AD_____

SRI-ORG-KM-89-168-6000-XII

# SYNTHESIS LABORATORY FOR THE U. S. ARMY MEDICAL RESEARCH INSTITUTE OF INFECTIOUS DISEASES SELECTION PANEL

ANNUAL PROGRESS REPORT

John A. Secrist III
Cecil D. Kwong
Charles A. Krauth
Angela G. Ford
Yajnanarayana H. R. Jois
Deborah A. Carter
Lisa K. Hanna
George S. McCaleb

FEBRUARY 13, 1989
(For the period 1 December 1987 - 30 November 1988)

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, MD 21701-5012

Contract No. DAMD17-86-C-6011

SOUTHERN RESEARCH INSTITUTE
2000 Ninth Avenue South
P. O. Box 55305
Birmingham, Alabama 35255-5305



DOD DISTRIBUTION STATEMENT

Distribution authorized to U. S. Government agencies only: proprietary information; February 1989. Other requests for this document must be referred to the Commander, U. S. Army Medical Research and Development Command (ATTN: SGRD-RMI-S), Fort Detrick, Frederick, Maryland 21701-5012.

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

Unclassified
SECURITY CLASSIFICATION OF THIS PAGE

# REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

| | |
|---|---|
| 1a. REPORT SECURITY CLASSIFICATION: Unclassified | 1b. RESTRICTIVE MARKINGS: ~~auth~~ |
| 2a. SECURITY CLASSIFICATION AUTHORITY | 3. DISTRIBUTION / AVAILABILITY OF REPORT: Distribution ~~limited~~ to U. S. Government Agencies only; Proprietary Information February 1989 |
| 2b. DECLASSIFICATION / DOWNGRADING SCHEDULE | |
| 4. PERFORMING ORGANIZATION REPORT NUMBER(S): SRI-ORG-KM-89-168-6000-XII | 5. MONITORING ORGANIZATION REPORT NUMBER(S) |
| 6a. NAME OF PERFORMING ORGANIZATION: Southern Research Institute; 6b. OFFICE SYMBOL (If applicable) | 7a. NAME OF MONITORING ORGANIZATION |
| 6c. ADDRESS (City, State, and ZIP Code): 2000 Ninth Avenue South, P. O. Box 55305, Birmingham, AL 35255-5305 | 7b. ADDRESS (City, State, and ZIP Code) |
| 8a. NAME OF FUNDING / SPONSORING ORGANIZATION: U. S. Army Med. Research & Develop. Com.; 8b. OFFICE SYMBOL (If applicable): SGRD-RMI-S | 9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: Contract Number DAMD17-86-C-6011 |
| 8c. ADDRESS (City, State, and ZIP Code): Fort Detrick, Frederick, MD 21701-5012 | 10. SOURCE OF FUNDING NUMBERS |

| PROGRAM ELEMENT NO. | PROJECT NO. | TASK NO. | WORK UNIT ACCESSION NO. |
|---|---|---|---|
| 637634 | 3172 63763D807 | 4D | 064 |

11. TITLE (Include Security Classification)
Synthesis Laboratory for the U. S. Army Medical Research Institute of Infectious Diseases Selection Panel

12. PERSONAL AUTHOR(S) John A. Secrist III, Cecil D. Kwong, Charles A. Krauth, Angela G. Ford, Yajnanarayana H. R. Jois, Deborah A. Carter, George S. McCaleb, and Lisa K. Hanna

| 13a. TYPE OF REPORT | 13b. TIME COVERED | 14. DATE OF REPORT (Year, Month, Day) | 15. PAGE COUNT |
|---|---|---|---|
| Annual Progress | FROM 12-1-87 TO 11-30-88 | 1989, February 13 | 85 |

16. SUPPLEMENTARY NOTATION

| 17. COSATI CODES | | |
|---|---|---|
| FIELD | GROUP | SUB-GROUP |
| 07 | 03 | |
| 06 | 15 | |

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
antiviral; synthesis laboratory; imidazole; adenosine; adenosine $N^1$-oxides; benzyloxyadenosines; tetraazadiphosphorines; selenadiazoles; triazolotriazoles; guanidines; pyrazoles; adamantanecarboxamides; adamantylthioureas; RAI

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

A synthesis laboratory has been established for the preparation of compounds to be evaluated against viruses of interest to U. S. Army Medical Research Institute of Infectious Diseases. The synthesis of known compounds as well as new compounds has been undertaken, and all compounds are being made in sufficient quantity to allow for full evaluation. Among the compounds prepared thus far are 1-benzyloxyadenosines, 9-substituted 1-benzyloxyadenines, 1,2,4,5,3,6-tetraazadiphosphorines, substituted imidazoles, selanadiazoles, triazoles, triazolotriazoles, guanidines, pyrazoles, adamantane derivatives, chloroquines, $N^1$-aminonucleosides, allopurinol acyclonuclosides, nucleotides of ribavirin and tiazofurin, and various other heterocyclic compounds. Keywords: antiviral agents; synthesis (chemistry); organic chemistry; (KT)

| 20. DISTRIBUTION / AVAILABILITY OF ABSTRACT | 21. ABSTRACT SECURITY CLASSIFICATION |
|---|---|
| ☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS | Unclassified |

| 22a. NAME OF RESPONSIBLE INDIVIDUAL | 22b. TELEPHONE (Include Area Code) | 22c. OFFICE SYMBOL |
|---|---|---|
| Mrs. Virginia M. Miller | 301/663-7325 | SGRD-RMI-S |

DD Form 1473, JUN 86 — Previous editions are obsolete. — SECURITY CLASSIFICATION OF THIS PAGE

Unclassified

## TABLE OF CONTENTS



## FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

**Introduction**

This report summarizes the activities supported by Contract No. DAMD17-86-C-6011 during Quarters 8-11 from 1 December 1987 through 30 November 1988. The purpose of this contract is to support the synthesis of a wide variety of compounds for evaluation in the USAMRIID viral screening program. These compounds will include: (1) known compounds that are needed in larger quantities for proper evaluation; and (2) new compounds whose structures have been determined by rational processes.

During this year, we submitted 69 more compounds for screening. Most of these were analogs of compounds that we either selected from the USAMRIID list of active antiviral compounds or found in our searches of the literature. We also synthesized and submitted a number of other compounds which had been specifically requested by Major Ussery. We have addressed 15 out of the 21 compounds specifically requested by Major Ussery. Thirteen of these compounds were synthesized, while no synthesis was required for two other compounds, bisdesethylchloroquine and 4-iminopyrazolo[3,4-*d*]-1,3-thiazin-6-thione. An alternate source was arranged for bisdesethylchloroquine, because we were having difficulty isolating this compound, and it was already available from this alternate source. We also decided not to make any additional quantities of 4-iminopyrazolo[3,4-*d*]-1,3-thiazin-6-thione. Our information indicated that USAMRIID already had 15 g of this compound in stock. We also repurified a USAMRIID-supplied sample of 4-acetyl-4-phenylpiperidine, and we began working toward the synthesis of four recently reported anti-HIV agents. Finally, we have continued to search the literature for other new lead compounds and are awaiting suggestions for other leads from USAMRIID.

**Personnel**

During the year covered by this report, we have had the following personnel changes: After the eighth quarter, Dr. Y. H. R. Jois was transferred from our project to another SRI project which had a greater need for his specific experience and training. Mr. George S. McCaleb joined our project in the ninth quarter. During the tenth quarter, Ms. Angela G. Ford left our group to return to pursue an advanced degree. Ms. Lisa K. Hanna joined our group at the beginning of the eleventh quarter.

The time charges made during the third year are listed below and are divided into various categories.

| Name | Hours 1 Dec 87 - 30 Nov 88 | Percent of Time |
|---|---|---|
| **Project Supervision:** | | |
| Dr. J. A. Secrist III | 186 | 10 |
| **Chemists:** | | |
| Dr. C. D. Kwong | 1,616 | 87 |
| C. A. Krauth | 1,836 | 100 |
| D. A. Carter | 1,870 | 99 |

| Name | Hours 1 Dec 87 - 30 Nov 88 | Percent of Time |
|---|---|---|
| Dr. Y. H. R. Jois | 518 | 28 |
| G. S. McCaleb | 1,394 | 78 |
| L. K. Hanna | 432 | 23 |
| A. G. Ford | 1,233 | 66 |
| D. J. Adamson | 18 | 1 |
| **Analytical Services:** | | |
| Dr. W. C. Coburn | 222 | 12 |
| Dr. J. M. Riordan | 302 | 16 |
| Dr. D. S. Weinberg | 2 | <1 |
| M. C. Kirk | 284 | 16 |
| C. Richards | 288 | 16 |
| R. T. Morris | 248 | 13 |
| M. D. Ochs | 54 | 3 |
| S. A. Campbell | 33 | 2 |
| M. L. Manier | 14 | 1 |
| **Glassware Technicians:** | | |
| W. Johnson | 149 | 8 |
| J. Crow | 319 | 17 |
| A. Jackson | 208 | 11 |
| R. Milton | 37 | 2 |

**Compounds Submitted**

The compounds that we submitted during the year for this annual report are shown on the following pages, in their approximate order of delivery. Our SRI numbers, AVS numbers (when available), and the amounts submitted are listed with each of these compounds. Of course, we can make additional quantities of any of these compounds, if warranted.

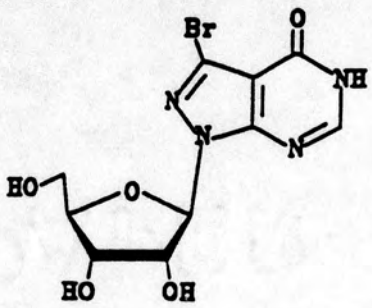
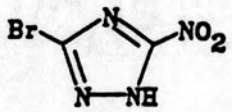
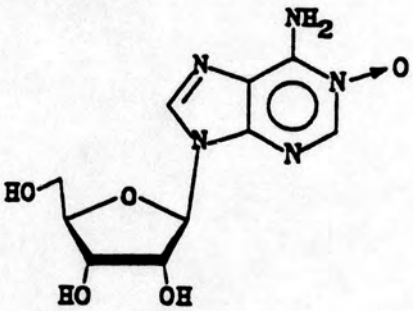
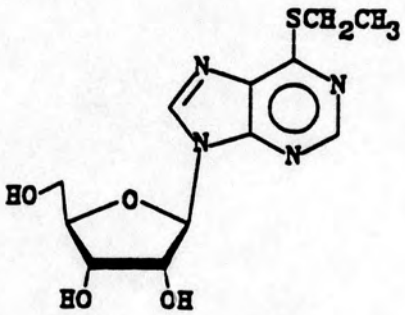
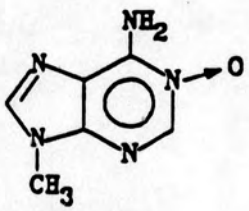
**Chemistry**

During this year, we continued to synthesize analogs of compounds which were either selected from the USAMRIID list of active antiviral compounds or found in the literature. Among the compounds investigated were analogs of adenosine-$N^1$-oxide, $N^1$-aminonucleosides, triazolotriazoles, allopurinol acyclonucleosides, ethyl 5-arylpyrazole-3-carboxylates, and di- and tetrahydroquinolines.

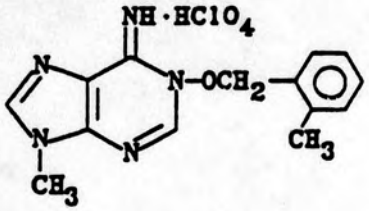
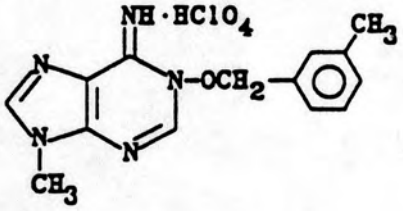
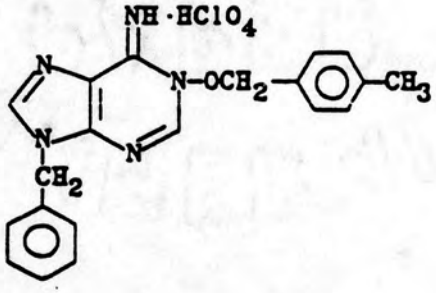
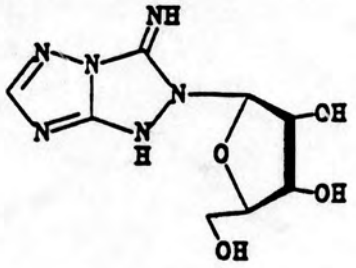
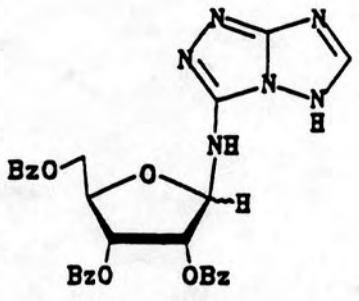
Schemes I-VII shows the approaches used to synthesize the adenosine-$N^1$-oxide analogs submitted this year. Scheme I shows that as with the previously submitted 1-benzyloxyadenosines, the precursor for compounds **2b-j** was adenosine-$N^1$-oxide **1**, which was prepared by oxidizing adenosine with *m*-chloroperbenzoic acid.[1-3] Alkylation of adenosine-$N^1$-oxide with the appropriately substituted benzyl bromides gave the corresponding 1-benzyloxyadenosines. These compounds were then treated with ammonium perchlorate, isolated, and submitted as their perchlorate salt **2b-j**. The procedures used to make these compounds were virtually identical to that used to make previously reported and submitted 1-(2-cyanobenzyloxy)adenosine, perchlorate salt, **2a**.[4,5] Because of this, only the detailed procedure for

## Compounds Submitted

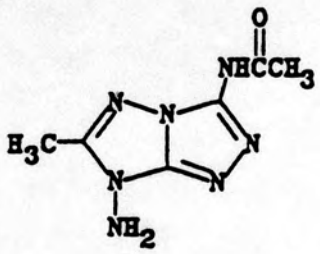
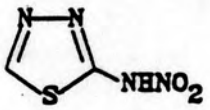
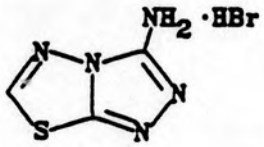
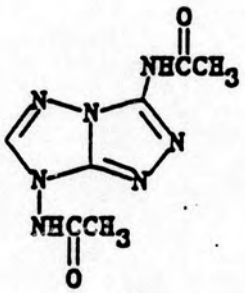
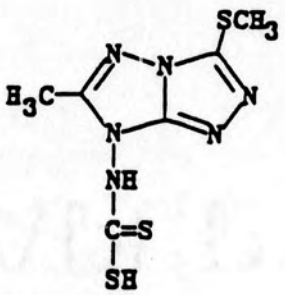
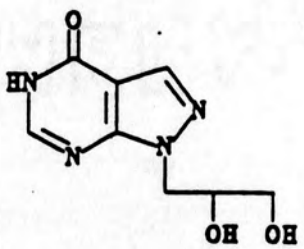
**December 1, 1987 to February 29, 1988**

| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7122 | 000161 | 3.0 g |
|  | 7123 | 000231 | 5.0 g |
|  | 4544 | 001985 | 5.0 g |
|  | 1215 | 002700 | 5.0 g |
|  | 7132 | 004121 | 0.5 g |

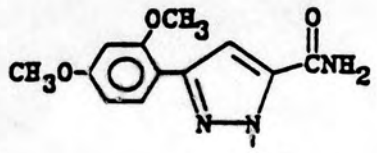
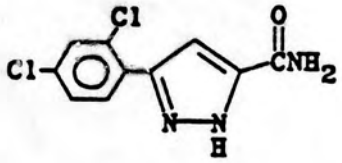
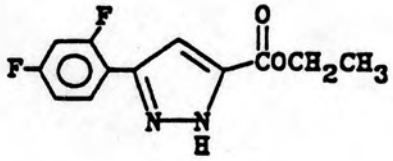
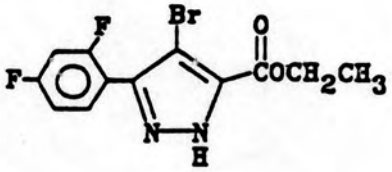
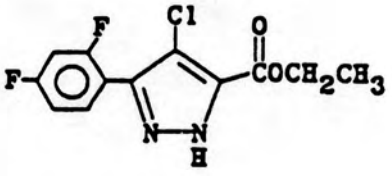
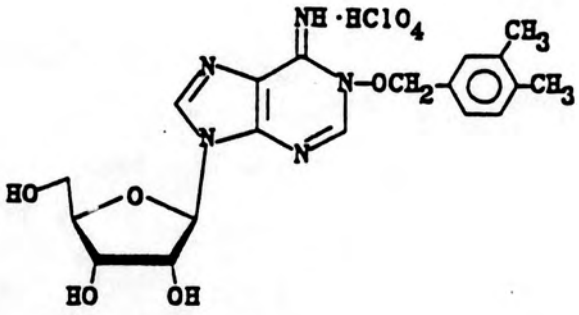
## Compounds Submitted (continued)

| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7133 | 004122 | 1.1 g |
|  | 7134 | 004123 | 1.2 g |
|  | 7135 | 004124 | 2.0 g |
|  | 7150 | 004204 | 0.7 g |
|  | 7151 | 004205 | 0.64 g |

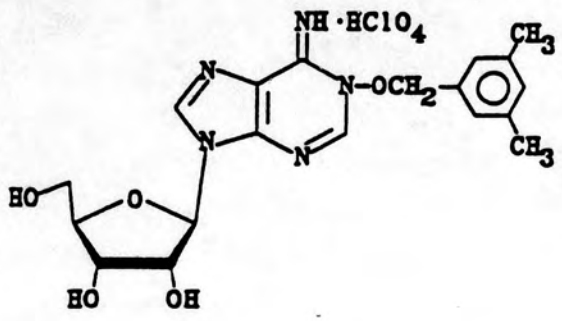
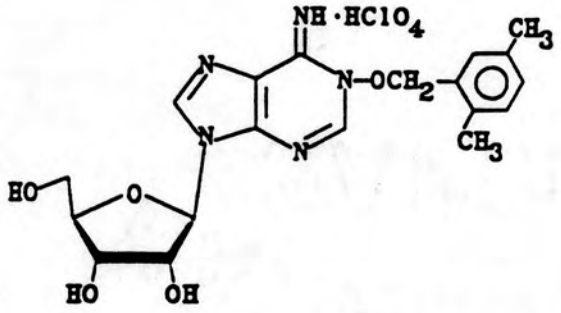
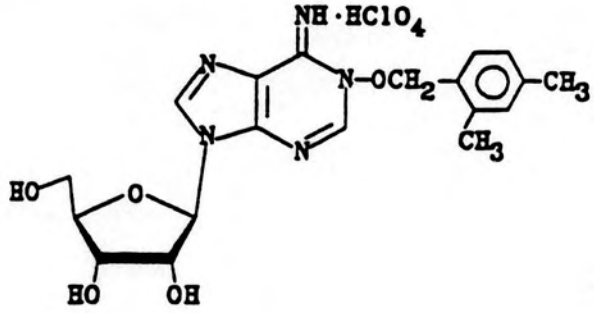
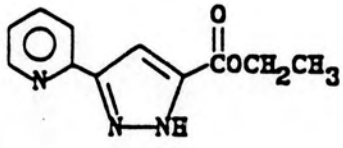
## Compounds Submitted (continued)

| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7152 | 004206 | 1.2 g |
|  | 7153 | 004207 | 1.15 g |
|  | 7154 | 004208 | 0.62 g |
|  | 7158 | 004213 | 0.6 g |
|  | 7159 | 004214 | 1.2 g |
|  | 7148 | 004215 | 0.6 g |

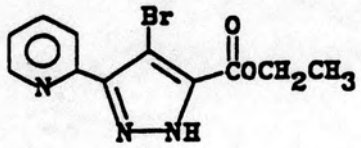
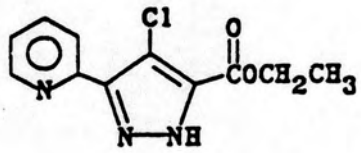
## Compounds Submitted (continued)

| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7160 | 004216 | 1.6 g |
|  | 7161 | 004217 | 1.3 g |
|  | 7162 | 004218 | 1.9 g |
|  | 7163 | 004219 | 1.1 g |
|  | 7164 | 004220 | 1.0 g |
|  | 7168 | 004224 | 1.5 g |

## Compounds Submitted (continued)

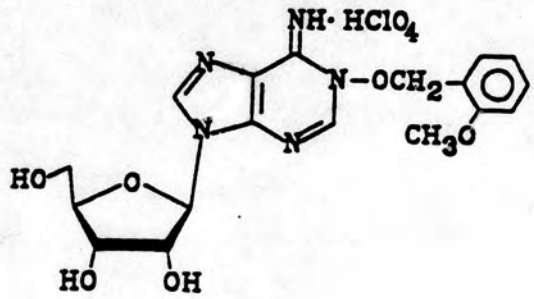
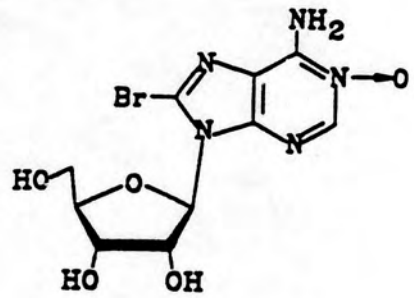
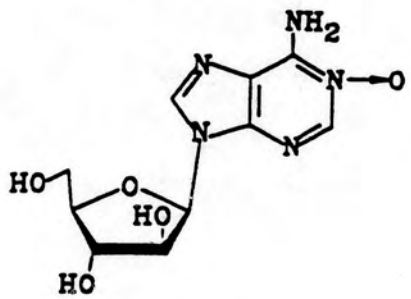
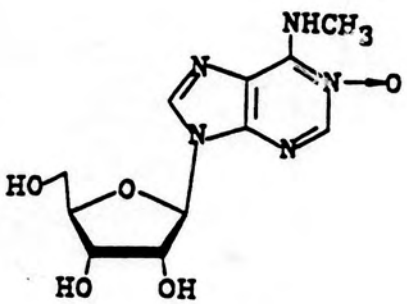
| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7169 | 004225 | 2.0 g |
|  | 7170 | 004226 | 1.2 g |
|  | 7171 | 004227 | 0.8 g |
|  | 7172 | 004228 | 1.6 g |

## Compounds Submitted (continued)

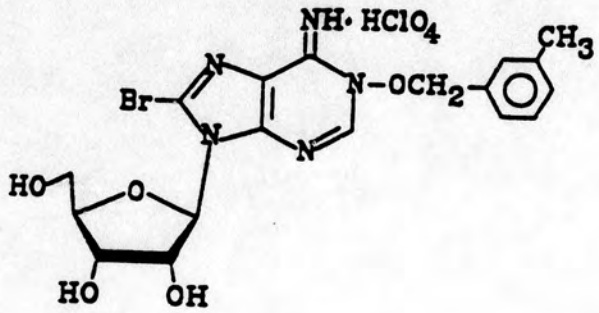
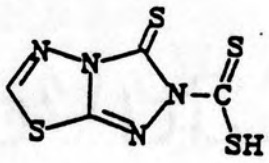
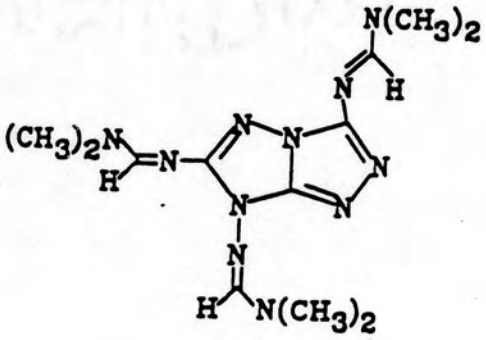
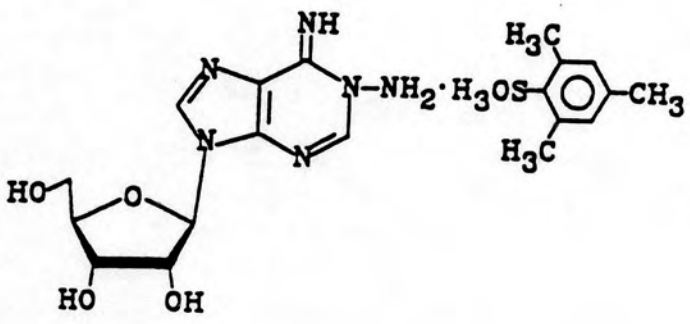
| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7173 | 004229 | 2.0 g |
|  | 7174 | 004230 | 1.8 g |

## Compounds Submitted

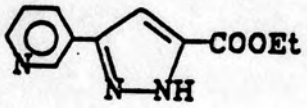
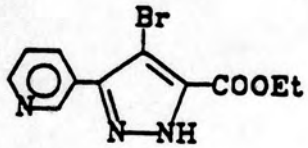
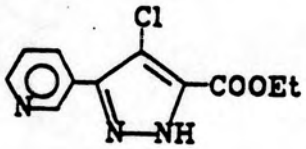
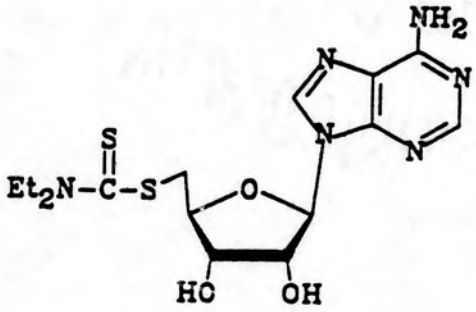
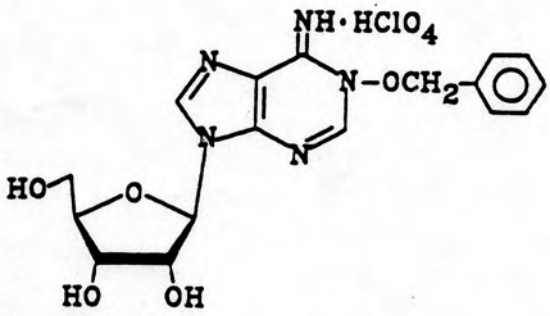
**March 1, 1988 to May 31, 1988**

| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7187 | 004533 | 650 mg |
|  | 7188 | 004532 | 440 mg |
|  | 7189 | 004531 | 700 mg |
|  | 7190 | 004530 | 500 mg |

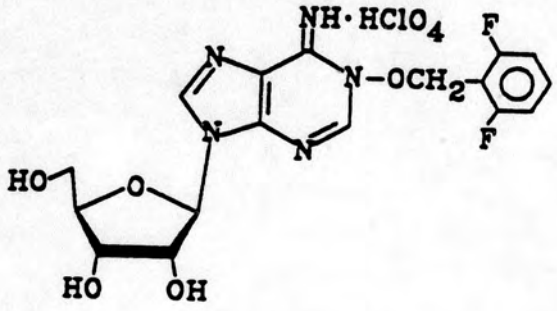
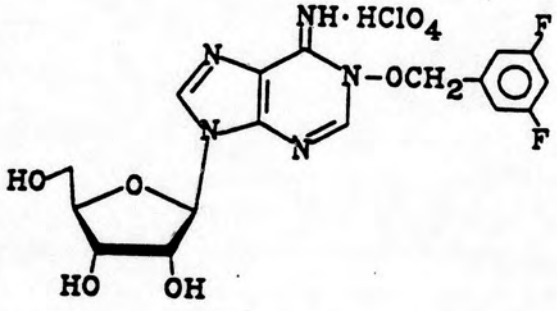
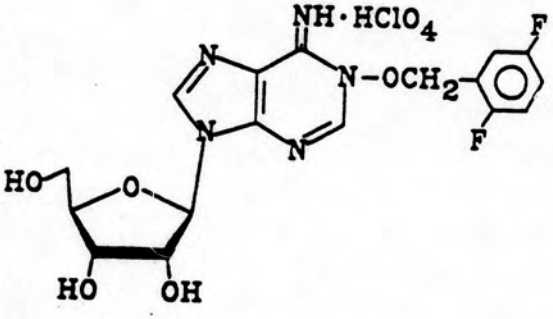
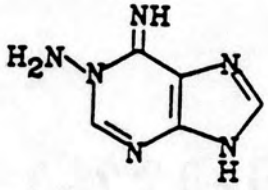
## Compounds Submitted (continued)

| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7191 | 004529 | 900 mg |
|  | 7192 | 004589 | 1.6 g |
|  | 7193 | 004587 | 1.5 g |
|  | 7194 | 004588 | 0.7 g |

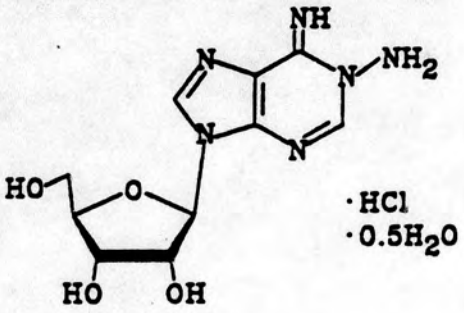
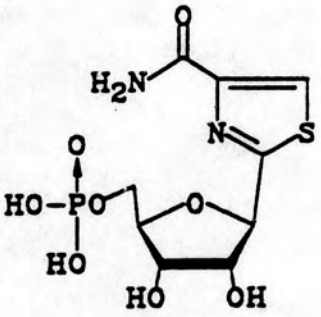
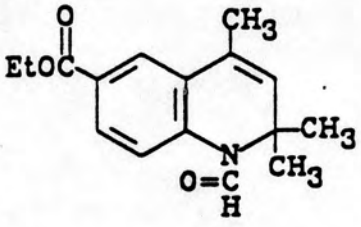
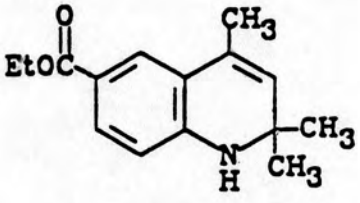
## Compounds Submitted (continued)

| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7205 | 004612 | 1.4 g |
|  | 7206 | 004613 | 1.5 g |
|  | 7207 | | 1.2 g |
|  | 7208 | 004618 | 0.6 g |
|  | 7214 | 004619 | 2.0 g |

## Compounds Submitted (continued)

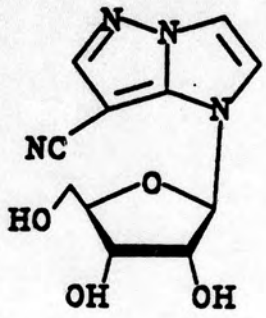
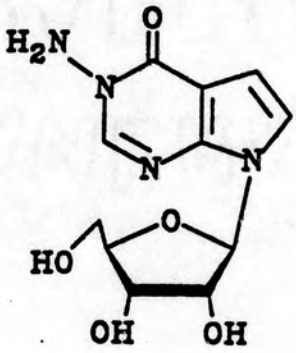
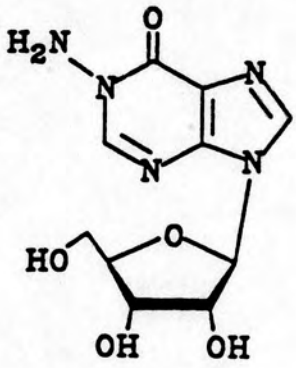
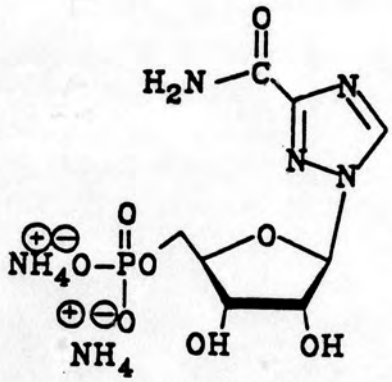
| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7215 | 004620 | 1.0 g |
|  | 7216 | 004621 | 1.0 g |
|  | 7217 | 004622 | 2.0 g |
|  | 7220 | 004623 | 450 mg |

## Compounds Submitted (continued)

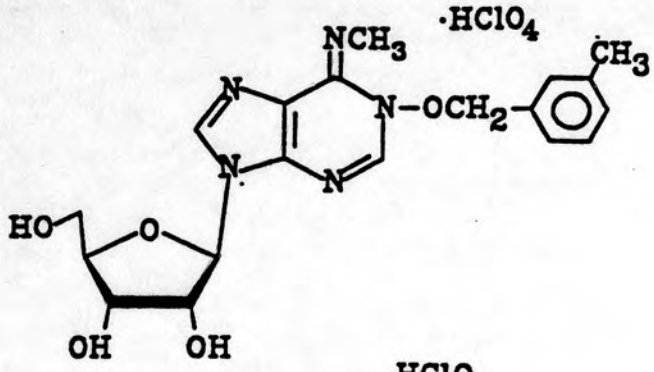
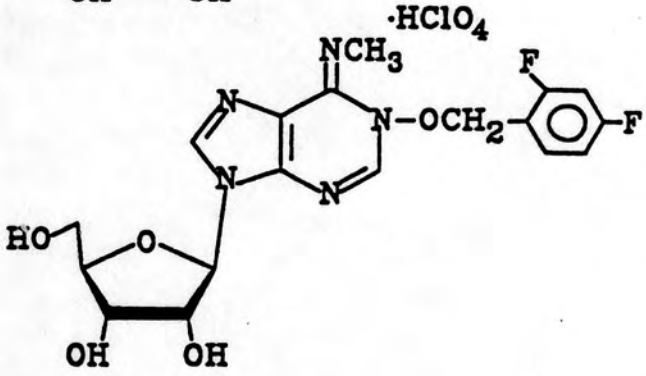
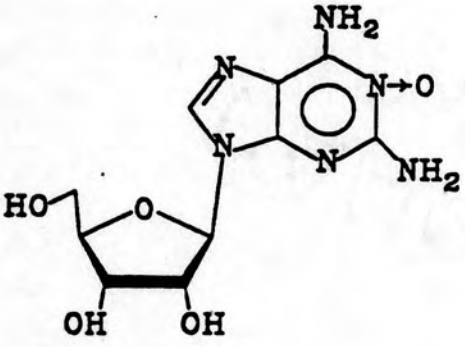
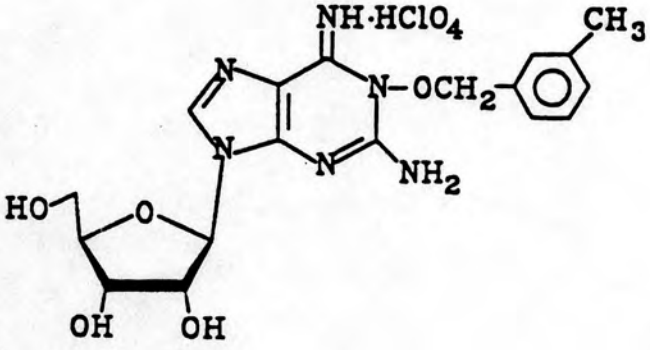
| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  ·HCl ·0.5$H_2O$ | 7221 | 004624 | 696 mg |
|  | 7186 | | 4.75 g |
|  | 7226 | 004721 | 1.0 g |
|  | 7227 | 004720 | 0.9 g |

## Compounds Submitted

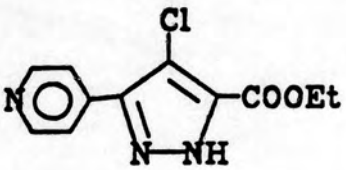
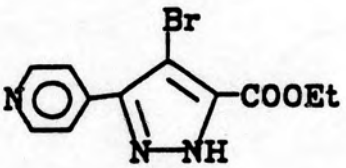
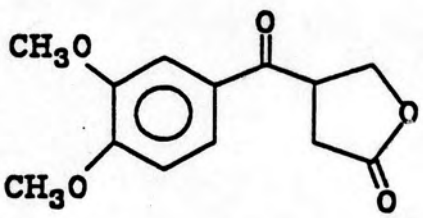
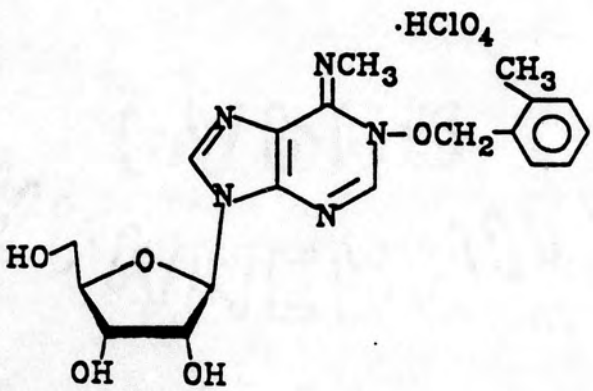
**June 1, 1988 to August 31, 1988**

| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7259 | 004926 | 0.4 g |
|  | 4991 | 004685 | 0.200 g |
|  | 7238 | 004866 | 0.247 g |
|  | 7251 | 004871 | 0.21[illegible] g |

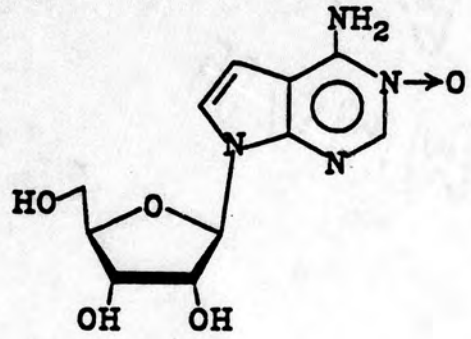
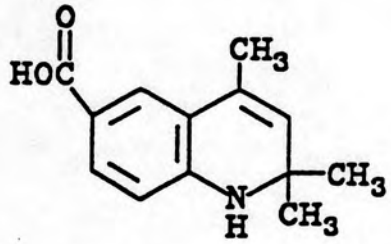
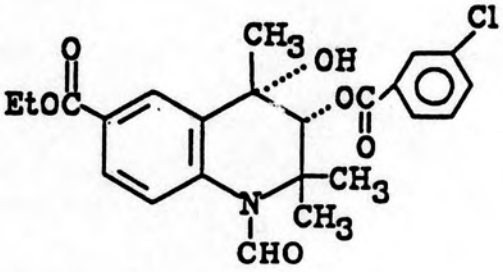
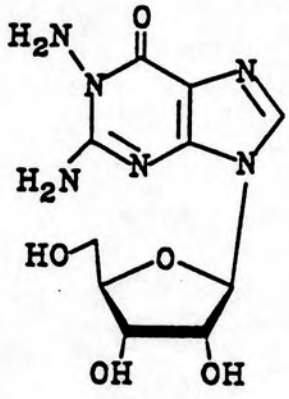
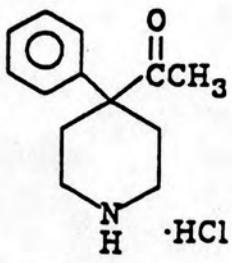
## Compounds Submitted (continued)

| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7252 | 004872 | 0.800 g |
|  | 7253 | 004873 | 0.450 g |
|  | 7254 | 004874 | 0.450 g |
|  | 7255 | 004875 | 0.500 g |

