) mp 204-207°; $[\alpha]_D^{24}$ -71.6° (c 0.3, DMF). (45) mp 207-208.5°; $[\alpha]_D^{25}$ -84.5° (c 1.01, DMF). (55) mp 212.5-214°.]

Anal. Calcd for $C_{13}H_{17}N_5O_4 \cdot C_2H_5OH$: C, 50.98; H, 6.56; N, 19.82. Found: C, 50.69; H, 6.38; N, 19.75.

9-[3,5-O-Isopropylidene-2-O-methanesulfonyl-β-D-xylofuranosyl]adenine (37) (56).

To a solution of 1 g (0.0033 mole) of 32 in 20 ml of dry, distilled pyridine was added 1 ml (0.013 mole) of methanesulfonyl chloride with stirring. The flask was stoppered and stirred for 6 hr. The yellow reaction mixture was poured into 150 ml of $H_2O$ and this solution was extracted with 6 x 50 ml of $CHCl_3$. The combined organic phase was washed with 100 ml of saturated aqueous $NaHCO_3$ solution, 100 ml of $H_2O$, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. Remaining traces of pyridine were removed by coevaporation with toluene. The yellow residue was dissolved in 2 ml of $CHCl_3$ and applied to a silica column (100 g, 2.3 x 50 cm). The column was washed with $CHCl_3$ (300 ml) and the compound was then eluted with MeOH-$CHCl_3$ (2:98). Evaporation of the appropriate fractions gave 0.960 g (77%) of 37 as a white powder: mp 218-219°; $[\alpha]_D^{24}$ -81.5° (c 0.98, MeOH); uv (MeOH) max 255 nm (ε 16,400), min 225 (2,200); nmr (DMSO-$d_6$) δ 1.25; 1.50 (s, s; 3, 3; $C(CH_3)_2$), 3.56 (s, 3, $-OSO_2CH_3$), 4.10-4.30 (m, 3, $H_{4'}$; $H_{5',5''}$), 4.71 (d, $J_{3'-4'}$ = 2 Hz, 1, $H_{3'}$), 5.27 (s, 1, $H_{2'}$), 6.35 (s, 1, $H_{1'}$), 7.32 (br s, 2, 6-$NH_2$), 8.18 (s, 1, $H_2$) 8.26 (s, 1, $H_8$); mass spectrum (200°) (% R.I., ion) 385 (4, M); 370 (7.5, M-15), 327 (2, $[M-(CH_3-\overset{\overset{O}{\|}}{C}-CH_3)]$), 248 (11.5), 232 (11.5), 218 (4),

202 (19), 178 (8, d), 164 (100, h), 148 (8, f), 136 (54, B+2H), 135 (46, B+H). [Reported (56) mp 212-212.5°; $[\alpha]_D^{25.9}$ -72° (c 1, MeOH)].

Anal. Calcd for $C_{14}H_{19}N_5O_6S$: C, 43.62; H, 4.97; N, 18.17; S, 8.32. Found: C, 43.59; H, 5.01; N, 18.07; S, 8.45.

9-(2-O-Methanesulfonyl-β-D-xylofuranosyl)adenine (37a) (56) (128).

To 50 ml of trifluoroacetic acid-$H_2O$ (45:5) was added 0.840 g (0.0022 mole) of 37 and the solution was stirred for 25 minutes. The solution was evaporated to give an off-white foam which was dissolved in MeOH and 4 g of silica gel was added. The mixture was evaporated to dryness and the impregnated powder was added to a column (80 g, 2.3 x 40 cm) of silica. The product was eluted using MeOH:$CHCl_3$ (1:9) and evaporation of the appropriate fractions gave 0.61 g (81%) of 37a as an off-white powder: mp 181-182°; uv (0.1 N HCl) max 255 nm (ε 15,700), min 225 (ε 3,150); uv ($H_2O$) max 258 nm (ε 16,000), min 228 (2,500); uv (0.1 N NaOH) max 256 (ε 15,700), min 225 (2,500). Nmr (DMSO-$d_6$) δ 3.36 (s, 3, O-$SO_2$-$CH_3$), 3.77 ("d", $J_{5',5''-4'}$ = 4 Hz, 2, $H_{5',5''}$), 4.19 ("q", 1, $H_{4'}$), 4.46 (m, 1, $H_{3'}$), 5.39 ("t", $J_{2'-3'} \simeq J_{2'-1'}$ = 2.5 Hz, 1, $H_{2'}$), 6.1 (br s, 2, 3'-OH, 5'-OH), 6.24 (d, $J_{1'-2'}$ = 2.5 Hz, 1, $H_{1'}$), 7.7 (br s, 6-$NH_2$), 8.26, 8.36 (s, s;

1, 1; $H_2$, $H_8$). Mass spectrum (Calcd for $C_{11}H_{15}N_5O_6S$: 345.0743; Found: m/e 345.0730) (200°) (% R.I., ion) 345 (19, M), 248 (5.5), 219 (5.5), 202 (5.5), 190 (4.5, i), 178 (4.5, d), 164 (100, h), 148 (12, f), 136 (47.5, B+2H), 135 (85.5, B+H). [Reported (56) mp 170.5-171°. (128) mp 172-173°.]

Anal. Calcd for $C_{11}H_{15}N_5O_6S$: C, 38.25; H, 4.38; N, 20.28; S, 9.28. Found: C, 38.40; H, 4.41; N, 20.03; S, 9.24.

9-(2,3-Anhydro-β-D-lyxofuranosyl)adenine (38). Method B.

To a solution of 0.35 g (0.001 mole) of 37a in 200 ml of MeOH was added 0.4 g (0.017 mole) of sodium. The solution was stirred at room temperature for 6 hr, neutralized with glacial HOAc, and evaporated to dryness. The residue was dissolved in 25 ml of $H_2O$ and the solution was applied to a column (2.3 x 52 cm) of Dowex 1-X2 ($OH^-$) resin. Elution with $H_2O$ gave 0.218 g (87%) of pure 38. This product was identical with a known sample (see above) by nmr, tlc (silica, 10% MeOH in $CHCl_3$); and mass spectrometry (Calcd for $C_{10}H_{11}N_5O_3$: 249.0862; Found: m/e 249.0868).

9-β-D-Arabinofuranosyladenine (17) (56) (107).

