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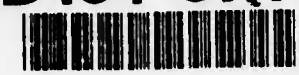

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(2)

SRI-ORG-91-059-6000-XXII

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
Deborah A. Carter
Lisa K. Hanna
George S. McCaleb

JANUARY 14, 1991
(For the period 1 December 1989 - 30 November 1990)

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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Synthesis Laboratory for the U.S. Army Medical Research Institute of Infectious Diseases Selection Panel

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17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
07	03		antiviral; synthesis laboratory; imidazole; adenosine; adenosine N^1-oxides; benzyloxyadenosines; tetraazadiphosphorines; selenadiazoles; triazolotriazoles; guanidines; pyrazoles; adamantanecarboxamides; adamantylthioureas; RAI
06	15		

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, selenadiazoles, triazoles, triazolotriazoles, guanidines, pyrazoles, adamantane derivatives, chloroquines, N^1-aminonucleosides, allopurinol acyclonucleosides, nucleotides of ribavirin and tiazofurin, and various other heterocyclic compounds.

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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 describes the activities supported by Contract No. DAMD17-86-C-6011 during the fifth and final year, 1 December 1989 through 30 November 1990. The purpose of this contract is to support the synthesis of a wide variety of compounds for evaluation in the USAMRIID viral testing program. These compounds will include: (1) known compounds that are needed in larger quantities for proper evaluation; and (2) new compounds whose structures are determined by rational processes.

During this year, we submitted thirty-three more compounds for screening:

4-(4′-ethylamino-1′-methylbutylamino)-7-chloroquinoline [AVS-3980]
ribavirin triphosphate
9-[2-(phosphonylmethoxy)ethyl]guanine (PMEG)
1-(phosphonylmethoxyethyl)-1,2,4-triazole-3-carboxamide
the diammonium salt of 1-[(phosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide
1-[2-(diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide
6-ethylsulfonyl-9-β-D-ribofuranosylpurine
3-acetamido-7-amino-6-methyl-7*H*-*S*-triazolo[5,1-*c*]-*S*-triazole (AVS-4206)
1,3-bis-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinone
1-morpholinomethyltetrahydro-2(1*H*)-pyrimidinethione
1-morpholinomethyltetrahydro-2(1*H*)-pyrimidinone
two batches of 5-chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (AVS-0124)
3-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (AVS-4205)
3-imino-2*H*-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole
3-amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole
multiple batches of 1-(3-methylbenzyloxy)-adenosine (AVS-1986)
6-amino-2,4-dithiouracil
1-(2-methylbenzyloxy)adenosine (AVS-2875)
6-carboxamidopurine riboside (AVS-0015)
4-thio-6-azauridine
the triacetate of 4-thio-6-azauridine
4-amino-1-(β-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (3-deazaadenosine) (AVS-303)
4-amino-1-[1α,2β,3β,4α)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]imidazo[4,5-*c*]pyridine (carbocyclic 3-deazaadenosine)
4-amino-1-(β-arabinofuranosyl)imidazo[4,5-*c*]pyridine (arabino-3-deazaadenosine)
(1α,2β,3β,4α)-(±)-4-(7-amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-2,3-dihydroxycyclopentanemethanol (carbocyclic 8-azaadenosine)
(1α,2β,4α)-(±)-4-(7-amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-2-hydroxycyclopentanemethanol (carbocyclic 2′-deoxy-8-azaadenosine)
(1β,3α,4β)-(±)-3,6-dihydro-3-[3-hydroxy-4-(hydroxymethylcyclopentyl)-7*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-7-one (carbocyclic 2′-deoxy-8-azainosine)
(1α,2β,4α)-(±)-4-(5,7-diamino-3*H*-1,2,3-triazolo[4,5,*d*]pyrimidin-3-yl-2-hydroxy-cyclopentanemethanol (carbocyclic 2,6-diamino-8-azapurine-2′-deoxyribofuranoside)
(1β,3α,4β)-(±)-5-amino-3,6-dihydro-3-[3-hydroxy-4-(hydroxymethyl)cyclopentyl]-7*H*-1,2,3-triazolo-[4,5-*d*]pyrimidin-7-one (carbocyclic 2′-deoxy-8-azaguanosine)
(1β,3α,4β)-(±)-5-amino-3,6-dihydro-3-[3-hydroxy-4-(hydroxymethyl)cyclopentyl]-7*H*-1,2,3-triazolo-[4,5-*d*]pyrimidin-7-thione (carbocyclic 2′-deoxy-8-aza-6-thioguanosine)
(1α,2β,4α)-(±)-4-(5-amino-7-methoxy-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-2-hydroxycyclopentanemethanol (carbocyclic 2-amino-6-methoxy-8-azapurine-2′-deoxyribofuranoside).