## Compounds Submitted (continued)

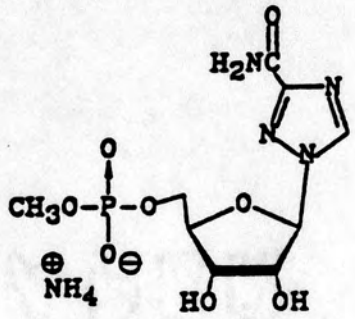
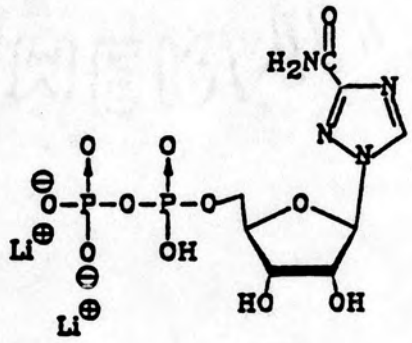
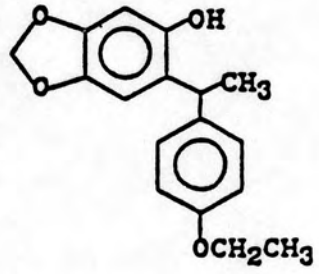
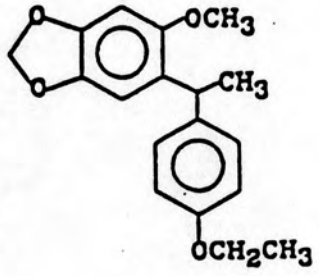
| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7269 | 005047 | 1.3 g |
|  | 7270 | 005031 | 1 4 g |
|  | 7271 | 005032 | 0.7 g |
|  | 7272 | 005033 | 1.5 g |
|  | 7274 | 005034 | 0.275 g |

## Compounds Submitted (continued)

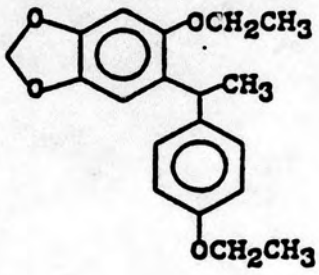
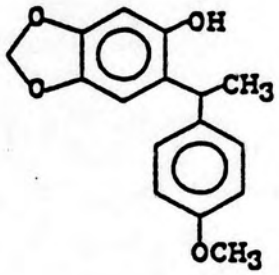
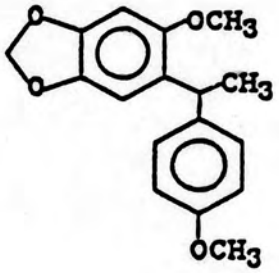
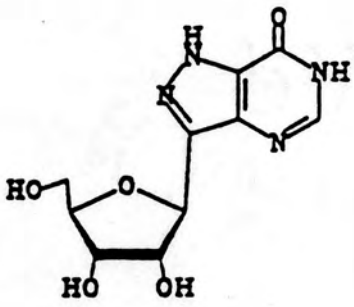
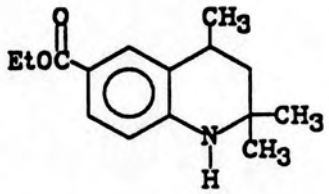
| Compound | SRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7275 | 005035 | 0.500 g |
|  | 7276 | 005036 | 0.600 g |
|  | 7277 | 005037 | 0.600 g |
|  | 7278 | 005038 | 2.2 g |
|  | 7288 | 005048 | 4.0 g |

## Compounds Submitted

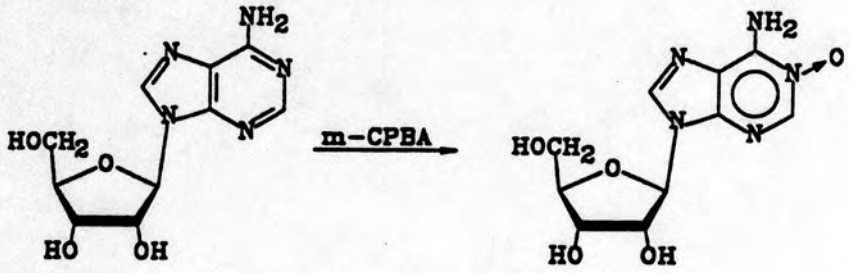
**September 1, 1988 to November 30, 1988**

| Compound | SoRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7301 | 005067 | 2.05 g |
|  | 7304 | 005075 | 190 mg |
|  | 7319 | 005082 | 1.2 g |
|  | 7320 | 005083 | 1.2 g |

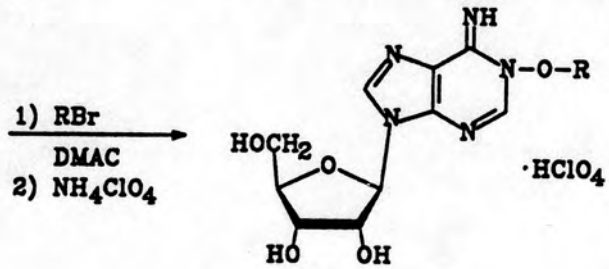
## Compounds Submitted (continued)

| Compound | SoRI Number | AVS Number | Amount Submitted |
|---|---|---|---|
|  | 7321 | 005084 | 1.2 g |
|  | 7322 | 005085 | 1.2 g |
|  | 7323 | 005086 | 1.2 g |
|  | 7328 | | 5.0 g |
|  | 7329 | 005223 | 0.6 g |

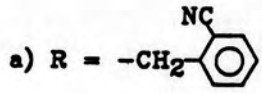
**Scheme I**

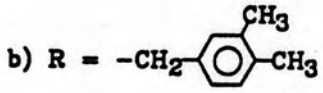


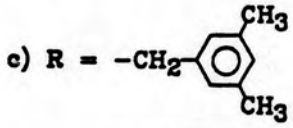

1

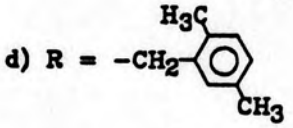


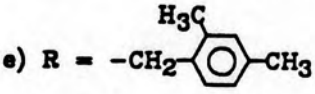

2

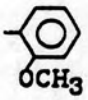
a) R = 


b) R = 

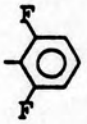

c) R = 

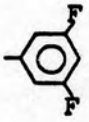

d) R = 

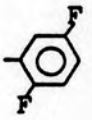

e) R = 


f) R = 

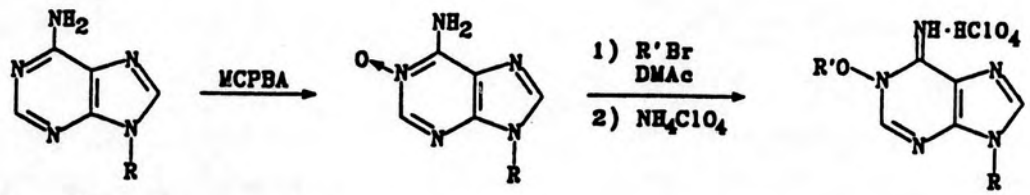

g) R = 

h) R = 

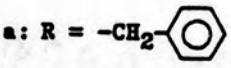

i) R = 


j) R = 

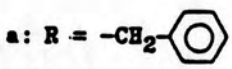

**Scheme II**



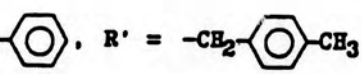

3 4 5

a: R = 

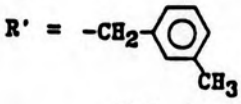

b: R = $CH_3$

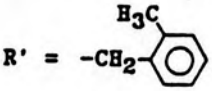
a: R = 


b: R = $CH_3$

a: R = 

, R' =

b: R = $CH_3$, R' = 


c: R = $CH_3$, R' = 

the synthesis of 1-(2-cyanobenzyloxy)adenosine will be presented in the experimental section. No detailed synthetic procedures will be presented for compounds **2b-j**.

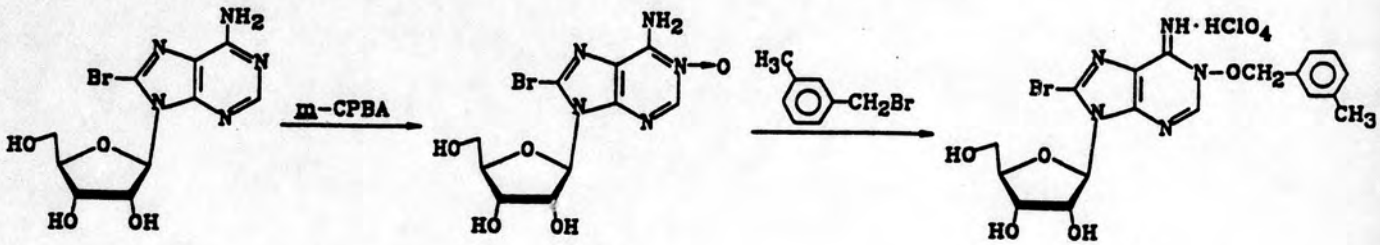
We also synthesized $N^1$-oxide and $N^1$-benzyloxy analogs of 2'-deoxyadenosine, 9-benzyladenine, and 9-methyladenine. As shown in Scheme II, these compounds were also made by following the general synthetic procedure for 1-(2-cyanobenzyloxy)adenosine **2a**. 9-Benzyladenine **3a** and 9-methyladenine **3b** were oxidized with *m*-chloroperbenzoic acid[1-3] to give their corresponding $N^1$-oxides **4a** and **b**. These $N^1$-oxides were then alkylated with the appropriately substituted benzyl bromides as indicated, and they were converted to their respective perchlorate salts **5a-c**. Since, the procedures for making all of these compounds again were essentially the same as the procedure for making 1-(2-cyanobenzyloxy)adenosine **2a**, we have supplied only summarized information and analytical data for these compounds in the experimental section. No detailed synthetic procedures have been provided for these compounds.

We also synthesized some $N^1$-oxide- and 1-benzyloxy- analogs of the following compounds: 8-bromoadenosine **6**, 9-$\beta$-D-arabinofuranosyladenine **9**, 9-$\beta$-D-ribofuranosyl-6-methylaminopurine **11**, 2,6-diamino-9-$\beta$-D-ribofuranosylpurine **14**, and 7-deazaadenosine **17**. Schemes III-VII show that essentially the same sequence of reactions was used to make these compounds as had been used for all of the other adenosine-$N^1$-oxide and 1-benzyloxyadenosine analogs. Oxidation of these nucleosides with *m*-chloroperbenzoic acid gave the corresponding nucleoside-$N^1$-oxides **7, 10, 12, 15,** and **18**. $N^1$-oxides **7, 12,** and **15** were then alkylated with the indicated benzyl bromides to give the 1-benzyloxyadenosine analogs **8, 13a-c,** and **16**.

We submitted $N^1$-aminoadenine and four $N^1$-aminonucleosides because of the structural similarities of these compounds to the adenosine-$N^1$-oxide analogs. As shown in Scheme VIII, a methanolic solution of O-mesitylenesulfonyl hydroxylamine was used to effect $N^1$-amination of adenine and adenosine to form the corresponding $N^1$-aminoadenine **19** and $N^1$-aminoadenosine **20**.[6] Two separate samples of 1-aminoadenosine **20** were submitted: one as the mesitylenesulfonate salt and one as the hydrochloride salt. To make $N^1$-aminonucleosides **22, 24,** and **26**, a slight procedural modification was used. An aqueous solution of hydroxylamine-O-sulfonic acid[7] was used to $N^1$-aminate the corresponding nucleosides **21, 23,** and **25**, and this also gave the desired $N^1$-aminonucleosides in reasonable yields.

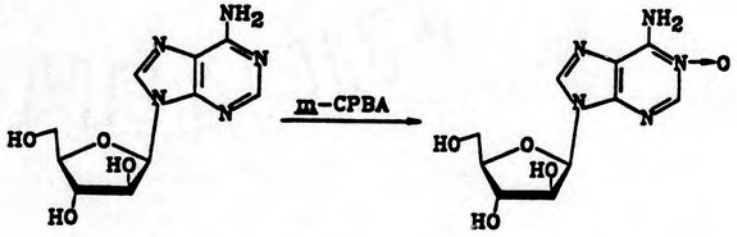
We also wanted to benzylate these $N^1$-aminonucleosides to get 1-benzylamino analogs similar to the 1-benzyloxyadenosine series that we had already been investigating. Unfortunately, we were never able to alkylate either $N^1$-aminoadenine or $N^1$-aminoadenosine. Our attempts to make either 1-benzylaminoadenine or 1-benzylaminoadenosine **27** with benzyl bromide or benzaldehyde using a number of variations of reagents and reaction conditions were all unsuccessful. We also tried to develop an *N*-benzylated hydroxylaminesulfonic acid reagent to try to circumvent the alkylation problem, but this approach was also unsuccessful since we were unable to make this reagent. Therefore, we decided that we would not pursue $N^1$-benzylaminonucleosides any further unless the submitted $N^1$-aminonucleosides show promising activities.

**Scheme III**



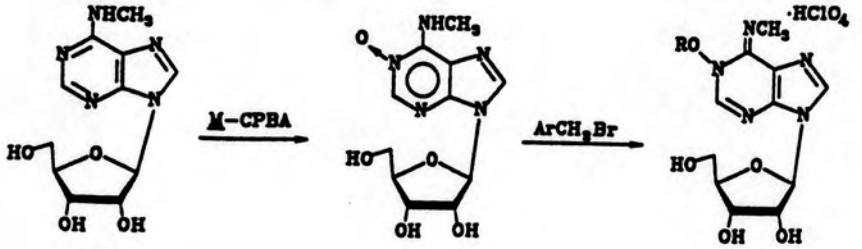

6 7 8

**Scheme IV**

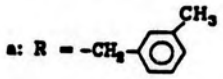


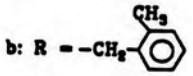

9 10

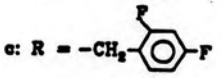
**Scheme V**



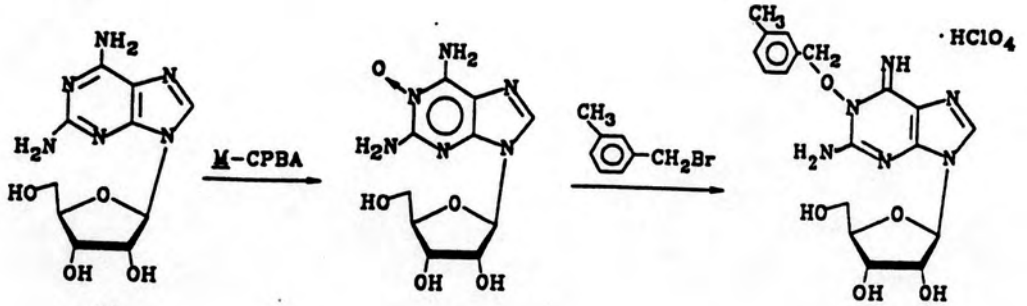

11 12 13

a: R = 

b: R = 

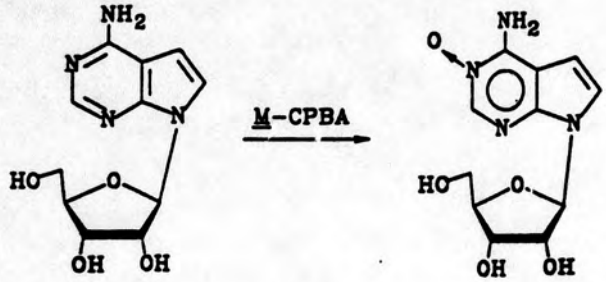
c: R = 

**Scheme VI**



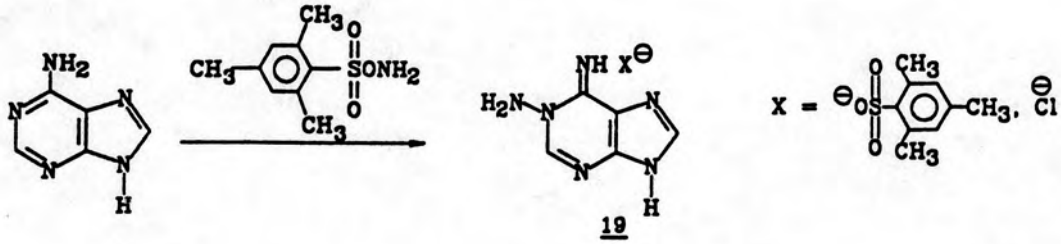

14 15 16

**Scheme VII**

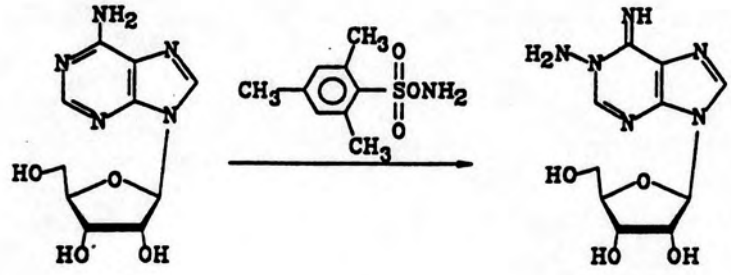



17 18

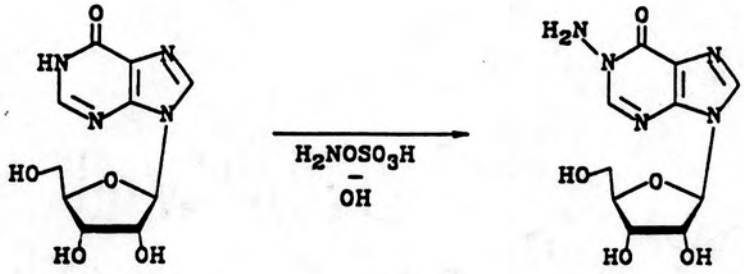
**Scheme VIII**



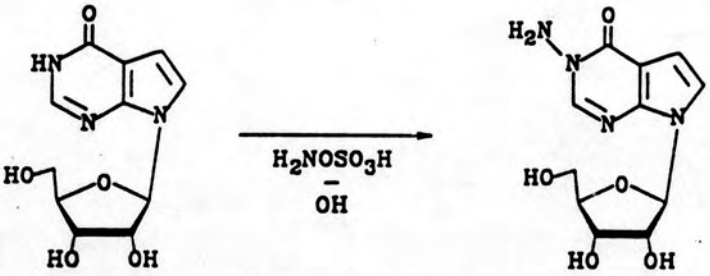

19




20



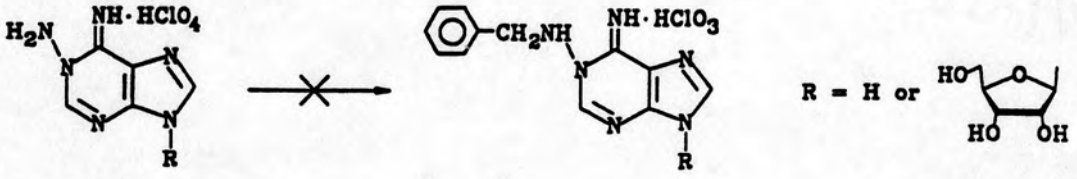

21 22




23 24

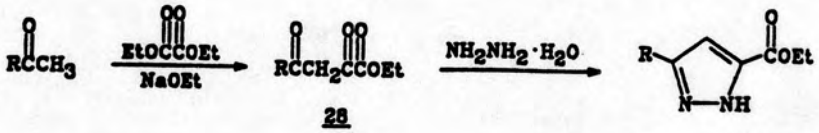
**Scheme VIII (continued)**


25 26




20 27

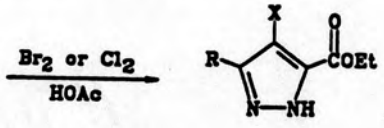
**Scheme IX**




28 29

a: R = c: R =

b: R = d: R =




30

a: R = , X = Br e: R = , X = Br

b: R = , X = Cl f: R = , X = Cl

c: R = , X = Br g: R = , X = Br

d: R = , X = Cl h: R = , X = Cl

Our continuing work with substituted pyrazoles produced 12 new compounds **29a-d** and **30a-h**. These compounds were synthesized by following the same general preparation used to synthesize our previously submitted pyrazoles.[8] As shown in Scheme IX, the necessary starting materials for these compounds, ethyl 4-(2′,4′-difluorophenyl)dioxobutyrate, 4-(2′-pyridyl)dioxobutyrate, 4-(3′-pyridyl)dioxobutyrate, and 4-(4′-pyridyl)dioxobutyrate were made by condensing the 2′,4′-difluoroacetophenone or the corresponding acetylpyridines with diethyl oxalate.[9] Treatment of these butyrates with hydrazine hydrate gave the corresponding pyrazoles **29a-d**. These compounds were then halogenated with either bromine or chlorine in acetic acid to give 4-halopyrazolecarboxylates **30a-h**.

In addition to these pyrazolecarboxylates, we also made pyrazolecarboxamides **32a** and **b**. As shown in Scheme X, these compounds were made by treating the corresponding ethyl pyrazolecarboxylates with ammonium hydroxide. Thus far, we have limited production of the pyrazolecarboxamides to just these two. However, if these compounds show promising activity, we will expand this series by converting other pyrazolecarboxylates to their corresponding carboxamides.

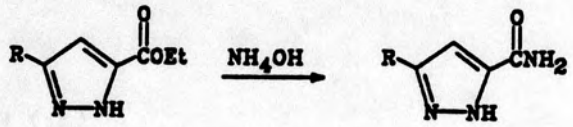
Our efforts to synthesize analogs of triazolotriazole **33** yielded four new triazolotriazole derivatives as well as two new ribosylated triazoles and two triazolothiadiazole compounds. As shown in Scheme XI, triazolotriazole **36** was obtained by the following two-step process. Triaminoguanidine **34** was heated with acetic acid, cyclizing to give triazole **35**.[10] Triazole **35** was then cyclized to triazolotriazole dithionide **36** via sequential treatment with carbon disulfide and methyl iodide.

Triazolotriazole acetates **38** and **40** were both made by treatment of the previously submitted parent compounds **37** and **39**[11] with acetic anhydride. Scheme XII shows that the ribosylated triazolotriazoles were made by treating the previously submitted triazolotriazole **41**[11] with stannous chloride and 2,3,5-tribenzoylribofuranosyl-1-acetate.[12] The major product from this reaction was adduct **42**, which was deprotected with NaOMe and MeOH to give ribosylated triazolotriazole **43**. One of the minor products, compound **44**, was also isolated in sufficient quantity to allow deprotection to give ribosylated triazolotriazole **45**. However, close inspection of the literature revealed that this compound had been made under a previous DAMD contract in 1979. Therefore, we assumed that USAMRIID already had access to this compound, and it was not submitted to USAMRIID. Another of the minor products of the ribosylation reaction was compound **46**. This compound was submitted in its benzoylated form, because even the mildest of deprotection conditions also cleaved the ribosyl linkage.

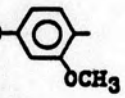
As shown in Scheme XIII, triazolothiadiazole **49** was made by following the same general sequence used to make the other triazolotriazoles. Aminothiadiazole **47** was nitrated[13,14] with fuming nitric acid to give nitroaminothiadiazole **48**. This compound was then reduced with zinc and acetic acid and cyclized with cyanogen bromide to give triazolothiadiazole **49**. Nitroaminothiadiazole **48** was also used to make another triazolothiadiazole. Reduction of **48** with zinc and acetic acid followed by treatment with carbon disulfide gave triazolothiadiazole **50**.

Scheme XIV shows the route followed for triaminotriazolotriazole derivative **52**. This compound was obtained by treating previously submitted triazolotriazole **51** with Gold's reagent.[15]

**Scheme X**

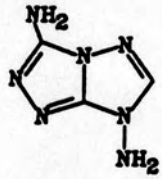


31 32

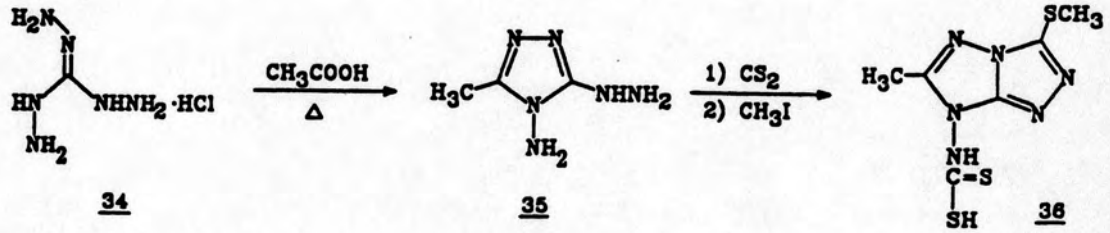
a: R = $CH_3O$ 

b: R = Cl 

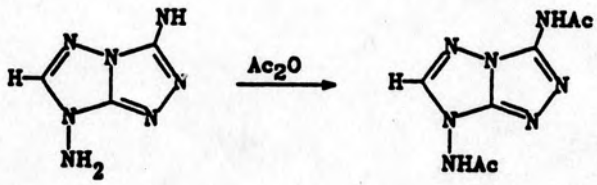
**Scheme XI**



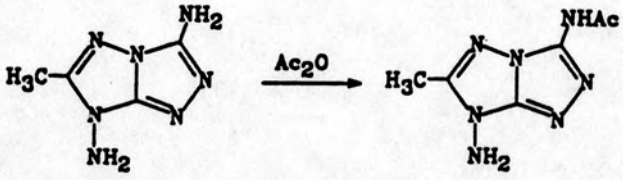
33 (AVS 000245)



34 35 36

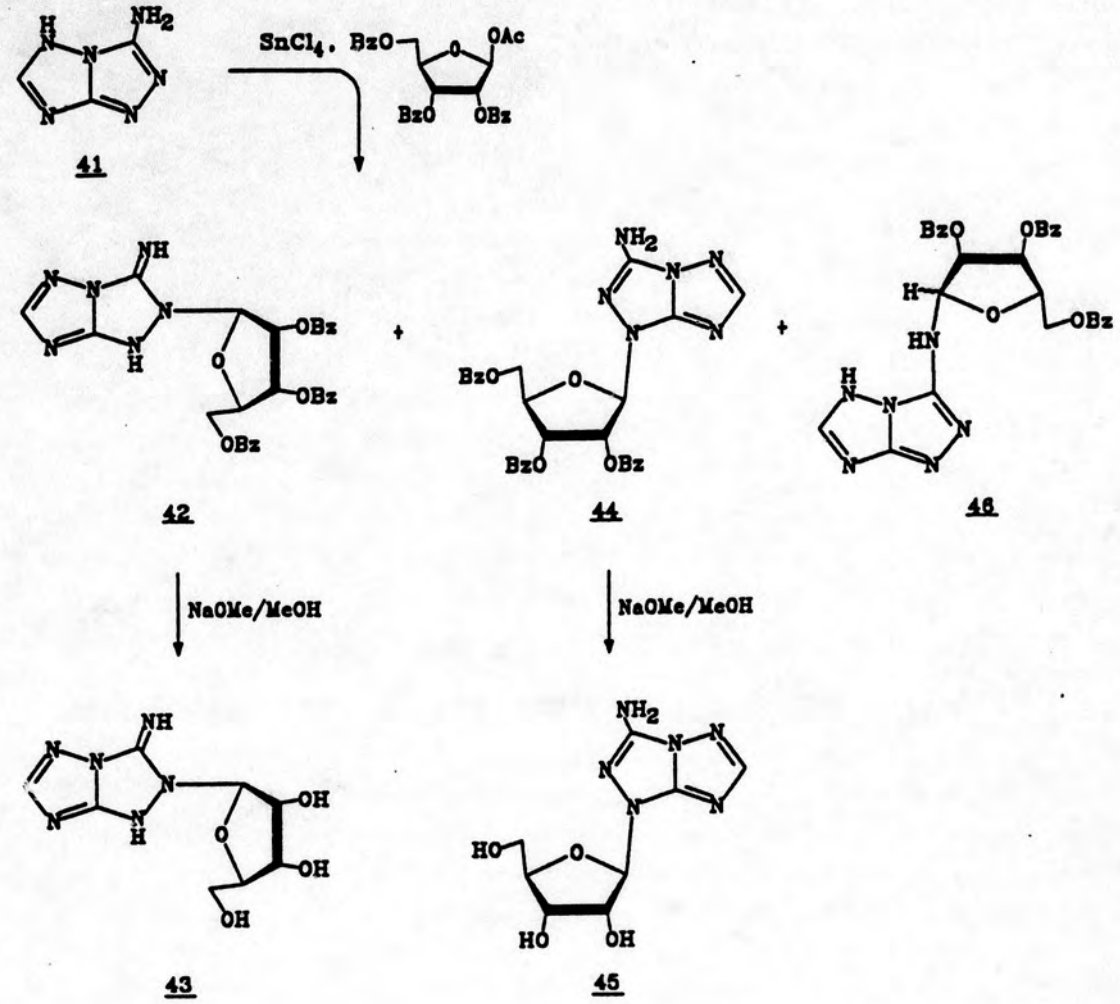


37 38

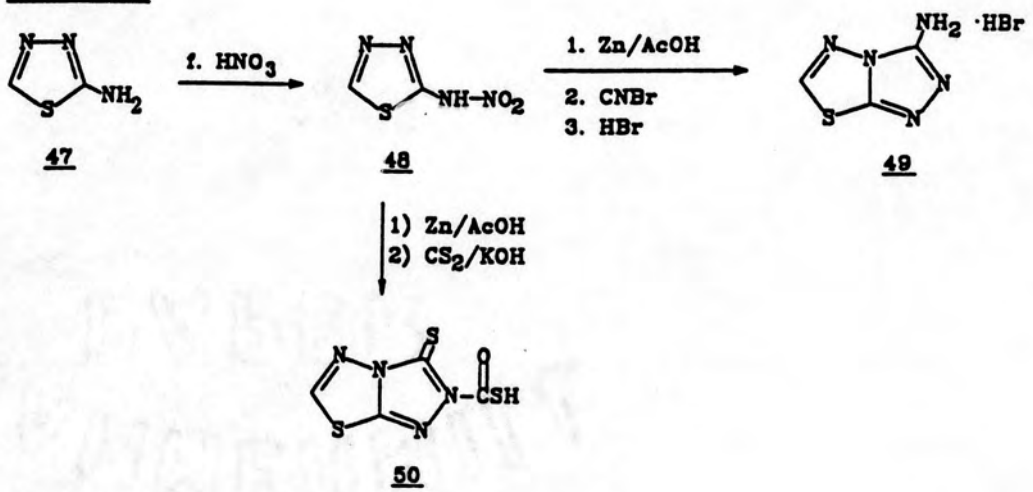


39 40

**Scheme XII**




**Scheme XIII**



Our pursuit of allopurinol acyclonucleosides yielded one more submittable compound, 1-(2',3'-dihydroxypropyl)allopurinol **56**. As shown in Scheme XV, this compound was made from previously submitted 3-bromo-(2',3'-dihydroxypropyl)allopurinol **55**[16] by removal of the 3-bromo group via catalytic hydrogenation.[17] We also pursued a number of other similar acyclonucleoside analogs with other functional groups at the 4-position. We had hoped that this pursuit would not only provide new products but it would also improve the selectivity of the site of alkylation with the acyclo sugar. Unfortunately, these efforts were totally unsuccessful. Not only were our product yields unreasonably low, but there was also no selectivity in the site of alkylation. Because of these problems, we decided to concentrate only on those structurally similar compounds that were specifically requested by Maj. Ussery and to phase out our efforts toward any other acyclonucleosides of allopurinol.

We also began to investigate dihydroquinolines and tetrahydroquinolines and modeled a study after the novel antibiotic virantmycin **57**. Virantmycin had been isolated from *streptomyces nitrosporeus*[18,19] and shown to have potent inhibitory activity against RNA and DNA viruses at considerably low concentrations. It was also found to exhibit weak antifungal activity against *Saccharomyces sake, Piricularia oryzae, Trichophyton interdigitale,* and *Aspergillus niger*. Since literature review showed little work with dihydroquinolines, we chose to pursue the development of analogs of this compound class. We specifically chose to simplify the side chains located at the 2-position, replacing the methoxymethyl and 2,3-dimethylpent-2-enyl sidechains with two methyl groups.

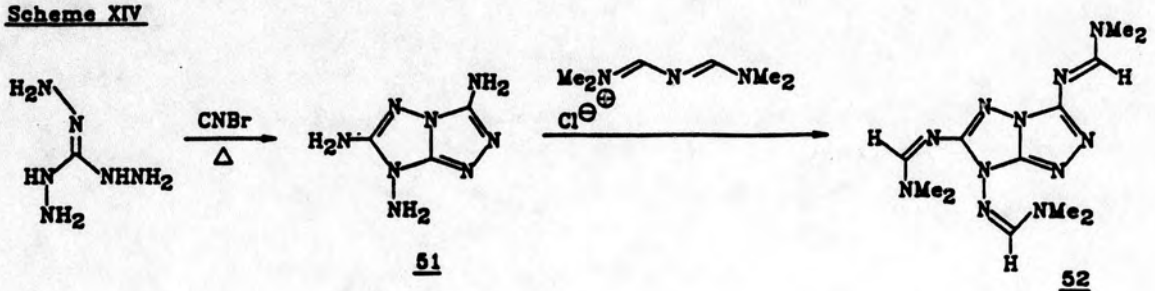
As shown in Scheme XVI, the precursor for our analog series was dihydroquinoline **58**. This compound was prepared by refluxing ethyl 4-aminobenzoate with acetone in toluene and iodine.[20] Dihydroquinoline **58** was then formylated with formic acetic anhydride[21] to give derivative **59**.

From our efforts to make simple derivatives of either dihydroquinoline **58** or formylated dihydroquinoline **59** key intermediates, we found that we could neither brominate nor epoxidize the 3- and 4-positions of either of these compounds. We attempted the straightforward addition of bromine to these compounds under a number of different reaction conditions, and invariably, we were not able to halogenate the double bond. We similarly tried a number of reagents and reaction conditions but could not epoxidize the double bond either. *m*-Chloroperbenzoic acid added across the double bond of **59** to give adduct **60**, but the resulting ester alcohol would not collapse to the corresponding epoxide **61**.

We were able to synthesize dihydroquinoline acid **62** from dihydroquinoline **58** by treatment with sodium hydroxide. Furthermore, we were able to reduce the 3,4-double bond of dihydroquinoline by catalytic hydrogenation with palladium on carbon to give tetrahydroquinoline **63**.

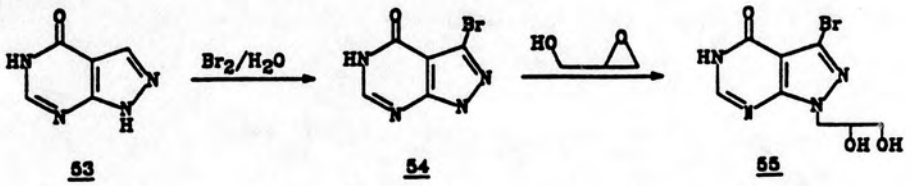
We also investigated nucleoside diethylthiocarbamates as possible lead compounds, because several dithiocarbamates are well-known fungicides,[22-24] and sodium diethyl dithiocarbamate (DTC or imuthiol) has been found to be an effective immune modulator in clinical trials.[25] In the latter study, AIDS and ARC patients treated with sodium diethyl dithiocarbamate were found to show more symptomatic improvement than untreated patients.