To a solution of 0.250 g (0.001 mole) of 38 in 50 ml of DMF containing 2 ml of $H_2O$ was added 0.3 g

(0.002 mole) of sodium benzoate. This mixture was heated at 100° for 5 hr with stirring and then evaporated *in vacuo* to give a yellow gum. This gum was dissolved in 80 ml of MeOH and 0.15 g (0.0063 g. at.) of Na was added. The solution was stirred for 16 hr at room temperature, neutralized with glacial acetic acid and evaporated. The residue was dissolved in 20 ml of $H_2O$ and the solution was applied to a column (2.2 x 50 cm) of Dowex 1-X2 ($OH^-$) resin packed in $H_2O$. The column was washed with $H_2O$ (2 ℓ) and then with MeOH-$H_2O$ (1:9) (2 ℓ). The concentration of MeOH in $H_2O$ was gradually increased to 65% (dry volume). A small quantity, 0.018 g (6.5%) of material indistinguishable from 23b by thin layer chromatography (tlc), paper chromatography, electrophoresis and mass spectroscopy was obtained. After increasing the concentration of MeOH to 85%, the desired product 17 was eluted. Evaporation of the appropriate fractions and crystallization of the residue from 95% EtOH (ether, desiccator) gave 0.210 g (80%) of 17: mp 265-266°. This product was shown to be free of the xylo-isomer by paper chromatography. $[\alpha]_D^{24}$ -12° (c 0.11, $H_2O$) -4° (c 0.53, DMF); uv (0.1 N HCl) max 256 nm (ε 13,300), min 225 (3,200); uv ($H_2O$) max 256 nm (ε 13,400), min 225 (1,350); uv (0.1 N NaOH) max 259 nm (ε 14,200), min 227 (2,650); nmr (DMSO-$d_6$) δ 3.65 (br s, 2, $H_{5',5''}$), 3.78

(br s, 1, $H_{3'}$), 4.12 ("d", 2, $H_{2'}$, $H_{4'}$), 5.2 (br s, 1, 5'-OH), 5.40 (br s, 2, 2'-OH, 3'-OH), 6.25 (d, 1, $J_{1'-2'}$ = 4 Hz, $H_{1'}$), 7.18 (br s, 2, 6-$NH_2$), 8.15, 8.18 (s, s; 1, 1; $H_2$, $H_8$); mass spectrum (215°); m/e (% R.I., ion) 267 (3, M), 250 (1.5, M-17), 237 (3, c), 194 (3, i), 178 (21, d), 164 (100, h), 148 (9, f), 136 (54, B+2H), 135 (81, B+H). [Reported (56) mp 257-257.5°; $[\alpha]_D^{27}$ -5° (c 0.25, $H_2O$). (107) mp 258-260°; $[\alpha]_D^{20}$ -1.7° (c 0.54, pyridine)].

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.20. Found: C, 44.99; H, 5.15; N, 25.98.

9-(3-Azido-3-deoxy-β-D-arabinofuranosyl)adenine (129a) (104).

To a suspension of 0.250 g (0.001 mole) of 38 in 50 ml of dry, distilled DMF was added 0.5 g (0.0075 mole) of sodium azide. The mixture was heated for 4 hr at 100° with stirring and then evaporated in vacuo. The resulting pale yellow solid was dissolved in 15 ml of $H_2O$ and this solution was applied to a column (3 x 50 cm) of Dowex 1-X2 ($OH^-$) resin. Elution with MeOH-$H_2O$ (7:3) and concentration of the appropriate fractions gave 0.20 g (68%) of 129a as white needles: mp 165-166°; $[\alpha]_D^{24}$ -39.2° (c 0.45, DMF); uv (MeOH) max 258 nm (ε 15,000), min 225 (2,700); nmr (DMSO-$d_6$) δ 3.65 ("d", 2, $H_{5'}$, $_{5''}$), 3.8 (m, 1, $H_{4'}$), 4.25-4.6

(br "s", 2, $H_{2'}$, $H_{3'}$), 5.25 ("t", 1, 5'-OH), 6.05 (br d, 1, 2'-OH), 6.22 (d, $J_{1'-2'}$ = 5 Hz, 1, $H_{1'}$), 7.2 (s, 2, 6-$NH_2$), 8.14 (s, 1, $H_2$), 8.28 (s, 1, $H_8$); mass spectrum (200°) m/e (% R.I., ion) 292 (1, M), 250 [1.5, M-42($N_3$)], 220 (4, c-42), 194 (7, i), 190 (4, j), 178 (8.5, d), 164 (21.5, h), 148 (18.5, f), 136 (53, B+2H), 135 (100, B+H). [Reported (104) compound does not melt under 340°, $[\alpha]_D^{23.5}$ -23° (c 0.496, pyridine); -41.5° (c 0.48, DMF)].

Anal. Calcd for $C_{10}H_{12}N_8O_3$: C, 41.09; H, 4.14; N, 38.34. Found: C, 41.19; H, 4.29; N, 38.20.

9-(3-Amino-3-deoxy-β-D-arabinofuranosyl)adenine (129b) (104).

A solution of 0.050 g (0.00017 mole) of 129a in 50 ml of 95% EtOH was hydrogenated at 45 psi (gauge pressure) for 22 hr at ambient temperature over 0.050 g of 5% Pd/C catalyst. The mixture was filtered, the filter cake washed with 10 ml of hot EtOH, and the combined filtrate evaporated to give a white solid which was crystallized from 5 ml of 95% EtOH (ether, desiccator))to give 0.036 g (84%) of 129b: mp 220-222°; $[\alpha]_D^{24}$ +4° (c 0.5, $H_2O$); uv (0.1 N HCl) max 255 nm (ε 14,400), min 225 (3,000); ($H_2O$) max 259 nm (ε 14,700), min 225 (1,850); (0.1 N NaOH) max 258 nm (ε 14,900), min 232 (3,250); nmr (DMSO-$d_6$) δ 1.75 (br s, 2, 3'-$NH_2$), 3.3 (s, 1, $H_{3'}$), 3.6 (br s, 3, $H_{4'}$, $H_{5',5''}$), 4.10 ("t",

$J_{2'-3} \cong J_{2'-1'} \cong 5.5$ Hz, 1, $H_{2'}$), 5.10-5.60 (br s, 2, 3'-OH, 5'-OH), 6.24 (d, $J_{1'-2'} = 5.5$ Hz, 1, $H_{1'}$), 7.18 (br s, 2, 6-$NH_2$), 8.12 (s, 1, $H_2$), 8.24 (s, 1, $H_8$). Mass spectrum (190°) m/e (% R.I., ion) 266 (1, M), 236 (1, M-30), 194 (43, i), 178 (12.5, d), 164 (25, h), 148 (10.5, f), 136 (100, B+2H), 135 (33, B+H). [Reported (104) mp 245-247°; $[\alpha]_D^{24}$ +3.8° (c 0.5, $H_2O$)].

Anal. Calcd for $C_{10}H_{14}N_6O_3$: C, 45.10, H, 5.29; N, 31.56. Found: C, 44.80; H, 5.30; N, 31.28.

9-(3-O-Methyl-β-D-arabinofuranosyl)adenine (131) and 9-(2-O-Methyl-β-D-xylofuranosyl)adenine (132).