During the year, we also directed our efforts toward the synthesis of a number of other compounds which were specifically requested by Dr. Gabrielsen. These compounds included: 9-[(phosphonylmethoxy)ethyl]-2-aminopurine (PMEMAP); 9-[(phosphonylmethoxy)ethyl]-2,6-diaminopurine (PMEDAP); the amidine analog of 6-carboxamidopurine riboside (AVS-0015); 7-*S*-substituted analogs of 5-chloro-3-β-D-ribofuranosyl-*s*-triazolopyrimidin-7-one (AVS-0124); and 6-ethylsulfinylpurine riboside. However, the syntheses of these compounds were not completed. Because none of these compounds were especially high priority, we decided to maximize the time remaining with this contract and to direct our efforts toward the other higher priority compounds which had been recently requested by Dr. Gabrielsen and the USAMRIID antiviral screening committee. As a result, we have been pursuing the following compounds: 4-amino-5-glucosamino-2-thiouracil; 4-amino-5-mannosamino-2-thiouracil; 2,4-dithio-6-azauridine; 5′-*O*-[[[[2′,3′,4′,6′-tetra-*O*-benzyl-α-D-gluco-pyranosyl)oxy]carbonyl]amino]sulfonyl]-2′,3′-isopropylidene-2-thio-6-azauridine; and carbocyclic adenosine.

Other activities during this year have included the completion of the preliminary drafts for our publication manuscripts describing the 1-benzyloxyadenosine and triazolotriazole nucleoside analogs. These manuscripts are now being reviewed by Dr. Secrist, and they should be submitted in the near future.

Finally, we also requested and were granted an "extension without additional funds" for this contract. The three-month period provided by this extension will be used primarily to continue our pursuit of compounds requested by Dr. Gabrielsen and the USAMRIID antiviral screening committee. We will also use this extension to prepare additional publication manuscripts and to write the Fifth Annual and the Final reports for this project.

Personnel

During the year covered by this report, there were no major changes. All of the time charges made during the fifth year are listed below and are divided into various categories.

Name	Hours 1 Dec 88 - 30 Nov 89	Percent of Time
Project Supervision:		
Dr. J. A. Secrist III	178.5	10
Chemists:		
D. A. Carter	1151	62
L. K. Hanna	476	25
C. A. Krauth	1845.5	100
Dr. C. D. Kwong	1369	74
G. S. McCaleb	1220.5	68

Name	Hours 1 Dec 88 - 30 Nov 89	Percent of Time
Chemists: (continued)		
C. A. O'Dell	14	1
R. J. Remy	1	<1
Analytical Services:		
D. J. Adamson	11	1
J. A. Alexander	3	<1
S. R. Campbell	7	>1
Dr. W. C. Coburn	123.5	7
R. J. Gray	55	3
M. C. Kirk	162	9
D. M. McCain	27	1
M. D. Ochs	73.5	4
C. Richards	203.25	11
Dr. J. M. Riordan	108.5	6
Glassware Technicians:		
A. D. Jackson	322	18
W. Johnson	172	10
R. W. Milton	10	1
J. C. Robinson	210.5	12
Support Services:		
B. F. Meadows	4.5	<1
T. D. Stringfellow	3.5	<1

Compounds Submitted

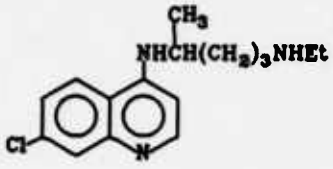
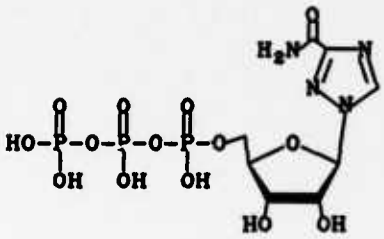
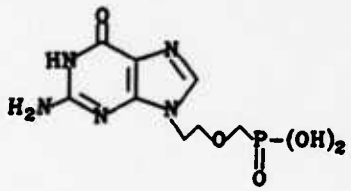
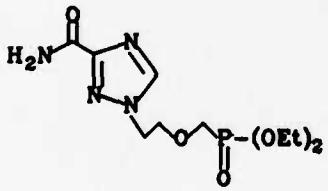
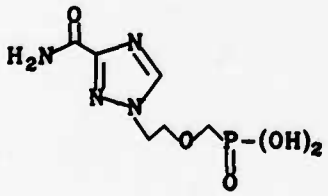
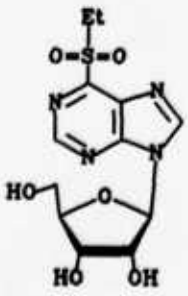
The compounds that we submitted during this report period are shown on the following page. We have included their SRI numbers, AVS numbers (if available), and the amounts submitted. Of course, we can make additional quantities of these compounds, if warranted.