**Scheme XIV**

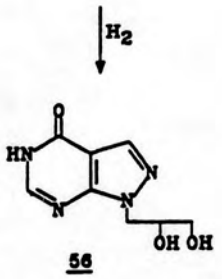



51 52

**Scheme XV**

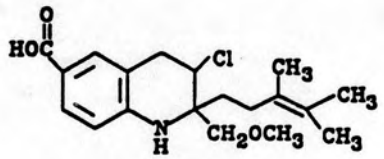



53 54 55

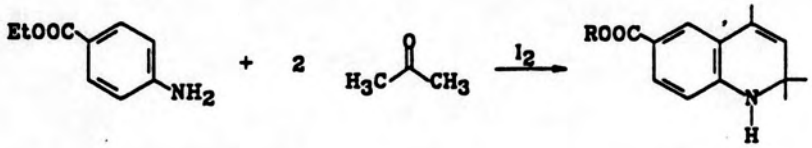



56

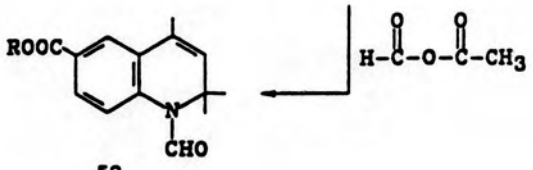
**Scheme XVI**



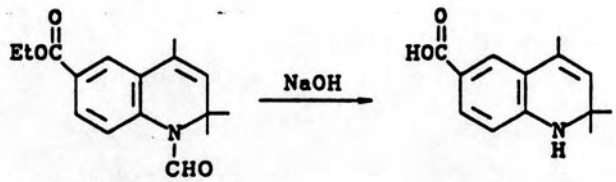
57




58

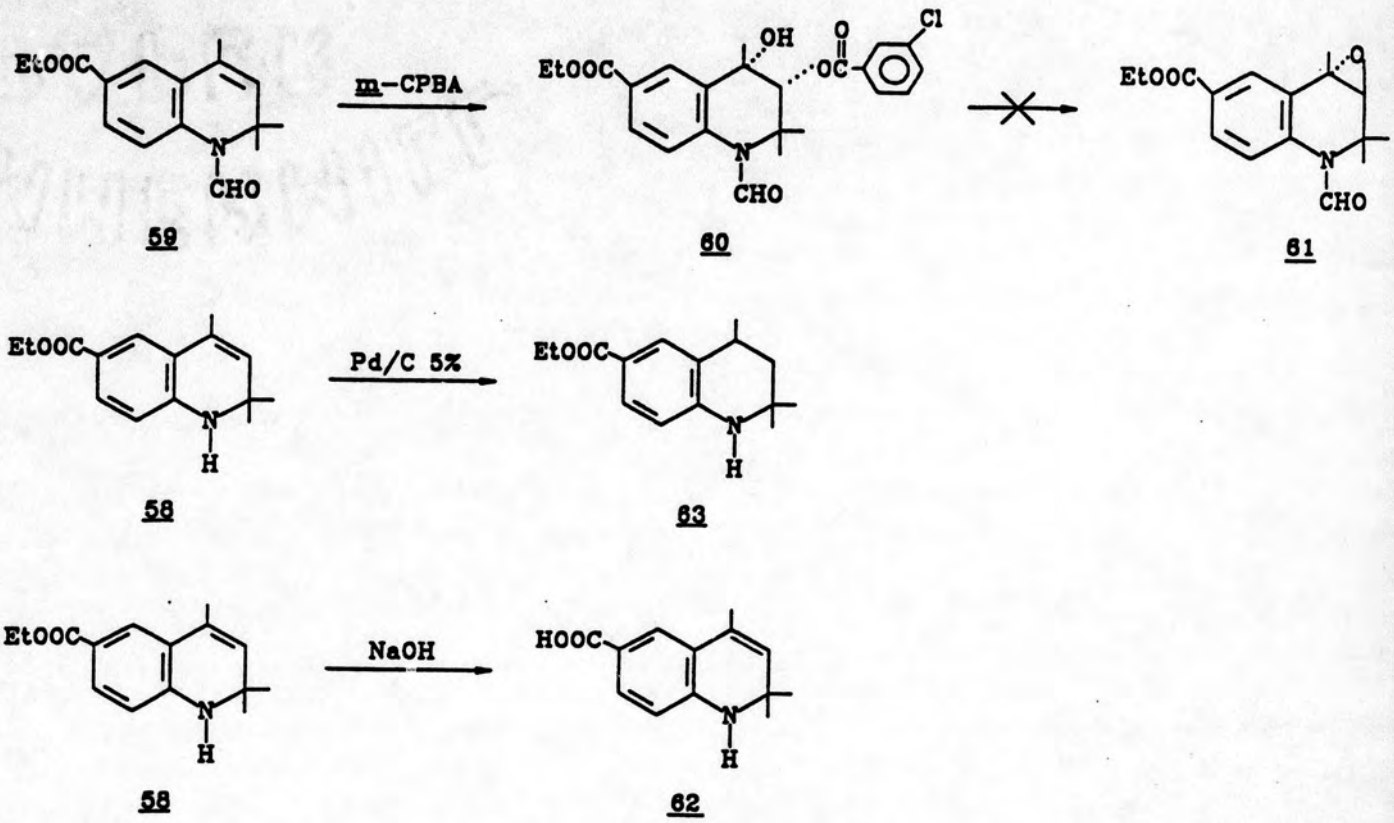



59

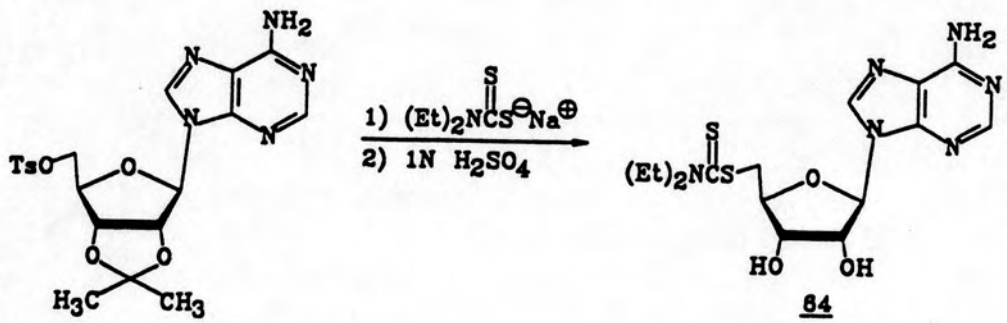



59 61

**Scheme XVI (continued)**




**Scheme XVII**



A review of the literature showed that there have not been any detailed studies on dithiocarbamate-substituted nucleosides, and therefore, we initiated the exploration of this potential area by preparing 5'-deoxythioadenosine, 5'-*N,N*-diethylthiocarbamate (**64**). This thiocarbamate **64** was made by refluxing commercially available sodium diethyldithiocarbamate trihydrate and 2',3'-O-methylethylidene adenosine in DMF and then treating the reaction mixture with 1*N* $H_2SO_4$ (Scheme XVII). Thus far, we have not prepared any other thiocarbamate nucleosides. However, if this compound shows any promising activity we will prepare a series of similarly substituted nucleoside analogs.

We also began synthesizing 6-benzyl-1,3-benzodioxole derivatives as analogs of the biologically active natural products, podophyllotoxin **65** and Justicidin B **66**. (We became especially interested in this series since Justicidin B was one of the USAMRIID requested compounds.) Our search of the literature yielded an antitumor activity study of these benzodioxole derivatives against the *in vivo* i.p. P388 murine lymphocytic leukemia.[26] This study compared the activities of these compounds with that of podophyllotoxin and reported that the most active of these benzodioxoles were as effective as podophyllotoxin against P388 murine lymphocytic leukemia, although its effectiveness required higher dosage levels. Because of this demonstrated biological activity, and because podophyllotoxin is structurally similar to Justicidin B, we felt that these derivatives would be an excellent series of compounds for antiviral screening.

Scheme XVIII shows the five benzodioxole derivatives that we submitted as well as the synthetic routes used to make these compounds. Compounds **68a-c** were selected because they were among the most active antitumor agents in the previously mentioned study. The others, compounds **67a-b** were also submitted since they were intermediates leading to the synthesis of compounds **68a-c**. As shown in the scheme, compounds **67a-b** were made by condensing sesamol in aqueous acidic medias with the appropriately substituted benzyl alcohol (obtained by sodium borohydride reduction of the corresponding substituted acetophenone). The resulting phenolic 1,3-benzodioxoles were then alkylated with either methyl iodide or ethyl iodide to give the corresponding alkylated 6-benzyl-1,3-benzodioxoles **68a-c**.

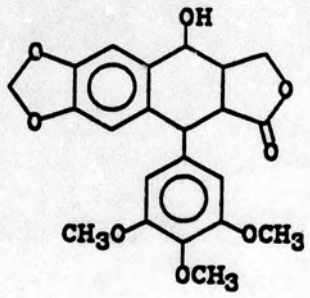
During this year, we also continued to synthesize compounds that were specifically requested by Major Ussery. As a result of this work, we have either submitted or addressed 15 out of the 21 requested compounds. Furthermore, our overall compound output for this project has been affected, because the preparations for these compounds have often been complex, multistep synthetic procedures.

All of the specifically requested compounds that we synthesized and the synthetic procedures used to make them are given in the following sections and schemes.

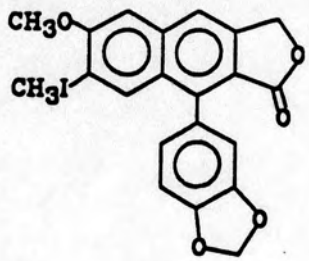
1. 3-Bromo-1-$\beta$-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine-4(5*H*)-one **72**[17,27] was synthesized by the approach shown in Scheme XIX. Commercially available allopurinol **69** (Pyrazolo[3,4-*d*]pyrimidin-4-(5*H*)-one) was first treated with bromine in water. The resulting 3-bromoallopurinol **70** was then ribosylated with 2,3,5-tribenzoylribofuranosyl-1-acetate, and the resulting protected nucleoside analog **71** was deprotected with ammonia and methanol to give compound **72**.

2. 5-Bromo-3-nitro-1,2,4-triazole **74**[28] was synthesized by direct bromination of 3-nitro-1,2,4-triazole with bromine and sodium hydroxide, as shown in Scheme XX.

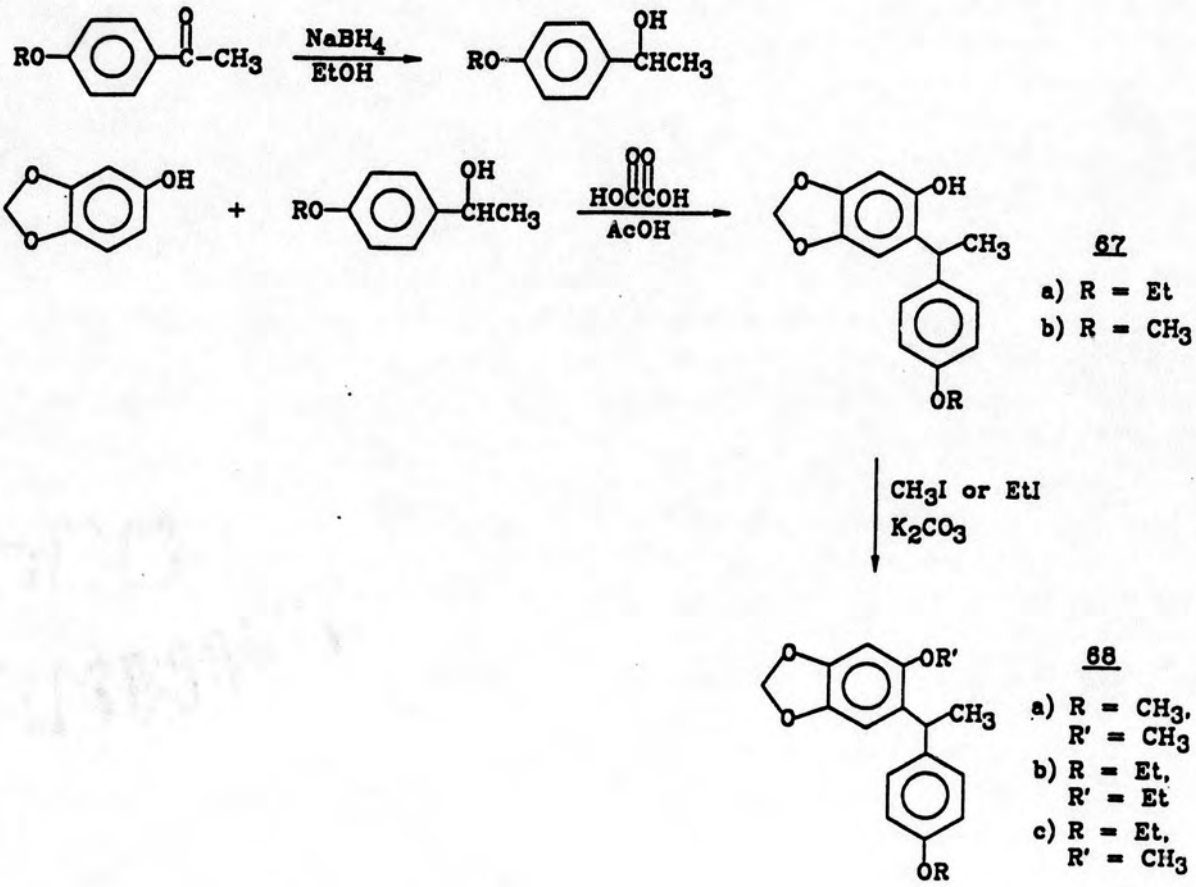
**Scheme XVIII**



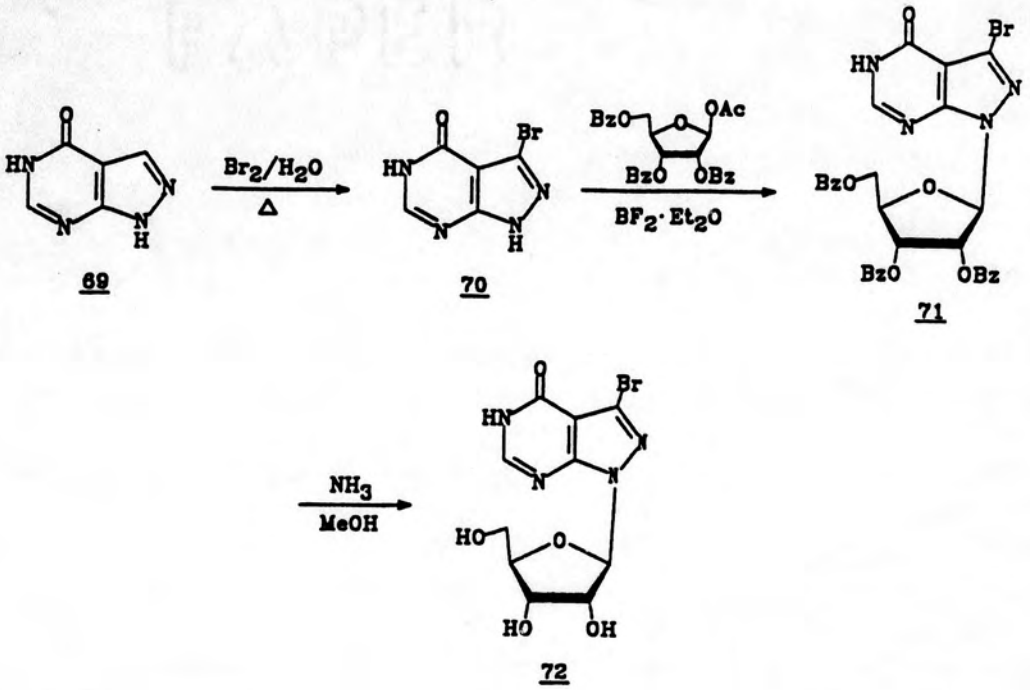
65



66

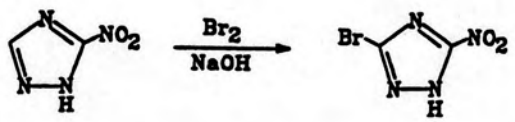


**Scheme XIX**



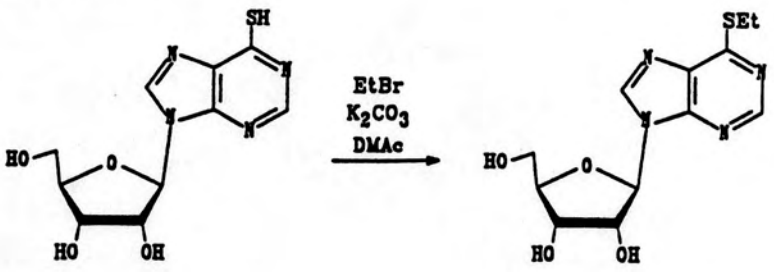

69 70 71 72

**Scheme XX**




73 74

**Scheme XXI**




75 76

3. The additional quantity of adenosine-$N^1$-oxide was prepared by the same procedure used to make the previously submitted samples.[1-3] This procedure, using *m*-chloroperbenzoic acid to oxidize adenosine, was presented earlier in Scheme I.

4. 6-Ethylmercaptopurine riboside **76** was prepared as shown in Scheme XXI by the alkylation of 6-mercaptopurine riboside **75**[29,30] with ethyl bromide in DMAC with potassium carbonate.

5. As previously mentioned, an alternate source was found for chloroquine **77**. Our efforts to isolate and purify this compound consistently yielded a mixture containing both **77** and **78** (Scheme XXII), and this indicated that our **77** must be spontaneously decomposing to **78**.

6. As previously mentioned, our information indicated that USAMRIID already had 15 g of 4-iminopyrazolo[3,4-*d*]-1,3-thiazin-6-thione **79** on hand, and therefore, we have not tried to make any more of this compound (Scheme XXII).

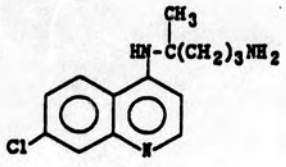
7. As shown in Scheme XXIII, tiazofurin 5′-phosphate **81**[31] was synthesized by treating tiazofurin with phosphorus oxychloride in pyridine.

8. The nucleoside of 7-cyanoimidazo[1,2-*b*]pyrazole **88**[32,33] was made by the procedure shown in Scheme XXIV. 2-Hydrazinoacetaldehyde diethylacetal **83** was made from hydrazine and chloroacetaldehyde diethylacetal **82**. Reaction of this diethylacetal (**83**) with ethoxymethylenemalononitrile gave 5-amino-1,3-(2,2-diethoxyethyl)pyrazole-4-carbonitrile **84**, which was cyclized to imidazolo[1,2-*b*]pyrazole-7-carbonitrile **85** by treatment with 1*N* HCl. Pyrazolecarbonitrile **85** was then ribosylated with 1-O-acetyl-2,3,5-tribenzoyl-D-ribofuranose and HMDS, giving a product mixture containing both protected nucleoside **86** and the isomeric nucleoside **87**. Chromatographic isolation of compound **86** followed by deprotection with methanolic ammonia gave the desired compound **88**.

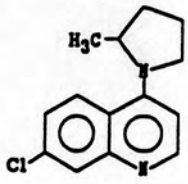
9, 10, and 11. Three out of the four ribavirin nucleotides requested by Major Ussery have been synthesized according to the routes shown in Scheme XXV.[34] Ribavirin 5′-phosphate **90** was made by treating ribavirin **89** with phosphoryl chloride and trimethylphosphite. Treatment of phosphate **90** with MeOH, triethylamine, and dicyclohexylcarbodiimide gave ribavirin 5′-methylphosphate **91**. Ribavirin 5′-phosphate **90** was also the precursor for ribavirin 5′-diphosphate. Phosphate **90** was first converted to its morpholidate **92**. Subsequent treatment of the morpholidate with orthophosphoric acid, pyridine, and tributylamine then gave the desired ribavirin 5′-diphosphate.

Our efforts to synthesize the fourth ribavirin nucleotide, ribavirin 5′-triphosphate has been hampered by the instability of the triphosphate during purification. According to thin-layer chromatographic and mass spectrometric data, we have been successful at cleanly synthesizing the desired triphosphate compound. Treatment of the morpholidate **92** in dry DMF (instead of pyridine as used in the syntheses of the other ribavirin nucleotides) with rigorously purified bis-tri-*n*-butylammoniumpyrophosphate gives the desired triphosphated compound without contamination with di- and monophosphated nucleoside. However, our procedure for synthesizing ribavirin 5′-triphosphate required a large excess (5X) of the pyrophosphate, and as a result the isolated product contained a significant amount of pyrophosphate in addition to the desired triphosphate. Furthermore, the chromatographic systems that had effectively separated the other ribavirin nucleotides from their

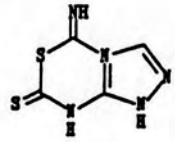
**Scheme XXII**



77

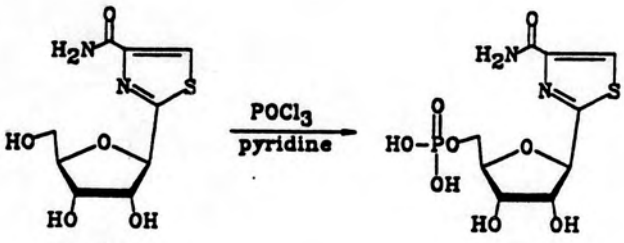


78



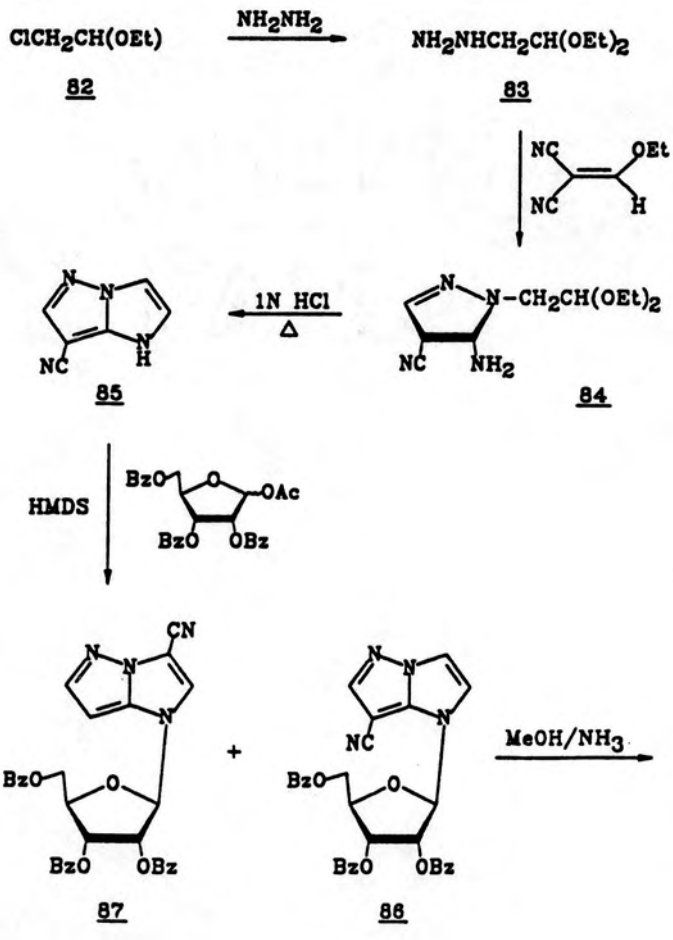
79

**Scheme XXIII**



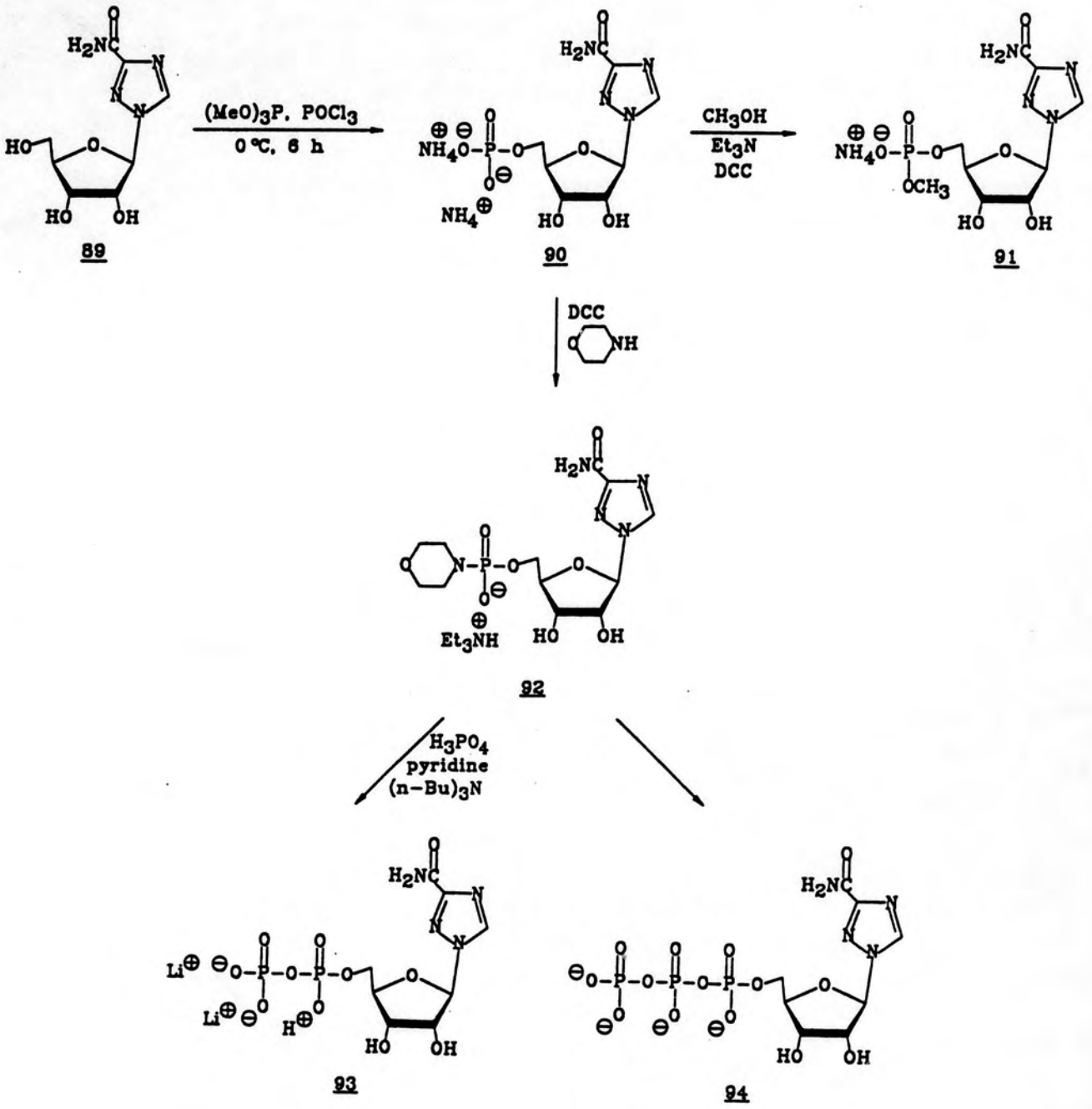

80 81

**Scheme XXIV**




82 83 84 85 86 87 88

**Scheme XXV**




89 90 91 92 93 94

corresponding reaction sideproducts were now totally ineffective at separating ribavirin 5'-triphosphate from the residual pyrophosphate. Other efforts to remove or reduce the level of pyrophosphate from the product mixture included lowering the pH (so that we might be able to extract out the pyrophosphate) and various ion exchanges with the appropriate ion-exchange resins have also been ineffective. These efforts consistently result in partial breakdown of the triphosphate, thereby contaminating the product mixture with significant amounts of both the mono- and diphosphated nucleotides.

We have recently tried a small-scale reaction using only about a 10% excess of the pyrophosphate. After overnight stirring at room temperature, thin layer chromatography indicated that only a small amount of the starting morpholidate remained. Analysis of this sample after workup is still ongoing, and therefore, at this time, we cannot report whether this procedural change has resolved our pyrophosphate dilemma.

12. Formycin B **104** was synthesized by following the procedure shown in Scheme XXVI.[35,36] Ribofuranose 1-acetate 2,3,5-tribenzoate **95** was converted to intermediate **100** by the following series of reactions. Treatment of ribofuranose **95** with HBr and $Hg(CN)_2$ gave 1-cyanosugar **96**. Hydrolysis of **96** followed by treatment with thionyl chloride gave acid chloride **97**. This intermediate was then treated with HCN followed by ylide **99**, to give cyanoester **100**. (Ylide **99** was generated from t-butylacetyltriphenylphosphorane HCl **98** with 10% sodium hydroxide in chloroform. Triphenylphosphorane HCl **98** was synthesized from chloroacetic acid and isobutene by treatment with sulfuric acid in benzene followed by triphenylphosphine.) Cyclization of cyanoester **100** with ethyl diazoacetate gave the ribosylated pyrazole ring of Formycin B, forming pyrazolediester **101**. Sequential treatment of this intermediate with formic acid followed by 2,2,2-trichloroethanol, triethylamine, and diphenylphosphoryl azide gave carbamoyl ester **102**. Further treatment with zinc/acetic acid, and formamidine acetate effected cyclization, forming the necessary pyrimidine ring, thus giving 2',3',5'-tribenzoylated Formycin B **103**. Deprotection was accomplished by using sodium methoxide in methanol to give Formycin B **104**.

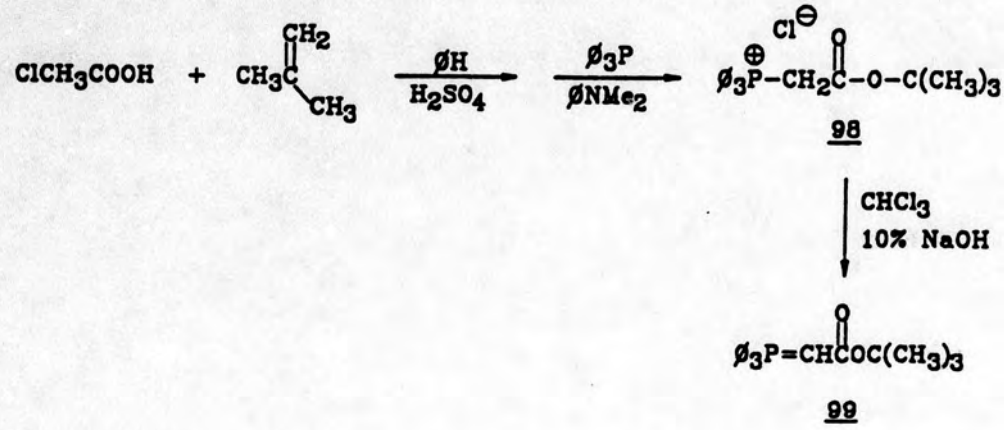
13. We have begun in-house screening of 3-deazacarbocyclic adenosine **105** (Scheme XXVII).

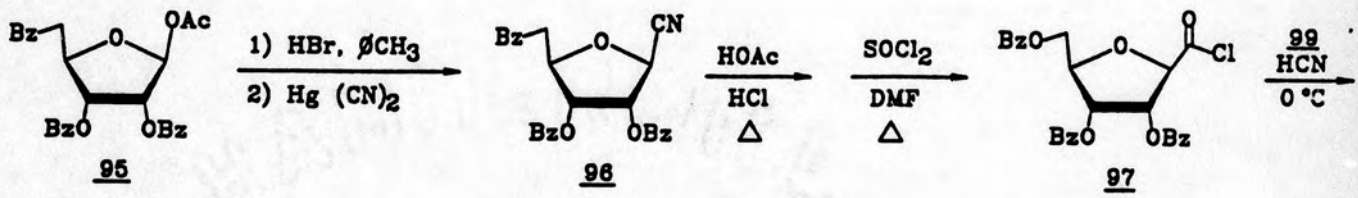
We rigorously purified a USAMRIID-supplied of 4-acetyl-4-phenylpiperidine **106**. Numerous attempts to crystallize compound **106** were unsuccessful, and therefore, it was submitted as its hydrochloride salt **107** (Scheme XXVII).

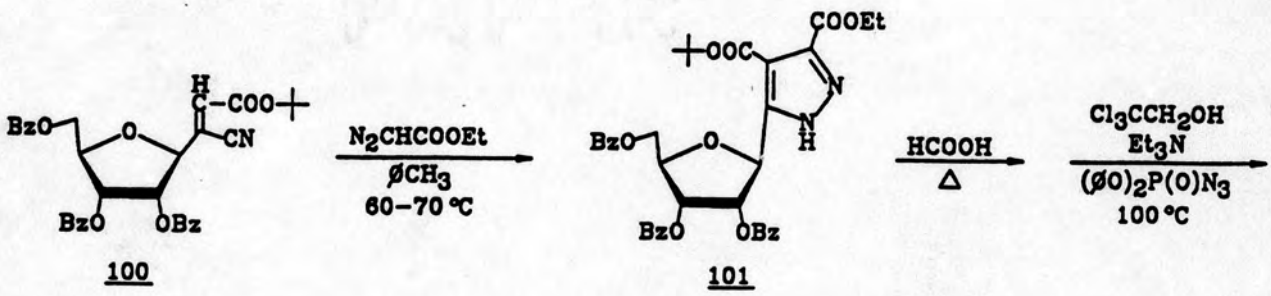
The remaining compounds from Major Ussery's lists are: ribavirin 5'-triphosphate; 6-carboxamidopurine riboside; 5-chloro-3-$\beta$-D-ribofuranosyl-S-triazolopyrimidin-7-one; Justicidin B; 4-amino-1-$\beta$-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine and 4-amino-1-$\beta$-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine 5'-acetate. We have also begun trying to synthesize the recently requested anti-HIV agents 9-(2-phosphonylmethoxyethyl)adenine (PMEA), 9-(2-phosphonylmethoxyethyl)diaminopurine (PMEDAP), 9-(2-phosphonylmethoxyethyl)-2-aminopurine (PMEMAP), and 9-(2-phosphonylmethoxyethyl)guanine (PMEG).

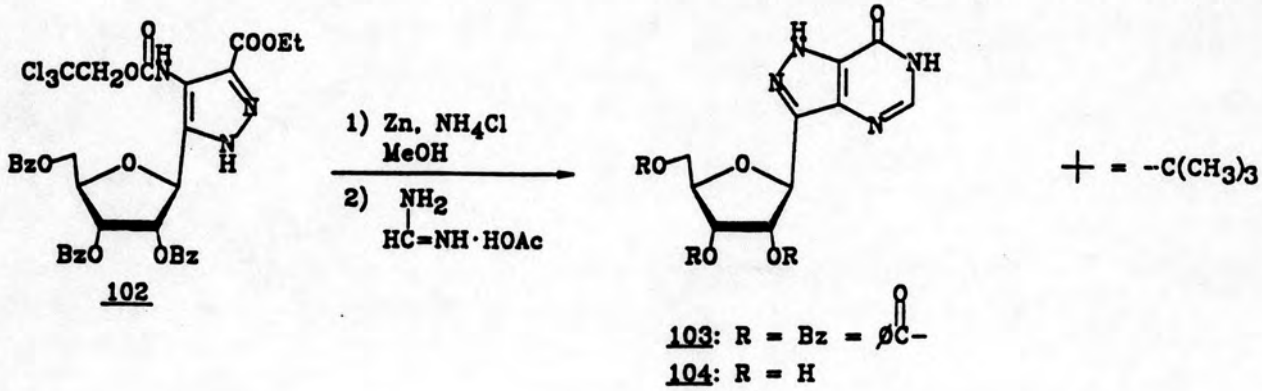
As previously mentioned, we have been able to synthesize ribavirin 5'-triphosphate **94** (Scheme XXV), but we have had difficulty isolating and purifying this compound. Our earlier efforts followed a procedure that used a large excess pyrophosphate reagent, and consequently, the resulting product

**Scheme XXVI**

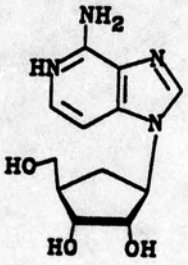

ClCH2COOH
CH2
CH3C
CH3
ØH
H2SO4
Ø3P
ØNMe2
Cl⊖
Ø3P⊕-CH2C-O-C(CH3)3
98
CHCl3
10% NaOH
Ø3P=CHCOC(CH3)3
99


Bz
OAc
BzO
OBz
95
1) HBr, ØCH3
2) Hg (CN)2
CN
96
HOAc
HCl
△
SOCl2
DMF
△
Cl
97
99
HCN
0 °C


H
C-COO+
CN
100
N2CHCOOEt
ØCH3
60-70 °C
COOEt
+OOC
N
N
H
101
HCOOH
△
Cl3CCH2OH
Et3N
(ØO)2P(O)N3
100 °C


Cl3CCH2OC
COOEt
102
1) Zn, NH4Cl
MeOH
2) NH2
HC=NH·HOAc
NH
RO
OR
+ = -C(CH3)3
103: R = Bz = ØC-
104: R = H

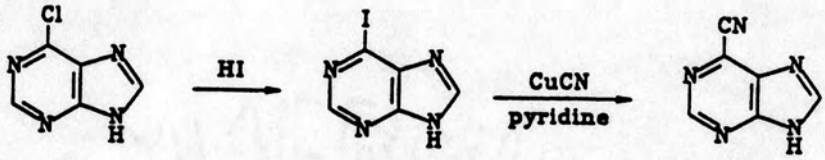
Scheme XXVII



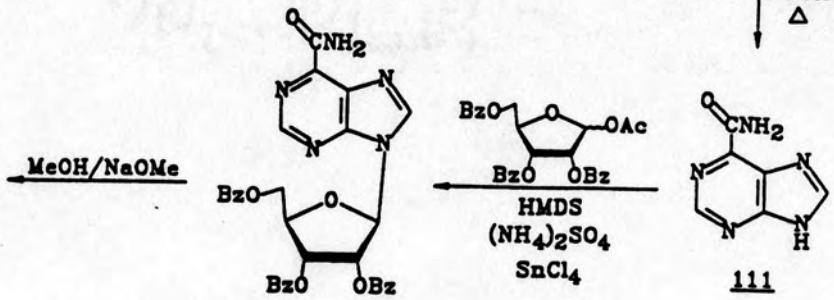
105

106 107

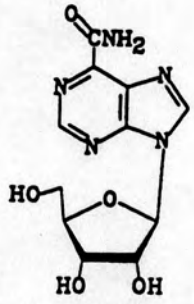
Scheme XXVIII



108 109 110



112 111



113

mixture was also contaminated with a significant amount of pyrophosphate. Unfortunately, our efforts to remove the excess pyrophosphate by chromatographic means or by any of a number of extraction or ion exchange methods have been unsuccessful. We are hopeful that altering the synthetic procedure (using a much smaller excess of pyrophosphate) will allow us to synthesize and isolate ribavirin 5′-triphosphate **94** with much less pyrophosphate contamination.

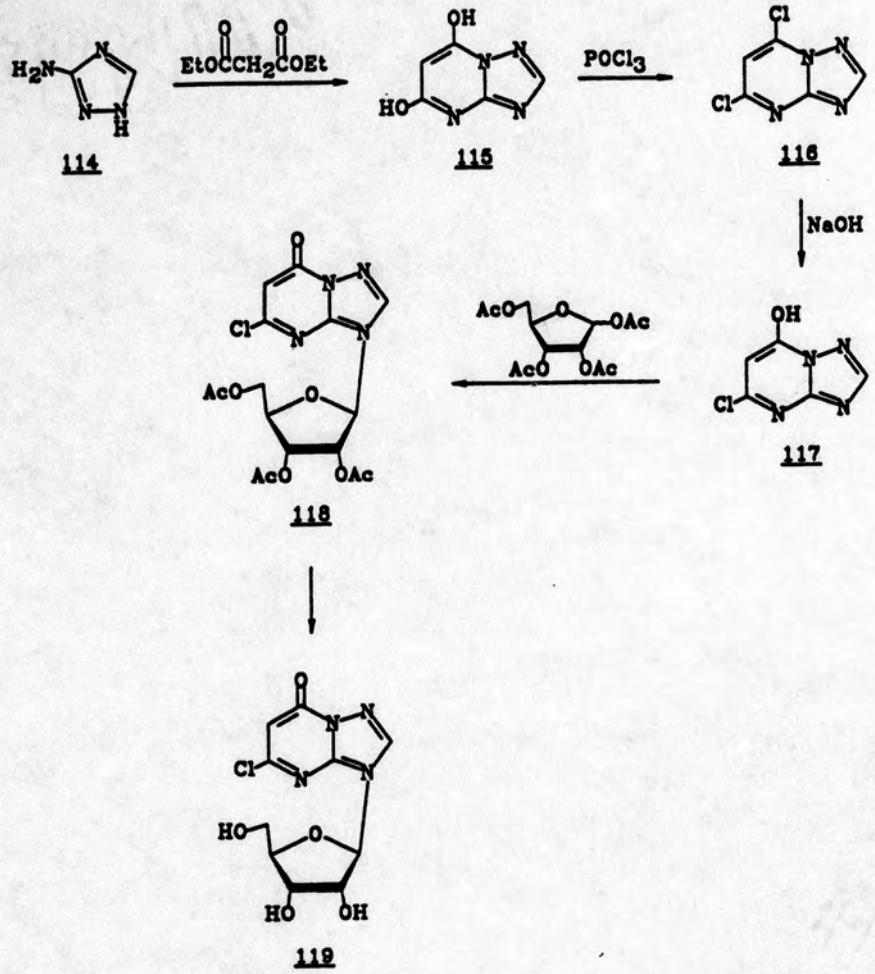
Until recently, we had been concentrating our efforts on the higher priority compounds. Since 6-carboxamidopurine riboside **113**[37-39] was not in this category, our pursuit of its synthesis was postponed. However, we have renewed our efforts to synthesize this compound, and we will be following the approach given in Scheme XXVIII to synthesize this compounds. 6-Chloropurine **108** will be converted to 6-iodopurine **109** by treatment with HI. Displacement of the iodide with copper (I) cyanide will give 6-cyanopurine **110** which can then be hydrolyzed with sodium hydroxide to give 6-carboxamidopurine **111**. Ribosylation followed by deprotection will give the desired 6-carboxamidopurine riboside **113**.