To a suspension of 0.2 g (0.0008 mole) of 38 in 50 ml of MeOH was added 0.3 g (0.008 mole) of $NaBH_4$. The mixture was heated for 5 hr at reflux. After cooling, the solution was neutralized with glacial HOAc and evaporated to give a white powder which was dissolved in 15 ml of $H_2O$ and applied to a column (2.3 x 33 cm) of Dowex 1-X2 ($OH^-$) resin. Elution with $H_2O$ gave 0.001 g of a product identical by thin layer chromatography and mass spectrometry to an authentic sample of 9-(2-Deoxy-β-D-threo-pentofuranosyl)adenine (133). Further elution with $H_2O$ gave 0.030 g (13%) of 132; nmr (DMSO-$d_6$) δ 3.40 (s, 3, $-OCH_3$), 3.7 (m, 2, $H_{5',5''}$), 3.95 -4.25 (m, 3, $H_{2'}$, $H_{3'}$, $H_{4'}$), 4.70 ("t", $J_{5'-OH-5,5''} \cong 5$ Hz, 1, 5'-OH), 6.00 (d, $J_{1'-2'} \cong 1.25$ Hz, 1, $H_{1'}$), 6.05 (br s, 1, 3'-OH), 7.38 (br s, 2, 6-

$NH_2$), 8.18 (s, 1, $H_2$), 8.30 (s, 1, $H_8$); mass spectrum (Calcd for $C_{11}H_{15}N_5O_4$: 281.1124; Found: m/e 281.1150) (210°) m/e (R.I., ion) 281 (3, M), 251 (2, c), 250 (0.5, M-31), 233 [5, M-(31+17)], 192 (39, d), 190 (2, j), 177 (6, v), 164 (100, h), 148 (16, f), 146 (42.5, w), 136 (100, B+2H), 135 (76, B+H).

Elution with MeOH-$H_2O$ (3:7) and evaporation of the appropriate fractions gave 0.185 g (79%) of 131 which was crystallized from 98% EtOH (ether, desiccator) and had mp 229-230°; $[\alpha]_D^{24}$ +6.3° (c 0.35, $H_2O$); uv (0.1 N HCl) max 255 nm (ε 14,200), min 228 (4,200); uv ($H_2O$) max 258 nm (ε 15,400), min (4,200); uv (0.1 N NaOH) max 258 nm (ε 16,000), min 228 (4,200); nmr (DMSO-$d_6$) δ 3.36 (s, 3, $OCH_3$), 3.75 (br s, 2; $H_{5',5''}$), 3.85 (m, 2, $H_{3'}$, $H_{4'}$), 4.3 (br s, 1, $H_{2'}$), 5.12 (br "t", $J_{5\text{-OH-}5',5''}$ = 5.5 Hz), 5.72 (br d, 1, 2'-OH), 621 (d, $J_{1'-2'}$ = 4.5 Hz, 1, $H_{1'}$), 7.2 (s, 2, 6-$NH_2$), 8.12, 8.18 (s, s; 1, 1; $H_2$, $H_8$); mass spectrum (200°) m/e (% R.I., ion) 281 (4, M), 266 (6.5, M-15), 251 (5.5, c), 220 (5.5, c-31), 194 (3, j), 178 (23.5, d), 164 (100, h), 148 (21, f), 136 (89, B+2H), 135 (97, B+H).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.37; N, 24.90. Found: C, 46.76; H, 5.46; N, 25.12.

9-(2-Deoxy-β-D-threo-pentofuranosyl)adenine (133), 9-(3-Deoxy-β-D-threo-pentofuranosyl) adenine (134) (92) and 9-(3-O-Ethyl-β-D-arabinofuranosyl)adenine (134a).

To a suspension of 1 g (0.004 mole) of 38 in 100 ml of 95% EtOH was added 1.5 g (0.04 mole) of $NaBH_4$. The mixture was heated for 6 hr at reflux and then evaporated to dryness. The residue was dissolved in 100 ml of MeOH and refluxed 10 min. The solution was neutralized with glacial acetic acid and then evaporated to dryness. The residue was dissolved in 20 ml of $H_2O$ and applied to a column (2.5 x 53 cm) of Dowex 1-X2 ($OH^-$) resin. Elution with $H_2O$ gave a small amount (0.017 g) of 133: mp 220-221°; $[\alpha]_D^{24}$ -73.5° (c 0.5, DMF); uv (0.1 N HCl) max 255 nm (ε 14,200), min 230 (3,500); uv ($H_2O$) max 258 nm (ε 14,700), min 228 (2,750); uv (0.1 N NaOH) max 258 nm (ε 15,000), min 228 (3,000); nmr (DMSO-$d_6$) δ 2.4 (d of d, $J_{2"-2'} \simeq 14$ Hz, $J_{2"-1'} \cong 2$ Hz, 1, $H_{2"}$), 2.9 ("sept", 1, $H_{2'}$), 3.8 (m, 2, $H_{5',5"}$), 4.0 (m, 1, $H_{4'}$), 4.5 ("t", 1, $H_{3'}$), 4.65 ("t", $J_{5'-OH-5',5"} = 5$ Hz, 1, 5'-OH), 5.9 (d, $J_{3'-OH,3'} = 5$ Hz, 1, 3'-OH), 6.42 (d of d, $J_{1'-2'} \cong 9$ Hz, $J_{1'-2"} \cong 2$ Hz, 1, $H_{1'}$), 7.36 (br s, 2, 6-$NH_2$), 8.22 (s, 1, $H_2$), 8.42 (s, 1, $H_8$); mass spectrum (200°) m/e (R.I., ion) 251 (8.5, M), 234 (3, M-17), 221 (4, c), 203 (8.5, M-(31+17)), 190 (8.5, i), 164 (8.5, h), 162 (58.5, d), 148 (2, f), 136 (41.5, B+2H), 135 (100, B+H).

[Reported (92) mp 218.9-219.5°; $[\alpha]_D^{24}$ -76 (c 1, DMF).].

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.21; N, 27.87. Found: C, 47.75; H, 5.00; N, 27.98.

Further elution with $H_2O$ gave 0.71 g (71%) of 134: mp 198-199°; $[\alpha]_D^{24}$ -26° (c 0.49, DMF); uv (0.1 N HCl) max 255 nm (ε 14,600), min 228 (3,600); uv ($H_2O$) max 258 nm (ε 14,600), min 225 (2,650); uv (0.1 N NaOH) max 258 nm (ε 15,200), min 228 (2,950); nmr (DMSO-$d_6$) δ 1.9-2.45 (m, 2, $H_{3',3''}$), 3.64 (br s, 2, $H_{5',5''}$), 4.10 (m, 1, $H_{4'}$), 4.53 (m, 1, $H_{2'}$), 5.14 (br s, 1, 5'-OH), 5.40 (d, $J_{2'\text{-OH},2'}$ = 5 Hz, 1, 2'-OH), 6.17 (d, $J_{1'-2'}$ = 5 Hz, 1, $H_{1'}$), 7.22 (br s, 2, 6-$NH_2$), 8.15 (s, 1, $H_2$), 8.30 (s, 1, $H_8$); mass spectrum (185°) m/e (R.I., ion) 251 (7.5, M), 234 (2.5, M-17), 221 (7.5, c), 202 (6, c-18), 178 (15, d), 164 (97, h), 148 (9, f), 136 (51.5, B+2H), 135 (100, B+H). [Reported (92) mp 195-196°; $[\alpha]_D^{22}$ -27° (c 1, DMF).]