Chemistry

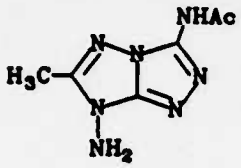
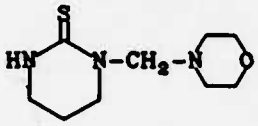
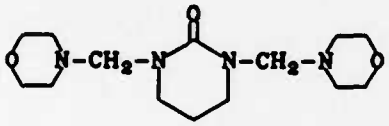
During this report period, the thirty-three compounds submitted for screening included: 4-(4′-ethylamino-1′-methylbutylamino)-7-chloroquinoline [AVS-3980]; ribavirin triphosphate; 9-[2-(phosphonylmethoxy)ethyl]guanine (PMEG); 1-(2-(phosphonylmethoxyethyl)-1,2,4-triazole-3-carboxamide (AVS-6469); the diammonium salt of 1-[(phosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide; 1-[2-(diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide; 6-ethylsulfonyl-9-β-D-ribofuranosylpurine; 3-acetamido-7-amino-6-methyl-7*H*-*S*-triazolo[5,1-*c*]-*S*-triazole (AVS-4206); 1,3-bis-(morpholinomethyl)-tetrahydro-2(1*H*)pyrimidinone; 1-morpholinomethyltetrahydro-2(1*H*)pyrimidinethione; 1-morpholinomethyltetrahydro-2(1*H*)-pyrimidinone; two batches of 5-chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (AVS-0124); 3-(2′,3′,5′-tri-*O*-benzoyl-D-ribofuranosyl)amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (AVS-4205); 3-imino-2*H*-2-(2,3,5-tri-*O*-benzoyl-β-D-

Compounds Submitted During the 17th Quarter

(December 1, 1989 - February 28, 1990)

Compound	SRI Number	AVS Number	Amount Submitted
	7086	3980	2.5 g
	7557	6753	255 mg
	7553	6754	710 mg
	7541	6468	350 mg
	7542	6469	30 mg 25 mg
	7547	6752	693 mg

Compounds Submitted (Continued)

Compound	SRI Number	AVS Number	Amount Submitted
	7152	4206	2.4 g
	7572	6781	1.1 g
	7573	6782	1.0 g

Compounds Submitted During the 18th Quarter

(March 1, 1990 - May 30, 1990)

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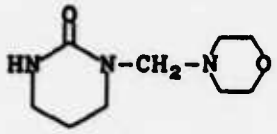
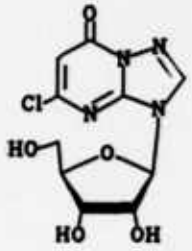
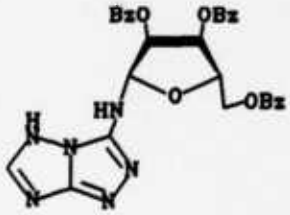
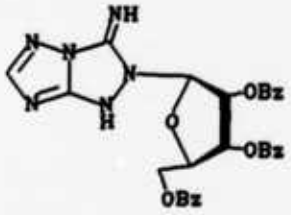
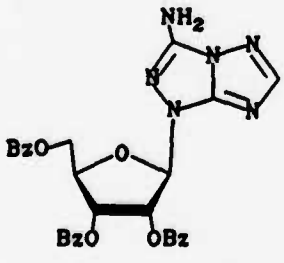
	7589	7120	2.3 g
	7597	124	100 mg
	7151	4205	666 mg
	7586	6787	2.2 g
	7587	6788	1.41 g

Compounds Submitted During the 19th Quarter

(June 1, 1990 - August 31, 1990)

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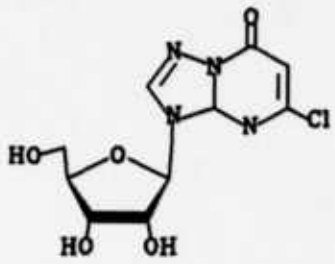
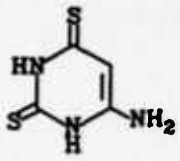
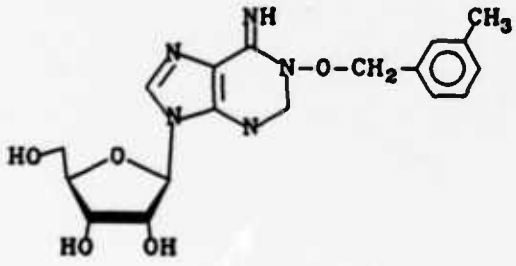
	7597	124	2.0 g
	7687		100 mg
	6767	1986	1.0 g