5-Chloro-7-$\beta$-D-ribofuranosyl-s-triazolopyrimidin-7-one **119**[40] is another low priority compound whose synthesis was postponed until recently. Scheme XXIX shows the synthetic approach that we will use to make this compound. Treatment of 3-aminotriazole **114** with diethyl malonate will give triazolopyrimidine **115**. Conversion of both hydroxyl groups with phosphorus oxychloride will give the dichloropurine analog **116** which then will be partially hydrolyzed to the 5-chloro-7-hydroxy analog **117** by treatment with sodium hydroxide. Ribosylation and deprotection should then give us the desired 5-chloro-7-$\beta$-D-ribofuranosyl-S-triazolopyrimidin-7-one **119**. In our earlier attempts to synthesize this compound, we obtained 5,7-dihydroxytriazolopyrimidine **115** with no difficulty. However, our attempts to convert this dihydroxy compound to the dichloro analog **116** were not as successful, and our yields were unreasonably low. Therefore, as we renew our efforts toward this compound, this will be the first hurdle in our pursuit.

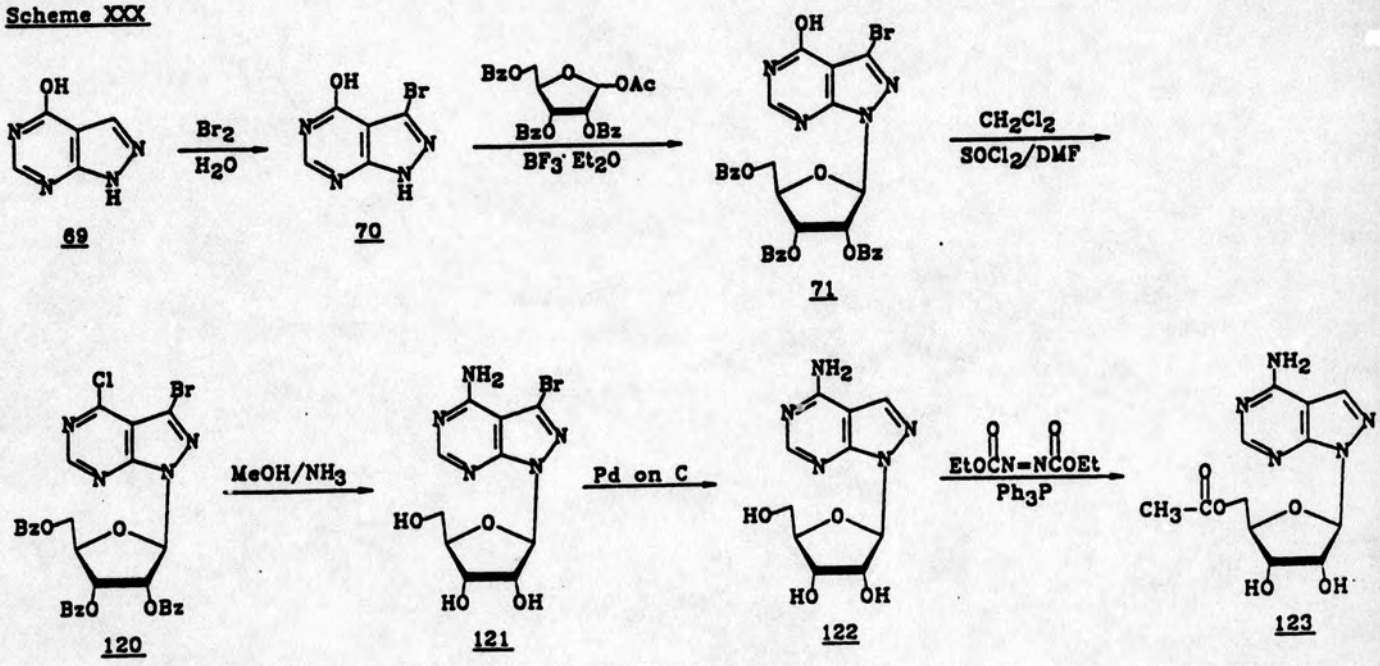
The syntheses of 4-amino-1-ribofuranosylpyrazolo[3,4-*d*]pyrimidine **122** and 4-amino-1-ribofuranosylpyrazolo[3,4-*d*]pyrimidine 5′-acetate **123**[41,42] are also still in progress. We have made pyrazolopyrimidine **122** by the two related approaches shown in Schemes XXX and XXXI. Both of these approaches are very similar to the approach used to synthesize previously discussed 3-bromo-1-$\beta$-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine **72**. As shown in Scheme XXX, allopurinol **69** is first 3-brominated and then ribosylated with ribofuranose-1-acetate-2,3,5-tribenzoate to give protected nucleoside **71**. Phosphorus oxychloride in DMF converts the 4-hydroxy to the more reactive 4-chloro analog. Treatment with methanolic ammonia deprotects the sugar and displaces away the 4-chloro group to give 3-bromonucleoside **121**. Catalytic reduction with palladium on carbon to remove the 3-bromo group then gives 4-amino-1-ribofuranosylpyrazolo[3,4-*d*]pyrimidine **122**.

Our second approach is shown in Scheme XXXI and was developed simply to allow us to cut out one synthetic step. This synthesis begins with 4-aminopyrazolo[3,4-*d*]pyrimidine **124**, and it follows

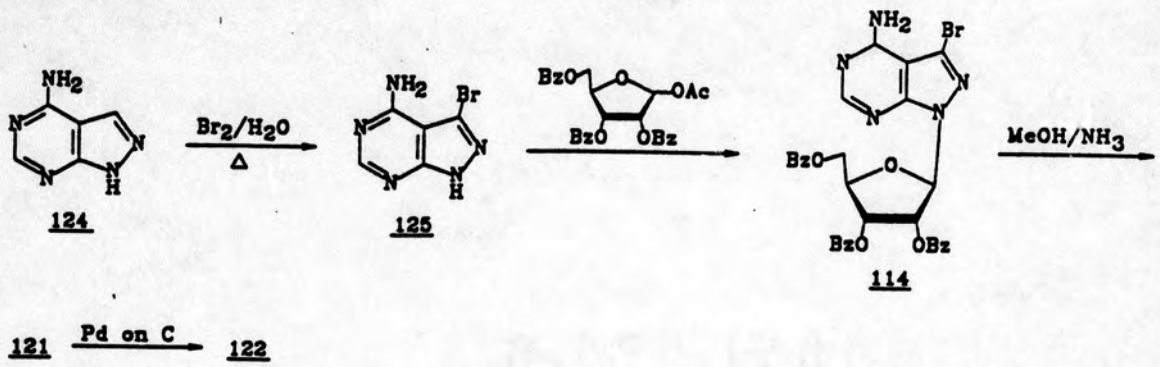
Scheme XXIX




Scheme XXX

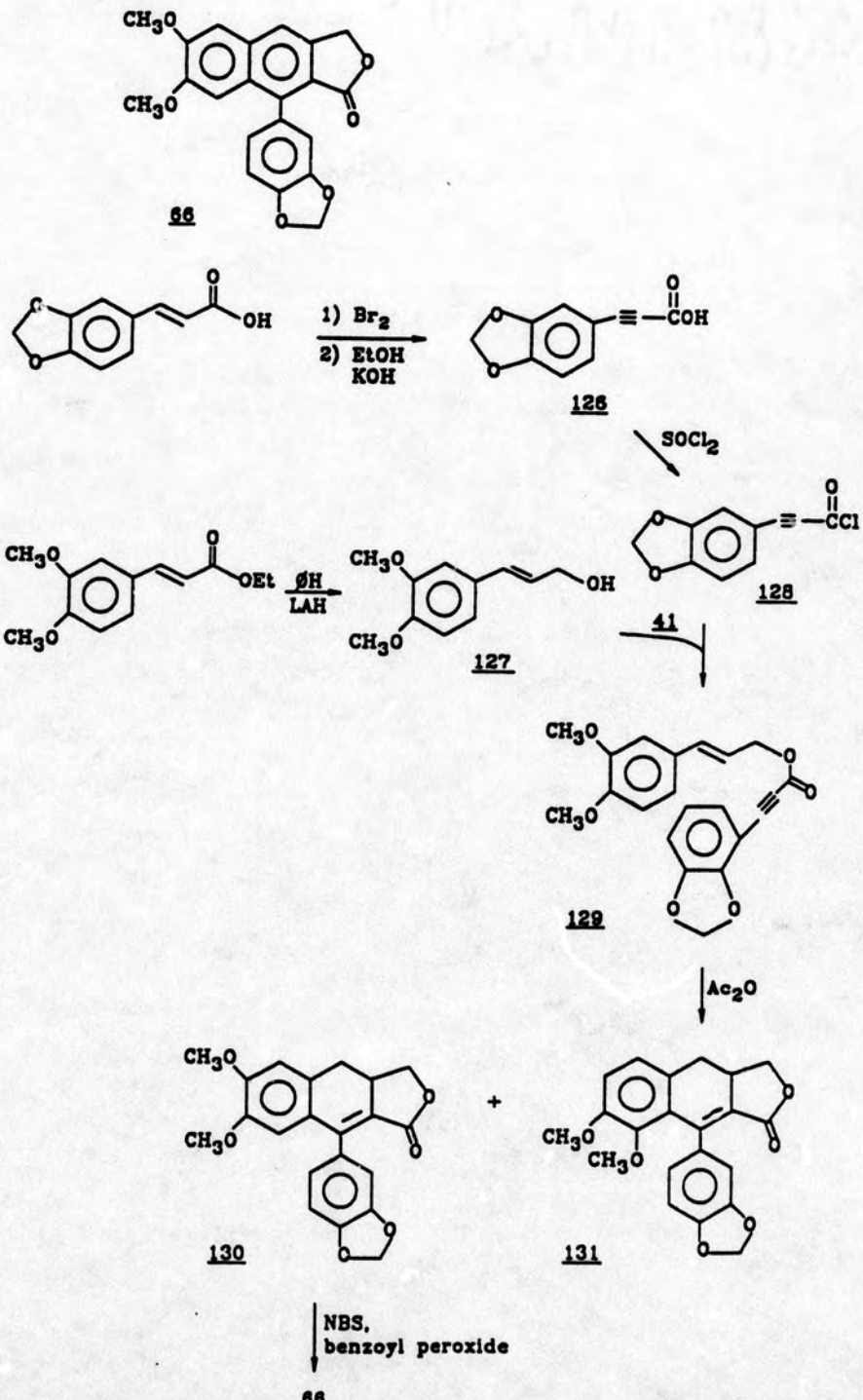


**Scheme XXXI**




121 —Pd on C→ 122

**Scheme XXXII**



a similar course to that in Scheme XXX. Bromination of 124 followed by ribosylation and deprotection again gives 3-bromonucleoside 121, and catalytic hydrogenolysis of 121 again gives nucleoside 122.

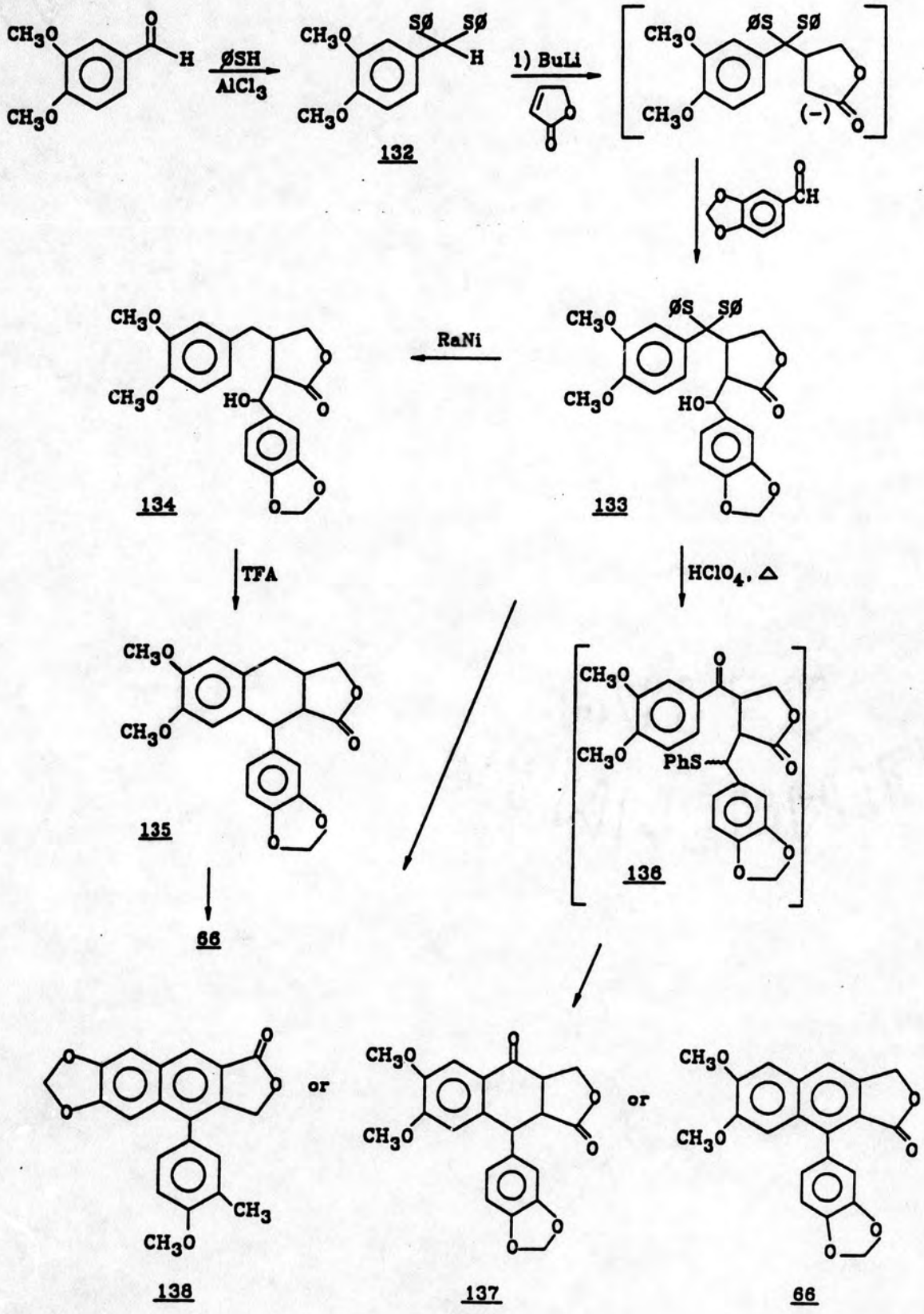
Therefore, we have been able to synthesize nucleoside 122 by following either of these approaches. However, we have not been able to isolate the requested quantity of this compound, because the final catalytic removal of the 3-bromo group consistently occurs with extremely low yield. We are currently investigating other catalysts as well as other isolation techniques that should improve our yields and allow us to isolate the necessary quantities of nucleoside 122 for sample submission as well as for the synthesis of the requested 5'-acetyl derivative 123 of this nucleoside. When we have sufficient quantities of allopurinol nucleoside 122, we should be able to obtain the 5'-acetyl derivative 123 by treatment with diethylazodicarboxylate.

Justicidin B is another low priority compound whose synthesis is progressing very slowly. Schemes XXXII-XXXVI have all been investigated as potential approaches to Justicidin B, and all of these have proven not to be simple and direct routes to this compound. We first tried the approach shown in Scheme XXXII[43] which used 3,4-methylenedioxycinnamic acid and 3,4-dimethoxycinnamic acid as the starting materials. 3,4-Methylenedioxycinnamic acid was brominated and dehydrohalogenated to propiolic acid 126, while 3,4-dimethoxycinnamic acid was reduced to alcohol 127 with LAH. Propiolic acid 126 was converted to acid chloride 128 with thionyl chloride and then treated with alcohol 127 to form ester 129. Efforts to cyclize this ester by refluxing in acetic anhydride gave a mixture of isomers 130 and 131, which were barely separable and only by preparative thin-layer chromatography. We had originally abandoned this approach, because the effort required for isolation and purification seemed unreasonable relative to the requested amount. We have begun to search again for alternate solvent systems that might facilitate sample purification.

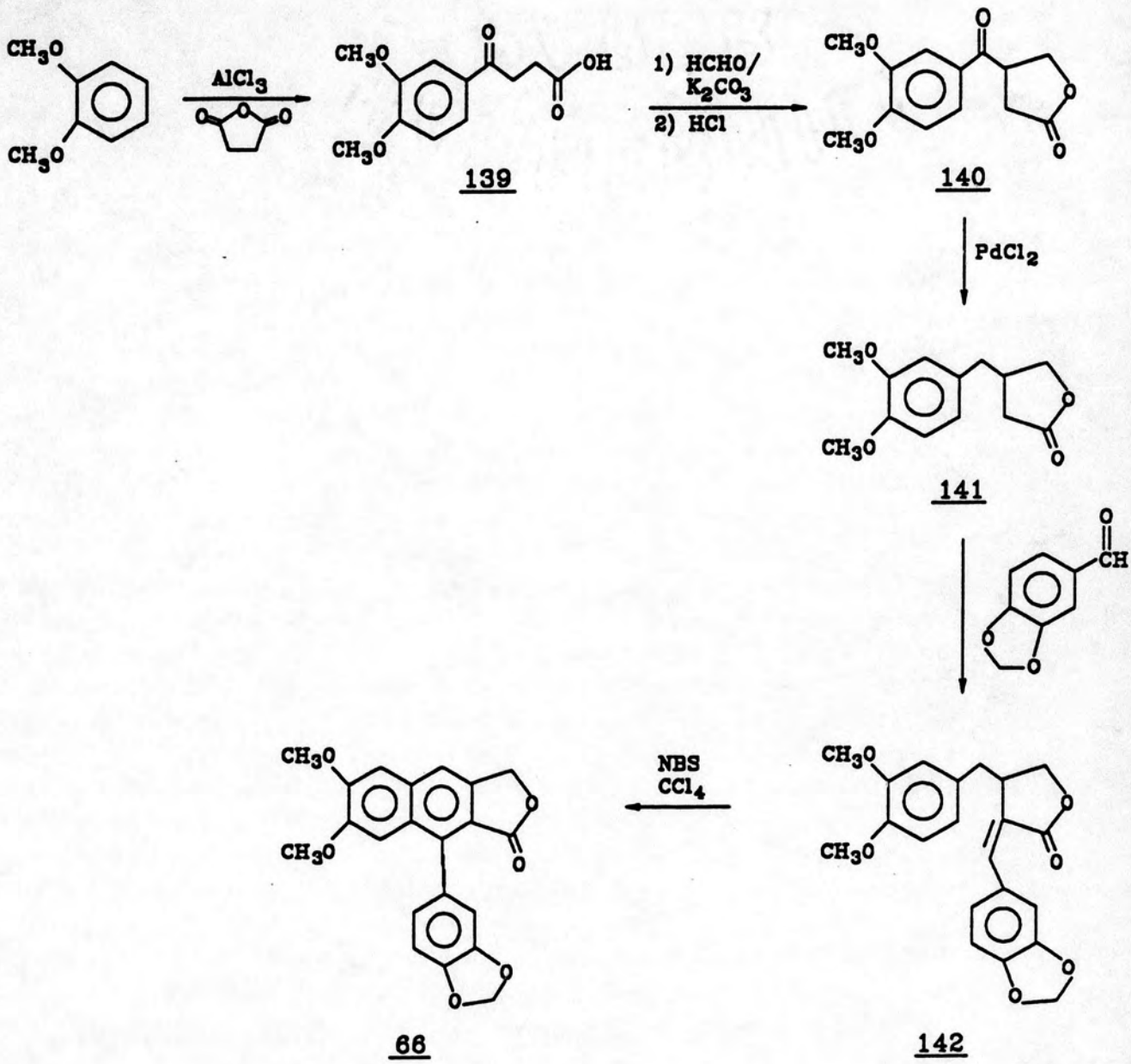
The second approach attempted to construct the entire carbon skeleton of Justicidin B in one step.[44] As shown in Scheme XXXIII, addition of 2(5*H*)-furanone with the *n*-butyllithium induced anion of 3,4-dimethoxybenzaldehyde diphenylthioacetal 132 followed by addition of piperonal gave adduct 133. According to our synthetic procedure, Raney nickel desulfurization of 133 should have easily given alcohol 134. Then, alcohol 134 should have been easily cyclized with trifluoroacetic acid to give 135, which would be easily oxidized to Justicidin B 66. Unfortunately, Raney Nickel desulfurization of this adduct has not been as easy as was described in the literature (reflux in ethanol for three hours). Instead, our reaction times have been much longer, and concurrent cleavage of the piperonal has also been encountered. However, in our pursuit of the Justicidin B analog 137, we found that heating a perchloric acid solution containing adduct 133 (and presumably dethioketalized intermediate 136 since this intermediate is known to form when thioketal 133 is treated with perchloric acid at room temperature) resulted in the formation of a mixture of products containing 135 as the primary product.

The third scheme[45] approached Justicidin B via butyrolactone 141. As shown in Scheme XXXIV, this intermediate was obtained by the following reaction series: 1,2-dimethoxybenzene (veratrole) was reacted with succinic anhydride and aluminum chloride to give ketoacid 139. Subsequent addition of

**Scheme XXXIII**



**Scheme XXXIV**




139 140 141 142 66

formalin solution and potassium carbonate followed by cyclization with concentrated HCl gave ketolactone **140**. Lactone intermediate **141** then should have easily obtained from keto-lactone **140** by reduction with palladium chloride (3 h at 50 psi $H_2$). Justicidin B could be synthesized from this intermediate after condensation with piperonal followed by cyclization with NBS in carbon tetrachloride.

However, when we tried this reaction sequence, we found that the simple palladium chloride reduction of ketolactone **140** did not occur as readily and easily as had been reported in the literature. We had only limited success in reducing the keto-carbonyl with palladium chloride in our small scale runs, and only when large excesses of catalyst are used over 5-7 day reaction periods. Because of the prohibitive time requirements of this approach, we decided to try to obtain lactone intermediate **141** by a different route, especially after a literature search yielded the quick synthesis of the analogous lactone **145**.

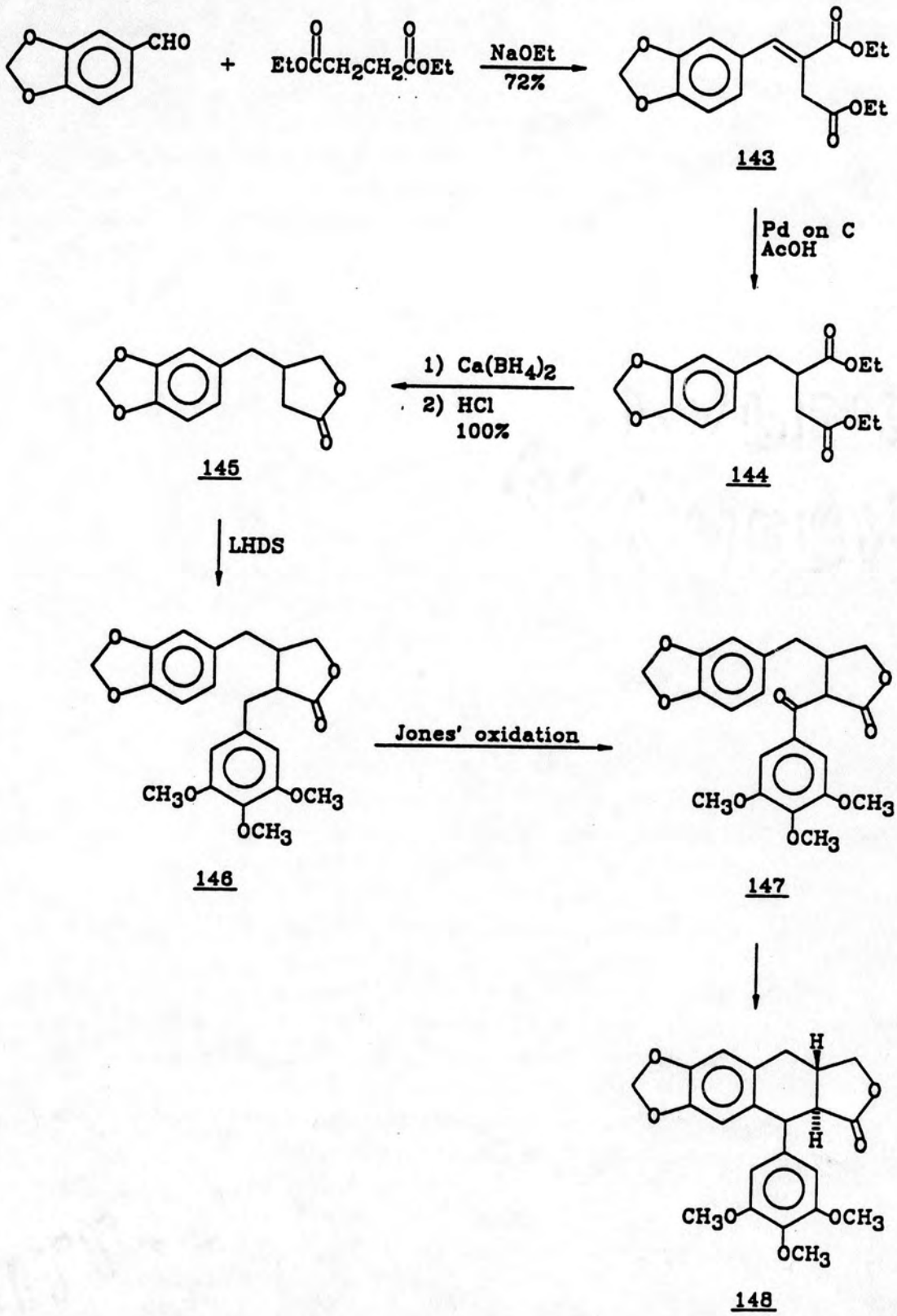
The analogous lactone synthesis was one that was presented in a synthesis for podorhizone **147** and isodeoxypodophyllotoxin **148** as shown in Scheme XXXV.[46] According to this approach, diethylsuccinate or dimethylsuccinate is reacted with piperonal with sodium ethoxide via the Stobbe condensation, giving ethylenic hemiester **143**. Hydrogenation of the hemiester double bond with palladium on carbon in acetic acid gave hemiester **144** which was cyclized to lactone **145** with $Ca(BH_4)_2$ reduction of the ester and subsequent treatment with HCl. Podorhizone **147** could then be made from this intermediate by the condensation of this lactone with 3,4,5-trimethoxybenzaldehyde. Treatment of podorhizone with palladium on carbon in either trifluoroacetic acid or perchloric acid would then give isodeoxypodophyllotoxin **148**.

Our efforts to mimic this reaction sequence are presented in Scheme XXXVI. Substituting veratraldehyde (3,4-dimethoxybenzaldehyde) for piperonal should have given the desired lactone intermediate **141**. Unfortunately, when we tried this alteration, the initial Stobbe condensation gave ethylenic hemiester **149**, but not in the desired yields or purity that we had hoped for. Furthermore, preliminary investigations into the subsequent steps have also given complex product mixtures which will require extensive chromatography. Therefore, we are still evaluating this approach as well as searching for other more straightforward approaches to Justicidin B.

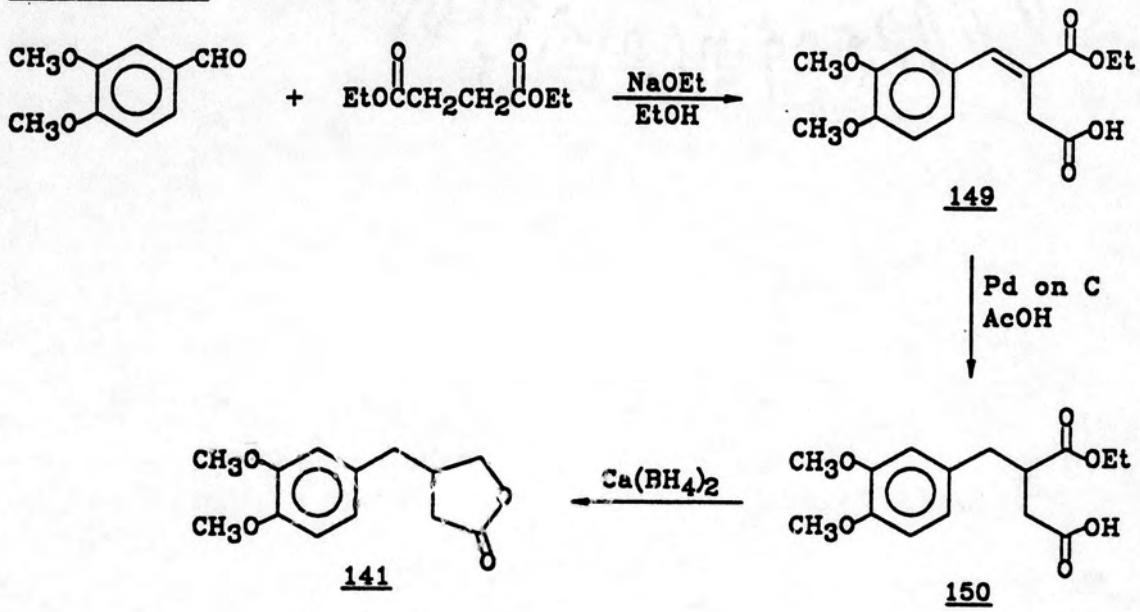
We will also be resynthesizing additional quantities of the nucleoside of 7-cyanoimidazo[1,2-*b*]pyrazole **88**,[32,33] since we previously were able to submit only a small (sub-600 mg) quantity of this compound. As presented earlier, this compound will be synthesized according to Scheme X. We hope that our experience with this reaction scheme will allow us to obtain this compound with less difficulty.

Finally, we have also begun working on the synthesis of four recently requested anti-HIV agents[47,48]: PMEA, PMEDAP, PMEMAP, and PMEG. Our initial efforts have been directed toward the synthesis of the acyclic sugar sidechain by the reaction shown in Scheme XXXVII. Our early attempts at reacting dioxolane **151** with acetyl chloride consistently gave low yields of 2-(chloromethoxy)ethyl acetate **152**. We have recently obtained a detailed synthetic procedure from Bristol Myers which gives much needed specific information regarding the synthesis of 2-(chloromethoxy)ethyl

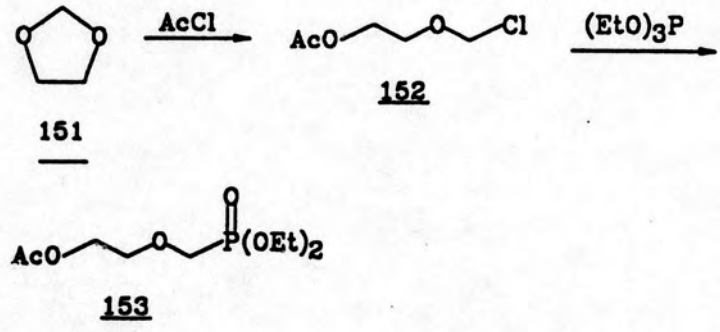
**Scheme XXXV**


CHO
+
EtOCCH2CH2COEt
NaOEt
72%
OEt
OEt
143
Pd on C
AcOH
1) Ca(BH4)2
2) HCl
100%
OEt
OEt
144
145
LHDS
CH3O
OCH3
OCH3
146
Jones' oxidation
CH3O
OCH3
OCH3
147
H
H
CH3O
OCH3
OCH3
148

**Scheme XXXVI**




**Scheme XXXVII**



acetate **152**. This procedure has enabled us to vastly improve our yields of the 2-chloromethoxyethyl acetate as well as to proceed on to the synthesis of 2-(diethylphosphonylmethoxy)ethyl acetate **153**.

**Experimental Section**

All solvents and materials were reagent grade and were either used as received or purified as required. $^1$H NMR and $^{13}$C NMR spectra were run with a Nicolet NMC NT-300 NB spectrometer operating at 300.65 MHz with tetramethylsilane as an internal reference. Chemical shifts ($\delta$) for multiplets were measured from the appropriate centers. The mass spectral data were obtained from a Varian MAT 311A mass spectrometer in fast atom bombardment (FAB) or electron-impact (EI) mode (direct probe temperature 20 °C), as indicated. Infrared data were obtained with a Nicolet 10-MX spectrometer. In most cases only strong or medium peaks in the 1800-600 cm$^{-1}$ range were reported. UV absorption spectra were determined in the appropriate pH 1 (0.1 *N* HCl), pH 7 buffer, and pH 13 (0.1 *N* NaOH) solutions with a Cary 17 spectrophotometer or a Perkin Elmer Model Lambda 9 UV/VIS/NIR spectrophotometer. Melting point data was obtained with a Mel-Temp Capillary Melting point apparatus, and all melting points were uncorrected. Elemental analysis data were obtained either from an in-house Perkin Elmer Model 240 Elemental Analyzer or from Atlantic Microlab of Atlanta, Georgia.

**Adenosine-$N^1$-oxide (1).** In a 1-L round-bottomed flask protected with a Drierite (calcium sulfate) drying tube was placed 5.0 g (18.7 mmol) of adenosine (1) and 500 mL of methanol. The mixture was stirred at room temperature and 4.85 g (22.5 mmol) of *m*-chloroperoxybenzoic acid (MCPBA) was added. Thin-layer chromatography after 24 h of stirring indicated the presence of starting material. Therefore an additional 0.5 g (2.9 mmol) of MCPBA was added and the reaction was stirred an additional 20 h. The reaction mixture was poured slowly in 1.5 L of ethyl acetate with good stirring. After having been stirred 2 h, the product was collected, washed with ethyl acetate and dried *in vacuo* over phosphorus pentoxide: yield 34.6 g. After one recrystallization from boiling ethanol 3.7 g (70%) of anhydrous adenosine-$N^1$-oxide, mp 222-225 °C was obtained. UV $\lambda_{max}$ 212 nm ($\epsilon$28,300), 257 (12,500), 265 (sh) at pH 1; 232 (41,900), 262 (8,300), 295 (2,400) at pH 7; 231 (24,900), 267 (8,800), 275 (sh), 307 (4,700) at pH 13; 235 (41,400), 263 (7,700), 304 (2,250) in EtOH; MS (FABMS) *m/e* 284 (M + 1); IR (strong and medium-strong bands 1800-600 cm$^{-1}$ region) 1670, 1500, 1225, 1210, 1135 sh, 1125, 1085, 1060, 640 cm$^{-1}$; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 3.57, 3.69 (2 m, 2, $J_{5'a,5'b}$ = 12.0, $CH_2$-5'), 3.96 (apparent q, 1, $J_{4',5'b}$ = 4.0 Hz, $J_{4',5'a}$ = 4.1 Hz, H-4'), 4.16 (apparent q, 1, $J_{3',4'}$ = 3.7 Hz, H-3'), 4.56 (apparent q, 1, $J_{2',3'}$ = 5.0 Hz, H-2'), 5.09 (apparent t, 1, 5'-OH), 5.28 (apparent d, 1, 3'-OH), 5.64 (apparent d, 1, 2'-OH), 5.89 (d, 1, H-1'), 8.55 (s, 1, H-2), 8.64 (s, 1, H-8). *Anal.* Calcd for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.48; H, 4.63; N, 24.68.

**1-(2-Cyanobenzyloxy)adenosine, Perchloric Acid Salt (2a).** In a 100-mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate drying tube was placed 2.5 g (8.83 mmol) of adenosine-N$^1$-oxide (1), 50 mL of molecular sieve (4A) dried *N,N*-dimethylacetamide (DMAC), and 5.2 g

(26.5 mmol) of α-bromo-*o*-cyanotoluene. The mixture was stirred at room temperature. The reaction was stirred for 2 h after complete solution was achieved. The reaction solution was poured into 300-500 mL of anhydrous ether with slight swirling. After the product stuck to the walls of the flask the supernatant was decanted. The gummy residue was washed with 400 mL ether, decanted, again covered with 400 mL of ether and ground to a powder. The powder was allowed to settle, the ether was decanted, and the residue was dried in a stream of argon. The residue was dissolved in 25 mL of $H_2O$ and added with stirring to a warm solution of 5 g (42.6 mmol) of ammonium perchlorate dissolved in 25 mL of $H_2O$. The product crystallized upon scratching and chilling. One recrystallization from $H_2O$ and drying at 78 °C for 16 h over phosphorus pentoxide yielded 3.5 g (79%); UV $\lambda_{max}$ 260 nm (12,700) at pH 1; 259 (12,560) at pH 7; 257 (12,160) at pH 13; MS (FAB) *m/e* 399 (M + 1); IR 2250, 1684, 1505, 1222, 1100 (broad), 772, and 623 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) δ 3.59, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.0 Hz, $CH_2$-5'), 3.99 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.8 Hz, H-2'), 5.0 (br s, 1, 5'-OH), 5.33 (br s, 1, 3'-OH), 5.60 (br, 1, 2'-OH), 5.60 (s, 2, O$CH_2$Ar), 5.94 (apparent d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.70 (t, 1, Ar-H, 4), 7.87, 7.90 (2 m, 2, Ar-H, 3,5), 7.99 (d, 1, Ar-H, 6), 8.81 (s, 1, H-2), 8.83 (s, 1, H-8), 9.8-10.6 (br, 2, H-$\overset{\oplus}{N}H_2$); $^{13}C$ NMR ($Me_2SO$-$d_6$) δ 60.81 (C-5'), 69.89 (C-3'), 74.44 (C-2'), 78.56 (C-O$CH_2$Ar), 85.83 (C-4'), 87.74 (C-1'), 112.53 (Ar-C-2), 117.12 (C-C≡N), 119.58 (C-5), 130.50, 131.71, 133.20, 133.38 (Ar-C-3,4,5,6), 135.16 (Ar-C-1), 142.81 (C-8), 144.23 (C-2), 145.16 (C-4), 148.38 (C-6).