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.21; N, 27.87. Found: C, 48.10, H, 5.00; N, 27.76.

A third product, 134a, was eluted with MeOH-$H_2O$ (1:1); yield 0.030 g; mp 201-202°; $[\alpha]_D^{24}$ -8.5° (c 0.47, DMF); uv (0.1 N HCl) max 255 nm (ε 15,900), min 228 (4,600); uv ($H_2O$) max 258 nm (ε 15,900), min 225 (2,750); uv (0.1 N NaOH) max 258 (ε 16,100), min 228 (3,450); nmr (DMSO-$d_6$) δ 1.18 (t, J = 7 Hz, 1, $OCH_2\underline{CH_3}$), 3.59 (q, J = 7 Hz, 2, -$O\underline{CH_2}CH_3$), 3.67 ("d", 2, $H_{5',5''}$),

3.84 ("s", 1, $H_{4'}$), 4.00 ("t", 1, $H_{3'}$), 4.25 (m, 1, $H_{2'}$), 5.13 (br s, 1, 5'-OH), 5.75 (br s, 1, 2'-OH), 6.22 (d, $J_{1'-2'}$ = 5 Hz, 1, $H_{1'}$), 7.18 (s, 2, 6-$NH_2$), 8.14, 8.18 (s, s; 1, 1; $H_2$ and $H_8$); mass spectrum (180°) m/e (R.I., ion) 295 (1, M), 266 (5.5, M-$C_2H_5$), 251 (10, M-44), 220 (4, c-45), 194 (3.5, i), 178 (16.5, d), 164 (100, h), 148 (9.5, f), 136 (54.5, B+2H), 135 (57.5, B+H).

Anal. Calcd for $C_{12}H_{17}N_5O_4$: C, 48.80; H, 5.80; N, 23.72. Found: C, 49.01; H, 6.01; N, 23.79.

9-(2-Fluoro-2-deoxy-β-D-xylofuranosyl)adenine (136) and 9-(3-Fluoro-3-deoxy-β-D-arabinofuranosyl)-adenine (135).

To a suspension of 0.25 g (0.001 mole) of 38 in 75 ml of dry distilled $CH_3CN$ was added 1 g (0.067 mole) of $Et_4NF$. The reaction mixture was heated at 90° with stirring for 19 hr. MeOH (10 ml) was added to the cooled reaction mixture and an insoluble non-uv absorbing solid was removed by filtration. A 2.5 g portion of silica was added and the mixture was evaporated to dryness. The impregnated powder was added to a column (2.3 x 37 cm, 50 g) of silica. The column was washed with 1.5 ℓ of $CHCl_3$ and the products were eluted with $CHCl_3$-MeOH (95:5). The first fractions contained a small amount (≈ 20 mg) of pure 136.

This product was identified by its mass spectrum (195°) m/e (R.I., ion): 269 (4, M), 239 (5, c), 252 (4, M-17), 221 [12.5, M-(31+17)], 180 (90, d), 164 (55, h), 136 (35, B+2H), 135 (100, B+H) and its $^1$H nmr spectrum (DMSO-$d_6$) δ 3.72 (m, 2, $H_{5',5''}$), 4.10-4.5 (m, 2, $H_{3'}$, $H_{4'}$), 4.87 ("t", 1, 5'-OH), 5.39 ("d of d", $J_{2'-2'F}$ = 49 Hz, $J_{2'-1'}$ = 1 Hz, 1, $H_{2'}$), 6.23 ("d of d", $J_{1'-2'F}$ = 21 Hz, $J_{1'-2'}$ = 1 Hz, 1, $H_{1'}$), 6.23 (d, $J_{3'-OH,3'}$ = 5.5 Hz, 1, 3'-OH), 7.35 (br s, 2, 6-$NH_2$), 8.15, 8.25 (s, s; 1, 1; $H_2$, $H_8$).

Further elution gave fractions containing 135 and 136 and finally a few dilute fractions containing very small quantities of pure 135; identified by its mass spectrum (195°) 269 (8.5, M), 239 (6, c), 252 (1.5, M-17), 178 (37.5, d), 164 (100, h), 148 (8.5, f), 136 (46, B+2H), 135 (92, B+H).

4-Amino-7-(2,3-anhydro-β-D-ribofuranosyl)pyrrolo-[2,3-d]pyrimidine (58) (61).

To 300 ml of MeOH saturated with $NH_3$ (at -5°), in a 500 ml round bottom flask was added 5.55 g (0.01 mole) of 51 at -5°. The flask was securely stoppered and allowed to stand at room temperature for 6 hr. The completion of the reaction was then verified by thin layer chromatography (tlc) (silica gel, 5% MeOH in $CHCl_3$). The $NH_3$ was removed by stirring the solu-

tion under vacuum (water pump). Silica gel (7 g) was then added and the mixture was evaporated at room temperature in vacuo. The impregnated powder was added to a wide column (ϕ: 5.5 cm, 150 g) of silica gel. The column was washed with $CHCl_3$ (2 ℓ) and the wash was discarded. The product was eluted using $CHCl_3$-MeOH (95:5) and evaporation (at room temperature) of appropriate fractions gave 58 as a white powder which was dried under high vacuum for 12 hr at room temperature to give 1.72 g (69%). A sample for analysis was rapidly recrystallized from 95% EtOH (ether, desiccator) to give 58 as white needles: mp 170-173°; $[\alpha]_D^{24}$ -46° (c 0.215, MeOH); uv (MeOH) max 271 nm (ε 11,500), min 227 (2,410); nmr (DMSO-$d_6$) δ 3.50 (m, 2, $H_{5',5''}$), 4.12 (t, $J_{4'-5',5''} \simeq 6$ Hz, 1, $H_{4'}$), 4.20 (d, $J_{3'-2'} = 2.5$ Hz, 1, $H_{3'}$), 4.28 (d, $J_{2'-3'} \simeq 2.5$ Hz, 1, $H_{2'}$), 5.04 (br s, 1, 5'-OH), 6.28 (s, 1, $H_{1'}$), 6.60 (d, 1, $H_5$), 7.05 (s, 2, 4-$NH_2$), 7.35 (d, 1, $H_6$), 8.08 (s, 1, $H_2$). Mass spectrum (190°) m/e (% R.I., ion) 248 (11.5, M), 218 (2, c) 217 (3, M-31), 201 (0.5, c-17), 189 (3 , i), 163 (50, h), 147 (6.5, f), 135 (21, B+2H), 134 (100, B+H). [Reported (61) mp 145-176°; $[\alpha]_D^{23}$ -42.6 (c 0.2, MeOH)].

Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.86; N, 22.57. Found: C, 53.17; H, 4.62; N, 22.34.

4-Amino-7-(3-iodo-3-deoxy-β-D-xylofuranosyl)pyrrolo-[2,3-d]pyrimidine (137).

A 0.54 g (0.001 mole) sample of 51 was dissolved in 100 ml of MeOH presaturated with ammonia at -20° and allowed to stand at that temperature for 3 hr. The ammonia was then evaporated in vacuo at -20° and 2 g of silica gel was added to the solution. The mixture was evaporated to dryness and the impregnated powder was added to a column (2 x 26 cm, 40 g) of silica. The column was washed with $CHCl_3$ and the wash discarded. The product was eluted using $CHCl_3$-MeOH (98:2) and evaporation of appropriate fractions gave 0.25 g (66%) of 137 as a white powder. A sample for analysis was recrystallized from 95% EtOH (ether, desiccator) and had mp 175-176°; $[\alpha]_D^{24}$ = -5° (c 0.6, DMF); uv (0.1 N HCl) max 265; 225 nm (ε 11,300; 22,200), min 245 (5,250); uv ($H_2O$) max 268 nm (ε 12,300), min 238 (3,200); uv (0.1 N NaOH) max 268 nm (ε 11,700), min 242 (6,000); nmr (DMSO-$d_6$) δ 3.70 (br s, 2, $H_{5',5''}$), 3.90 (m, 1, $H_{4'}$), 4.46 ("t", $J_{3'-2'} = J_{2'-3'}$ = 5.5 Hz, 1, $H_{3'}$), 4.83 (m, 1, $H_{2'}$), 5.40 ("t", $J_{5'-OH-5',5''}$ = 5.5 Hz, 1, 5'-OH), 5.91 (d, $J_{1'-2'}$ = 5 Hz, 1, $H_{1'}$), 6.14 (d, $J_{3'-OH-3'}$ = 3 Hz, 1, 2'-OH), 6.65 (d, $J_{5-6}$ = 4 Hz, 1, $H_5$), 7.10 (br s, 2, 4-$NH_2$), 7.40 (d, $J_{6-5}$ = 4 Hz, 1, $H_6$), 8.10 (s, 1, $H_2$); mass spectrum (180°) m/e (R.I., ion) 376 (8, M), 248 (8, M-127), 230 [4, M-(127+18)],

219 [12, M-(127+30)], 189 (2, i), 164 (44, h), 147 (4, f), 135 (28, B+2H), 134 (100, B+H).

Anal. Calcd for $C_{11}H_{13}IN_4O_3$: C, 35.12; H, 3.48; N, 14.89; I, 33.74. Found: C, 35.12; H, 3.84; N, 14.61; I, 33.87.

4-Amino-7-(3-deoxy-β-D-erythro-pentofuranosyl)-pyrrolo[2,3-d]pyrimidine (139) (60).

To a suspension of 0.20 g (0.0008 mole) of 58 in 80 ml of 98% EtOH was added 0.7 g (0.018 mole) of $NaBH_4$. The mixture was heated for 4 hr at reflux with a further addition of 1.3 g of $NaBH_4$ after 45 min. The solution was evaporated and the white residue was dissolved in 100 ml of MeOH and refluxed for 10 min. After acidification with glacial HOAc, the solution was evaporated and the white residue was dissolved in 20 ml of $H_2O$ and applied to a column (2.5 × 40 cm) of Dowex 1-X2 ($OH^-$) resin. The product was eluted with $H_2O$, and evaporation of appropriately pooled fractions gave 0.037 g (18.5%) of 139. Recrystallization of this material from 95% EtOH gave 0.028 g of 139 as white crystals: mp 183.5-184°; $[\alpha]_D^{24}$ -75.5° (c 0.51, EtOH); uv (0.1 N HCl) max 270; 227 nm (ε 11,000; 23,400), min 245 (4,000); uv ($H_2O$) max 267 nm (ε 12,000), min 236 (2,250); uv (0.1 N NaOH) max 270 nm (ε 11,500), min

240 (3,500); nmr (DMSO-$d_6$) δ 1.90 (d of q, 1, $H_{3''}$), 2.20 ("sept", 1, $H_{3'}$), 3.57 ("q", 2, $H_{5'}$, $H_{5''}$), 4.20-4.55 (br m, 2, $H_{2'}$, $H_{4'}$), 5.06 ("t", $J_{5'\text{-OH-}5',5''}$ = 5.5 Hz, 1, 5'-OH), 5.50 (d, $J_{2'\text{-OH-}2'}$ = 5.5 Hz, 1, 2'-OH), 6.01 (d, $J_{1'-2'}$ = 3 Hz, 1, $H_{1'}$), 6.6 (d, $J_{5-6}$ = 4 Hz, 1, $H_5$), 6.98 (s, 2, 4-$NH_2$), 7.34 (d, $J_{6-5}$ = 4 Hz, 1, $H_6$), 8.10 (s, 1, $H_2$); mass spectrum (150°) m/e (R.I., ion) 250 (10, M), 220 (1.5, c), 202 [1, c-18($H_2O$)], 177 (4, d), 163 (32, h), 147 (4, f), 135 (22, B+2H), 134 (100, B+H). [Reported (60) mp 180-181°; $[\alpha]_D^{27}$ -75.1° (c, 1, EtOH)].

Anal. Calcd for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 53.01; H, 5.94; N, 22.13.

N,N-Dibenzoyl-4-amino-7-(5-O-benzoyl-2,3-anhydro-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (140).

To a suspension of 1 g (0.004 mole) of 58 in 30 ml of dry pyridine was added 3 ml (0.026 mole) of freshly distilled benzoyl chloride and the resulting clear solution was stirred for 8 hr at room temperature. Ice chips were added and the solution was poured slowly into 2000 ml of ice and water with vigorous stirring. The resulting white precipitate was filtered, washed with 1000 ml of cold water, and dried (finally in vacuo at 50°) to give 2 g (89%) of 140. Recrystallization of 0.065 g of this product from 5 ml of a

mixture of EtOH and $CHCl_3$ gave 0.060 g of pure 140: mp 201-202°; uv (MeOH) shoulder at 270 nm (ε 17,500), max 215 nm (ε 59,500); nmr (DMSO-$d_6$) δ 4.2-4.60 (m, 5, $H_{5',5''}$; $H_{4'}$, $H_{3'}$, $H_{2'}$), 6.38 (d, $J_{5-6}$ = 4 Hz, 1, $H_5$), 6.48 (s, 1, $H_1$), 7.3-7.95 (m, 16, aromatic, $H_6$), 8.56 (s, 1, $H_2$); mass spectrum (200°) m/e (R.I., ion) 560 (68, M), 455 (100, M-$COC_6H_5$), 439 (23, M-$OCOC_6H_5$), 218 (40, s).