Compounds Submitted During the 20th Quarter

(September 1, 1990 - November 30, 1990)

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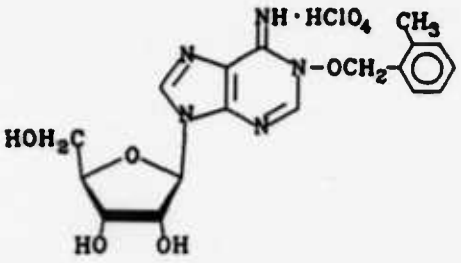
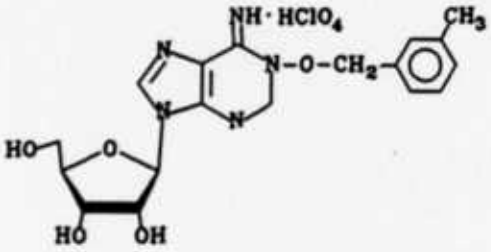
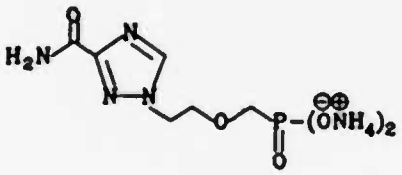
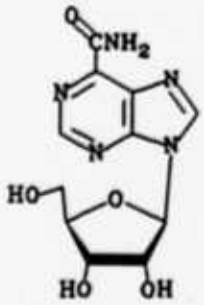
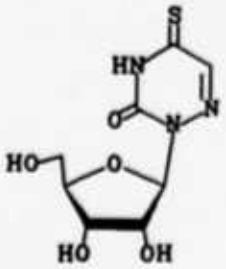
	6887	2875	1.0 g
	6767	1986	1.0 g
	7700	8354	497 mg
	7718	0015	1.9 g
	7717	8355	100 mg

Compounds Submitted (Continued)

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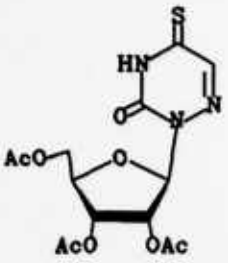
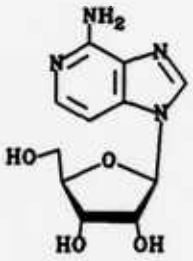
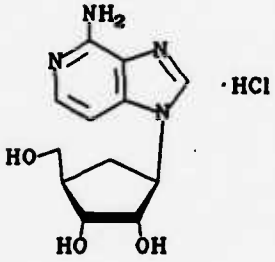
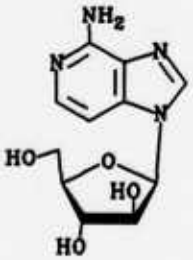
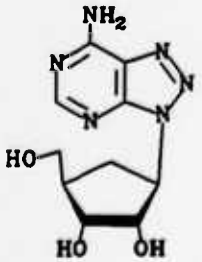
	7699	8353	300 mg
	5944		98 mg
	6251	303	97 mg
	5970		98 mg
	4395		20 mg

Compounds Submitted (Continued)

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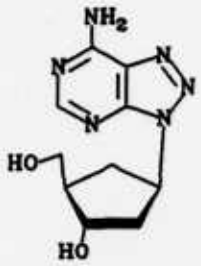
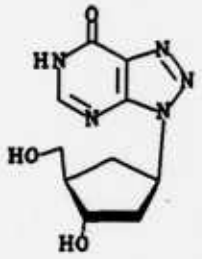
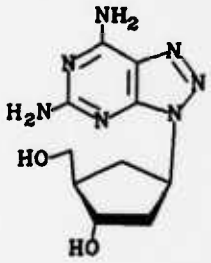
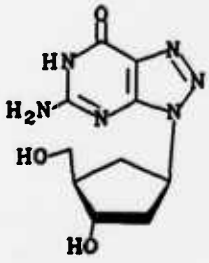
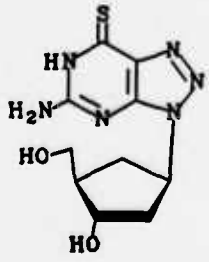
	4541		20 mg
	4552		20 mg
	5160		20 mg
	5174		20 mg
	5566		20 mg

Compounds Submitted (Continued)