**1-(3,4-Dimethylbenzyloxy)adenosine, Perchloric Acid Salt (2b).** The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt (2a) was used. From 1.5 g (5.32 mmol) of adenosine-$N^1$-oxide, 3 mL of 3,4-dimethylbenzylbromide (prepared from 3,4-dimethylbenzyl alcohol and HBr) and 3 g (25.5 mmol) of $NH_4ClO_4$ in 45 mL warm $H_2O$ was obtained 2.25 g (84%); mp 139-142 °C cap dec; UV $\lambda_{max}$ 259 nm (13,300) at pH 1; 259 (13,300) at pH 7; 258 (13,600) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR 1691, 1510, 1100 (broad), 624 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) δ 2.25 (s, 6, Ar-$CH_3$) 3.58, 3.69 (2 m, 2, $J_{4,5'a}$ = $J_{4,5'b}$ = 3.87 Hz, $J_{5'a,5'b}$ = 12.1 Hz, $CH_2$-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.85 Hz, H-3'), 4.49 (apparent q, 1, $J_{2',3'}$ = 4.88 Hz, H-2'), 5.09 (br s, 1, OH-5'), 5.33 (s, 2, O$CH_2$Ar), 5.60 (br d, 1, $J_{2',2'}$-OH = 4.57 Hz, OH-2'), 5.94 (d, 1, $J_{1'2'}$ = 5.4 Hz, H-1'), 8.81 (s, 1, H-8), 8.91 (s, 1, H-2), 9.72, 10.41 (2 br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{19}H_{24}ClN_5O_9 \cdot H_2O$: C, 43.89; H, 5.04; N, 13.47. Found: C, 44.00; H, 5.02; N, 13.38.

**1-(3,5-Dimethylbenzyloxy)adenosine, Perchloric Acid Salt (2c).** The procedure for 1-(2-cyanobenzyloxy)adenosine, perchloric acid (2a) salt was followed. From 2.5 g (8.83 mmol) of adenosine-$N^1$-oxide, 5 g (25.1 mmol) of 3,5-dimethylbenzylbromide (prepared from 3,5-dimethylbenzyl alcohol and HBr) and 5 g (42.6 mmol) of $NH_4ClO_4$ was obtained 4.0 g of crude product. One recrystallization from warm $H_2O$, and drying over phosphorus pentoxide at 78 °C overnight yielded, 3.5 g (80%); mp 154-158 °C cap; UV $\lambda_{max}$ 259 nm (12,900) at pH 1; 259 (13,100) at pH 7; 258 (13,000) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR 1693, 1510, 1225, 1100 (broad), 890, 853, 638, 623 $cm^{-1}$; $^1H$ NMR

($Me_2SO$-$d_6$) $\delta$ 2.30 (s, 6, Ar-$CH_3$), 3.59, 3.69 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.0 Hz, $CH_2$-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.8 Hz, H-3'), 4.49 (br s, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.09 (br s, 1, OH-5'), 5.32 (s, 2, O$CH_2$Ar), 5.60 (br d, 1, OH-2'), 5.95 (d, 1, $J_{1',2'}$ = 5.38 Hz, H-1'), 7.11, 7.28 (2 s, 3, Ar-H), 8.82 (s, 1, H-8), 8.96 (s, 1, H-2), 9.72, 10.42 (2 br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{19}H_{24}ClN_5O_9 \cdot 0.625H_2O$: C, 44.47; H, 4.96; N, 13.65. Found: C, 44.46; H, 5.11; N, 13.74.

**1-(2,5-Dimethylbenzyloxy)adenosine, Perchloric Acid Salt (2d).** The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt (2a) was repeated with the following quantities: 1.5 g (5.32 mmol) of adenosine-$N^1$-oxide, 2 mL of 2,5-dimethylbenzyl bromide (prepared from 2,5-dimethylbenzyl alcohol and HBr), and 3 g of $NH_4ClO_4$. After one recrystallization from $H_2O$ and drying at 78 °C over phosphorus pentoxide overnight an analytical sample was obtained; yield, 1.8 g (67%); mp 117-123 °C cap; UV $\lambda_{max}$ 259 nm (13,100) at pH 1; 259 (13,200) at pH 7; 258 (13,200) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR 1688, 1508, 1415, 1225, 1100 (broad), 915, 900, 880, 875, 825, 685, 655, 622 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 2.26, 2.39 (2 s, 6, Ar-$CH_3$), 3.58, 3.68 (2 m, 2, $J_{4,5'a}$ = $J_{4',5'b}$ = 3.8 Hz, $J_{5'a,5'b}$ = 12.1 Hz, $CH_2$-5'), 3.99 (apparent q, 1, H-4'), 4.15 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.48 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.09 (br s, 1, OH-5'), 5.32 (br s, 1, OH-3'), 5.41 (s, 2, O$CH_2$Ar), 5.59 (apparent d, 1, OH-2'), 5.93 (d, 1, $J_{1',2'}$ = 5.37 Hz, H-1'), 7.18, 7.20, 7.30 (m, 3, H-Ar), 8.65 (s, 1, H-2), 8.82 (s, 1, H-8), 9.75, 10.45 (2 br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{19}H_{24}ClN_5O_9 \cdot H_2O$: C, 43.89; H, 5.04; N, 13.47. Found: C, 43.96; H, 5.12; N, 13.58.

**1-(2,4-Dimethylbenzyloxy)adenosine, Perchloric Acid Salt (2e).** The procedure of 1-(2-cyanobenzyloxy)adenosine perchloric acid salt (2a) was repeated using the following quantities: 2.0 g (7.09 mmol) of adenosine-$N^1$-oxide, 3 mL of 2,4-dimethylbenzylbromide, and 4 g of $NH_4ClO_4$. One recrystallization from $H_2O$ and drying over phosphorus pentoxide at 78 °C for 6 h yielded, 1.1 g (31%); mp 120-130 °C cap; UV $\lambda_{max}$ 259 nm (13,300) at pH 1; 259 (13,400) at pH 7; 258 (13,200) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR 1689, 1615, 1510, 1430, 1220, 1100 (broad), 895, 645, 623 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 2.31, 2.42 (2 s, 6, Ar-$CH_3$), 3.57, 3.67 (2 m, 2, $CH_2$-5'), 3.98 (apparent q, 1, H-4'), 4.15 (apparent t, 1, H-3'), 4.48 (apparent t, 1, H-2'), 5.09 (br s, 1, OH-5'), 5.33 (br s, 1, OH-3'), 5.40 (s, 2, O$CH_2$Ar), 5.60 (br s, 1, OH-2'), 5.91 (d, 1, $J_{1',2'}$ = 5.35 Hz, H-1'), 7.03, 7.15, 7.31 (m, 3, H-Ar), 8.52 (s, 1, H-2), 8.82 (s, 1, H-8), 9.76, 10.45 (2 br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{19}H_{24}ClN_5O_9 \cdot 0.75H_2O$: C, 44.28; H, 4.99; N, 13.59. Found: 44.38; H, 4.90; N, 13.65.

**1-(2-Methoxybenzyl)adenosine, Perchloric Acid Salt (2f).** In a 100-mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate drying tube was placed 2.5 g (8.83 mmol) of adenosine-$N^1$-oxide (1), 40 mL of molecular sieve (4A) dried *N,N*-dimethylacetamide (DMAC), and 5 g of 2-methoxybenzyl bromide (prepared from 2-methoxybenzyl alcohol and HBr). The mixture was stirred at room temperature for 2 h after complete solution was achieved. The reaction solution was poured into 300-500 mL of anhydrous ether with slight swirling. After the product stuck to the walls of the flask the supernatant was decanted. The gummy residue was washed with 400 mL ether, decanted, and

again covered with 400 mL of ether and ground to a powder. The powder was allowed to settle, the ether was decanted, and the residue was dried in a stream of argon. The residue was dissolved in 25 mL of $H_2O$ and added with stirring to a warm solution of 5 g (42.6 mmol) of ammonium perchlorate, the solution was warmed, filtered, chilled in an ice bath and scratched to induce crystallization. The product was collected after 2 h in the ice bath, washed with a little $H_2O$ and dried; crude yield 4.2 g. The product was dissolved in about 350 mL hot EtOH, treated with silica gel and filtered through a layer of silica gel. The clear solution was slowly diluted with ØH until cloudy, chilled overnight, and the precipitate was collected. This product still contained $NH_4^+$ according to the $^1H$ NMR spectrum. However, a second crop obtained from the filtrate which was washed with ether and dried at 56 °C over phosphorus pentoxide overnight was found to be free of $NH_4^+$. The yield was 900 mg (20%); mp 157-162 °C cap; UV $\lambda_{max}$ 259 nm (12,800) at pH 1; 259 (12,600) at pH 7; 259 (13,000) at pH 13; MS (FAB) *m/e* 404 (M + 1); IR 1684, 1605, 1505, 1500, 1250, 1225, 1100 (broad), 1025, 1015, 860, 624 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.65 (s, 3, $OCH_3$), 3.57, 3.68 (2 m, 2, $CH_2$-5′), 3.99 (apparent q, 1, H-4′), 4.15 (apparent q, 1, H-3′), 4.47 (apparent q, 1, H-2′), 5.18 (apparent t, 1, OH-5′), 5.31 (apparent d, 1, OH-3′), 5.42 (s, 2, $OCH_2Ar$), 5.59 (apparent d, 1, OH-2′), 5.93 (d, 1, H-1′), 7.02 (m, 1, Ar-H-4,5), 7.48 (m, 2, Ar-H-3,6), 8.65 (s, 1, H-2), 8.80 (s, 1, H-8), 9.54, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{18}H_{22}ClN_5O_{10}\cdot 0.25(C_2H_5)_2O$: C, 43.68; H, 4.73; N, 13.41. Found: C, 43.72; H, 4.56; N, 13.34.

**1-Benzyloxyadenosine, Perchloric Acid Salt (2g).** The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt (**2a**) was followed using the following proportions: 2.5 g (8.83 mmol) of adenosine-$N^1$-oxide (**1**), 50 mL of dry DMAC, 4.5 g of benzyl bromide, and 5 g of $NH_4ClO_4$. One recrystallization from $H_2O$, and drying at 78 °C for 5 h over phosphorus pentoxide yielded 3.1 g (74%); mp 150-154 °C cap (dec); UV $\lambda_{max}$ 259 nm (13,100) at pH 1; 259 (13,200) at pH 7; 257 (13,100) at pH 13; MS (FAB) *m/e* 374 (M + 1); IR 1686, 1515, 1415, 1230, 1100 (broad), 755, 622 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.58, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.1 Hz, $CH_2$-5′), 3.99 (apparent q, 1, H-4′), 4.15 (apparent q, 1, $J_{3',4'}$ = 3.9 Hz, H-3′), 4.49 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-4′), 5.18 (apparent t, 1, $J_{5',5'\text{-OH}}$ = 5.1 Hz, OH-5′), 5.33 (d, 1, $J_{3',3'\text{-OH}}$ = 5.1 Hz, OH-3′), 5.42 (s, 2, $OCH_2Ar$), 5.60 (d, 1, $J_{2',2'\text{-OH}}$ = 6.1 Hz, OH-2′), 5.94 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1′), 7.48, 7.66 (2 m, 5, H-Ar), 8.82 (s, 1, H-8), 8.97 (s, 1, H-2). *Anal.* Calcd for $C_{17}H_{20}ClN_5O_9\cdot H_2O\cdot 0.10Et_2O$: C, 41.86; H, 4.64; N, 14.03. Found: C, 42.00; H, 4.50; N, 14.12.

**1-(2,6-Difluorobenzyloxy)adenosine, Perchloric Acid Salt (2h).** The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was repeated with the following proportions: 2.5 g (8.83 mmol) of adenosine-$N^1$-oxide, 50 mL of dry DMAC, 5 g of 2,6-difluorobenzylbromide, and 5 g of $NH_4ClO_4$. One recrystallization from $H_2O$, and drying at 78 °C for 5 h over phosphorus pentoxide yielded 1.75 g (39%); mp 114-122 °C cap; UV $\lambda_{max}$259 nm (14,000) at pH 1; 259 (13,900) at pH 7; 257 (13,400) at pH 13; MS (FAB) *m/e* 410 (M + 1); IR 1685, 1629, 1515, 1476, 1415, 1405, 1245, 1230, 1100 (broad), 920, 910, 800, 675, 622 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.58, 3.68 (2 m, 2, $J_{4',5'a}$

= 3.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.1 Hz, $CH_2$-5'), 3.99 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.49 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.10 (br s, 1, OH-5'), 5.33 (br s, 1, OH-3'), 5.57 (s, 2, $OCH_2Ar$), 5.62 (apparent d, 1, OH-2'), 5.94 (d, 1, H-1'), 7.23 (t, 2, H-Ar-3,5), 7.63 (m, 1, H-Ar-4), 8.83 (s, 1, H-8), 8.87 (s, 1, H-2), 9.83, 10.48 (2 br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{17}H_{18}ClF_2N_5O_9 \cdot H_2O$: C, 38.68; H, 3.82; N, 13.27. Found: C, 38.81; H, 3.81; N, 13.24.

**1-(3,5-Difluorobenzyloxy)adenosine, Perchloric Acid Salt (2i).** The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt (2a) was followed using these proportions: 2.5 g (8.83 mmol) of adenosine-$N^1$-oxide (1), 50 mL of dry DMAC, 5 g of 3,5-difluorobenzyl bromide, and 5 g of $NH_4ClO_4$. One recrystallization from $H_2O$, and drying at 78 °C for 5 h over phosphorus pentoxide yielded 2.0 g (44%); mp 129-134 °C cap; UV $\lambda_{max}$ 259 nm (13,600) at pH 1; 259 (13,500) at pH 7; 257 (12,700) at pH 13; MS (FAB) *m/e* 410 (M + 1); IR 1697, 1686 (sh), 1630, 1605, 1455, 1380, 1330, 1230, 1100 (broad), 870, 860 (sh), 845, 665, 624 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.59, 3.70 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, $CH_2$-5'), 4.01 (apparent q, 1, H-4'), 4.17 (apparent d, 1, $J_{3',4'}$ = 3.8 Hz, OH-3'), 4.50 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.10 (br s, 1, OH-5'), 5.34 (apparent d, 1, H-3), 5.40 (s, 1, $OCH_2Ar$), 5.61 (apparent d, 1, $J_{2',2'\text{-OH}}$ = 6.1 Hz, OH-2'), 5.96 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.39 m, 1, H-Ar-4), 7.50 (m, 2, H-Ar-2,6), 8.83 (s, 1, H-8), 9.07 (s, 1, H-2), 9.78, 10.47 (2 br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{17}H_{18}ClF_2N_5O_9 \cdot 0.625H_2O$: C, 39.18; H, 3.72; N, 13.44. Found: C, 39.22; H, 3.74; N, 13.36.

**1-(2,5-Difluorobenzyloxy)adenosine, Perchloric Acid Salt (2j).** The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was repeated with the following proportions: 2.5 g (8.83 mmol) of adenosine-$N^1$-oxide (1), 50 mL dry DMAC, 5 g of α-bromo-2,5-difluorotoluene and 5 g of $NH_4ClO_4$. One recrystallization from $H_2O$, and drying at 78 °C for 5 h over phosphorus pentoxide yielded 3.4 g (76%); mp 108-118 °C cap; UV $\lambda_{max}$ 260 nm (13,800) at pH 1; 260 (13,800) at pH 7; 258 (13,200) at pH 13; MS (FAB) *m/e* 410 (M + 1); IR 1691, 1510, 1500, 1435, 1240, 1230, 1195, 1100 (broad), 975, 880, 735, 624 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.59, 3.70 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, $CH_2$-5'), 4.01 (apparent q, 1, H-4'), 4.17 (apparent q, 1, $J_{3',4'}$ = 3.8 Hz, H-3'), 4.50 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.11 (t, 1, $J_{5',5'\text{-OH}}$ = 5.3 Hz, OH-5'), 5.85 (d, 1, $J_{3',3'\text{-OH}}$ = 5.2 Hz, OH-3'), 5.49 (s, 2, $OCH_2Ar$), 5.63 (d, 1, $J_{2',2'\text{-OH}}$ = 6.1 Hz, OH-2'), 5.96 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.40, 7.64 (2 m, 3, H-Ar), 8.83 (s, 1, H-8), 8.89 (s, 1, H-2). *Anal.* Calcd for $C_{17}H_{18}ClF_2N_5O_9 \cdot 0.75H_2O$: C, 39.02; H, 3.76; N, 13.38. Found: C, 39.00; H, 3.76; N, 13.30.

**9-Methyladenine-$N^1$-oxide (4b).** In a 2-L round-bottomed flask closed with a calcium sulfate drying tube 9.5 g (63.8 mmol) of 9-methyladenine was suspended in 800 mL of methanol. *m*-Chloroperoxybenzoic acid (16.5 g, 76.6 mmol) was added to the well stirred mixture in 7 portions at 15 min intervals. The reaction mixture was stirred an additional 4 h then poured into 4 L of ethyl acetate and stirred until the peroxide had decomposed. The product was collected by filtration, washed with ethyl acetate and dried; crude yield, 5.3 g. The filtrate was evaporated *in vacuo* and the residue

was triturated with ethyl acetate, the product was collected by filtration, washed with ethyl acetate, and dried, crude yield of second crop, 5.2 g.

After 1.5 g of the first crude product was recrystallized from EtOH and dried 15 h at 78 °C, 750 mg of pure product was obtained; mp >300 °C; UV $\lambda_{max}$ 259 nm (11,300) at pH 1; 262 (7,700) at pH 7; 268 (8,100) at pH 13; MS (FAB) *m/e* 166 (M + 1); IR 1678, 1511, 1233, 1150, 1039, 692, 438 $cm^{-1}$; $^1H$ NMR ($D_2O$) $\delta$ 3.84 (s, 3, $CH_3$), 8.17 (s, 1, H-2), 8.57 (s, 1, H-8). *Anal.* Calcd for $C_6H_7N_5O$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.62; H, 4.30; N, 42.36.

**9-Benzyl-1-(4-methylbenzyloxy)adenine, Perchloric Acid Salt (5a).** 9-Benzyladenine-$N^1$-oxide (1.5 g, 6.22 mmol) was suspended with stirring in 30 mL of dry *N,N*-dimethylacetamide, protected from moisture with a calcium sulfate tube, and α-bromo-p-xylene (3.5 g, 18.7 mmol) was added. The mixture was stirred 24 h (complete solution within 4 h), poured into 800 mL ether, the ether solution was decanted and the precipitate was washed with 2 x 400 mL of ether and dried in a stream of nitrogen. The residue was dissolved in 75 mL $H_2O$ and 50 mL EtOH and a hot solution of 3 g of $NH_4ClO_4$ in 15 mL $H_2O$ was added. The reaction mixture was heated to dissolve the product, filtered, allowed to crystallize, collected and dried over phosphorus pentoxide 5 h at 78 °C; yield 2.65 g (95%); mp 190-194 °C cap; UV $\lambda_{max}$ 261 nm (12,900) at pH 1; 261 (13,100) at pH 7; 259 (13,600) at pH 13; MS (FAB) *m/e* 346 (M + 1); IR 1689, 1620, 1514, 1425, 1100 (broad), 725, 710, 622 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 2.33 (s, 3, $CH_3$Ar), 5.35 (s, 2, $OCH_2$Ar), 5.49 (s, 2, $NCH_2$Ar), 7.22-7.52 (3 m, 9, H-Ar), 8.69 (s, 1, H-8), 8.85 (s, 1, H-2), 9.67, 10.34 (2 br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{20}H_{20}ClN_5O_5 \cdot 0.125(C_2H_5)_2O$: C, 54.10; H, 4.71; N, 15.39. Found: C, 54.28; H, 4.80; N, 15.26.

**9-Methyl-1-(3-methylbenzyloxy)adenine, Perchloric Acid Salt (5b).** In a 100-mL round-bottomed flask equipped with a calcium sulfate drying tube was placed 1 g (6.06 mmol) of 9-methyladenine-$N^1$-oxide and 20 mL of *N,N*-dimethylacetamide (DMAC). With good stirring 2.8 g (15.15 mmol) of α-bromo-*m*-xylene was added and the mixture was stirred at room temperature for 24 h. TLC in 4:1 acetonitrile 1N $NH_4OH$ indicated no starting material. The reaction mixture was poured into 800 mL of anhydrous ether. After the salt settled the ether solution was decanted. The residue was washed with 2 x 500 mL ether and the residue dried in a stream of $N_2$. The residue was dissolved in 25 mL $H_2O$-50 mL EtOH. A hot solution of 2 g $NH_4ClO_4$ dissolved in 25 mL hot water was added to the aqueous EtOH solution, and this solution was filtered, and allowed to crystallize. The product was collected, washed with $H_2O$ and dried 18 h at 78 °C over phosphorus pentoxide, yield 1.65 g (74%); UV $\lambda_{max}$ 261 nm (12,300) at pH 1; 260 (12,700) at pH 7; 258 (12,800) at pH 13; MS (FAB) *m/e* 270 (M + 1); IR 1686, 1525, 1410, 1385, 1230, 1100 (broad), 793, 692, 644, 623 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 2.34 (s, 3, $CH_3$Ar), 3.83 (s, 3, $CH_3$-9), 5.37 (s, 2, $OCH_2$Ar), 7.28-7.42 (m, 3, Ar-H-4,5,6), 7.48 (s, 1, Ar-H-2), 8.50 (s, 1, H-8), 8.89 (s, 1, H-2), 9.64, 10.29 (2 br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{14}H_{16}ClN_5O_5 \cdot 0.125EtOH$: C, 45.58; H, 4.50; N, 18.65. Found: 45.68; H, 4.41; N, 18.80.

**9-Methyl-1-(2-methylbenzyloxy)adenine, Perchloric Acid Salt (5c).** The procedure of 9-methyl-1-(3-methylbenzyloxy)adenine, perchloric acid salt was repeated using the same amounts. After drying the product at 78 °C for 18 h over phosphorus pentoxide a pure specimen was obtained, yield, 1.5 g

(68%); mp 202-204 °C cap; UV $\lambda_{max}$ 261 nm (12,400) at pH 1; 261 (12,000) at pH 7; 259 (12,300) at pH 13; MS (FAB) *m/e* 270 (M + 1); IR 1689, 1526, 1410, 1100 (broad), 768, 749, 654, 622 $cm^{-1}$, $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 2.46 (s, 3, $CH_3Ar$), 3.83 (s, 3, $CH_3$-9), 5.45 (s, 2, $OCH_2Ar$), 7.20-7.44 (3 m, 4, *H*-Ar), 8.49 (s, 1, H-2), 8.51 (s, 1, H-8), 9.71, 10.36 (2 br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{14}H_{16}ClN_5O_5$: C, 45.47; H, 4.36; N, 18.94. Found: C, 45.53; H, 4.38; N, 18.92.

**8-Bromoadenosine-$N^1$-oxide (7).**[1] The procedure used for adenosine-$N^1$-oxide was followed using the following proportions: 2.0 g (5.8 mmol) of 8-bromoadenosine, 175 mL of MeOH, and 1.5 g (8.7 mmol) of *m*-chloroperoxybenzoic acid (MCPBA). The reaction was followed by TLC and two additional portions of MCPBA were added until little starting material remained. The reaction mixture was poured into 1 L of ethyl acetate and stirred 3 h to decompose the peroxide. The solution was concentrated to about 50 mL, the product was collected, washed with ethyl acetate and dried: 1.76 g. In order to remove small amounts of starting material, the sample was treated with MeOH and $CHCl_3$/MeOH (5:1) and passed through a flash column of 200 g of silica gel. The appropriate fractions identified by TLC were combined and evaporated. The residue was recrystallized from MeOH; yield, 490 mg (23%); mp 180-190 °C cap (dec); UV $\lambda_{max}$ 263 nm (15,300), 214 (27,700) at pH 1; 298 (2,700), 265 (10,500), and 237 (40,400) at pH 7; 315 (5,700), 278 (9,000), and 236 (23,100) at pH 13; MS (FAB) *m/e* 362 (M + 1); IR 1678, 1466, 1295, 1275 (sh), 1270, 1142, 1100, 1075, 1070 (sh), 1057, 1051, 1025 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.49, 3.64 (2 m, 2, $J_{5'a,5'b}$ = 11.8 Hz, $CH_2$-5'), 3.91 (apparent q, 1, $J_{4',5'a}$ = 5.7 Hz, $J_{4',5'b}$ = 4.9 Hz, H-4), 4.21 (apparent q, 1, $J_{3',4'}$ = 3.4 Hz, H-3'), 4.83 (t, 1, $J_{5'a,5'\text{-OH}}$ = 6.5 Hz, $J_{5'b,5'\text{-OH}}$ = 5.4 Hz, OH-5'), 5.09 (q, 1, $J_{2',3'}$ = 5.3 Hz, H-2'), 5.26 (d, 1, $J_{3',3'\text{-OH}}$ = 5.0 Hz, OH-3'), 5.49 (d, 1, $J_{2',2'\text{-OH}}$ = 6.0 Hz, OH-2'), 5.81 (d, 1, $J_{1',2'}$ = 6.1 Hz, H-1'), 8.65 (s, 1, H-2). *Anal.* Calcd for $C_{10}H_{12}BrN_5O_5$·0.10MeOH: C, 33.20; H, 3.42; N, 19.17. Found: C, 33.38; H, 3.37; N, 19.16.

**8-Bromo-1-(3-methylbenzyloxy)adenosine, Perchloric Acid Salt (8).** One gram (2.76 mmol) of 8-bromoadenosine-$N^1$-oxide (7) was suspended in 10 mL DMAC with stirring and 1.37 g (7.41 mmol) of 3-methylbenzylbromide was added. The mixture went into solution in less than 10 min and was stirred 2.5 h. The solution was poured into 400 mL ether, allowed to settle, decanted, and washed with 2 x 250 mL more ether. After the last portion of ether was decanted and the residue was dried in a stream of argon, dissolved in a minimum of $H_2O$ and added 650 mg (5.56 mmol) of $NH_4ClO_4$. The mixture was warmed to effect solution, filtered, scratched and chilled. The product was collected, washed with a little $H_2O$ and dried for 5 h at 78 °C over phosphorus pentoxide; yield, 1.1 g (71%); mp 151-153 °C cap, 160 °C dec; UV $\lambda_{max}$ 265 nm (16,500) at pH 1; 264 (15,800) at pH 7; 260 (13,700) at pH 13; MS (FAB) *m/e* 466 (M + 1); IR 1685, 1475, 1410, 1300, 1100 (broad), 985, 890, 880, 800, 765, 623, 610 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 2.35 (s, 3, $CH_3Ar$), 3.51, 3.67 (2 m, 2, $J_{4',5'a}$ = 5.6 Hz, $J_{4',5'b}$ = 5.4 Hz, $J_{5'a,5'b}$ = 11.7 Hz, $CH_2$-5'), 3.96 (apparent q, 1, H-4'), 4.22 (apparent t, 1, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.96 (t, 1, $J_{2',3'}$ = 5.3 Hz, H-2'), 5.36 (s, 2, $OCH_2Ar$), 5.90 (d, 1, $J_{1',2'}$ =

6.0 Hz, H-1'), 7.28-7.50 (m, 4, H-Ar), 9.01 (s, 1, H-2), 9.89, 10.57 (br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{18}H_{21}BrClN_5O_9 \cdot 0.05NH_4ClO_4$: C, 37.75; H, 3.73; N, 12.35. Found: C, 37.79; H, 3.74; N, 12.48.

**9-β-D-Arabinofuranosyladenine-$N^1$-oxide (10).** The procedure used for adenosine-$N^1$-oxide (1) was followed using the following proportions: 930 mg (3.48 mmol) 9-β-D-arabinofuranosyladenine, 100 mL MeOH and 900 mg *m*-chloroperoxybenzoic acid (MCPBA). Poured into 500 mL of ethyl acetate, stirred 4 h, collected the product, washed thoroughly with ethyl acetate and dried: crude yield, 980 mg. The product was dissolved in 40 mL $H_2O$-20 mL hot EtOH, filtered and diluted with 1 L of EtOH. The white product was collected, washed with EtOH and dried at 78 °C for 5 h over phosphorus pentoxide: yield, 840 mg (85%); mp >250 °C cap; UV $\lambda_{max}$ 258 nm (12,600), 213 nm (28,300) at pH 1; 293 (2,700), 261 (8,500), 232 (42,200) at pH 13; MS (FAB) *m/e* 284 (M + 1); IR 1669, 1505, 1425, 1385, 1210, 1135 (sh), 1130, 1115, 1083, 1040, 1035 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) δ 3.66 (m, 1, $CH_2$-5'), 3.80 (apparent q, 1, H-4'), 4.12 (apparent q, 1, H-3'), 4.19 (apparent q, 1, H-2'), 5.10 (t, 1, OH-5'), 5.17 (d, 1, OH-3'), 5.69 (d, 1, OH-2'), 6.22 (d, 1, H-1'), 8.37 (s, 1, H-2), 8.63 (s, 1, H-8). *Anal.* Calcd for $C_{10}H_{13}N_5O_5 \cdot 0.05EtOH$: C, 42.48; H, 4.69; N, 24.53. Found: C, 42.59; H, 4.69; N, 24.46.

**6-Methylamino-9-β-D-ribofuranosylpurine-$N^1$-oxide (12).** The procedure of adenosine-$N^1$-oxide (1) was followed using some of the modifications used in 8-bromoadenosine-$N^1$-oxide (7). The following proportions were used: 2.0 g (7.12 mmol) 6-methylaminopurine riboside, >2.3 g (10.7 mmol) of *m*-chloroperoxybenzoic acid (MCPBA), and 80 mL of MeOH. Since the reaction did not want to go to completion, the reaction was stirred over two nights and several additional (unweighed) portions of MCPBA were added. The crude product was passed through a flash column of 400 g of silica gel and developed with chloroform/ethanol (5:1) and eluted with $CHCl_3$/EtOH (3:1) and $CHCl_3$/EtOH (2:1). The appropriate fractions, as identified by TLC, were combined and evaporated. The product was dried at 78 °C for 5 h over phosphorus pentoxide; yield 620 mg (30%); mp shrinks 125-130 °C; UV $\lambda_{max}$ 215 nm (25,800), 262 nm (13,900) at pH 1; 235 (37,900), 270 (9,800) at pH 7; 235 (38,000), 271 (9,500) at pH 13; MS (FAB) *m/e* 298 (M + 1); IR 1656, 1580, 1500, 1425, 1215, 1090 (broad), 1050, 1025 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) δ 3.45 (apparent d, 3, $NCH_3$), 3.54, 3.66 (2 m, 2, $J_{4',5'a}$ = 4.0 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.0 Hz, $CH_2$-5'), 3.93 (apparent q, 1, H-4'), 4.16 (apparent q, 1, $J_{3',4'}$ = 3.8 Hz, H-3'), 4.51 (apparent q, 1, $J_{2',3'}$ = 5.0 Hz, H-2'), 5.07 (t, 1, $J_{5',5'\text{-OH}}$ = 5.5 Hz, OH-5'), 5.24 (d, 1, $J_{3',3'\text{-OH}}$ = 5.1 Hz, OH-3'), 5.59 (d, 1, $J_{2',2'\text{-OH}}$ = 5.9 Hz, OH-2'), 5.88 (d, 1, $J_{1',2'}$ = 5.5 Hz, H-1'), 8.39 (br d, 1, $CH_3N$-*H*), 8.55 (s, 1, H-2), 8.62 (s, 1, H-8). *Anal.* Calcd for $C_{11}H_{15}N_5O_5 \cdot 0.25CHCl_3 \cdot 0.30EtOH$: C, 42.03; H, 5.08; N, 20.68. Found: C, 42.12; H, 5.02; N, 20.74.

**6-Methylamino-1-(3-methylbenzyloxy)-9-β-D-ribofuranosylpurine, Perchloric Acid Salt (13a).** The basic procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was used with the following proportions: 1.65 g (5.55 mmol) of $N^6$-methyladenosine-$N^1$-oxide, 30 mL dry DMAC, 3.1 g (16.6 mmol) of α-bromo-*m*-xylene, and 2 g of $NH_4ClO_4$. One recrystallization from 10 mL of hot $H_2O$ and drying at 78 °C for 5 h over phosphorous pentoxide: yield, 1.06 g (38%); mp 94-102 °C; UV $\lambda_{max}$ 263 nm (13,500) at pH 1; 263 (13,600) at pH 7; 261 (12,600) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR 1662, 1595,

1509, 1425, 1350, 1220, 1100 (broad), 975, 870, 690, 665, 624 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 2.35 (s, 3, $CH_3Ar$), 3.56 (s, 3, $CH_3N$), 3.56, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, $CH_2$-5'), 3.99 (apparent q, 1, H-4'), 4.15 (apparent q, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.48 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.10 (apparent t, 1, OH-5'), 5.43 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 5.2 Hz, OH-3'), 5.47 (s, 2, $OCH_2Ar$), 5.62 (d, 1, $J_{2',2'\text{-OH}}$ = 6.0 Hz, OH-2'), 5.96 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.27-7.47 (m, 4, H-Ar), 8.83 (s, 1, H-8), 8.95 (s, 1, H-2), 9.82 (br s, 1, H-$CH_3\overset{\oplus}{N}H$). *Anal.* Calcd for $C_{19}H_{21}ClN_5O_9 \cdot 0.25H_2O$: C, 45.06; H, 4.88; N, 13.83. Found: C, 45.04; H, 4.92; N, 13.70.

**6-Methylamino-1-(2-methylbenzyloxy)-9-$\beta$-D-ribofuranosylpurine, Perchloric Acid Salt (13b).** The basic procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was used with the following proportions: 1.0 g (3.36 mmol) of $N^6$-methyladenosine-$N^1$-oxide, 10 mL DMAC, 1.86 g $\alpha$-bromo-*o*-xylene and 1.2 g of $NH_4ClO_4$. One recrystallization from 5 mL of $H_2O$ and drying at 78 °C for 16 h over phosphorus pentoxide yielded 310 mg (18%) of analytically pure product. Mp 174-177 °C; UV $\lambda_{max}$ 263 nm (12,900) at pH 1; 263 (13,200) at pH 7; 260 (11,700) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR 1667, 1595, 1505, 1425, 1100 (broad), 1020, 985, 895, 620 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 2.46 (s, 3, $CH_3Ar$), 3.59 (s, 3, $CH_3N$), 3.59, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.0 Hz, H-5'), 3.98 (apparent q, 1, H-4'), 4.14 (apparent q, 1, $J_{3',4'}$ = 4.4 Hz, H-3'), 4.47 (apparent q, 1, $J_{2',3'}$ = 5.1 Hz, H-2'), 5.10 (apparent t, 1, OH-5'), 5.33 (apparent d, 1, OH-3'), 5.46 (s, 2, $OCH_2Ar$), 5.61 (apparent d, 1, $J_{2',2'\text{-OH}}$ = 5.9 Hz, OH-2'), 5.94 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.20-7.46 (3 m, 4, H-Ar), 8.62 (s, 1, H-2), 8.85 (s, 1, H-8), 9.89 (br s, 1, H-$CH_3\overset{\oplus}{N}H$). *Anal.* Calcd for $C_{19}H_{24}ClN_5O_9 \cdot 0.3H_2O$: C, 44.98; H, 4.89; N, 13.81. Found: C, 44.86; H, 4.92; N, 13.94.

**6-Methylamino-1-(2,4-difluorobenzyloxy)-9-$\beta$-D-ribofuranosylpurine, Perchloric Acid Salt (13c).** The basic procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was used with the following proportions: 800 mg (2.69 mmol) of $N^6$-methyladenosine-$N^1$-oxide, 15 mL of dry DMAC, 1.68 g (8.07 mmol) of $\alpha$-bromo-2,4-difluorotoluene and 2 g of $NH_4ClO_4$. The white product began to crystallize as the solution cooled. After chilling, the product was collected, washed with a little $H_2O$, and dried at 78 °C for 5 h over phosphorus pentoxide: yield 500 mg (36%); mp 165-169 °C; UV $\lambda_{max}$ 263 nm (14,400) at pH 1; 263 (14,300) at pH 7; 260 (12,600) at pH 13; MS (FAB) *m/e* 424 (M + 1); IR 1671, 1595, 1510, 1505, 1100 (broad), 985, 860, 623 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.56 (s, 3, $CH_3N$), 3.56, 3.66 (2 m, 2, $J_{4',5'a}$ = $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 11.9 Hz, $CH_2$-5'), 3.99 (apparent q, 1, H-4'), 4.15 (apparent q, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.50 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.11 (apparent t, 1, $J_{5',5'\text{-OH}}$ = 5.2 Hz, OH-5'), 5.84 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 5.2 Hz, OH-3'), 5.49 (s, 2, $OCH_2Ar$), 5.62 (d, 1, $J_{2',2'\text{-OH}}$ = 6.1 Hz, OH-2'), 5.96 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.23, 7.42 (2 m, 2, H-Ar-3,5), 7.73 (m, 1, H-Ar-6), 8.85 (apparent d, 2, H-8,2), 9.90 (br s, 1, H-$CH_3\overset{\oplus}{N}H$). *Anal.* Calcd for $C_{18}H_{20}ClF_2N_5O_9 \cdot 0.50H_2O$: C, 40.57; H, 3.97; N, 13.14. Found: C, 40.56; H, 3.80; N, 13.08.

**2,6-Diamino-9-$\beta$-D-ribofuranosylpurine-$N^1$-oxide (15).** To a well stirred mixture of 780 mg (2.77 mmol) of 2,6-diaminopurineriboside in 100 mL of methanol in a 250-mL round-bottomed flask and

protected from moisture by a calcium sulfate drying tube was added 780 mg of *m*-chloroperoxybenzoic acid (MCPBA) in portions over 1-1.5 h. After 1.5 h of stirring ~200 mg more of MCPBA was added and the mixture was stirred overnight. Thin-layer chromatography indicated little or no starting material remaining. The reaction mixture was poured into 700 mL of EtOAc and stirred until the peroxy acid had decomposed. The product was collected, washed with EtOAc and dried, crude yield 750 mg.

The product was dissolved in 400 mL of hot EtOH, filtered, and chilled. The cold solution was diluted with heptane and stored in the freezer until crystallization was complete. The yellow-beige product was collected, washed with heptane and dried at 78 °C for 5 h over phosphorus pentoxide: yield, 630 mg (76%); mp >250 °C dec. UV $\lambda_{max}$ 213 nm (26,200), 253 (11,100), 289 (10,200) at pH 1; 211 (16,200), 233 (33,700), 260 (9,000), 292 (6,900) at pH 7; 233 (31,700), 262 (9,200), 288 (7,200) at pH 13; IR 1672, 1633, 1618, 1420, 1225, 1125, 1100, 1055, 1040 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.56, 3.64 (2 m, 2, $J_{4',5'a}$ = 4.2 Hz, $J_{4',5'b}$ = 4.1 Hz, $J_{5'a,5'b}$ = 12.0 Hz, H-5'), 3.89 (apparent q, 1, H-4'), 4.10 (apparent q, 1, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.45 (apparent q, 1, $J_{2',3'}$ = 5.0 Hz, H-2'), 5.02 (apparent t, 1, $J_{5',5'\text{-OH}}$ = 5.5 Hz, OH-5'), 5.15 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 4.8 Hz, OH-3'), 5.43 (d, 1, $J_{2',2'\text{-OH}}$ = 6.0 Hz, OH-2'), 5.25 (d, 1, $J_{1',2'}$ = 5.9 Hz, H-1'), 7.23 (br s, 2, H-$NH_2$), 8.15 (s, 1, H-8). *Anal.* Calcd for $C_{10}H_{14}N_6O_5 \cdot 0.60H_2O \cdot 0.30EtOH$: C, 39.43; H, 5.26; N, 26.03. Found: C, 39.42; H, 5.10; N, 25.91.