Anal. Calcd for $C_{32}H_{24}N_4O_6$: C, 68.56; H, 4.31; N, 9.99. Found: C, 68.43; H, 4.54; N, 10.27.

4-Amino-7-β-D-xylofuranosylpyrrolo[2,3-d]-pyrimidine (141).

To a solution of 0.56 g (0.001 mole of 140 in 50 ml of DMF containing 1 ml of water was added 0.35 g (0.002 mole) of sodium benzoate. This mixture was heated at 100° for 34 hr with stirring and then evaporated in vacuo. The resulting gum was dissolved in 240 ml of MeOH and 0.6 g (0.025 g at.) of sodium was added. The solution was stirred for 21 hr at room temperature, neutralized with glacial acetic acid and evaporated. The residue was partitioned between 20 ml of $H_2O$ and 50 ml of $Et_2O$ and the aqueous phase was applied to a column (2.5 x 22 cm) of Dowex 1-X2 ($OH^-$) resin packed in $H_2O$. The column was washed with $H_2O$ (2 ℓ)

and then with a mixture of MeOH-$H_2O$ (1:9). The ratio of MeOH in $H_2O$ was gradually increased to 6:4 which eluted the product. Evaporation of the appropriate fractions gave 0.19 g (60%) of 141; which was crystallized from MeOH (ether, desiccator)' to give 0.18 g of 141: mp 223-224°; $[\alpha]_D^{24}$ -135° (c 0.5, DMF); uv (0.1 N HCl) max 270, 227 nm (ε 10,600; 22,400), min 245 (3,950); ($H_2O$) max 270 nm (ε 11,500), min 237 (1,950); (0.1 N NaOH) max 270 nm (ε 11,400), min 240 (3,550); nmr (DMSO-$d_6$) δ 3.6-3.7 (m, 2, $H_{5',5''}$), 3.95-4.10 (m, 2, $H_{3'}$, $H_{4'}$), 4.22 (br s, 1, $H_{2'}$), 5.15 (t", $J_{5'\text{-OH-}5',5''} \cong$ 5 Hz, 1, 5'-OH), 5.7 (d, 1, 2'-OH), 5.88 (s, 1, 3'-OH), 5.94 (d, $J_{1'-2'}$ = 2 Hz, 1, $H_{1'}$), 6.55 (d, $J_{5-6}$ = 4 Hz , 1, $H_5$), 7.0 (br s, 2, 4-$NH_2$), 7.38 (d, 1, $J_{6-5}$ = 4 Hz, $H_6$), 8.08 (s, 1, $H_2$), mass spectrum (170°) m/e (R.I., ion) 266 (3, M), 177 (45, d), 163 (66, h), 147 (19.5, f), 135 (61.5, B+2H), 134 (100, B+H).

Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.42; H, 5.32; N, 20.75.

Further elution with MeOH-$H_2O$ (7:3) gave 0.018 g of 142. This product had essentially identical mobility to a sample of authentic 142 by thin layer chromatography paper chromatography, and electrophoresis. The mass spectrum was identical to that of 142. The nmr spectrum

(DMSO-$\underline{d}_6$) of the product obtained from similar experimental batches was identical with that of 142. ($H_1$, at δ 6.42, $J_{1',2'} \cong 4$ Hz).

4-Amino-7-(3-azido-3-deoxy-β-D-xylofuranosyl-pyrrolo[2,3-d]pyrimidine (143).

To a solution of 0.560 g (0.001 mole) of 140 in 50 ml of dry, distilled DMF was added 0.5 g (0.0075 mole) of sodium azide. The mixture was heated for 22 hr at 100° with stirring and then evaporated to dryness in vacuo. The resulting yellow gum was partitioned between 200 ml of $CHCl_3$ and 50 ml of $H_2O$ and the aqueous layer was extracted with 2 x 50 ml of $CHCl_3$. The combined organic phase was washed with 2 x 100 ml of $H_2O$, dried over $Na_2SO_4$, filtered, and dissolved in 120 ml of MeOH and stirred with 0.46 g (0.002 g.at.) of sodium for 18 hr at room temperature. The solution was neutralized with glacial HOAc and evaporated. The residue was partitioned between 50 ml of $Et_2O$ and 20 ml of $H_2O$ and the aqueous layer was applied to a column (2.3 x 25 cm) of Dowex 1-X2 ($OH^-$) resin. The product was eluted using MeOH-$H_2O$ (6:4). Evaporation of the appropriate fractions and recrystallization of the residue from 5 ml of 95% EtOH (ether, desiccator) gave 0.11 g (38%) of crystalline 143: mp 220-221°; $[\alpha]_D^{24}$ -132° (c 0.55, DMF); uv ($H_2O$) max 268

nm (ε 13,500), min 238 (1,950); (0.1 N HCl) max 270, 227 nm (ε 12,000; 24,000), min 245 (3,900); (0.1 N NaOH) max 270 nm (ε 13,900), min 242 (3,900); nmr (DMSO-$d_6$) δ 3.65 (br s, 2, $H_{5',5''}$), 4.25-4.35 (m, 2, $H_{3'}$, $H_{4'}$), 4.6 ("t", $J_{2'-1'}$ = 5 Hz, $J_{2'-3'}$ ≅ 5 Hz, 1, $H_{2'}$), 5.28 ("t", 1, 5'-OH), 6.0 (d, $J_{1'-2'}$ = 5 Hz, 1, $H_{1'}$), 6.12 (br s, 1, 2'-OH), 6.62 (d, $J_{5-6}$ = 4 Hz, 1, $H_5$), 7.1 (s, 2, 4-$NH_2$); 7.35 (d, $J_{6-5}$ = 4 Hz, 1, $H_6$), 8.08 (s, 1, $H_2$). Mass spectrum (190°) m/e (% R.I., ion) 291 (4.5, M), 263 [1, M-28($N_2$)], 249 [2, M-42($N_3$)], 219 [6.5, c-42($N_3$)], 177 (5.5, d), 163 (29.5, h), 147 (16.5, f), 135 (27, B+2H) 134 (100, B+H).

Anal. Calcd for $C_{11}H_{13}N_7O_3$: C, 45.35; H, 4.49; N, 33.66. Found: C, 45.28; H, 4.64; N, 33.51.

4-Amino-7-(3,5-O-isopropylidene-β-D-xylofuranosyl)-pyrrolo[2,3-d]pyrimidine (145).