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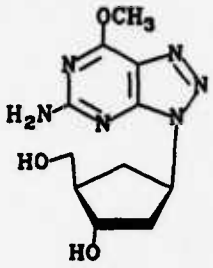
	6560		20 mg

triazole; 6-amino-2,4-dithiouracil; multiple batches of 1-(3-methylbenzyloxy)adenosine (AVS 1986); 1-(2-methylbenzyloxy)adenosine (AVS-2875); 6-carboxamidopurine riboside (AVS-0015); 4-thio-6-azauridine; the triacetate of 4-thio-6-azauridine; 3-deazaadenosine; carbocyclic 3-deazaadenosine; arabino-3-deazaadenosine; carbocyclic 8-azaadenosine; carbocyclic 2′-deoxy-8-azaadenosine; carbocyclic 2′-deoxy-8-azainosine; carbocyclic 2,6-diamino-8-azapurine-2′-deoxyribofuranoside; carbocyclic 2′-deoxy-8-azaguanosine; carbocyclic 2′-deoxy-8-aza-6-thioguanosine; and carbocyclic 2-amino-6-methoxy-8-azapurine-2′-deoxyribofuranoside.

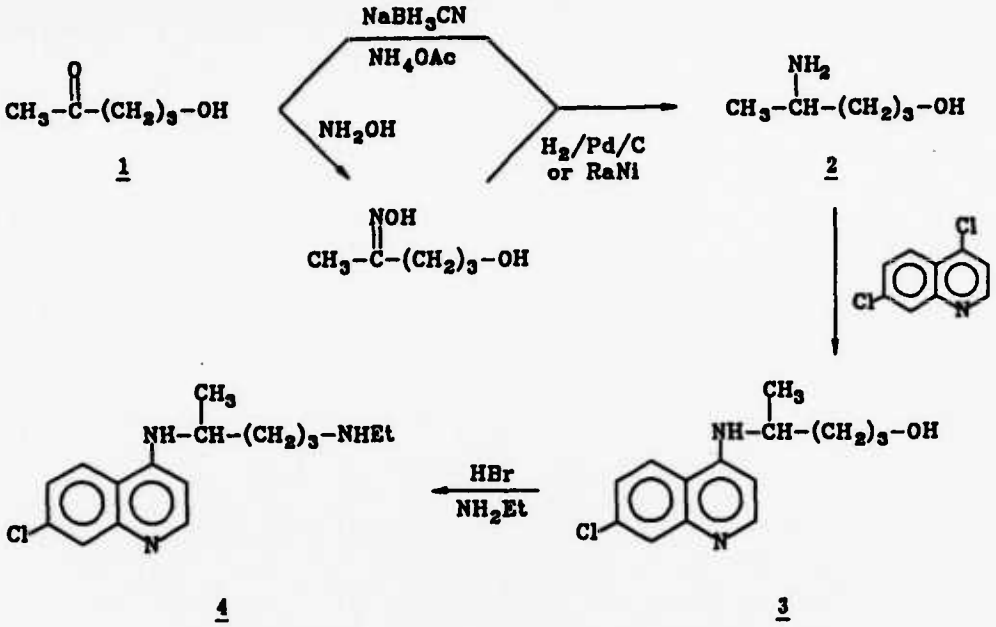
Scheme I shows the approach that we followed in our resynthesis of 4-(4′-ethylamino-1′-methylbutylamino)-7-chloroquinoline (**4**).[1,2] This compound first required the synthesis of the sidechain precursor by the reduction of 3-acetylpropanol (**1**) with $NaBH_3CN$ and ammonium acetate to give 4-aminopentanol (**2**). The 4-aminopentanol was then reacted with 4,7-dichloroquinoline to give adduct **3**, and this compound was then treated with HBr and ethylamine to give 4-(4′-ethylamino-1′-methylbutylamino)-7-chloroquinoline (**4**).

We had previously reported that we had synthesized ribavirin 5′-triphosphate (**7**)[3] by the two routes shown in **Scheme II**. Unfortunately, the products obtained from both methods were contaminated with residual inorganic pyrophosphate. When informed that we were unable to significantly reduce the amount of pyrophosphate either chromatographically or by manipulating reaction conditions, Dr. Gabrielson agreed to accept the obtained compound for screening.