**2,6-Diamino-1-(3-methylbenzyloxy)-9-β-D-ribofuranosylpurine, Perchloric Acid Salt (16).** The basic procedure for 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was used with the following proportions: 750 mg (2.52 mmol) of 2,6-diamino-9-β-D-ribofuranosylpurine-$N^1$-oxide, 10 mL of DMAC, 960 mg (5.18 mmol) of α-bromo-*m*-xylene, and 885 mg of $NH_4ClO_4$. The product which crystallized from the reaction mixture, was collected, washed with a little $H_2O$ and dried at 78 °C for 5 h over phosphorus pentoxide: yield, 780 mg (62%); mp 152-156 °C; UV $\lambda_{max}$ 256 nm (10,900), 295 nm (9,200) at pH 1; 256 (11,200), 295 (9,300) at pH 7; 268 (16,000) at pH 13; MS (FAB) *m/e* 403 (M + 1); IR 1696, 1644, 1634, 1594, 1420, 1100 (broad), 860, 624 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 2.30 (s, 3, $CH_3$-Ar), 3.55, 3.64 (2 m, 2, $J_{4',5'a}$ = $J_{4',5'b}$ = 4.1 Hz, $J_{5'a,5'b}$ = 12.0 Hz, H-5'), 3.91 (apparent q, 1, H-4'), 4.10 (apparent q, 1, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.40 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.13 (apparent t, 1, OH-5'), 5.18-5.28 (2 m, 2, O$CH_2$Ar), 5.23 (apparent d, 1, OH-3'), 5.47 (apparent d, 1, OH-2'), 5.71 (d, 1, $J_{1',2'}$ = 5.8 Hz, H-1'), 7.22-7.43 (m, 4, H-Ar), 8.19 (br s, 2, $NH_2$-2), 8.35 (s, 1, H-8), 9.03, 9.81 (2 br s, 2, H-$\overset{\oplus}{N}H_2$). *Anal.* Calcd for $C_{18}H_{23}ClN_6O_9 \cdot 0.50H_2O$: C, 42.23; H, 4.73; N, 16.42. Found: C, 42.36; H, 4.64; N, 16.30.

**7-Deazaadenosine-$N^1$-oxide (18).** The basic procedure for 2,6-diamino-9-β-D-ribofuranosylpurine-$N^1$-oxide was used with the following proportions: 1.0 g (3.76 mmol) of tubercidin (7-deazaadenosine), 960 mg of MCPBA and 100 mL of methanol. The reaction was poured into 800 mL of EtOAc, the precipitate which crystallized was collected, washed with EtOAc, and dried 5 h at 56 °C over phosphorus pentoxide: yield, 1.03 g (97%); mp >250 °C; UV $\lambda_{max}$ 210 nm (21,900), 223 (22,900), 272 (8,000) at pH 1; 234 (33,900), 271 (5,500), 303 (3,400) at pH 7; 234 (30,800), 273 (5,900), 305

(3,800) at pH 13; MS (FAB) *m/e* 283 (M + 1); IR 1729, 1655, 1502, 1240, 1120, 1084, 1047, 1025, 1000, 800, 745, 645 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.52, 3.60 (2 m, 2, H-5'), 3.88 (apparent q, 1, H-4'), 4.07 (apparent d, 1, H-3'), 4.33 (apparent q, 1, H-2'), 5.10 (apparent t, 1, OH-5'), 5.17 (apparent d, 1, OH-3'), 5.43 (apparent d, 1, OH-2'), 6.00 (d, 1, H-1'), 6.68 (d, 1, H-7), 7.56 (d, 1, H-8), 8.05 (br s, 1, H-$NH_2$), 8.45 (s, 1, H-2). *Anal.* Calcd for $C_{11}H_{14}N_4O_5 \cdot 0.40EtOAc \cdot 0.10H_2O$: C, 47.40; H, 5.49; N, 17.54. Found: C, 47.41; H, 5.46; N, 17.39.

**1-Amino-6-iminopurine (19).** A stirred suspension of adenine (1.35 g, 10.0 mmol) in ethanol (250 mL) was treated with *o*-mesitylenesulfonylhydroxylamine (6.0 g, 28.0 mmol). After 1 h all of the suspended solid had dissolved, and stirring was continued for 0.5 h, and a white solid separated. The mixture was chilled in a dry ice-isopropanol bath, and the solid was collected, washed with cold methanol, and dried *in vacuo*: yield 1.93 g (55%) [a second crop was obtained from the filtrate, and was crystallized to give another isomer (by MS and TLC)]. The product (1.93 g) was crystallized from methanol to give 1.25 g (which still contained a trace of an impurity by TLC). This mesitylenesulfonate salt of 1-aminoadenine was dissolved in a solution of acetonitrile and 1*N* ammonium hydroxide (4:2), and evaporated with 6 g of silica gel (230-400 mesh, Aldrich) and then was chromatographed on a flash column (silica gel), and eluted with acetonitrile and 1*N* ammonium hydroxide (4:1). Fractions containing the product were combined, evaporated, and dried *in vacuo* to give the free base of 1-amino-6-iminopurine: 500 mg (93% recovery); mp 205-207 °C (dec); IR (KBr) (strong 1680-1625), 1545, 1470, 1425, 1375, 1335, 1185, 1175, 1120, 975, 645, 555. UV $\lambda_{max}$ 207 (21,320), 257 (10,500) at pH 1; 208 (19,400), 260 (9,700) at pH 7; 269 (12,700) at pH 13. $^1H$ NMR ($D_2O$) $\delta$ 8.04 (s, 1, H-3), 8.32 (s, 1, H-8). *Anal.* Calcd for $C_5H_6N_6 \cdot 0.86H_2O$: C, 36.25; H, 4.70; N, 50.74. Found: C, 36.56; H, 4.42; N, 50.57.

**1-Aminoadenosinium Mesitylene Sulfonate (20).** Freshly prepared *o*-mesitylenesulfonylhydroxylamine (6 g) was added to a solution of adenine (2.67 g) in methanol (200 mL). The solution was stirred at room temperature for 30 min and then immersed in a dry ice-isopropyl alcohol bath. The precipitate (2.7 g) was collected and dried; mp 178-182 °C dec; MS (FAB) 283 (M + 1); UV 202 (70,000), 258 (12,200); IR (KBr) 3282, 3149, 3650-2800 (broad, $NH_2$, NH, OH, $SO_3H$), 2930 (CH), 1692 ($SO_3H$), 1635, 1605 (aromatic), 1560, 1510, 1420, 1230, 1210, 1175, 1120, 1085, 1065, 1015, 905, 860 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 10.15-10.05 and 9.25-9.15 (br s, 2, C=NH and MesO*H*), 6.65-6.50 (br s, 2, $NH_2$), 5.95 (d, 1, $C_{1'}$-H, $J$ = 5 Hz), 4.52 (t, 1, $C_{2'}$-H), 4.18 (t, 1, $C_{3'}$-H), 4.0 (q, 1, $C_{4'}$-H), 3.64 (dq, 2, $C_{5'}$-H), 2.5 (s, 6, ortho protons of MesOH), 2.15 (s, 3, para protons of MesOH); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 151.4 (C-6), 148.9 (C-2, $^1J_{CH}$ = 218.8 Hz), 145.7 (C-4, $^3J_{C_4,H_8}$ = 13.15, $^3J_{C_4,H_2}$ = 5.1 Hz), 142.5 (C-8, $^1J_{C_8,H_8}$ = 217.8 Hz, $^3J_{C_8,H_{1'}}$ = 4.05 Hz), 142.2 (C-$SO_3H$), 136.3 (*p*-C-$CH_3$), 135.7 (*o*-C-$CH_3$), 129.7 (*m*-C-H), 118.5 (C-5), 87.7 ($C_{1'}$-H, $^1J_{C_{1'},H_{1'}}$ = 167.2), 85.8 (C-4'), 74.3 (C-2'), 70.0 (C-3'), 60.9 (C-5'), 22.6 (*o*-C-$CH_3$), 20.2 (*p*-C-$CH_3$). *Anal.* Calcd for $C_{19}H_{26}N_6SO_7$: C, 47.29; H, 5.43; N, 17.42. Found: C, 47.46; H, 5.54; N, 17.77.

**1-Aminoadenosine, Hydrochloride (21).** Freshly prepared *o*-mesitylenesulfonylhydroxylamine (6 g, 0.028 mol) was added to a solution of adenosine (2.67 g, 0.01 mol) in methanol (200 mL). The solution was stirred at 25 °C for 1 h, and was then chilled in a dry-ice/isopropyl alcohol bath. The solid was collected and dried *in vacuo*: yield 2.7 g (56%); mp 178-182 °C (dec). This product (1.8 g, 0.0037 mol) was passed through a Dowex 1-X2 ($Cl^-$ form) to get the chloride salt (1.15 g). The crude product was dissolved in a small amount of water, stirred with activated carbon and filtered. The clear solution was diluted with ethanol until cloudy and then added ether to aid crystallization. The mixture was stirred, and then chilled. The product was collected, washed with ether, and dried *in vacuo*: yield 777 mg (24%); mp 200-203 °C; MS (FAB) 283 (M + 1); IR (KBr) 3400-3050 (broad, NH, $NH_2$, DH's, HCl), 1780, 1500, 1425, 1410, 1165, 1030, 1000, 820, 730, 710, 700 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.58, 3.68 (2 m, 2, $CH_2$-5'), 3.99 (apparent q, 1, H-4'), 4.17 (apparent q, 1, H-3'), 4.52 (q, 1, H-2'), 5.16 (t, 1, 5'-OH), 5.35 (d, 1, 3'-OH), 5.68 (d, 1, H-1'), 6.74 (s, 2, $NH_2$-1), 8.68 (s, 1, H-8), 8.78 (s, 1, H-2), 9.39, 10.11 (2 br s, 2, H-$\overset{\oplus}{N}H_2$-6); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 60.83 (C-5'), 70.03 (C-3'), 74.35 (C-2'), 85.83 (C-4'), 87.66 ($^1J_{C_1',H_1'}$ = 166.3 Hz, C-1'), 118.48 ($^3J_{C_5,H_8}$ = 11.9 Hz, C-5), 142.60 ($J_{C_8,H_1'}$ = 3.9 Hz, $J_{C_8}$ = 218.0 Hz, C-8), 145.82 ($^3J_{C_4,H_8}$ = 131.1 Hz, $^3J_{C_4,H_2}$ = 5.3 Hz, $J_{C_4,H_1'}$ = 2.6 Hz, C-4), 148.82 ($^1J_{C_2,H_2}$ = 218.7 Hz, C-2), 151.39 ($^3J_{C_6,H_2}$ = 5.5 Hz, C-6). *Anal.* Calcd for $C_{10}H_{15}ClN_6O_4 \cdot 0.5H_2O$: C, 36.64; H, 4.92; N, 25.65. Found: C, 36.83, 36.79; H, 5.27, 5.21; N, 25.68, 25.54.

**1-Amino-7-deazainosine (24).** A solution of 7-deazainosine, 14, (534 mg, 2.0 mmol) in 1*N* sodium hydroxide (6 mL) was treated with a solution of hydroxylamine-*O*-sulfonic acid (340 mg, 3.00 mmol) in water (4 mL). The reaction solution was left in the refrigerator overnight. The solid that had formed was collected, and dried *in vacuo*: yield, 383 mg. This product was crystallized from water, and dried *in vacuo*: yield, 323 mg (57%); mp 220-222 °C dec. IR (KBr) 3430, 3310, 1665, 1495, 1420, 1226, 1085, 1055, 1030, 740 $cm^{-1}$. UV $\lambda_{max}$ 205 nm (20,730), 213 (20,710), 261 (6,610) at pH 1; 213 (20,630), 261 (6,580) at pH 7; 216 (17,750), 262 (6,500) at pH 13; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.56 (2 m, 2, $J_{4',5'a}$ = 4.0 Hz, $J_{4',5'b}$ = 4.1 Hz, $J_{5'a,5'b}$ = 11.9 Hz, $CH_2$-5'), 3.88 (q, 1, H-4'), 4.07 (q, 1, $J_{3',4'}$ = 4.2 Hz, H-3'), 4.31 (q, 1, $J_{2',3'}$ = 5.6 Hz, H-2'), 5.0 (t, 1, $J_{5',5'\text{-OH}}$ = 5.4 Hz, 5'-OH), 5.13 (d, 1, $J_{3',3'\text{-OH}}$ = 4.9 Hz, 3'-OH), 5.33 (d, 1, $J_{2',2'\text{-OH}}$ = 6.04 Hz, 2'-OH), 5.75 (s, 2, $NH_2$-1), 6.00 (s, 1, $J_{1',2'}$ = 6.1 Hz, H-1'), 6.57 (d, 1, $J_{H_7,H_8}$ = 3.6 Hz, H-7), 7.41 (d, 1, H-8), 8.23 (s, 1, H-2). *Anal.* Calcd for $C_{11}H_{14}N_4O$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.53; H, 5.17; N, 19.89.

**1-Aminoguanosine (26).** Guanosine hydrate (5.7 g, 20 mmol) was dissolved in 1*N* sodium hydroxide (60 mL), and was then treated with a solution of hydroxylamine-*O*-sulfonic acid (3.4 g, 30 mmol) in water (30 mL). The solution was stirred at room temperature for 15 min and a white solid began to separate. This mixture was stirred at room temperature overnight. The solid that formed was chilled, collected, washed with water, acetone, and dried under nitrogen: yield, 3.5 g (59%). This product was crystallized from dilute ammonium hydroxide followed by one crystallization from water. The product was dried *in vacuo* ($P_2O_5$): yield, 2.3 g (39%); mp 240 °C; IR (KBr) 3480, 3465, 3350,

3120, 1670, 1625, 1590, 1575, 1505, 1415, 1100, 1055, 1035, 1020. UV $\lambda_{max}$ 257 nm (11,093), 277 (8,029) at pH 1; 208 (15,086), 257 (11,093) at pH 7; 254 (12,931), 274 (sh) at pH 13; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 3.56 (2 m, 2, $CH_2$-5'), 3.77 (q, 1, H-4'), 4.09 (t, 1, H-3'), 4.92 (t, 1, H-2'), 5.70 (d, 1, H-1'), 7.10 (s, 2, $NH_2$-1), 7.95 (s, 1, H-8). *Anal.* Calcd for $C_{10}H_{14}N_6O_5$: C, 40.27; H, 4.73; N, 28.18. Found: C, 40.50; H, 4.77; N, 28.42.

**Ethyl 5-(2',4'-Difluorophenyl)pyrazole-3-carboxylate (29a).** Ethyl 4-(2',4'-difluorophenyl)-2,4-dioxobutyrate (13.0 g, 0.051 mol) was mixed with 150 mL water. Hydrazine hydrate (2.54 g, 0.051 mol) was slowly added with stirring, and then the mixture was stirred overnight at room temperature. The resulting light yellow powdery precipitate was filtered and dried, giving about 12 g of the crude product. The solid was chromatographed with silica gel (ether/petroleum ether, 2:3) yielding 9.8 g of the desired product as a white solid; mp 44-45 °C; MS (EI) *m/e* 252 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 14.14 (s, 1, NH) 7.98, 7.40, 7.25 (m, 3, PhH), 7.09 (d, $J$ = ~3.2 Hz, 1, pyr. H), 4.34 (q, 2, -O$CH_2$$CH_3$), 1.33 (t, 3, -OCH$_2$$CH_3$); IR (KBr) 3226, 3132, 3007, 1723, 1489, 1276, 1256, 1141, 1108, 996, 980, 842, 780 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 162.1 (dd, $^1J_{C_{4'},F_4}$ = 248.2 Hz, $^3J_{C_{4'},F_2}$ = 1.23 Hz, C4'), 160.3 (C=O), 159.2 (dd, $^1J_{C_{2'},F_2}$ = 251.2 Hz, $^3J_{C_{2'},F_4}$ = 12.2 Hz, C2'), 141.3 (C5), 138.8 (C3), 129.5 (dd, $^3J_{C_{6'},F_2}$ = 4.8 Hz, C6'), 115.6 (dd, $^2J_{C_{1'},F_2}$ = 12.7 Hz, $^4J_{C_{1'},F_4}$ = 3.3 Hz, C1'), 112.2 (dd, $^2J_{C_{5'},F_4}$ = 21.5 Hz, $^4J_{C_{5'},F_2}$ = 3.3 Hz, C-5'), 107.7 (d, $^4J_{C_4,F_2}$, C4), 104.8 (t, $^2J_{C_{3'},F_2}$ = $^2J_{C_{3'},F_4}$ = 26.0 Hz, C3'), 60.7 (O$CH_2$$CH_3$), 14.2 (-OCH$_2$$CH_3$). *Anal.* Calcd for $C_{12}H_{10}F_2N_2O_2$: C, 57.15; H, 4.00; N, 11.11. Found: C, 56.92; H, 4.16; N, 10.98.

**Ethyl 5-(2'-Pyridyl)pyrazole-3-carboxylate (29b).** Ethyl 4-(2-pyridyl)-2,4-dioxybutyrate (13.1 g, 0.059 mol) was mixed with 200 mL $H_2O$. Hydrazine hydrate (2.96 g, 0.059 mol) was slowly added with swirling, and the mixture was stirred overnight at room temperature. The resulting light brown solid was filtered, dried, filtered through silica gel with 9.5:1, $CHCl_3$:MeOH as solvent. Evaporation gave 9.0 g of a thick brown resin which solidified upon cooling. A 2.3 g portion of this solid was further washed with cold ether and filtered giving 1.6 g of the desired product as an off-white granular solid; mp 103-4 °C; MS (EI) *m/e* 217 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 14.19 (s, 1, NH), 8.64 (m, 1, C6'-H), 7.98 (m, 1, C3'-H), 7.90 (m, 1, C4'-H), 7.37 (br s, 2, C5'-H and C4-H), 4.32 (apparent q, 2, -O$CH_2$$CH_3$), 1.33 (t, 3, -OCH$_2$$CH_3$); IR (KBr) 3151, 3102, 2981, 1743, 1408, 1232, 1195, 1156, 1141, 1068, 1007, 766 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 160.5 (C=O), 147.8 (C6'), 147.8 (C2'), 145.6 (C5), 140.0 (C3), 139.5 (C4'), 123.9 (C5'), 121.0 (C6'), 147.8 (C2'), 145.6 (C5), 140.0 (C3), 139.5 (C4'), 123.9 (C5'), 121.0 (C3'), 107.1 (C4), 60.8 (-O$CH_2$$CH_3$), 14.2 (-OCH$_2$$CH_3$). *Anal.* Calcd $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.67; H, 5.24; N, 19.28.

**Ethyl 5-(3'-Pyridyl)pyrazole-3-carboxylate (29c).** Ethyl 4-(3'-pyridyl)-2,4-dioxybutyrate (12.3 g, 0.056 mol) was mixed with 150 mL $H_2O$. Hydrazine hydrate (2.8 g, 0.056 mol) was slowly added with swirling, and the mixture was stirred overnight at room temperature Four grams of the resulting light yellow solid was recrystallized from EtOH giving 1.5 g yellow needles (and a second crop, 1.4 g of a yellow solid); mp 162-163 °C; MS (EI) *m/e* 217 (M); $^1$H NMR ($Me_2SO$-$d_6$, tautomeric mixture) $\delta$ 14.22,

14.11 (s, 1, H-2), 9.10, 9.06 (2 s, 1, H-2'), 8.56 (m, 1, H-6'), 7.50 (m, 1, H-5'), 7.46, 7.35 (2 s, 1, H-4), 4.35 (m, 2, -OC$H_2$CH$_3$), 1.34 (m, 3, -OCH$_2$C$H_3$); IR (KBr) 3107, 2988, 1725, 1332, 1284, 1254, 1187, 1034, 959, 814 cm$^{-1}$; $^{13}$C NMR (Me$_2$SO-$d_6$) $\delta$ 159.5 (C=O), 144.7 (C-5), 143.2 (C-2'), 140.8 (C-6'), 138.9 (C-4'), 137.6 (C-3), 130.3 (C-3'), 126.6 (C-5'), 107.1 (C-4), 61.1 (-OC$H_2$CH$_3$), 14.2 (-OCH$_2$C$H_3$). *Anal.* Calcd for C$_{11}$H$_{11}$N$_3$O$_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.70; H, 5.27; N, 19.48.

**Ethyl 5-(4'-Pyridyl)pyrazole-3-carboxylate (29d).** Ethyl 4-(4'-pyridyl)-2,4-dioxybutyrate (11.9 g, 0.054 mol) was mixed with 150 mL $H_2O$. Hydrazine hydrate (2.8 g, 0.056 mol) was slowly added with swirling, and the mixture was stirred overnight at room temperature. Two grams of the resulting light yellow solid was chromatographed through silica gel with 3:1 EtOAc:petroleum ether giving 1.4 g of a white granular solid: mp 211-213 °C; MS (EI) 217 (M); $^1$H NMR (Me$_2$SO-$d_6$) $\delta$ 14.34 (br s, 1, H-2), 8.14 (d, $J$ = 6 Hz, 2, H-2'), 7.86 (m, 2, H-3'), 7.52 (s, 1, H-4), 4.35 (q, 2, -OC$H_2$CH$_3$), 1.34 (t, 3, -CH$_3$); IR (KBr) 1727, 1610, 1448, 1283, 1249, 1207, 1154, 1005, 957, 840 cm$^{-1}$; $^{13}$C NMR (Me$_2$SO-$d_6$) $\delta$ 159.0 (C=O), 147.5 (C-4'), 145.6 (C-5), 142.7 (C-2'), 137.5 (C-3), 122.1 (C-3'), 109.5 (C-4), 61.3 (-OC$H_2$), 14.2 (-C$H_3$). *Anal.* Calcd for C$_{11}$H$_{11}$N$_3$O$_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.64; H, 5.43; N, 19.27.

**Ethyl 5-(2',4'-Difluorophenyl)-4-bromopyrazole-3-carboxylate (30a).** Ethyl 5-(2',4'-difluorophenyl)pyrazole-3-carboxylate (2.4 g, 0.0095 mol) was dissolved in 30 mL glacial acetic acid. Bromine (1.71 g, 0.01 mol) was added and the mixture was stirred for 6 h. The reaction mixture was poured over ice water (~400 mL) and neutralized with sodium carbonate. The resulting gummy yellow solid was filtered and dried. Since mass spectrometric and TLC analysis of this product showed the presence of starting material, the solid was redissolved in glacial acetic acid, and about 1 g of bromine was added. Overnight stirring was followed by the mixture again being poured over ice water (~400 mL) and neutralized with sodium carbonate. The resulting white solid was isolated and chromatographed (silica gel, 2:3, ether:petroleum ether), giving 1.3 g of a white granular solid; mp 87.8 °C; MS (EI) *m/e* 295 (M); $^1$H NMR (Me$_2$SO-$d_6$, mixture of tautomers) $\delta$ 14.62, 14.38 (s, 1, NH), 7.62, 7.48, 7.28 (m, 3, C3',5',6'-H), 4.35 (m, 2, -OC$H_2$CH$_3$), 1.34 (t, 3, -OCH$_2$C$H_3$); IR (KBr) 3245, 1732, 1444, 1266, 1147, 1123, 1051, 980, 955, 849 cm$^{-1}$. $^{13}$C NMR (Me$_2$SO-$d_6$) $\delta$ 163.4 (q, $^1J_{C_{4'},F_4}$ = 249.2 Hz, $^3J_{C_{4'},F_2}$ = 11.8 Hz, C4'), 159.6 (C=O), 160.0 (q, $^1J_{C_{2'},F_2}$ = 251.2 Hz, $^3J_{C_{2'},F_4}$ = 12.3 Hz, C2'), 141.5 (C5), 136.4 (C3), 133.3 (dd, $^3J_{C_{6'},F_4}$ = 10.1 Hz, $^3J_{C_{6'},F_2}$ = 4.1 Hz, C6'), 114.4 (dd, $^2J_{C_{1'},F_2}$ = 15.2 Hz, $^4J_{C_{1'},F_4}$ = 3.7 Hz, C1'), 112.1 (dd, $^2J_{C_{5'},F_4}$ = 21.7 Hz, $^4J_{C_{5'},F_4}$ = 21.7 Hz, $^4J_{C_{5'},F_2}$ = 3.7 Hz, C5'), 97.1 (C4), 61.1 (-OC$H_2$CH$_3$), 14.2 (-OCH$_2$C$H_3$). *Anal.* Calcd for C$_{12}$H$_9$BrF$_2$N$_2$O$_2$: C, 43.53; H, 2.74; N, 8.46. Found: C, 43.50; H, 2.78; N, 8.45.

**Ethyl 5-(2',4'-Difluorophenyl)-4-chloropyrazole-3-carboxylate (30b).** Ethyl 5-(2',4'-difluorophenyl)pyrazole-3-carboxylate (2.1 g, 0.0083 mol) was dissolved in glacial acetic acid (30 mL). Chlorine (scrubbed with conc. $H_2SO_4$) was bubbled through the solution and the reaction mixture was stirred for 6 h at room temperature. It was then poured over ~400 mL ice-water, and the solution

was neutralized with $NaHCO_3$. The resulting gummy yellow solid was filtered, dried, and chromatographed (silica gel, 2:3, ether: pet. ether), giving 1.3 g of a granular white solid. Further drying in vacuum resulted in a yield of 1.2 g of the granular white powder; mp 102-3 °C; MS (EI) *m/e* 286 (M); $^1$H NMR ($Me_2SO$-$d_6$, mixture of tautomers) $\delta$ 14.60, 14.24 (s, 1, NH), 7.45 (m, 3, C3′, 5′, 6′-H), 4.36 (m, 2, -OC$H_2$CH$_3$), 1.32 (m, 3, -OCH$_2$C$H_3$); IR (KBr) 3251, 1729, 1444, 1270, 1245, 1148, 1058, 950, 957, 850 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 163.3 (dd, $^1J$ = 249.6 Hz, $^3J$ = 11.6 Hz, C4′), 159.9 (dd, $^1J$ = 252.3 Hz, $^3J$ = 12.7 Hz, C2′), 159.3 (C=O), 139.5 (C5), 134.6 (C3), 132.9 (m, $^3J_{C_{6'},F_4}$ = 9.9 Hz, $^3J_{C_{6'},F_2}$ = 4.2 Hz, C6′), 113.6 (dd, $^2J_{C_{1'},F_2}$ = 15.4 Hz, $^4J_{C_{1'},F_4}$ = 3.3 Hz, C1′), 112.2 (dd, $^2J_{C_{5'},F_4}$ = 21.6 Hz, $^4J_{C_{5'},F_2}$ = 3.6 Hz, C5′), 111.5 (C4), 104.8 (t, $^2J_{C_{3'},F_2}$ = $^2J_{C_{3'},F_4}$ = 26.0 Hz, C3′), 61.1 (-OC$H_2$CH$_3$), 14.2 (-OCH$_2$C$H_3$). *Anal.* Calcd for $C_{12}H_9ClF_2N_2O_2$: C, 50.28; H, 3.16; N, 9.77. Found: C, 49.97; H, 3.29; N, 9.51.

**Ethyl 5-(2′-Pyridyl)-4-bromopyrazole-3-carboxylate (30c).** Ethyl 5-(2′-pyridyl)pyrazole-3-carboxylate (2.1 g, 0.0097 mol) was dissolved in glacial acetic acid (30 mL). Bromine (1.55 g, 0.0097 mol) was added, and the reaction mixture was stirred overnight at room temperature. It was then poured over ice water (≈400 mL) and neutralized with $NaHCO_3$. The resulting solid was filtered, dried, and filtered through silica gel with ethyl acetate. Solvent evaporation gave 2.5 g of a fluffy light brown solid; mp 107-8 °C; MS (EI) *m/e* 295 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 14.51 (s, 1, NH), 8.73 (m, 1, C6′-H), 8.11 (br s, 1, C3′-H), 7.99 (br s, 1, C4′-H), 7.49 (m, 1, C5′-H), 4.33 (q, 3, -OC$H_2$CH$_3$), 1.34 (t, 3, -OCH$_2$C$H_3$); IR (KBr) 3175, 2928, 1732, 1600, 1468, 1446, 1265, 1246, 1192, 1047, 786 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 159.6 (C=O), 148.2 (C6′), 146.4 (C2′), 142.2 (C5), 139.6 (C4′), 139.1 (C3), 124.7 (C5′), 122.7 (C3′), 95.1 (C4), 61.0 (-OCH$_2$C$H_3$). *Anal.* Calcd for C, 44.62; H, 3.40; N, 14.19. Found: C, 44.75; H, 3.63; N, 14.23.

**Ethyl 5-(2′-Pyridyl)-4-chloropyrazole-3-carboxylate (30d).** Ethyl 5-(2′-pyridyl)pyrazole-3-carboxylate (1.7 g, 0.0078 mol) was dissolved in glacial acetic acid (30 mL). Chlorine (scrubbed with conc. $H_2SO_4$) was bubbled through the reaction mixture with stirring for 1.5 h, at room temperature. The reaction mixture was poured over ice water (~400 mL) and neutralized with $NaHCO_3$. The resulting solid was filtered, dried and chromatographed (silica gel, ether) giving 1.8 g of the desired product as a light brown solid; mp 127-8 °C; MS (EI) *m/e* 251 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 13.5 (br s, 1, NH), 8.73 (d, 1, C6′-H), 8.05 (m, 2, C2′-H, C3′-H), 7.49 (m, 1, C5′-H), 4.34 (q, 2, -OC$H_2$CH$_3$), 1.34 (t, 3, -OCH$_2$C$H_3$); IR (KBr) 3185, 1731, 1480, 1251, 1198, 1158 1068, 1052, 1002, 787, 680 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 159.5 (C=O), 148.3 (C6′), 146.0 (C2′), 140.4 (C5), 139.8 (C4′), 136.6 (C3), 124.7 (C5′), 122.3 (C2′), 110.5 (C4), 61.1 (-OC$H_2$CH$_3$), 14.2 (-OCH$_2$C$H_3$). *Anal.* Calcd for $C_{11}H_{10}ClN_3O_2$: C, 52.50; H, 4.01; N, 16.70. Found: C, 52.16; H, 4.17; N, 16.83.

**Ethyl 5-(3′-Pyridyl)-4-bromopyrazole-3-carboxylate (30e).** Ethyl 5-(3′-pyridyl)pyrazole-3-carboxylate (2.1 g, 0.0097 mol) was dissolved in glacial acetic acid (30 mL). Bromine (1.55 g, 0.0097 mmol) was added, and the reaction mixture was stirred for 3 h at room temperature. It was then poured over ice-water (~400 mL) and neutralized with $NaHCO_3$. The resulting solid was filtered, dried, and filtered through

silica gel with ether. Solvent evaporation gave 1.5 g of a fluffy white solid (further elution gave an additional 0.7 g of a slightly impure light brown solid); mp 162-163 °C; MS (EI) *m/e* 295 (M); $^1$H NMR ($Me_2SO$-$d_6$, tautomeric mixture) $\delta$ 14.66, 14.46 (br s, 1, H-2), 8.988 (s, 1, H-2'), 8.68 (m, 1, H-6'), 8.18 (2 s, 1, H-4'), 7.68 (m, 1, H-5'), 4.38 (apparent q, 2, -O*C*$H_2$CH$_3$), 1.36 (t, 3, -OCH$_2$*C*$H_3$; IR (KBr) 2792, 2730, 2678, 1739, 1561, 1414, 1229, 959, 812, 705 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 158.4 (C=O), 144.6 (C-2'), 143.1 (C-6', C-5), 140.8 (C-4'), 135.1 (C-3), 128.9 (C-3'), 126.2 (C-5'), 95.9 (C-4), 61.3 (O*C*H$_2$CH$_3$), 14.1 (-OCH$_2$*C*H$_3$). *Anal.* Calcd for $C_{11}H_{10}BrN_3O_2$: C, 44.62; H, 3.40; N, 14.19. Found: C, 44.71; H, 3.68; N, 14.03.

**Ethyl 5-(3'-Pyridyl)-4-chloropyrazole-3-carboxylate (30f).** Ethyl 5-(3'-pyridyl)pyrazole-3-carboxylate (1.8 g, 0.0083 mol) was dissolved in glacial acetic acid (30 mL). Chlorine (scrubbed with conc. $H_2SO_4$) was bubbled through the reaction mixture with stirring for 2 h, at room temperature. The reaction mixture was poured over ice-water (~400 mL) and neutralized with $NaHCO_3$. The resulting solid was filtered, dried and chromatographed (silica gel, ether) giving 1.2 g of the desired product as a light brown granular solid; mp 180-181 °C; MS (EI) *m/e* 251 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 14.35 (br s, 1, NH), 9.2 (m, 1, H-2'), 6.7 (d, 1, H-6'), 8.19 (2 t, 1, H-4'), 7.57 (2 d, 1, H-5'), 4.36 (q, 2, -O*C*$H_2$CH$_3$), 1.35 (t, 3, -OCH$_2$*C*$H_3$); IR (KBr) 1726, 1717, 1385, 1230, 1219, 1205, 1196, 961, 811, 700 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 158.3 (C=O), 144.7 C-2'), 142.8 (C-6'), 141.3 (C-5), 140.0 (C-4'), 133.4 (C-3), 128.2 (C-3'), 126.2 (C-5'), 110.8 (C-4), 81.3 (-O*C*$H_2$CH$_3$), 14.1 (-OCH$_2$*C*$H_3$). *Anal.* Calcd for $C_{11}H_{10}ClN_3O_2$: C, 52.50; H, 4.01; N, 16.70. Found: C, 52.36; H, 4.08; N, 16.79.

**Ethyl 5-(4'-Pyridyl)-4-bromopyrazole-3-carboxylate (30g).** Ethyl 5-(4'-pyridyl)pyrazole-3-carboxylate (2.0 g, 0.0092 mol) was dissolved in glacial acetic acid (30 mL). Bromine (1.47 g, 0.0092 mol) was added, and the reaction mixture was stirred for 3 h at room temperature. It was then poured over ice-water (~400 mL) and neutralized with $NaHCO_3$. The resulting solid was filtered, dried, and filtered through silica gel with ether. Solvent evaporation gave 1.8 g of a fluffy white solid; mp 192-194 °C; MS (EI) *m/e* 295 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 14.70 (s, 1, H-2), 8.72 (br d, $J$ = 4 Hz, 2, H-2'), 7.83 (br d, $J$ = 6 Hz, 2, H-3'), 4.37 (q, 2, -O*C*$H_2$), 1.36 (t, 3, -OCH$_2$*C*$H_3$); IR (KBr), 1720, 1607, 1410, 1380, 1220, 1206, 1008, 958, 834, 776 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 158.1 (C=O), 144.6 (C-2'), 144.3 (C-4'), 143.2 (C-5), 135.1 (C-3), 123.1 (C-3'), 97.1 (C-4), 61.5 (-O*C*$H_2$), 14.1 (-*C*$H_3$). *Anal.* Calcd for $C_{11}H_{10}BrN_3O_2$·0.2$H_2O$: C, 44.07; H, 3.50; N, 14.02. Found: C, 43.71; H, 3.62; N, 13.70.

**Ethyl 5-(4'-Pyridyl)-4-chloropyrazole-3-carboxylate (30h).** Ethyl 5-(4'-pyridyl)pyrazole-3-carboxylate (2.0 g, 0.0092 mol) was dissolved in glacial acetic acid (30 mL). Chlorine (scrubbed with conc. $H_2SO_4$) was bubbled through the reaction mixture with stirring for 4 h, at room temperature. The reaction mixture was poured over ice-water (~400 mL) and neutralized with $NaHCO_3$. The resulting dark yellow solid was filtered through silica gel with ether, and recrystallized from ether giving two crystal fractions (0.9 and 0.8 g). The first fraction was found to be sufficiently pure compound **21** as a yellow granular solid; mp 180-182 °C; MS (EI) *m/e* 251 (M); $^1$H NMR ($Me_2SO$-$d_6$, mixture of tautomers) $\delta$ 14.74-14.56 (br s, 1, H-2), 8.72 (br s, 2, H-2'), 7.86 (br s, 2, H-3'), 4.36 (m, 2, -O*C*$H_2$CH$_3$), 1.34 (t, 3,

-$OCH_2CH_3$); IR (KBr) 1716, 1609, 1407, 1384, 1237, 1218, 1209, 1009, 954, 833 $cm^{-1}$; $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 157.8 (C=O), 145.5 (C-4'), 143.4 (C-2'), 141.4 (C-5), 133.4 (C-3), 123.0 (C-3'), 112.8 (C-4), 61.6 (-$OCH_2$), 14.1 (-$CH_3$). *Anal.* Calcd for $C_{11}H_{10}ClN_3O_2$: C, 52.50; H, 4.01; N, 16.70. Found: C, 52.26; H, 4.08; N, 16.99.

**5-(2',4'-Dimethoxyphenyl)pyrazole-3-carboxamide (32a).** Ethyl 5-(2',4'-dimethoxyphenyl)pyrazole-3-carboxylate (2.0 g, 0.0072 mol) was dissolved in conc. $NH_4OH$ (50 mL) and stirred at room temperature for 80 h. The reaction mixture was then poured into ~100 mL water and acidified to pH 5-6 with dil. $H_2SO_4$. The resulting solid was filtered, dried, and chromatographed (silica gel, 1:9, MeOH: $CHCl_3$) giving 1.8 g of an off white granular solid; mp 174-5 °C; MS (EI) *m/e* 247 (M); $^1H$ NMR ($Me_2SO$-$d_6$, mixture of tautomers) $\delta$ 13.38, 13.12 (s, 1, NH), 7.92, 7.80, 7.42, 7.20 (m's, 2, $NH_2$), 7.12 (d, 1, C6'-H), 6.92 (s, 1, C4-H), 6.67 (s, 1, C3'-H), 6.65 (d, 1, C5'-H), 3.89 (s, 3, -$OCH_3$), 3.81 (s, 3, -$OCH_3$); IR (KBr) 3229, 1680, 1639, 1612, 1602, 1594, 1498, 1310, 1297, 1210 $cm^{-1}$; $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 163.5 (C=O), 160.9 (C-4'), 157.3 (C-2'), 145.0 (C-3), 142.1 (C-5), 128.8 (C-6'), 111.4 (C-1'), 105.7 (C-5'), 104.7 (C-4), 98.9 (C-3'), 55.7 (-$OCH_3$), 55.4 (-$OCH_3$). *Anal.* Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.56; H, 5.62; N, 16.96.