To a stirred solution of 6 ml of freshly distilled acetone containing 0.84 g of p-toluenesulfonic acid and 1.5 ml (0.014 mole) of 2,2-dimethoxypropane was added 0.3 g (0.0011 mole) of 141. The flask was stoppered and stirred for 20 hr. The red solution was poured, with stirring, into 30 ml of saturated aqueous sodium bicarbonate solution. After a few minutes the solution was extracted with 7 x 30 ml of $CHCl_3$. White crystals appeared upon concentration of the

combined organic phase and were filtered to yield 0.680 g (100%) of 145: mp 251°-252°; $[\alpha]_D^{24}$ -81.5 (c 0.5, DMF); uv (0.1 N HCl) max 266, 225 nm, (ε 10,300, 21,400), min min 242 (4,000); uv ($H_2O$) max 270 nm (ε 11,100), min 237 (280); uv (0.1 N NaOH) max 267 nm (ε 10,800), min 240 (ε 4,000); nmr (DMSO-$d_6$) δ 1.34; 1.44 (s, s; 3, 3; $C(CH_3)_2$), 3.8-4.3 (m, 5, $H_{2'}$, $H_{3'}$, $H_{4'}$; $H_{5',5''}$), 5.90 (br s, 1, 2'-OH), 6.16 (s, 1, $H_{1'}$), 6.52 (d, $J_{5-6}$ = 4 Hz, 1, $H_5$), 6.96 (br s, 2, 4-$NH_2$), 7.42 (d, $J_{6-5}$ = 4 Hz, 1, $H_6$), 8.08 (s, 1, $H_2$); mass spectrum (185°) (% R.I., ion) 306 (85, M), 291 (4, M-15), 219 (1), 193 (2, i), 177 (5.5, d), 163 (70, h), 147 (3, f), 135 (32, B+2H), 134 (100, B+H).

Anal. Calcd for $C_{14}H_{18}O_4N_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 55.09; H, 6.13; N, 18.02

4-Amino-7-(3,5-O-isopropylidene-2-O-methanesulfonyl-β-D-xylofuranosyl)pyrrolo[2,3-d]pyrimidine (146)

To a solution of 0.6 g (0.0019 mole) of 145 in 10 ml of dry distilled pyridine was added 0.6 ml (0.007 mole) of methanesulfonyl chloride with stirring. The flask was stoppered and stirred for 3 hr. The solution was poured into 150 ml of ice and water and this mixture was extracted with 4 x 50 ml of $CHCl_3$. The combined organic phase was washed with 100 ml of

saturated aqueous $NaHCO_3$, 100 ml of $H_2O$, dried over $Na_2SO_4$, filtered, and evaporated *in vacuo* to give a white powder. This powder was dissolved in 5 ml of $CHCl_3$ and applied to a column of silica gel (2.3 x 50 cm, 100 g). The column was washed with 200 ml of $CHCl_3$ and the compound was then eluted with MeOH-$CHCl_3$ (3:97). The appropriate fractions were evaporated to give 0.58 g (77%) of 146 as a white powder: mp 80-83°; uv (MeOH) max 270 nm (ε 11,200) min 230 (3,670); nmr (DMSO-$d_6$) δ 1.32; 1.50 (s, s; 3, 3; $C(CH_3)_2$), 3.48 (s, 3, $-OSO_2CH_3$), 3.90-4.3 (m, 3, $H_{4'}$; $H_{5',5''}$), 4.65 (d, $J_{3',4'}$ = 2 Hz, 1, $H_{3'}$), 5.05 (s, 1, $H_{2'}$), 6.40 (s, 1, $H_{1'}$), 6.60 (d, $J_{5-6} \simeq 3.8$ Hz, 1, $H_5$), 7.1 (br s, 2, 4-$NH_2$), 7.40 (d, $J_{6-5} \simeq 3.8$ Hz, 1, $H_6$), 8.08 (s, 1, $H_2$); mass spectrum (Calcd for $C_{15}H_{20}N_4O_6S$: 384.1103; Found: m/e 384.1111) (180°) (% R.I., ion) 384 (5.5, M), 369 (3.5, M-15), 247 (5.5), 231 (7), 217 (2), 201 (10.5), 163 (95, h), 147 (9, f), 135 (32, B+2H), 134 (100, B+H).

4-Amino-7-(2-O-methanesulfonyl-β-D-xylofuranosyl)-pyrrolo[2,3-d]pyrimidine (147)

A 0.55 g (0.0014 mole) sample of 146 was dissolved in 50 ml of 90% trifluoroacetic acid. The solution was stirred at room temperature for 20 min and was then evaporated. After removal of traces of water and acid

by coevaporation of the residue with benzene, 0.42 g (85%) of 147 was obtained as a white solid foam: mp 179-180°; uv (MeOH) max 270 nm (ε 11,200), min 230 (3,670); nmr (DMSO-$d_6$) δ 3.22 (s, 3, $-CH_3$), 3.71 (m, 2, $H_{5',5''}$), 4.09 (m, 1, $H_{4'}$), 4.42 (m, 1, $H_{3'}$), 4.91 ("t", $J_{5\text{-}OH\text{-}5',5''}$ = 5 Hz, 1, 5'-OH), 5.21 ("t", $J_{2'-3'}$ = $J_{2'-1'}$ = 2.5 Hz, 1, $H_{2'}$), 6.25 (d, $J_{1'-2'}$ = 5 Hz, 1, $H_{1'}$), 6.35 (d, $J_{2'\text{-}OH\text{-}2',2''}$ = 5.5 Hz, 1, 2'-OH), 6.60 (d, $J_{5-6}$ = 4 Hz, 1, $H_5$), 7.12 (br s, 2, $4\text{-}NH_2$), 7.36 (d, $J_{6-5}$ = 4 Hz, 1, $H_6$), 8.08 (s, 1, $H_2$); mass spectrum (200°) m/e (R.I., ion) 344 (Calcd for $C_{12}H_{15}N_4O_6S$: 344.0791; Found: m/e 344.0788) (2.5 M), 248 (27, M-($OSO_2CH_3$ and OH)), 217 (7, 248-31), 201 (6), 189 (9, j), 163 (93, h), 147 (18, f), 135 (44.5, B+2H), 134 (100, B+H).

Anal. Calcd for $C_{12}H_{16}N_4O_6S$: C, 41.85; H, 4.68; N, 16.27; S, 9.31. Found: C, 41.67; H, 4.47; N, 16.00; S, 9.28.