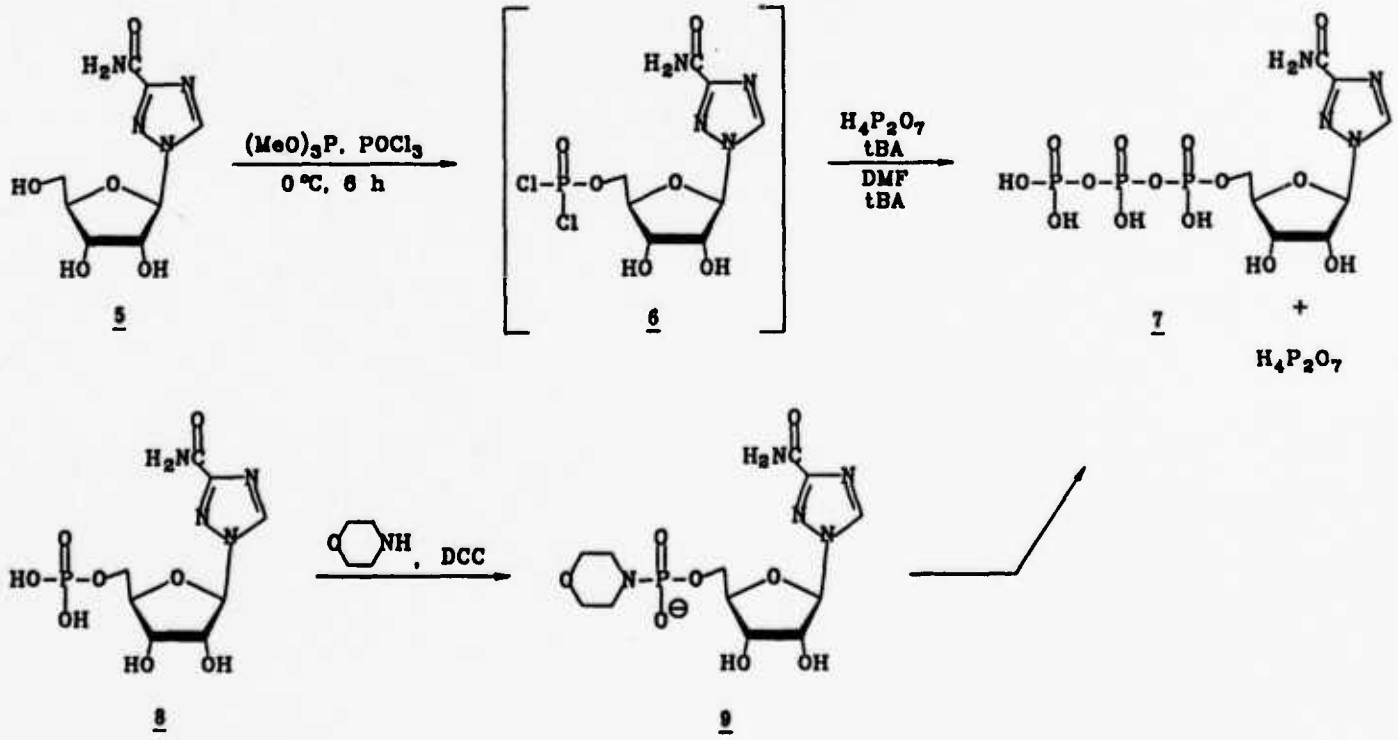
We have discussed the many routes pursued in our synthesis 9-[2-(phosphonylmethoxy)ethyl]guanine (PMEG) (**18**), the guanine analog of 9-[2-(phosphonylmethoxy)ethyl]adenine (PMEA). **Scheme III** shows the synthetic route to this compound that was successful for us. The key intermediate for this compound (as well as for the other PMEA analogs) was synthesized using a sidechain precursor, which differed from that suggested by the procedure[4] that we had initially followed. Our modified sidechain precursor, 2-(diethylphosphonylmethoxy)ethyl-1-tosylate (**14**), was synthesized by first treating chloroacetate **11** with triethylphosphite to give phosphonate **12**. We then hydrolyzed **12** with acetone:water (4:1) and concentrated HCl and tosylated the resulting diethylphosphonylmethoxyethanol (**13**) with *p*-toluenesulfonyl chloride and triethylamine in methylene chloride to obtain precursor **14**. Coupling of this sidechain precursor with 2-amino-6-chloropurine (**15**) with potassium carbonate in anhydrous DMF (at room temperature for 3 days under argon),[5] gave intermediate **16**. PMEG (**18**) was then obtained after the hydrolysis of the phosphonate ester with bromotrimethylsilane and hydrolysis of the 6-chloro group to the required 6-oxo group.