**5-(2',4'-Dichlorophenyl)pyrazole-3-carboxamide (32b).** Ethyl 5-(2',4'-dichlorophenyl)pyrazole-3-carboxylate (2.1 g, 0.0074 mol) was dissolved in 50 mL conc. $NH_4OH$ and the solution was stirred at room temperature for two days. Since starting material still was detectable by mass spectrometric analysis, dioxane (20 mL) was added and the solution was heated to 40-50 °C for two more days. The reaction mixture was cooled and poured into ~100 mL water. The solution was acidified to pH 5-6 with dil. $H_2SO_4$. The resulting off-white solid was filtered and dried, yielding 1.5 g of the desired product; mp 294-5 °C; MS (EI) *m/e* 255, 257 (M, M + 2); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 13.69 (s, 1, NH), 7.90 (s, 1, C4-H), 7.80 (d, $J$ = 8.2 Hz, 1, C6'-H), 7.74 (d, $J$ = 2 Hz, 1, C3'-H), 7.53 (dd, $J$ = 2.2 Hz, $J$ = 8.5 Hz, C5'-H), 7.46 (s, 1, $NH_2$), 7.29 (s, 1, $NH_2$); IR (KBr) 3390, 3280, 3218, 3179, 1706, 1689, 1606, 1481, 1408, 815 $cm^{-1}$; $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 161.1 (C=O), 144.2 (C-5), 141.2 (C-3), 133.1 (C-4'), 131.7 (C-2'), 131.4 (C-6'), 129.6 (C-3'), 129.5 (C-1'), 127.5 (C-5'), 106.2 (C-4). *Anal.* Calcd for $C_{10}H_7N_3Cl_2O$: C, 46.90; H, 2.76; N, 16.42. Found: C, 47.04; H, 2.90; N, 16.04.

**7-*N*-(6-Methyl-3-methylthio-7*H*-*s*-triazolo[5,1-*c*]triazolyl)dithiocarbamate (36).** A solution of 4-amino-3-hydrazino-5-methyltriazole dihydrochloride (12.4 g) and potassium hydroxide (10.8 g) in 70% aqueous ethanol (300 mL) was refluxed with carbon disulfide (50 mL) for 38 h. The solvent was removed and the residue was dissolved in water (50 mL). The solution was acidified to pH 3 by addition of conc. HCl. The pale yellow solid obtained was filtered and recrystallized from water. This thiol (11.53 g) was refluxed in methanol (150 mL) in the presence of equimolar quantities of sodium hydroxide (2.98 g) and methyl iodide (4.7 mL) for 2 h. Partial evaporation of the solvent and dilution with water precipitated the desired product. Pure methylthio derivative was obtained by crystallizing twice from water, followed by silica gel column filtration (eluted with 10% methanol in chloroform), 3.0 g, mp 186-189 °C; MS (EI) 260 (M); UV $\lambda_{max}$ 321 (12,600), 228 (10,100) at pH 1; 320 (13,000), 228 (10,700)

at pH 7; 320 (10,800) at pH 13; IR (KBr) 3219, 3102, 3015, 2925 (NH, $CS_2H$, CH), 1660, 1542, 1527 (thioureido band), 1480, 1306, 1254, 1169, 1045 ($CS_2H$), 816 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 6.15-5.9 (br s, NH, SH, $H_2O$), 2.65 (s, 3, $SCH_3$), 2.4 (s, 3, $CH_3$); $^{13}C$ NMR ($Me_2SO$-$d_6$) 188.8 ($CS_2H$), 159.1 (C-3, $^3J_{CH}$ = 5.5 Hz), 153.5 (C-6, $^2J_{CH}$ = 7.3 Hz), 145.9 (C-8), 15.2 ($SCH_3$, $^1J_{CH}$ = 143.6 Hz), 9.95 ($CH_3$, $^1J_{CH}$ = 130.4 Hz). *Anal.* Calcd for $C_6H_8N_6S_3 \cdot 0.2H_2O$: C, 27.30; H, 3.21; N, 31.85; S, 36.44. Found: C, 27.16; H, 3.02; N, 31.78; S, 36.32.

**3,7-Diacetamido-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (38).** 3,7-Diamino-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (5.0 g) was stirred with acetic anhydride (150 mL) at room temperature for 3 days. The solid obtained was filtered, washed with diethyl ether and dried (2.45 g). Further purified by crystallizing from water, mp 220-224 °C; MS (EI) 223 (M); UV $\lambda_{max}$ 238 (5800); IR (KBr) 3216, 3194 (NH), 3040, 2980 (CH), 1700, 1683 (C=O), 1615, 1564, 1531, 1505, 1440, 1380, 1263, 1245, 1180 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 11.7-11.55 (s, 1, NH), 10.75-10.6 (s, 1, NH), 8.8 (s, 1, CH), 2.1 (s, 6, $CH_3$); $^{13}C$ NMR ($Me_2SO$-$d_6$) 169.4 (CO), 169.3 (CO), 149.9 (C-8, $^3J_{CH}$ = 4.0 Hz), 149.2 (C-6, $^1J_{CH}$ = 221.3 Hz), 135.4 (C-3), 22.2 ($CH_3$), 20.1 ($CH_3$). *Anal.* Calcd for $C_7H_9N_7O_2$: C, 37.66; H, 4.06; N, 43.94. Found: C, 37.71; H, 4.09; N, 43.88.

**3-Acetamido-7-amino-6-methyl-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (40).** 3,7-Diamino-6-methyl-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (2.0 g) was stirred with acetic anhydride (100 mL) at room temperature for 3 days. The solid obtained was filtered, washed with diethyl ether and dried. Further purified by crystallizing from water (1.89 g), mp 239-241 °C (dec); MS (EI) 195 (M); IR (KBr) 3320, 3280 ($NH_2$), 3102 (NH), 2965, 2925, 2850, 2750 (CH), 1708 (C=O), 1635, 1617, 1579, 1558, 1425, 1405, 1373, 1270, 1250, 1215, 1035, 860, 775, 715, 675, 655 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 10.55-10.4 (br s, 1, NH), 6.0 (s, 2, $NH_2$), 2.35 (s, 3, $CCH_3$), 2.05 (s, 3, $COCH_3$); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 169.4 (CO), 158.0 (C-6), 152.5 (C-8), 134.3 (C-3), 22.2 ($COCH_3$), 10.4 ($CCH_3$). *Anal.* Calcd for $C_6H_9N_7O$: C, 36.91; H, 4.65; N, 50.24. Found: C, 36.93; H, 4.77; N, 50.08.

**Synthesis of Ribofuranosyl Triazolotriazoles 44, 45, 46.** 3-Amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole[9] (6.97 g) was suspended in a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (28.35 g) in anhydrous acetonitrile (915 mL). Stannic chloride (14.7 mL) was added slowly at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature for 24 h. It was then concentrated to a small volume and saturated sodium bicarbonate was added till the vigorous evolution of carbon dioxide had ceased. The mixture was evaporated under reduced pressure and the residual gum was extracted several times with hot chloroform. The combined extracts dried and concentrated. Thin-layer chromatographic analysis of this crude product (silica gel, chloroform-methanol, 9:1 v/v) showed three spots with $R_f$ values of 0.45, 0.81 and 0.9 along with unchanged as well as decomposed sugar derivatives ($R_f$ 0.97). The mixture was applied to a column of silica gel and eluted with chloroform followed by 1%, 2%, and 3% methanol in chloroform. The above three products were separated and further purified by repeating silica gel column chromatography. Structures of these compounds were assigned on the basis of spectral data as follows:

**3-Imino-2*H*-2-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole (42).** Compound with $R_f$ 0.45 cited above, yield 9.46 g (30%); mp 125-127 °C; MS (FAB) 569 (M + 1); UV $\lambda_{max}$ 234 (39,400), shoulder at 280 (3200) at pH 1; 236 (33,000), shoulder at 276 (17,300) at pH 7; 225 (29,300), 276 (8600) at pH 13; IR (KBr) 3500-2500 (broad peak, NH, NH, CH), 1727 (C=O), 1666 (C=N), 1615, 1602 (aromatic), 1585, 1475, 1450, 1315, 1267, 1200, 1175, 1116, 1093, 1070, 1024 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 8.1-7.8 and 7.6-7.1 (m, 18, NH, NH, $C_6$-H and benzoyl protons), 6.35 (d, 1, $C_{1'}$-H, $J_{1',2'}$ = 1.7 Hz), 6.25 (dd, 1, $C_{2'}$-H, $J_{2',3'}$ = 5.2 Hz), 6.19 (dd, 1 H, $C_{3'}$-H, $J_{3',4'}$ = 6.8 Hz), 4.92-4.82 (m, 1, $C_{4'}$-H, $J_{4',5'a}$ = 5.2 Hz, $J_{4',5'b}$ = 3.6 Hz), 4.82-4.77 (d, 1, $C_{5'b}$-H), 4.74-4.65 (dd, 1, $C_{5'a}$-H, $J_{5'a,5'b}$ = 12.1 Hz); $^{13}C$ NMR ($CDCl_3$) δ 166.3, 165.2, 165.1 (C=O), 160.3 (C-6, $^1J_{C_6H}$ = 202.6 Hz), 160.1 (C-8, $J_{C_8H}$ = 4.4 Hz), 138.3 (C-3), 133.7, 133.4, 133.0, 129.7, 129.64, 129.6, 129.2, 128.6, 128.4, 128.43, 128.39 (aromatic carbons), 88.8 (C-1′, $^1J_{C_1'H}$ = 167.8 Hz), 80.4 (C-4′), 75.3 (C-2′), 71.7 (C-3′) and 63.9 (C-5′). *Anal.* Calcd for $C_{29}H_{24}N_6O_7 \cdot H_2O$: C, 59.34; H, 4.47; N, 14.33. Found: C, 59.12; H, 4.42; N, 14.50.

**3-(2′,3′,5′-Tri-*O*-benzoyl-D-ribofuranosyl)amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (46).** Compound with $R_f$ 0.81 cited above, yield 7.5 g (23%); mp 189-192 °C; MS (FAB) 569 (M + 1); UV $\lambda_{max}$ 233 (19,500), shoulder at 278 (1350) at pH 1; 236 (18,800), shoulder at 280 (5400) at pH 7; 226 (14,000) at pH 13; IR (KBr) 3200, 3070, 3010, 2975-2900 (NH and CH), 1734, 1725, 1716 (C=O), 1630, 1587 (broad, aromatic), 1465, 1450, 1315, 1284, 1267, 1180, 1155, 1126, 1114, 1093 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) δ 12.45-12.7 (br s, 1, $N_5$-H), 8.67 (b d, 1, NH), 8.1-7.83, 7.8-7.3 (m, 16, $C_6$-H and benzoyl protons), 6.39-6.32 (m, $C_{1'}$-H of α-isomer), 5.97-5.77 (m, 3, $C_{1',2',3'}$-H), 4.8-4.5 (m, 3, $C_{4',5'}$-H); $^{13}C$ NMR ($Me_2SO$-$d_6$) of the compound showed mixture of α,β-isomers. *Anal.* Calcd for $C_{29}H_{24}N_6O_7$: C, 61.26; H, 4.26; N, 14.79. Found: C, 61.42; H, 4.56; N, 14.78.

**3-Amino-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole (44).** Compound with $R_f$ 0.9 cited above, yield 2.34 g (7.3%), mp 86-87 °C; MS (FAB) 569 (M + 1); UV $\lambda_{max}$ 239 (30,500), shoulder at 280 (13,300) at pH 1; 240 (30,700), shoulder at 280 (13,300) at pH 7; 229 (27,700), shoulder at 275 (2200) at pH 13; IR (KBr) 3425, 3335, ($NH_2$), 3175, 3065 (CH), 1727 (C=O), 1655 (C=N), 1600, 1570 (aromatic), 1452, 1317, 1269, 1175, 1160, 1121, 1096, 1070, 1025, 709 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 8.15-7.25 (m, 16, $C_6$-H and benzoyl protons), 6.31 (d, 1, $C_{1'}$-H, $J_{1',2'}$ = 3.86 Hz), 6.28 (dd, 1, $C_{2'}$-H, $J_{2',3'}$ = 5.32 Hz), 6.15 (dd, 1, $C_{3'}$-H, $J_{3',4'}$ = 5.31 Hz), 4.88-4.5 (m, 3, $C_{4',5'}$-H); $^{13}C$ NMR ($CDCl_3$) δ 166.1, 165.2, 165.0 (C=O), 158.3 (C-6, $^1J_{CH}$ = 207.4 Hz), 156.0 (C-8, $^3J_{CH}$ = 9.8 Hz), 140.9 (C-3), 133.6, 133.5, 133.0, 129.8, 129.77, 129.7, 129.6, 128.8, 128.7, 128.4, 128.37, 128.3 (aromatic), 88.5 (C-1′), 79.9 (C-4′), 73.7 (C-2′), 71.7 (C-3′), 63.8 (C-5′).

**3-Imino-2*H*-2-β-D-ribofuranosyl-*s*-triazolo[5,1-*c*]-*s*-triazole (43).** The tribenzoyl ribofuranoside 44 (8.6 g) was deprotected by stirring with sodium methoxide (0.85 g) in methanol (200 mL) under dry conditions for 3 h at room temperature. The pH of the solution was brought to 7 by the careful addition of 6*N* HCl. Reaction mixture was concentrated under reduced pressure and charged on a silica gel column. Methyl benzoate was removed by eluting with chloroform. Elution with chloroform-

methanol (4:1) yielded the pure product, 2.81 g (73%), mp 160-162 °C (dec); MS (FAB) 257 (M + 1); UV $\lambda_{max}$ 248 (7200) at pH 1; 264 (8500) at pH 7; 277 (9100) at pH 13; IR (KBr) 3650-2600 (broad, OH, NH, CH), 1678, 1613 (C=N, C=NH), 1480, 1445, 1415, 1350, 1208, 1120, 1045 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 8.5-8.0 (br s, 1, NH), 7.9 (s, 1, $C_6$-H), 5.83 (d, 1, $C_{1'}$-H), 5.6-5.4, 5.25-5.1, 5.1-4.7 (br s, 3, OH), 4.53 (dd, 1, $C_{2'}$-H), 4.2 (dd, 1, $C_{3'}$-H), 3.92 (m, 1, $C_{4'}$-H), 3.64-3.42 (m, 2, $C_{5'}$-H); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 160.1 (C-6), 159.9 (C-8), 138.3 (C-3), 89.8 (C-1', $^1J_{CH}$ = 164.8 Hz), 85.3 (C-4'), 73.2 (C-2'), 70.6 (C-3'), 62.1 (C-5'). *Anal.* Calcd for $C_8H_{12}N_6O_4 \cdot 0.3CH_3OH \cdot 0.2H_2O$: C, 37.00; H, 5.09; N, 31.20. Found: C, 37.01; H, 4.99; N, 31.24.

**3-Amino-1-$\beta$-D-ribofuranosyl-*s*-triazolo[5,1-*c*]-*s*-triazole (45).** The tribenzoyl derivative 44 (2.0 g) was stirred with sodium methoxide (0.2 g) in methanol (100 mL) under dry conditions for 5 h at room temperature. The pH of the solution was brought to 7 by the careful addition of 6*N* HCl. Reaction mixture was concentrated under reduced pressure and charged on a silica gel column. Methyl benzoate was removed by eluting with chloroform. Elution with chloroform-methanol (4:1) yielded the pure product, 0.86 g (96%), mp 141-143 °C (lit.[12] mp 144-5 °C); MS (FAB) 257 (M + 1); UV $\lambda_{max}$ 240 (6400) at pH 1; 240 (7000) at pH 7; 242 (6800) at pH 13; IR (KBr) 3600-2600 (broad, OH, $NH_2$, CH), 1657, 1626 (C=N), 1580, 1505, 1455, 1445, 1410, 1325, 1285, 1265, 1215, 1185, 1140, 1105 and 1052 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 8.02 (s, 1, $C_6$-H), 6.85 (s, 2, $NH_2$), 5.48 (d, 1, $C_{1'}$-H), 5.43 (d, 1, $C_{2'}$-OH), 5.15 (d, 1, $C_{3'}$-OH), 4.82 (t, 1, $C_{5'}$-OH), 4.57 (m, 1, $C_{2'}$-H), 4.09 (m, 1, $C_{3'}$-H), 3.85 (m, 1, $C_{4'}$-H), 3.58-3.33 (m, 2, $C_{5'}$-H); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 157.8 (C-6, $^1J_{CH}$ = 206.7 Hz), 155.2 (C-8, $^3J_{C8H6}$ = 3.7 Hz, $^3J_{C8H1'}$ = 9.6 Hz), 141.2 (C-3), 90.5 (C-1'), 84.9 (C-4'), 72.0 (C-2'), 70.3 (C-3'), 62.0 (C-5'). *Anal.* Calcd for $C_8H_{12}N_6O_4$: C, 37.50; H, 4.72; N, 32.81. Found: C, 37.24; H, 4.93; N, 32.47.

**2-Nitroamino-1,3,4-thiadiazole (48).** Nitration of 3-amino-1,2,4-triazole was followed. Fuming nitric acid (d 1.52, 17.5 mL) was added slowly over 15 min to 2-amino-1,3,4-thiadiazole (5 g) at 0 °C with vigorous stirring. The reaction mixture was stirred further for 30 min at 10-20 °C and quenched by pouring it into ice-water. The solid was filtered and recrystallized from water to afford pure product (2.93 g), mp 168-170 °C (dec); MS (EI) 146 (M); IR (KBr) 3120 (broad), 3080 (NH), 3025, 3000, 2860 (CH), 1532, 1484, 1437, 1350, 1280, 1268, 1234, 1218, 1100, 1005, 897 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 14.5-11.5 (broad, NH), 9.1 (s, 1, CH); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 170.5 (C-2, $^3J_{CH}$ = 2.5 Hz), 148.0 (C-5, $^1J_{CH}$ = 218.6 Hz). *Anal.* Calcd for $C_2H_2N_4SO_2$: C, 16.44; H, 1.38; N, 38.35. Found: C, 16.67; H, 1.60; N, 38.25.

**5-Amino-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole, hydrobromide (49).** 2-Nitroamino-1,3,4-thiadiazole (12.24 g) and activated zinc dust (21.8 g) were moistened with water and ground to a paste. The paste was suspended in water (50 mL) at 10 °C and treated with 50% aqueous acetic acid (100 mL) over 2 h, while maintaining the temperature between 10-20 °C. The mixture was stirred at 20 °C for an additional 4 h, heated to 60 °C for 1 h, and allowed to cool. The excess zinc was removed by filtration and the filtrate saturated with hydrogen sulfide for 2 h. After removal of zinc sulfide, the filtrate and washings were treated with 10N HCl. The hydraziño compound obtained (12.0 g, MS (EI)

116 (M)) was refluxed with cyanogen bromide (11.0 g) in 85% aqueous methanol (425 mL) for 48 h. The solvent was removed by evaporation, and the solid residue was dissolved in water and neutralized with sodium acetate, giving a solid precipitate. The product was recrystallized from water and treated with one equivalent of hydrobromic acid, giving a pure product (1.23 g), mp 240-250 °C (dec); MS (EI) 141 (M); IR (KBr) 3400-2700 ($NH_2$, CH, HBr), 1685, 1588, 1500, 1485, 1325, 1275, 1200, 1020, 970, 780 $cm^{-1}$; $^1H$ NMR ($MeSO_2$-$d_6$) $\delta$ 9.4 (s, 1, C-H), 9.2-8.8 (br s, $NH_2$, $H_2O$, $H^+$); $^{13}C$ NMR ($Me_2SO$-$d_6$) 157.7 (C-2, $^1J_{CH}$ = 223.6 Hz), 149.7 (C-8, $^3J_{CH}$ = 3.3 Hz), 144.7 (C-5). *Anal.* Calcd for $C_3H_3N_5S$•HBr•0.5$H_2O$: C, 15.59; H, 2.18; N, 30.30. Found: C, 15.52; H, 1.90; N, 30.01.

**5-Thio-s-triazolo[3,4-*b*]-1,3,4-thiadiazole-6,N-dithiocarboxylic Acid (50).** 2-Nitroamino-1,3,4-thiadiazole (22 g) and activated zinc dust (32.8 g) were moistened with water and ground to a paste. The paste was suspended in water (82 mL) at 10 °C and treated with 50% aqueous acetic acid (164 mL) over 2 h, while maintaining the temperature between 10-20 °C. The mixture was stirred at 20 °C for an additional 4 h, heated to 60 °C for 1 h, and allowed to cool. The excess zinc was removed by filtration and the filtrate saturated with hydrogen sulfide for 2 h. After removal of zinc sulfide, the filtrate and washings were treated with 10*N* HCl to yield the hydrazino compound (15 g, MS (EI) 116 (M)). This compound (12.7 g) was refluxed with KOH (12.4 g), carbon disulfide (50 mL) in 70% aqueous ethanol (300 mL), for 30 h. The solvent was removed and the residue was dissolved in water, acidified (pH 3) by addition of conc. HCl. The yellow solid obtained was filtered and recrystallized from water, charged on silica gel column chromatograph, eluted with chloroform/methanol (9:1). Pure product was obtained by the treatment with dilute HCl (200 mL, pH 2), filtered and dried (4.01 g); mp 121-123 °C; MS (EI) 234 (M); UV 356 (5700), 282 (17,800), 244 (10,300); IR (KBr) 3650-3150 (broad, CSSH), 3050 (C-H), 1640 (C=S), 1515, 1488, 1453, 1427, 1406, 1323, 1268, 1220, 1080, 1040, 1010 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 9.5 (s, 1, CH), 3.95-3.8 (br s, SH, $H_2O$, $H^+$); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 186.8 (CSSH), 163.1 (C-5), 156.7 (C-8, $^3J_{CH}$ = 4.3 Hz), 152.0 (C-2, $^1J_{CH}$ = 214.2 Hz) ppm. *Anal.* Calcd for $C_4H_2N_4S_4$•0.4$H_2O$•0.4HCl: C, 18.77; H, 1.26; N, 21.88; S, 50.07. Found: C, 18.84; H, 1.27; N, 21.86; S, 50.00.

**3,6,7-Tri[dimethylaminomethyleneamino]-7*H*-*s*-triazolo[5,1-*c*]-triazole (52).** 3,6,7-Triaminotriazolotriazole (2.5 g) was suspended in dry 1,4-dioxane (160 mL) under nitrogen atmosphere. Gold's reagent [7] (6.43 g, Aldrich) was added all at once and the reaction mixture was refluxed for 24 h. Cooled to room temperature, anhydrous sodium acetate (1.6 g) and glacial acetic acid (3.3 mL) were added and was refluxed for 3 h. Solvent was removed *in vacuo*. The residue was taken up in chloroform and washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and concentrated. Silica gel column chromatography (10% methanol in chloroform) followed by precipitation in chloroform-ether, yielded the pure product (2.1 g), mp 213-214 °C (dec); MS (EI) 119 (M); UV $\lambda_{max}$ 283 (32,800), 219 (19,200); IR (KBr) 2915, 2875, 2810 (CH), 1630 (C=N), 1592 (C=N), 1527, 1489, 1458, 1431, 1393, 1350, 1285, 1260, 1230, 1200, 1109, 1100 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 8.37 and 8.35 (s, 3, olefin protons), 3.13, 3.07, 2.99, 2.94 (s, 18, methyl protons; $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 158.4 (C-6),

157.0, 155.9, 155.6 (N=CH), 149.5 (C-8), 147.7 (C-3), 40.8, 40.5, 38.0, 34.7, 34.5 (methyl carbons). *Anal.* Calcd for $C_{12}H_{21}N_{11}\cdot 0.7H_2O$: C, 43.41; H, 6.80; N, 46.42. Found: C, 43.69; H, 6.57; N, 46.27.

**3-Bromo-1-(2,3-dihydropropyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (55).** In a round-bottomed flask equipped with a magnetic stirrer and calcium sulfate drying tube was mixed 3-bromo-4-hydroxypyrazolo-[3,4-*d*]pyrimidine (8 g, 37 mmol), DMF (100 mL), glycidol (38 mmol), and a trace of $K_2CO_3$. The solution was stirred at 78-80 °C for 48 h. The resulting orange-brown solution was cooled to room temperature and filtered. The solvent was evaporated under reduced pressure to yield a residual oil. Crystallization from methanol/ethanol (1:1) gave off-white crystals. Yield 3.5 grams (32.7%). (Other analytical data consistent with previously submitted sample. See Quarterly Report No. 6.)

**1-(2,3-Dihydroxypropyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (56).** To a solution of 3-bromo-1-(2,3-dihydroxypropyl)pyrazolo[3,4-*d*]pyrimidine-4,5-one (3.5 g 12 mmol) in 50% aqueous ethanol (300 mL) was added Pd/C (5%) 600 mg, and the mixture was hydrogenated at 48 psi at room temperature for 24 h. The reaction mixture was filtered through Celite pad and the filtrate was evaporated to dryness. Crystallization of the residual solid from 50% aqueous methanol gave white crystals yield 0.9 g (35.7%) mp 232-234 °C; MS (FAB) *m/e* 210 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 3.40 (m, 2, 3′-H), 4.00 (m, 1, 2′-H), 4.26 (m, 2, 1′-H), 4.81 (br s, 2, OH's), 8.05 (s, 1, 3-H), 12.1 (s, 1, 5-H)); IR (KBr) 3270, 3262, 3250, 3085, 1700, 1651, 1595, 1580, 1535, 782 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 157.3 (C-4), 152.2 (C-7a), 147.5 (C-6), 134.0 (C-3), 105.6 (C-3a), 70.1 (C-2′), 63.7 (C-3′), 50.4 (C-1′). *Anal.* Calcd for $C_8H_8N_4O_3$: C, 45.71; H, 4.79; N, 26.66. Found: C, 45.72; H, 5.11; N, 26.29.

**Ethyl 2,2,4-Trimethyldihydroquinoline-6-carboxylate (58).** A mixture of ethyl 4-aminobenzoate (50 g, 0.302 mol) and iodine (3 g, 0.012 mol) in acetone (200 mL) and toluene (1000 mL) was refluxed for 24 h with stirring. The refluxing apparatus was equipped with a distillation receiver to collect the acetone-water distillate which after cooling was replaced with dry acetone before refluxing was removed. After the reaction had gone to completion, the solution was cooled to room temperature. The mixture was then evaporated to yield a brown residue which was taken up in ethyl acetate (200 mL), washed with 10% NaOH (2 x 100 mL), water (2 x 100 mL), and dried over $MgSO_4$. The ethyl acetate was evaporated to yield a dark solid which was washed with $CHCl_3$ and pet ether. Crystallization from $CHCl_3$ and pet. ether (1:2) yielded pale green crystals. MS (FAB) 245 (M + 1); IR 3346, 1684, 1660, 1598, 1368, 1289, 1270, 1258, 1219, 111 cm$^{-1}$; UV $\lambda_{max}$ 255 nm at pH 1; 233 nm at pH 7 and 13. $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.25 (t, 9, -$CH_2CH_3$, -$CH_3$), 1.92 (s, 3, -$CH_3$), 4.20 (q, 2, O$CH_2CH_3$), 5.34 (s, 1, H-3), 6.42 (d, 1, aromatic), 6.77 (s, 1, N-H), 7.5 (d, aromatic); $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 51.8 (C-2), 31.6 (C-2′ + C-2″), 128.3 (C-3), 115.5 (C-4), 181.0 (C-4′), 126.6 (C-4a), 124.5 (C-5), 118.5 (C-6), 130.5 (C-7), 111.2 (C-8), 148.2 (C-8a), 165.9 (C-6′), 59.5 (C-6″), 14.4 (C-6‴). *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.81; N, 6.07. Found: C, 72.95; H, 8.12; N, 6.07.

**Ethyl 1-N-Formyl-2,2,4-trimethyldihydroquinoline-6-carboxylate (59).** Formic acetic anhydride[12] (18.05 g) was added dropwise to ethyl 2,2,4-trimethyldihydroquinoline-6-carboxylate (58) in a round-bottomed flask equipped with a calcium sulfate drying tube. The reaction stirred at room temperature for 24

h and the solution formed was evaporated to yield a residual green oil. The product was taken up into chloroform (100 mL) and washed with $NaHCO_3$ (100 mL), water (100 mL) and dried over $NaSO_4$. The solvent was filtered through 50 g of silica gel and then concentrated by evaporation. Crystallization with chloroform and pet. ether (1:2) gave a 26% yield of the compound; mp 68-69 °C; MS (FAB) 273 (M + 1); IR 1718, 1704, 1666, 1602, 1340, 1290, 1261, 1421, 1109, 767 $cm^{-1}$; UV $\lambda_{max}$ 252 nm at pH 1 and 7; 247 nm at pH 13; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 1.40 (t, 3, $-OCH_2CH_3$, 1.54 (s, 6, $C(CH_3)_2$), 2.10 (s, 3, $-CH_3$), 5.6 (s, 1, H-3), 7.92 (s, 2, aromatic), 8.60 (s, 1, C=OH); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 56.5 (C-2), 27.4 (C-2′ + C-2″), 134.4 (C-3), 126.2 (C-4), 175.5 (C-4′), 126.9 (C-4a), 128.5 (C-5), 127.7 (C-6), 124.0 (C-7), 121.8 (C-8), 138.5 (C-8a), 165.3 (C-6′), 60.6 (C-6″), 14.2 (C-6‴), 161.2 (C-1′). *Anal.* Calcd for $C_{16}H_{19}NO_3$: C, 70.30; H, 7.01; N, 5.12. Found: C, 69.83; H, 7.22; N, 4.83.

**2,2,4-Trimethyl-1,2-dihydroquinoline-6-carboxylic Acid (62).** A 250-mL round-bottomed flask fitted with a reflux condenser was used to mix 2,2,4-trimethyl-1,2-dihydroquinoline carboxylate (5 g, 20 mmol) in a 1*N* NaOH (100 ml) aqueous solution. Ethanol (40 mL) was added dropwise to help the compound to go into solution. The reaction mixture was heated at reflux (105 °C) for 18 h. After cooling to room temperature the reaction mixture was diluted with an equal volume of water (150 mL) and poured with stirring into 50 mL of HCl. The mixture was filtered and the filtrate was evaporated down to yield 3 g of crude product. Recrystallization from ethanol gave beige crystals (2 g); mp 226-228 °C; MS (EI) *m/e* 217; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 1.24 (s, 6, $-(CH_3)_2$), 1.9 (s, 3, $-CH_3$), 5.32 (s, 1, H-vinyl), 6.42 (d, 1, H-8 aromatic), 6.68 (s, 1, N-H), 7.5 (m, 2, H-7,5 aromatic), 11.96 (br s, 1, OH); IR (KBr) 2967, 1653, 1597, 1437, 1339, 1293, 1276, 1256, 1229, 1162 $cm^{-1}$; $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 18.1 (1-Me), 31.5 (3-Me), 51.6 (C-2), 128.1 (C-3), 118.3 (C-4), 126.6 (C-4a), 124.7 (C-5), 116.2 (C-6), 113.1 (C-7), 111.0 (C-8), 147.9 (C-8a). *Anal.* Calcd for $C_{13}H_{15}NO_2 \cdot 0.5H_2O$: C, 69.00; H, 7.12; N, 6.19. Found: C, 69.14; H, 7.11; N, 6.15.

**1-Formyl-2,2,4-trimethyl-3-[(3-chlorophenyl)carbonyloxy]-1,2,3,4-tetrahydro-4-hydroxyquinoline-6-carboxylic Acid Ethyl Ester (60).** In a 200-mL round-bottomed flask *m*-chloroperoxybenzoic acid (3.58 g, 20.8 mmol) was added to a solution of 1-*N*-formyl-2,2,4-trimethyl-1,2-dihydroquinoline carboxylate and $CH_2Cl_2$ (100 mL). The reaction mixture was allowed to reflux (50 °C) with stirring for 18 h. After allowing the reaction mixture to cool to room temperature, the mixture was poured over cooled water (300 mL) and stirred for 30 min. The layers were separated and the organic layer was washed with saturated $NaHCO_3$ (2 x 100 mL), $H_2O$ (1 x 100 mL), and dried over $Na_2SO_4$. Solvent was removed *in vacuo*. The residue was taken up in chloroform and pet. ether (1:3) and precipitation followed yielding pure product (1 g); mp 180-182 °C; MS (EI) *m/e* 445 (M); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 1.32 (t, 3, $-OCH_2CH_3$), 1.49 (s, 3, $-CH_3$), 1.55 (s, 3, $-CH_3$), 1.78 (br s, 3, $-CH_3$), 4.34 (q, 2, $-OCH_2CH_3$), 5.26 (s, 1, H-3), 5.85 (s, 1, -OH), 7.5-7.7 (m, 5, H-aromatic-3′), 7.92 (m dd, 1, $J_{7,8}$ = 60.9 Hz, $J_{7,5}$ = 2.4 Hz, H-7), 8.19 (d, 1, H-aromatic-5), 8.74 (s, 1, NCO-H); IR (KBr) 1724, 1694, 1685, 1674, 1667, 1609, 1336, 1292, 1266, 744 $cm^{-1}$; $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 59.3 (C-2), 83.9-81.3 (C-3), 69.7 (C-4), 135.9 (C-4a), 128.4 (C-

5), 126.1 (C-6), 120.6 (C-8), 139.4 (C-8a), 161.9 (C=O), 165.2 (C=O), 27.7-26.3, 23.5, 14.2 (-$CH_3$), 60.6 (-$CH_2$), 163.9 (C=O), 128.3, 130.6, 131.3, 133.1, 133.2 (aromatic). *Anal.* Calcd for $C_{23}H_{24}ClNO_6 \cdot 0.3H_2O$: C, 61.21; H, 5.49; N, 3.10. Found: C, 61.38; H, 5.50; N, 3.07.

**Ethyl 2,2,4-Trimethyl-1,2,3,4-tetrahydroquinoline-6-carboxylate (63).** To a solution of ethyl 2,2,4-trimethyl-1,2-dihydroquinoline-6-carboxylate (2 g) in 50% aqueous ethanol (250 mL) was added Pd/C (5%, 425 mg). The mixture was hydrogenated at 25 psi for 72 h at room temperature. The reaction mixture was filtered through a Celite pad which was then further washed with hot ethanol. The filtrates were combined and evaporated to dryness. The resulting crude crystalline solid was recrystallized from aqueous ethanol (50%) to give off-white crystals. The compound was dried *in vacuo* over $P_2O_5$ (yield 1.6 g, 80%). Mp 108-109 °C; MS (EI) 247 (M); IR (KBr) 3366, 3351, 1689, 1600, 1517, 1364, 1291, 1261, 1250, 1202 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 1.11 (s, 1, H-3), 1.21 (m, 12, -$CH_3$'s), 1.72 (dd, 1, H-3), 2.81 (m, 1, H-4), 4.20 (q, 2, -$OCH_2CH_3$), 6.44 (d, 1, H-8), 6.51 (s, 1, N-H), 7.48 (d, 1, H-7), 7.65 (s, 1, H-5); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 165.9 (CO), 148.6 (C8a), 128.4 (C7), 127.9 (C5), 122.6 (C4a), 115.1 (C6), 112.3 (C8), 59.2 (-$OCH_2CH_3$), 48.7 (C1), 43.3 (C3), 30.4 (-$CH_3$), 28.1 (-$CH_3$), 26.7 (C4), 19.7 (-$CH_3$), 14.4 ($OCH_2CH_3$). *Anal.* Calcd for $C_{15}H_{21}N_1O_2 \cdot 0.1H_2O$: C, 72.30; H, 8.59; N, 5.63. Found: C, 72.37; H, 8.83, N, 5.70.

**5'-Deoxyadenosine, 5'-*N*,*N*-Diethylthiocarbamate (64).** A solution of sodium diethyldithiocarbamate trihydrate 3 g and 2',3'-*O*-methylethylidene-5'-tosyladenosine (4.5 g) in dry DMF (200 mL) was refluxed for 3 h in a Dean-Stark water separation set-up. Reaction mixture was then concentrated under reduced pressure to a gummy solid. Product was purified by silica gel column chromatography, eluting with 5% methanol in chloroform (3.68 g) [MS (FAB) 439 (M + 1)]. This compound in ethanol (10 mL) was stirred with 1*N* $H_2SO_4$ (30 mL) at room temperature for 3 days. Reaction mixture was then triturated several times with ethanol. The residue obtained was taken up in ethanol (200 mL) and pH of the solution brought to 7.0. Solid obtained was filtered. Filtrate was concentrated, charged on a silica gel column, eluting with 10% methanol in chloroform. Product obtained was further purified by crystallization from methanol (1.65 g); mp 101-102 °C; MS (FAB) 399 (M + 1); UV 258 (20,600), 206 (23,400); IR (KBr) 3500, 3129, 2975, 2925, 3450-2800 (broad) [$NH_2$, OH and CH], 1672 (C=S), 1642, 1602 (aromatic), 1575, 1489, 1470, 1421, 1415, 1335, 1295, 1270, 1206 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 8.37 (s, 1 H, $C_8$-H), 8.16 (s, 1 H, $C_2$-H), 7.3 (br s, 2 H, $NH_2$), 5.9 (d, 1 H, $C_{1'}$-H, $J$ = 6 Hz), 5.53 (d, 1 H, $C_{2'}$-OH, $J$ = 6 Hz), 5.4 (d, 1 H, $C_{3'}$-OH, $J$ = 5 Hz), 4.86 (dd, 1 H, $C_{2'}$-H), 4.18 (dd, 1 H, $C_{3'}$-H), 4.14-4.04 (m, 1 H, $C_{4'}$-H), 3.97 (q, 2 H, -$CH_2N$-), 3.87-3.68 and 3.68-3.52 (m, 4 H, $C_{5'}$-H and -$CH_2N$), 1.18 and 1.15 (t, 6 H, 2 x $CH_3$; $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 193.2 (C=S), 156.0 (C-$NH_2$, $^3J_{C_6,H_2}$ = 11.3 Hz), 152.5 (C-2, $^1J_{C_2,H_2}$ = 198.9 Hz), 149.3 (C-4, $^3J_{C_4,H_8}$ = 12.4, $^3J_{C_4,H_2}$ = $^3J_{C_4,H_{1'}}$ = 4.1 Hz), 140.0 (C-8, $^1J_{C_8,H_8}$ = 212.8, $^3J_{C,H_{1'}}$ = 4.2 Hz), 119.2 (C-5, $^3J_{C_5,H_8}$ = 11.6, $^3J_{C_5,NH}$ = 3.6 Hz), 87.4 (C-1', $^1J_{C_{1'},H_{1'}}$ = 164.9 Hz), 82.5 (C-4'), 72.7 (C-3'), 72.5 (C-2'), 49.2 and 46.4 (-$CH_2NCH_2$-), 39.1 (C-5'), 12.3 and 11.2 (2 x $CH_3$) ppm. *Anal.* Calcd for

$C_{15}H_{22}N_6S_2O_3 \cdot 0.5H_2O \cdot 0.5EtOH$: C, 44.64; H, 6.09; N, 19.53; S, 14.90. Found: C, 44.87; H, 5.80; N, 19.51; S, 14.90.