4-Amino-7-(2,3-anhydro-β-D-lyxofuranosyl)-pyrrolo[2,3-d]pyrimidine (144)

To a solution of 0.237 g (0.0007 mole) of 147 in 80 ml of MeOH was added 0.2 g of sodium. The solution was stirred at room temperature for 12 hr, neutralized with glacial HOAc, and evaporated to dryness. The residue was dissolved in 25 ml of $H_2O$

and the solution applied to a column (2 x 60 cm) of Dowex 1-X2 (C[illegible]) resin. Elution with $H_2O$ and evaporation of appropriate pooled fractions gave 0.140 g (82%) of 144. Recrystallization of this material from 95% EtOH gave pure 144: mp 110-112° (dec); $[\alpha]_D^{24}$ -50.5 (c 0.4, DMF) uv (0.1 N HCl) max 270, 225 nm (ε 11,100; 23,000), min 245 (4,250); uv ($H_2O$) max 270 nm (ε 12,500), min 247 (7,500); uv (0.1 N NaOH) max 270 nm (ε 12,000), min 238 (4,100); nmr (DMSO-$d_6$) δ 3.58 (d, 2, $H_{5',5''}$), 3.95-4.2 (m, 3, $H_{2'}$, $H_{3'}$, $H_{4'}$), 5.0 (br s, 1, 5'-OH), 6.40 (s, 1, $H_{1'}$), 6.65 (d, $J_{5-6}$ = 4 Hz, 1, $H_5$), 7.08 (br s, 2, 4-$NH_2$), 7.30 (d, $J_{6-5}$ = 4 Hz, 1, $H_6$), 8.12 (s, 1, $H_2$); mass spectrum (Calcd for $C_{11}H_{12}N_4O_3$: 248.0909; Found: m/e 248.0905) (140°) m/e (R.I., ion) 248 (11.5, M), 231 (1.5, M-17), 218 (5.5, c), 217 (8.5, M-31), 201 (5.5, c-17), 189 (8.5, j), 163 (97, h), 147 (23, f), 135 (49, B+2H), 134 (100, B+H).

Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.86; N, 22.57. Found: C, 53.04; H, 5.09; N, 22.81.

4-Amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-d]-pyrimidine (142)

To a solution of 0.13 g (0.0005 mole) of 144 in 25 ml of DMF containing 1 ml of $H_2O$ was added 0.15 g (0.001 mole) of sodium benzoate. This mixture was

heated at 100° for 12 hr with stirring and then evaporated *in vacuo*. The residue was dissolved in 40 ml of MeOH and 0.07 g (0.003 g . at.) of Na was added. The solution was stirred for 1 hr at room temperature, neutralized with glacial HOAc and evaporated. The residue was dissolved in 25 ml of $H_2O$ and the solution was applied to a column (2 x 32 cm) of Dowex 1-X2 ($OH^-$) resin. The column was washed with $H_2O$ (2 ℓ) and then with MeOH:$H_2O$ (1:9). The concentration of MeOH in water was gradually increased. A small quantity, 0.006 g (4.5%) of material indistinguishable from 141 by thin layer chromatography, paper chromatography, electrophoresis, mass spectrometry and nmr was eluted with MeOH: $H_2O$ (6:4). Further elution gave 0.102 g (74%) of the desired 142. Recrystallization of 0.1 g of this material from MeOH/ether, desiccator) gave 0.095 g of pure 142: mp 125-126°; $[\alpha]_D^{24}$ +6.9° (c 0.5, DMF); uv (0.1 N HCl) max 268; 225 nm ( 11,100; 23,800), min 245 (4,150); uv ($H_2O$) max 268 nm (ε 11,900), min 240 (4,500); uv (0.1 N NaOH) max 280 nm (ε 11,200), min 240 (4,150); nmr (DMSO-$d_6$) 3.55-3.8 (m, 3, $H_3$', $H_5$',5"), 3.95-4.20 (m, 2, $H_2$', $H_4$'), 5.01 (t, 1, 5'-OH), 5.41 (d, 2, 2'-OH, 3'-OH), 6.42 (d, $J_{1'-2'}$ = 4 Hz, 1, $H_1$'), 6.52 (d, $J_{5-6}$ = 4 Hz, 1, $H_5$), 6.90 (br s, 2, 4-$NH_2$),

7.29 (d, $J_{6-5}$ = 4 Hz, 1, $H_6$), 8.05 (s, 1, $H_2$), mass spectrum (200°) m/e (R.I., ion) 266 (7, M), 236 (1, c), 193 (1, i), 190 (0.5, j), 177 (10.5, d), 163 (60, h), 147 (8, f), 135 (32, B+2H), 134 (100, B+H).

Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.92; H, 5.40; N, 20.86.

9-(2,3-Anhydro-5-O-p-toluenesulfonyl-β-D-ribofuranosyl)adenine (148).

To a cold (0°) suspension of 0.125 g (0.0005 mole) of 31 in 500 ml of dry pyridine was added 0.385 g (0.002 mole) of recrystallized p-toluenesulfonyl chloride. The resulting yellow solution was stirred at 0° for 6 days and was then poured into 200 ml of 10% aqueous $NaHCO_3$ solution. This mixture was extracted with 3 x 50 ml of $CHCl_3$. The combined organic phase was washed with 200 ml of 10% aqueous $NaHCO_3$ solution, 2 x 50 ml of $H_2O$, and dried over $Na_2SO_4$. Drying agent was removed by filtration and the filtrate was evaporated to give a yellow foam. This foam was dissolved in 5 ml of $CHCl_3$ and applied to a column (2 x 17 cm, 12 g) of silica gel. The product was eluted using $CHCl_3$-MeOH (98:2) and evaporation of the appropriate fractions gave 0.150 g (74%) of 148 as a white powder: mp 165-167°; uv (MeOH) max 260 nm (ε 15,050) min 240 (8,700). The maximum shifts to 272 nm (ε 13,850) on

standing in MeOH at room temperature. Nmr ($CDCl_3$ and a little DMSO-$\underline{d}_6$) δ 2.40 (s, 3, $-CH_3$), 4.1-4.5 (m, 5, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5',5''}$) 6.2 (s, 1, $H_{1'}$), 7.10-7.60 (m, 6, aromatic, 6-$NH_2$), 8.02; 8.18 (s, s; 1, 1; $H_2$ and $H_8$). Nmr (DMSO-$\underline{d}_6$): in this solvent 148 is rapidly converted to the $\underline{N}^3 \rightarrow 5'$ cyclonucleoside δ 2.3 (s, 3, $-CH_3$), 4.1 (q, 2, $H_{5',5''}$), 4.3-4.5 (m, 1, $H_{4'}$), 5.1-5.0 (m, 2, $H_{2'}$, $H_{3'}$), 6.55 (s, 1, $H_{1'}$), 7.1 (d, 2, aromatic), 7.5 (d, 2, aromatic), 8.5 (s, 1, $H_2$), 8.75 (s, 1, $H_8$). Mass spectrum (255°) m/e (% R.I., ion), 403 (very small, $\underline{\underline{M}}$), 231 (2, $\underline{\underline{M}}$-$\underline{p}$-$CH_3$-Ph-$SO_3H$), 172 (20, $\underline{p}$-$CH_3$-Ph-$SO_3H$), 155 (41%, $\underline{p}$-$CH_3$-Ph-$SO_2$), 136 (10, $\underline{\underline{B}}+\underline{\underline{2H}}$), 135 (100, $\underline{\underline{B}}+\underline{\underline{H}}$). An analytical sample, mp 165-166°, was obtained by crystallization of this powder from EtOH.

Anal. Calcd for $C_{17}H_{17}N_5SO_5$: C, 50.61; H, 4.25; N, 17.36; S, 7.94. Found: C, 50.56; H, 4.56, N, 17.09; S, 8.17.

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