Our routes to the synthesis of ribavirin analog **23** have also been given in previous quarterly reports. As shown in **Scheme IV**, we were able to alkylate methyl 1,2,4-triazole-3-carboxylate with compound **14**, the same modified sidechain precursor used in our successful PMEG synthesis. Coupling of the two components in anhydrous DMF with potassium carbonate at 90 °C under inert atmosphere[5] gave a mixture of products containing the desired intermediate **19** as well as structural isomer **20** and decarboxylated analog **21**. Because **19** and **21** could not be easily separated, this mixture was then treated with concentrated ammonium hydroxide to give an easily separable mixture containing 1-[2-(diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide **22** and **21**. Carboxamide phosphonate ester **22** was isolated and then hydrolyzed with bromotrimethylsilane

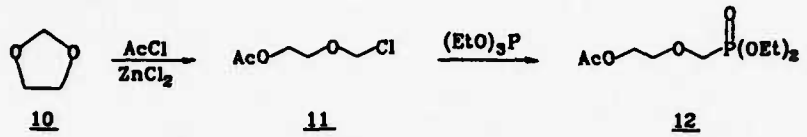
Scheme I



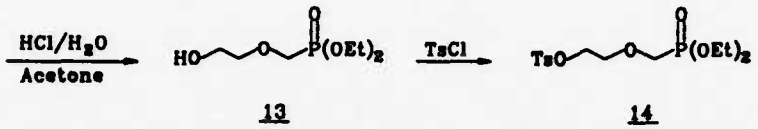
Scheme II



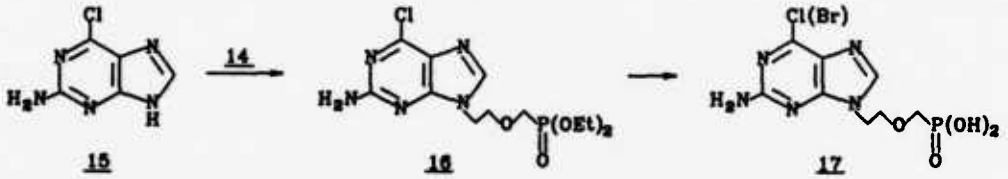
Scheme III



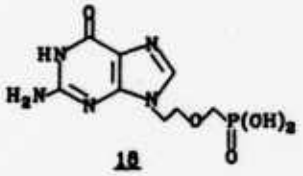
10 11 12



13 14

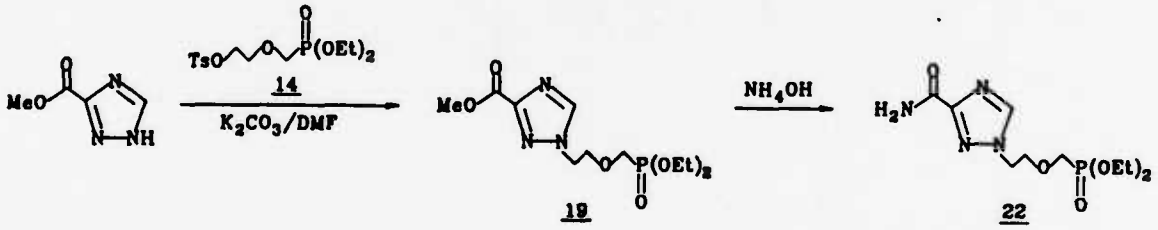


15 16 17



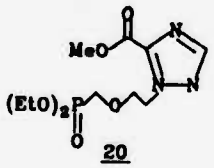
18

Scheme IV



19 22

+



20

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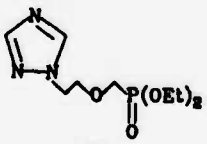

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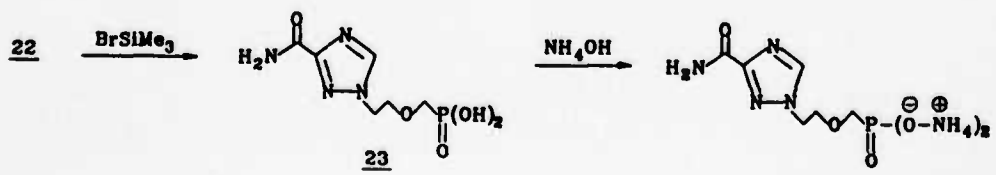


23

ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole;3-amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-to give the desired target compound **23**. Purification of this compound has proven to be difficult primarily because of solubility problems. Our attempts to recrystallize from acetone/water (as was suitable for the purification for PMEA) were unsuccessful, probably due to the extreme water solubility of this compound. Our results from this approach were inconsistent, and at best, we obtained only <10 % yields of pure **23**, relative to the total amount being produced. Therefore, a number of other purification methods were investigated before we determined that the simple treatment of **23** with dilute ammonium hydroxide followed by evaporation under vacuum gives a better yield of the desired compound as the diammonium salt.