**6-[1-(4-Ethoxyphenyl)ethyl]-1,3-benzodioxol-5-ol (67a).** 4-Ethoxyacetophenone (16.4 g, 0.1 mol) was dissolved in 50 mL ethanol. Sodium borohydride (1.9 g, 0.05 mol) was slowly added and the mixture was refluxed for 2 h. Water (10.2 mL) was added and the solution was cooled to give a precipitate which was collected by filtration. The remaining mother liquor was evaporated to an oil which also solidified to a white solid (17.6 g). The combined solid products were refluxed for 5 h with sesamol (13.8, 0.1 mol), oxalic acid (1 g, 0.008 mol), acetic acid (30 mL), and water (2.5 mL). An excess of water was added to cause the separation of an oil which was extracted with ether. Solvent removal under vacuum gave a brown solid which was recrystallized with cyclohexane. Cooling resulted in the formation of fine white needle-like crystals (1.8 g, mp 845-855 °C) which were collected from the top of the precipitated mass. The remaining light brown solid was recrystallized using hot benzene and ether. The resulting off-white needle like crystals were collected by filtration (5.5 g), mp 84.5-85.5 °C. MS (EI) *m/e* 286 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 9.04 (s, 1, OH), 7.12 (m, 2, Ph-H), 6.78 (m, 2, Ph-H's), 6.58 (s, 1, Ph-H), 6.38 (s, 1, Ph-H), 5.85, 5.83 (2 d, 2, $-OCH_2O-$), 4.34 (q, 1, $-CH_2CH_3$), 3.96 (q, 2, $-OCH_2CH_3$), 1.42 (d, 3, $-CH_3$), 1.30 (t, 3, $-OCH_2CH_3$); IR (KBr) 3463, 1510, 1436, 1248, 1230, 1199, 1179, 1040, 930, 853 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 156.4, 148.4, 145.0, 140.0, 138.2, 128.1, 124.7, 113.8, 106.8, 100.2, 97.4, 62.8, 35.6, 20.8, 14.6 ppm. *Anal.* Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.14; H, 6.48.

**6-[1-(4-Methoxyphenyl)ethyl]-1,3-benzodioxol-5-ol (67b).** 4-Methoxyacetophenone (15 g, 0.1 mol) was added to 50 mL of stirring ethanol. Sodium borohydride (1.9 g, 0.5 mol) was then slowly added and the mixture was stirred for 3 h. An excess of water was added to precipitate an oil which was isolated by extracting with ether. The resulting oil (21.8 g) was refluxed with sesamol (13.8 g, 0.1 mol), oxalic acid (1 g, 0.008 mol), acetic acid (30 mL) and water (2.5 mL) for 5 h. An excess of water was again added to cause separation of an oil. Extracting with ether, drying with sodium sulfate, and solvent evaporation gave an oil which was crystallized using hexane/benzene/petroleum ether, giving a brown solid (22.7 g). 4 g of this solid was further purified by recrystallization with ether/hexane, giving brown needle-like crystals (2.3 g, mp 90-92 °C). MS (EI) *m/e* 272 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 9.04 (s, 1, -OH), 7.13 (m, 2, Ph-H's), 6.81 (m, 2, Ph-H's), 6.61 (s, 1, Ph-H), 6.41 (s, 1, Ph-H), 5.84, 5.83 (s, d, 2, $-OCH_2O-$), 4.35 (q, 1, $-CHCH_3$), 3.69 (s, 3, $-OCH_3$), 1.43 (d, 3, $-CH_3$). IR (KBr) 3471, 1510, 1437, 1248, 1231, 1200, 1178, 1039, 926, 854 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 157.1, 148.4, 144.9, 139.6, 138.3, 128.0, 124.6, 113.3, 106.8, 100.2, 97.3, 54.8, 35.5, 20.8 ppm. *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.45; H, 5.94.

**5-Ethoxy-6-[1-(4-ethoxyphenyl)ethyl]-1,3-benzodioxol (68b).** 6-[1-(4-Ethoxyphenyl)ethyl]-1,3-benzodioxol-5-ol (2 g, 0.007 mol) and ethyl iodide (3.3 mL, 0.041 mol) were added to acetone (20 mL) with stirring. Then potassium carbonate (6 g, 0.04 mol) was added, and the mixture was refluxed for 48 h. The potassium salts were removed by filtration and rinsed thoroughly with acetone. The solution

was evaporated to an oil, and water was added to dissolve any remaining $K_2CO_3$. The crude product was isolated by extracting with ether followed by solvent evaporation. The crude compound was then purified by column chromatography using ethyl acetate/petroleum ether (1:15). The desired compound was isolated as an oil which after several days solidified as an off-white clump (1.6 g, mp 47-49 °C). MS (EI) *m/e* 314 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 7.12 (m, 2, Ph-H), 6.80 (m, 2, Ph-H's), 6.74 (s, 1, Ph-H), 6.68 (s, 1, Ph-H), 5.90, 5.89 (2 d, 2, -$OCH_2O$-), 4.37 (q, 1, -*CH*$CH_3$), 3.95 (q, 2, -$OCH_2CH_3$), 3.89 (m, 2, -$OCH_2CH_3$), 1.44 (d, 3, -$CHCH_3$), 1.28 (t, 3, -$OCH_2CH_3$), 1.25 (t, 3, -$OCH_2CH_3$); IR (KBr) 1510, 1504, 1486, 1477, 1233, 1225, 1185, 1049, 1034, 928 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 156.4, 150.2, 145.4, 140.5, 138.1, 128.0, 127.4, 113.8, 106.9, 100.6, 96.2, 64.5, 62.7, 35.8, 20.9, 14.6 ppm. *Anal.* Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.51; H, 7.02.

**5-Methoxy-6-[1-(4-ethoxyphenyl)ethyl]-1,3-benzodioxol (68c).** 6-[1-(4-Ethoxyphenyl)ethyl]-1,3-benzodioxol-5-ol (2 g, 0.007 mol) was refluxed for 48 h with methyl iodide (3 mL, 0.01 4 mol), acetone (6 mL) and potassium carbonate (7 g, 0.05 mol). The solution was cooled and the potassium salts were removed by filtration. The filtered salts were further rinsed with acetone, and the combined acetone solutions were then evaporated to dryness. Water was added to the residue and the resulting solid was collected by filtration. Recrystallization using hot methanol gave brown, thick needle-like crystals (1.7 g, mp 67-69 °C). MS (EI) *m/e* 300 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 7.10 (m, 2, Ph-H's), 6.80 (m, 2, Ph-H's), 6.72 (2 s, 2, Ph-H's), 5.91, 5.89 (2 d, 2, -$OCH_2O$), 4.35 (q, 1, -*CH*$CH_3$), 3.95 (g, 2, -$OCH_2CH_3$), 3.67 (s, 3, -$OCH_3$), 1.43 (d, 3, -$CHCH_3$), 1.29 (t, 3, -$OCH_2CH_3$); IR (KBr) 1505, 1482, 1478, 1470, 1241, 1202, 1180, 1170, 1042, 856 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 156.4, 151.0, 145.5, 140.5, 137.9, 128.0, 127.0, 113.9, 107.0, 100.6, 95.2, 62.7, 56.5, 35.6, 20.9, 14.6 ppm. *Anal.* Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.64; H, 6.90.

**5-Methoxy-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxol (68a).** 6-[1-(4-Methoxyphenyl)ethyl]-1,3-benzodioxol-5-ol (1.9 g, 0.007 mol) and methyl iodide (3.3 mL, 0.041 mol) was added to acetone (20 mL). Potassium carbonate (7 g, 0.05 mol) was slowly added and the mixture was refluxed for 24 h. The potassium salts were removed by filtration and rinsed thoroughly with acetone. Evaporation of solvent gave an oil. Water was added and the oil was extracted with ether. Removal of ether by evaporation gave an oil, which was purified on a silica gel column using ethyl acetate/petroleum ether (1:15). The desired compound was isolated as a yellow oil (1.2 g). MS (EI) *m/e* 286 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 7.12 (m, 2, Ph-H's), 6.82 (m, 2, Ph-H's), 6.72 (2 s, 2, Ph-H's), 5.92, 5.89 (2 d, 2, -$OCH_2O$), 4.37 (q, 1, -*CH*$CH_3$), 3.70 (s, 3, -$OCH_3$), 3.68 (s, 3, -$OCH_3$), 1.44 (d, 3, -$CHCH_3$); IR (KBr) 1511, 1483, 1465, 1423, 1246, 1191, 1170, 1038, 854, 831 cm$^{-1}$; $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 157.2, 151.1, 145.6, 140.6, 138.1, 128.0, 127.0, 113.4, 107.0, 100.7, 95.2, 56.5, 54.8, 35.6, 20.9 ppm. *Anal.* Calcd for $C_{17}H_8O_4$: C, 71.31; H, 6.33. Found: C, 70.91; H, 6.27.

**3-Bromo-1-(2′,3′,5′-tri-O-benzoyl-$\beta$-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (71).** 3-Bromo allopurinol (11 g, 51 mmol) and $\beta$-D-ribofuranose 1-acetate 2,3,5-tribenzoate (30 g, 50 mmol) were added to dry nitromethane (125 mL) and brought to reflux temperature. $BF_3$•$Et_2O$ (9.9 g, 8.8 mL, 69.7

mmol) was added. The suspension became clear within 5 min and refluxing continued for 2.5 h. The solvent was evaporated to yield a dark brown foam which was dissolved in ethyl acetate (800 mL) and washed with saturated $NaHCO_3$ (2 x 300 mL) and then water (2 x 300 mL) and dried over $NaSO_4$. The solvent was removed to yield a brown foam. The foam was applied to a silica gel column using ethylacetate and cyclohexane (2:1) as the eluting solvents. The unreacted sugar eluted first and was followed by the N-1 isomer ($R_f$ 0.37). The N-1 isomer was recrystallized from ethyl acetate and methanol (4:1) yield 4.7 g, 15%; mp 213-215 °C; MS (FAB) *m/e* 658 (M + 1); $^1$H NMR ($Me_2SO$-$d_5$) $\delta$ 4.63 (m, $J_{5'a,5'b}$ = 12.5 Hz, 2, 5'-H), 4.91 (m, $J_{4',5'b}$ = 3.3 Hz, $J_{4',5a}$ = 3.8 Hz, 1, 4'-H), 6.15 (t, $J_{3',4'}$ = 6.50 Hz, 1, 3'-H), 6.25 (q, $J_{2',3'}$ = 5.35 Hz, 1, 2'-H), 6.68 (d, $J_{1,2'}$ = 3.09 Hz, 1, 1'-H), 7.45-8.07 (Ph-H), 8.2 (s, 1, 7-H), 12.59 (s, 1, 5-H).

**3-Bromo-1-β-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-4-(5*H*)-one (72).** 3-Bromo-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (4.7 g, 7 mmol) was combined with methanolic ammonia (329 mL saturated at 0 °C) and placed in a steel bomb. The solution heated at 90-100 °C for 4 h at 0 psi overnight. The solution was evaporated to a clear brown residual oil and washed with benzene to remove benzamide. Crystals were formed from water and ethyl-acetate (4:1), yield 1.5 g (60.7%); mp 228-230 °C; MS (FAB) *m/e* 346 (M + 1); IR (KBr) 3399, 3392, 3377, 3373, 3370, 1697, 1599, 1533, 1093, 1044 cm$^{-1}$; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 3.44 (m, 2, $J_{4',5'a}$ = 60 Hz, 1, 5'-$CH_2$), 3.55 (m, 2, $J_{4,,5b,}$ = 4.7 Hz, 1, 5'-$CH_2$, 3.90 (q, 1, 4'-H), 4.15 (q, 1, $J_{3',4'}$ = 4.3 Hz, 1, 4'-H), 4.52 (q, 1, $J_{2,,3,}$ = 4.9 Hz, 1, 2'-H), 4.75 (t, $J_{5,5,OH}$ = 5.6 Hz, 1, OH), 5.28 (d, 1, $J_{3,,3\text{-}OH}$ = 5.4 Hz, 1, 3'-OH), 5.54 (d, 1, $J_{2,,2\text{-}OH}$ = 5.8 Hz, 1, 2'-OH), 6.02 (d, 1, $J_{1',2}$ = 4.7 Hz, 1, 1'-H), 8.16 (s, 1, 6-H), 12.56 (s, 1, 5-H); $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 149.7 (C6), 156.1 (C4), 105.0 (C4a), 122.2 (C3), 153.7 (7a), 88.2 (C1'), 85.3 (C2'), 73.1 (C3'), 70.5 (C4'), 62.0 (C5'). *Anal.* Calcd for $C_{10}H_{11}N_4O_5Br$: C, 34.59; H, 3.19; N, 16.13. Found: C, 34.67; H, 3.43; N, 16.45.

**5-Bromo-3-nitro-1,2,4-triazole (74).** A solution of 3-nitro-1,2,4-triazole (5.7 g, 0.05 mol), sodium hydroxide (2.0 g, 0.05 mol) and bromine (3.0 mL) in water (25 mL) was heated at 80 °C until the bromination appeared to be complete as shown by TLC (ethyl acetate developer). Because MS revealed the presence of some starting material, an additional 0.5 mL of bromine was added to the reaction solution, and the solution was stirred at 80 °C for 1 h, then stirred at room temperature for two days. A small aliquot was worked up and was found to still contain starting material, so another 1 mL addition of bromine was made and the solution was again stirred at room temperature for another couple of days. Work-up of another small aliquot still showed starting material, and therefore, a final addition of 1 mL bromine along with 1 mL 50% NaOH was made. The final reaction solution was acidified to pH 2 with 1N HCl and extracted (4 x 50 mL) with ethyl acetate. The ethyl acetate solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness yielding 5.0 g of an orange solid. Recrystallization from EtOAc/benzene gave 7 g of an off-white solid; mp 146-149 °C; MS (EI); *m/e* 192 (M); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 13.68 (br s, 1, $H_2O$ + $H^+$ + NH);

$^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 162.5 ($CNO_2$), 131.0 (CBr). *Anal.* Calcd for $C_2HN_4O_2Br$: C, 13.02; H, 0.64; N, 28.64. Found: C, 13.05; H, 0.68; N, 28.12.

**6-Ethylthiopurine Riboside (76).** In a 250-mL round-bottomed flask stoppered with a calcium sulfate drying tube was mixed 11 g (38.7 mmol) of 6-mercaptopurine riboside, 5.9 g (42.6 mmol) of freshly dried $K_2CO_3$ and 150 mL of dry *N,N*-dimethylacetamide. To this well stirred mixture was added 4.2 g (38.7 mmol) of ethylbromide. The addition was dropwise over 3-5 min. The reaction was run under a nitrogen atmosphere. After 1-1/2 h of stirring at room temperature, thin-layer chromatography (TLC) indicated much product but some starting 6-MPR. The reaction mixture was heated at 55-60 °C for 1 h, filtered hot through a Celite pad, the flask and residue were washed with several portions of acetone, and the combined filtrate and washings was evaporated *in vacuo* to a syrup <50 C°. The syrup was treated twice with 150 mL portions of EtOH and evaporated. The syrup was then pumped at maximum vacuum for several hours. The residue was dissolved in 150 mL of hot acetone, filtered, concentrated to ~100 mL, cooled and scratched to induce crystallization. The white product was collected, washed with a little acetone and dried at 65 °C for 18 h over phosphorus pentoxide; yield, 6.3 g (51%); mp 100-107 °C cap; UV $\lambda_{max}$ 294 nm (17,600) 225 nm (10,300) at pH 1; 292 (19,300) 225 (10,800) at pH 7; 293 (19,400) 225 (10,700) at pH 13; MS (FAB) *m/e* 313 (M + 1); IR 1567, 1435, 1420, 1335, 1211, 1170, 1127, 1119, 1084, 1058, 944 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 1.37 (t, 3, $SCH_2CH_2$), 3.36 (q, 2, $SCH_2CH_3$), 3.57, 3.70 (2 m, 2, $CH_2$-5'), 3.98 (apparent q, 1, H-4'), 4.18 (apparent q, 1, H-3'), 4.61 (q, 1, H-2'), 5.13 (t, 1, OH-2'), 5.24 (d, 1, OH-3'), 5.53 (d, 1, OH-5'), 6.00 (d, 1, H-1'), 8.71 (s, 1, H-8), 8.74 (s, 1, H-2). *Anal.* Calcd for $C_{12}H_{16}N_4O_4S$: C, 46.14, H, 5.16, N, 17.94. Found: C, 46.02; H, 5.18; N, 17.84.

**2-β-D-Ribofuranosyl-5'-phosphate-1,3-thiazole-4-carboxamide (81).** Water (1.7 g, 94.5 mmol) was added carefully to a cold solution (0 °C) of freshly distilled phosphoryl chloride (22.5 g, 141.3 mmol) pyridine (13.5 g, 172.1 mmol), and acetonitrile (25.9 g, 630 mmol). Predried tiazofurin (9.0 g, 34.6 mmol) was added, and the mixture was stirred at 0 °C for 4.5 h. The reaction mixture was poured into ice-water (350 mL), stirred, and the pH was adjusted to 2.0 with 2*N* sodium hydroxide. The solution was stirred for 1.5 h with preswelled, acid-washed carbon-Celite mixture (1.5:1). The column was washed thoroughly with water until the eluate was salt-free. The column was eluted with a solution of ethanol/water/concentrated ammonium hydroxide (10:10:1), and 25 mL fractions were taken. The fractions containing the nucleotide were combined and evaporated to dryness in vacuum. This anhydrous solid was dissolved in water and passed through a column of Dowex 50W-X8 (50-100 mesh, $H^+$ form, 200 mL). Fractions containing the nucleotide were combined, concentrated under reduced pressure, and lyophilized: yield 7.17 g (60%). This product was converted to the sodium salt by passing its water solution through Dowex 50W-X8 resin (50-100 mesh, $Na^+$ form, 200 mL). The fractions containing the nucleotide were lyophilized to give the product which was contaminated with a small amount of sodium chloride. This impure product (6.45 g) was dissolved in water and passed through a column of Dowex 50W-X8 (50-100 mesh, $H^+$ form, 200 mL) to give product fractions which were combined, concentrated, and lyophilized to give a solid. This product was taken up in ethanol

and precipitated by adding ether to give an oil that solidified after trituration in acetonitrile. The product was dried *in vacuo*: yield 4.85 g (41%); mp <80 °C; MS (FAB) 341 (M + 1); IR (KBr) 3340 (broad), 2975, 2940, 1660, 1580, 1210, 1030, 476; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 3.92 (m, 2, $CH_2$-5′), 4.04 (m, 2, H-4′,3′), 4.11 (t, 1, H-2′), 4.98 (d, 1, H-1′), 7.57, 7.71 (2 br s, 2, C-$NH_2$-4), 8.23 (s, 1, H-5). *Anal.* Calcd for $C_9H_{13}N_2O_8PS{\cdot}0.33C_2H_5OH{\cdot}0.45H_2O$: C, 31.91; H, 4.40; N, 7.71. Found: C, 31.91; H, 4.75; N, 8.06.

**1-β-D-Ribofuranosylimidazo[1,2-*b*]pyrazole-7-carbonitrile (88).** A solution of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazo[1,2-b]pyrazole-7-carbonitrile (approximately 2.5 g) in MeOH/$NH_3$ (saturated at 0 °C) was allowed to stir at room temperature over the weekend in a pressure bottle. The solvent was removed *in vacuo* and the residue triturated with boiling benzene (3 x 45 mL) to remove the benzamide. The residual gum was crystallized from EtOH to yield 0.42 g of white crystals: mp 186-187 °C; MS (FAB) *m/e* 265 (M + 1); IR 1699, 1543, 1494, 1474, 1447, 1426, 1352, 1299, 1273 cm$^{-1}$; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 8.15 (d, 1, H-6), 7.95 (d, 1 H, H-3), 7.68 (m, 1, H-2), 5.66 (q, 1, H-1′, OH-2′), 5.34 (d, 1, OH-3′), 5.04 (t, 1, OH-4′), 4.35 (q, 1, H-2′), 4.06 (m, 1, H-3′), 3.96 (m, 1, H-4′), 3.62 (m, 2, $CH_2$-4′); $^{13}$C NMR ($Me_2SO$-$d_6$) $\delta$ 146.21 (C-6), 139.84 (C-8), 119.60 (C-2), 114.52 (C≡N), 110.40 (C-3), 89.60 (C-1′), 85.50 (C-4′), 73.67 (C-2′), 70.12 (C-3′), 66.17 (C-7), 61.45 (C-5′). *Anal.* Calcd for $C_{11}H_{12}N_4O_4{\cdot}0.1H_2O$: C, 49.65; H, 4.63; N, 21.06. Found: C, 49.75; H, 4.71; N, 20.71.

**1-β-D-Ribofuranosyl-5′-phosphate-1,2,4-triazole-3-carboxamide, Diammonium Salt (90).** A cold (0 °C) stirred solution of phosphoryl chloride (3.3 mL, 32.6 mmol) in 66 mL of trimethylphosphite was treated with ribavirin (2.68 g, 11 mmol). This suspension was stirred at 0 °C for 6 h. Most of the solid dissolved after the first 2 h of stirring. The reaction solution was then kept in the refrigerator overnight. The solution was poured into 120 mL of water (0 °C), and the pH was adjusted to 2 with 2*N* sodium hydroxide. The solution was extracted with two 150 mL portions of chloroform. This aqueous solution was applied to a plug column of activated carbon (acid-washed) and Celite (60 mL:30 mL). The column was washed with water until salt-free. The nucleotide was eluted with a solution of ethanol-water-conc ammonium hydroxide (10:10:1). The solvent was removed under reduced pressure, and the residue was dissolved in dilute ammonia. Ethanol was added to the solution and the precipitate was collected and dried *in vacuo*: yield, 1.97 g (38%). IR (KBr) 3500-2800 (broad), 1680, 1475 (broad), 1295, 1065 (broad), 970 cm$^{-1}$. UV $\lambda_{max}$ 206 (11,236) at pH 1; 207 (11,236) at pH7. $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 3.70 (t, 2, $CH_2$-5′), 4.07 (d, 1, H-4′), 4.23 (t, 1, H-3′), 4.48 (t, 1, H-2′), 5.77 (d, 1, H-1′), 7.64 (s, 2, $NH_2$-3), 7.96 (s, 1, $NH_2$-3), 8.96 (s, 1, H-5). *Anal.* Calcd for $C_8H_{13}N_4O_8P{\cdot}0.25C_2H_5OH{\cdot}2NH_3{\cdot}2H_2O$: C, 25.16; H, 6.08; N, 20.71. Found: C, 25.14; H, 5.89; N, 20.62.

**1-β-D-Ribofuranosyl-5′-O-methylphosphate-1,2,4-triazole-3-carboxamide, Ammonium Salt (91).** The 5′-phosphate of ribavirin (3.24 g, 10 mmol) was dissolved in a solution of methanol (400 mL) containing triethylamine (7.5 mL). Dicyclohexylcarbodiimide (16.6 g, 82 mmol) was added, and this solution was

kept at 37 °C overnight The solution was first concentrated to about 150 mL under reduced pressure and then was diluted with water, stirred for 4 h, chilled, and filtered to remove the dicyclohexylurea. The filtrate was concentrated to an oil under reduced pressure and then dried *in vacuo*. This residue was dissolved in water (50 mL), filtered, and the clear filtrate was passed through a column of Dowex 50Wx2 resin ($NH_4^+$, 200 mL). The product-containing eluates were combined, and evaporated *in vacuo*. The semi-solid residue was stirred in ethanol (50 mL), and the white solid product was collected, and dried *in vacuo*: yield 2.18 g (55%). IR (KBr) 3600-2800 (broad), 1685, 1615, 1470, 1290, 1215, 1060, 820 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.30 (d, $J$ = 11 Hz, 3, $CH_3O$-5'), 3.78 (m, 2, $CH_2$-5'), 4.05 (q, 1, H-4'), 4.2 (t, 1, H-3'), 4.41 (t, 1, H-2'), 5.83 (d, 1, H-1'), 6.19 (d, 1, H-1'), 7.39 (s, 4, $NH_4^+$-5'), 7.65 (s, 2, $NH_2$-3), 8.05 (s, 2, $NH_2$-3), 8.20 (s, 2, $NH_2$-3), 8.92 (s, 1, H-5), 8.94 (s, 1, H-5). *Anal.* Calcd for $C_9H_{18}N_5O_8P \cdot 0.75C_2H_5OH \cdot 0.5H_2O$: C, 31.62; H, 5.93; N, 17.56. Found: C, 31.90; H, 6.21; N, 17.52.

**1-β-D-Ribofuranosyl-5'-O-diphosphate-1,2,4-triazole-3-carboxamide, Dilithium Salt (93).** The triethylammonium salt of ribavirin 5'-phosphoromorpholidate dihydrate (800 mg, 1.5 mmol) was dried by two repetitions of dissolution in pyridine (15 mL) and evaporation *in vacuo*. Orthophosphoric acid (85%) (0.31 mL, 4.5 mmol) was dissolved in pyridine (15 mL) containing tri-n-butylamine (1.07 mL, 4.5 mmol), and evaporated *in vacuo*. Three evaporations with pyridine (3 x 15 mL) rendered this mixture anhydrous.

Both of the above residues were dissolved in pyridine, combined, and the evaporation procedure was repeated two more times. The residue was dissolved in dry pyridine (20 mL), and stirred for 3 days (until no morpholidate remained). The solvent was removed *in vacuo* and the residue was evaporated several times with water. The pH of the aqueous solution was adjusted to pH 6.5 with 0.5*M* LiOH, and the aqueous solution was washed several times with ether. The pH of the aqueous phase was adjusted to 12 with LiOH (total volume, 45 mL). This suspension was chilled at 0 °C for 0.5 h, and the lithium phosphate was removed by filtration, and washed with a small amount of 0.01*N* LiOH. The pH of the aqueous solution was adjusted to pH 8 with Dowex 50 ($H^+$)-resin, and applied to a column of Dowex 2-x8 ($Cl^-$) resin (2.5 x 15 cm). The column was washed with water and then eluted with increasing concentrations of lithium chloride in 0.003 *N* HCl: 0.0125*N*, 0.025*N*, 0.075*N*, 0.1*N*, 0.25*N*, and 0.5*N* for over 2 L. Fractions containing the product were combined and evaporated *in vacuo*. The residue was treated with methanol, diluted with acetone, centrifuged, and the liquid was decanted to remove the LiCl. This procedure was repeated several times. The residue (250 mg) was dissolved in water, and freeze-dried to give the nucleoside diphosphate dilithium salt: yield 230 mg (26%). IR (KBr) 3600-3100 (broad), 1685, 1640, 1490, 1300, 1220, 1110 (broad), 940 $cm^{-1}$; $^{31}P$ NMR (1.6 mL Hepes Buffer, pH 7.4; 0.4 mL $D_2O$ and 0.05 mL EDTA) $\delta$ -5.98 (2, 1, P, d, $^3J_{1,2}$ = 22.1 Hz) and -9.97 (1, 1 P, dqt). *Anal.* Calcd for $C_8H_{12}N_4O_{11}P_2Li_2 \cdot 4.5H_2O \cdot 2LiCl$: C, 16.51; H, 3.64; N, 9.63. Found: C, 16.51; H, 3.56; N, 9.61.

**Formycin B. (Pyrazolo-[4,3-*d*]-6*H*-7-pyrimidone, 3-β-D-ribofuranosyl-) (104).** Formycin B was synthesized following a 14 step reaction sequence by L. Kalvoda. Mp 248-51 °C cap; UV $\lambda_{max}$ 276 nm (7,700) at pH 1; 278 (7,700) at pH 7; 292 (8,400) at pH 13; MS (FAB) *m/e* 269 (M + 1); IR 1700, 1668, 1587, 1530, 1122, 1115, 1076, 1014, 930, 900 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) δ 3.48, 3.62 (2 m, 2, $CH_2$-5'), 3.88 (q, 1, H-4'), 4.60 (s, 1, H-3'), 4.43 (apparent q, 1, H-2'), 4.90 (d, 1, H-1'), 7.89 (s, 1, H-5), 12.3, 14.06 (2 br s, 2, H-NH).

**4-Acetyl-4-phenylpiperidine Hydrochloride (107).** 4-Acetyl-4-phenylpiperidine (10 g) was chromatographically purified by elution with $CHCl_3$/MeOH (95:5) through silica gel.[11] Dissolution of the crystallizable clear oil in EtOH (125 mL) followed by bubbling HCl gas, solvent evaporation (x3), charcoaling in hot ethanol, and solvent evaporation to about 20% of the original volume gave a white granular solid (4.0 g). (Further evaporation gave 0.8 g of a slightly impure sample of 39.) Mp (darkens at 160 °C) 229-230 °C partial, 239-40 °C. $^1H$ NMR ($Me_2SO$-$d_6$) δ 9.20 (s, 2, $-\overset{\oplus}{N}H_2$), 7.40 (m, 5, Ar-H's), 3.10 (m, 2, 2 eq-H), 2.95 (m, 2, 2 ax-H), 2.52 (m, 2, 3 eq-H), 2.24 (m, 2, 3 ax-H), 1.94 (s, 3, $-CH_3$). *Anal.* Calcd for $C_{13}H_{18}ClNO$: C, 65.12; H, 7.58; N, 5.84. Found: C, 64.74; H, 7.58; N, 5.84.

**DL-β-(3,4-Dimethoxybenzoyl)-γ-butyrolactone (140).**[17] 3,4-Dimethoxybenzoyl-β-propionic acid (4.76 g, 0.02 mol) was slowly added to a solution of 2 g $K_2CO_3$ in 10 mL of water. Formalin (1.8 mL, 39% solution) was then slowly added, and the mixture was stirred at room temperature for two days and at ~50 °C for three more days. Concentrated HCl (3 mL) was added to effect lactonization and the resulting solution was heated at ~80 °C for 1 h. Cooling and extraction with methylene chloride, washing the $CH_2Cl_2$ with 10% $Na_2CO_3$ and water, drying over sodium sulfate, and evaporation of the solvent gave a viscous brown oil. Recrystallization of this oil from methanol gave a light brown granular solid (3.2 g). Mp 105-106 °C; $^1H$ NMR ($Me_2SO$-$d_6$) δ 7.70 (dd, $J_{aa} = J_{bb} = 9$ Hz, $J_{ab} =$ 2 Hz, 1, H-6'), 7.49 (m, 1, H-2'), 7.10 (d, $J = 9$ Hz, 1, H-5'), 4.60 (m, 2, H-4), 4.33 (m, 1, H-3), 3.87 (s, 3, $-OCH_3$), 3.84 (s, 3, $-OCH_3$), 2.90 (m, 1, H-2), 2.73 (m, 1, H-2). IR (KBr) 1757, 1661, 1582, 1514, 1267, 1251, 1198, 1161, 1156, 1012 $cm^{-1}$. $^{13}C$ NMR ($Me_2SO$-$d_6$) δ 196.1 (C=O), 175.9 (C=O, lac), 153.6 (C-4'), 148.7 (C-3'), 127.6 (C-1'), 123.4 (C-6'), 110.9 (C-5'), 110.5 (C-2'), 69.2 (C-4), 55.7 ($CH_3$), 55.5 ($CH_3$), 41.2 (C-3), 30.8 (C-2). *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.60; H, 5.90.

**References**


1. Lewis, A. F.; Townsend, L. B., *J. Am. Chem. Soc.*, 1982, *104*, 1073-1077.
2. Robins, M. J.; Uznanski, B., *Can. J. Chem.*, 1981, *59*, 2601-2607.
3. Shortnacy, A. T., personal communication.
4. Shinkai, I.; Vander Zwan, M. C.; Hartner, F. W.; Reamer, R. A.; Tull, R. J.; Weinstock, L. M., *J. Heterocycl. Chem.*, 1981, *18*, 197-198.
5. Weinstock, L. M.; Tull, R. J.; Douglass, A. W.; Shinkai, I., *J. Org. Chem.* 1980, *45*, 5419-5421.

6. Weimer, D. F.; Leonard, N. J., *J. Org. Chem.*, 1974, *39*, 3438.
7. Broom, A. D.; Robins, R. K., *J. Org. Chem.*, 1969, *34*, 1025.
8. Knorr, L., *Ann.*, 1984, *279*, 188-232.
9. Marvel, C. S.; Dreger, E. E., *Org. Syn. Coll. Vol. I*, 1941, 238-240.
10. Kroger, C.-F.; Etzdd, G.; Beyer, H., *Ann.*, 1963, *664*, 146-155.
11. Henry, R. A.; Makosky, R. C.; Smith, G. B. L., *J. Am. Chem. Soc.*, 1950, *73*, 474.
12. Saneyoshi, M.; Satoh, E., *Chem. Pharm. Bull.*, 1979, *27*, 2518-2521.
13. Kroger, C.-F.; Miethchen, R., *Z. Chem.*, 1969, *9*, 378-379.
14. Potts, K. T.; Hirsch, C., *J. Org. Chem.*, 1968, *33*, 143-150.
15. Gupton, J. T.; Corrcia, K. F.; Foster, B. S., *Synth. Commun.*, 1986, *16*, 365.
16. Veda, N.; Kawabata, T.; Takemoto, K., *J. Heterocycl. Chem.*, 1971, *8*, 827.
17. Cottam, H. B.; Petrie, C. R.; Revankar, G. R.; Robins, R. K., *J. Med. Chem.*, 1984, *27*, 1119-1127.
18. Omura, S.; Nakegawa, A., *Tetrahedron Lett.*, 1981, *22*, 2199-2202.
19. Omura, S., *J. Antibiot.*, 1981, *31*, 1395-1436.
20. Vaughan, W. R., *Org. Syn. Coll. Vol. III*, 1955, 329-332.
21. Fieser, L.; Fieser, M., *Reagents for Organic Synthesis*, 1967, *1*, 4.
22. Halls, D. J., *Mikrochim. Acta [Wien]*, 1969, 62.
23. Kitson, T., *Ed. Chem.*, 1985, 43.
24. Takami, F.; Ikawa, K.; Tokuyama;, Wakahara, S.; Maeda, T., *Chem. Pharm. Bull.*, 1974, *22*, 275.
25. Dagani, R., Chem. Eng. News, 1987, *65*, 47, 41.
26. Jurd. L.; Narayanan, V. L.; Paull, K. D., *J. Med. Chem.*, 1987, *30*, 1752-1756.
27. Leonova, T. S.; Yashunskii, V. G., *Khim. Geterotsik. Soedin.*, 1982, *7*, 982-984.
28. Witkowski, I. T.; Robins, R. K., *J. Org. Chem.*, 1970, *35*, 2635-2641.
29. Montgomery, J. A.;; Johnston, T. P.; Gallagher, A.; Stringfellow, C. R.; Schabel, F. M., *J. Med. Chem.*, 1961, *3*, 265-288.
30. Clayton, S. J., personal communication.
31. Srivastava, P. C.; Revankar, G. R.; Robins, R. K., *J. Med. Chem.*, 1984, *27*, 266.
32. Elguero, J.; Jacquier, R.; Mignonac-Mondon, S., *J. Heterocycl. Chem.*, 1973, *10*, 411-412.
33. Wood, S. G.; Dalley, N.; George, R.; Robins, R. K.; Revankar, G. R., J. Org. Chem., (1984) 49, 3534-3540.
34. Robins, R. K.; Christensen, L. F., *J. Med. Chem.*, 1978, *21*, 742.
35. Bobek, M.; Farkas, J., *Coll. Czech. Chem. Commun.*, 1969, *34*, 247-252.
36. Kalvoda, L., *Coll. Czech. Chem. Commun.*, 1978, *43*, 1431-1437.
37. Elion, G. B.; Hitchings, G. H., *J. Am. Chem. Soc.*, 1956, *78*, 3508-3510.
38. Elion, G. B.; Hitchings, G. H., *J. Am. Chem. Soc.*, 1956, *78*, 3511-3513.
39. Westover, J. D.; Revankar, G. R.; Robins, R. K., *J. Med. Chem.*, 1981, *24*, 941-946.

40. Makisumi, Y., *Chem. Pharm. Bull.*, **1961**, *9*, 801.

41. Revankar, G., *J. Med. Chem.*, **1984**, *27*, 1119-1127.

42. Shimokawa, S.; Kimura, J.; Mitsonobu, O., *Bull. Soc. Chem. Jap.*, **1976**, *49*, 3357-3358.

43. Block, E.; Stevenson, R. J., *J. Org. Chem.*, **1971**, *36*, 3453-3455.

44. Pelter, A.; Ward, R. S.; Pritchard, M. C.; Kay, I. T., *Tetrahedron Lett.*, **1985**, *26*, 6377-6380.

45. Rothe, J.; Zimmer, H., *J. Org. Chem.*, **1959**, *24*, 586.

46. Mellor, J. M.; Stibbard, J. H. A.; Rawlins, M. F., *J. Chem. Soc., Chem. Commun.*, **1978**, 556-557.

47. Pauwels, R.; Balzarini, J.; Schols, D.; Baba, M.; Desmyter, J.; Rosenberg, I.; Holy, A.; DeClercq, E., *Antimicrob. Agents Chemother.*, **1988**, *32*, 7, 1025-1030.

48. Bronson, J. (Bristol-Myers), personal communication.

## DISTRIBUTION LIST

| | |
|---|---|
| 4 Copies | Commander<br>U. S. Army Medical Research Institute of Infectious Diseases<br>ATTN: SGRD-UIZ-M<br>Fort Detrick, MD 21701-5011 |
| 1 Copy | Commander<br>U. S. Army Medical Research and Development Command<br>ATTN: SGRD-RMI-S<br>Fort Detrick<br>Frederick, MD 21701-5012 |
| 2 Copies | Defense Technical Information Center (DTIC)<br>ATTN: DTIC-FDAC<br>Cameron Station<br>Alexandria, VA 22304-6145 |
| 1 Copy | Dean, School of Medicine<br>Uniformed Services<br>University of the Health Sciences<br>4301 Jones Bridge Road<br>Bethesda, MD 21084-4799 |
| 1 Copy | Commandant<br>Academy of Health Sciences, U. S. Army<br>ATTN: AHS-CDM<br>Fort Sam Houston, TX 78234-6100 |