We synthesized 6-ethylsulfonyl-9-β-D-ribofuranosylpurine (**25**) by the approach shown in **Scheme V**. Oxidation of 6-ethylthiopurine riboside (AVS-2700) (**24**) with *m*-chloroperbenzoic acid in acetone[6] gave the corresponding sulfonyl compound.

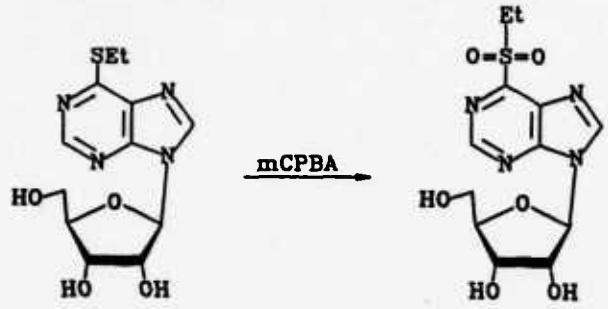
An additional quantity of 3-acetamido-7-amino-6-methyl-7*H*-*S*-triazolo[5,1-*c*]-*S*-triazole [AVS-4206] (**29**) was also prepared by the approach shown in **Scheme VI**. The required precursor for this compound, 3,7-diamino-6-methyl-7*H*-*S*-triazolo[5,1-*c*]-*S*-triazole (**28**) was synthesized from triaminoguanidine (**26**). Sequential treatment of triaminoguanidine with acetic acid and hydrochloric acid gave triazole **27**.[7] This intermediate was then further cyclized by treatment with cyanogen bromide to give precursor **28**,[8] which after acetylation with acetic anhydride gave **29**.

Mannich condensation products 1,3-bis-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinone (**32**) and 1-morpholinomethyltetrahydro-2(1*H*)-pyrimidinethione (**34**) were both synthesized by similar routes.[9] As shown in **Scheme VII**, both 1-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinone (**31**) and 1,3-bis-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinone (**32**) were synthesized by the condensation of tetrahydro-2(1*H*)-pyrimidinone (**30**) with morpholine in formalin solution. Although the literature preparation for these compounds reported that the desired products could be isolated and sufficiently purified by recrystallizations from ethyl acetate, our efforts to duplicate this procedure immediately gave only the monomorpholinomethyl product **31** in sufficient purity. However, we were able to isolate pure 1,3-bis-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinone (**32**) after column chromatography (silica gel, $CHCl_3$:MeOH, 9:1, iodine) followed by recrystallization from ethyl acetate.

Scheme VIII shows that a similar route was used to synthesize 1-morpholinomethyltetrahydro-2(1*H*)-pyrimidinethione (**34**). Condensation of tetrahydro-2(1*H*)-pyrimidinethione with morpholine and formalin solution gave the desired compound, which was purified by numerous recrystallizations from ethanol.

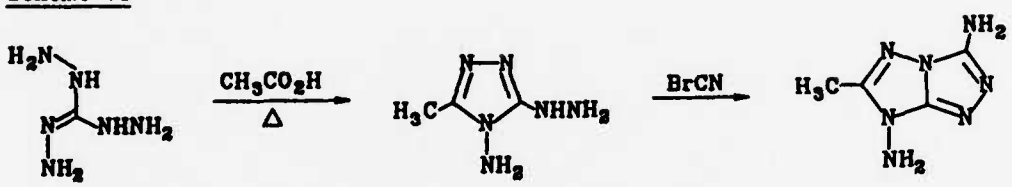
We synthesized 5-chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**39**) by the approach shown in **Scheme IX**. Our synthesis started with the condensation and cyclization of diethylmalonate with 3-amino-1,2,4-triazole to give triazolopyrimidin-5,7-dione (**35**). This dione was converted to dichlorotriazolopyrimidine (**36**) by treatment with phosphorus oxychloride, and it was hydrolyzed by treatment with NaOH to intermediate **37**.[10] The coupling[11] of **37** with 1,2,3,5-tetraacetylribofuranose then gave protected nucleoside **38**, which was purified by flash chromatography (silica gel, 97:3 chloroform:methanol). Our difficulties in the synthesis of this compound occurred during the deprotection of **38**. In our early attempts, we determined that we were not only deblocking the sugar moiety but also opening of the triazole ring. Initially, we had been pursuing

Scheme V

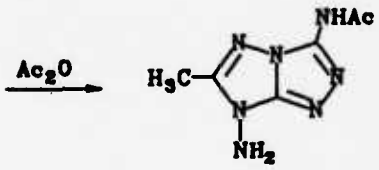


24 25

Scheme VI

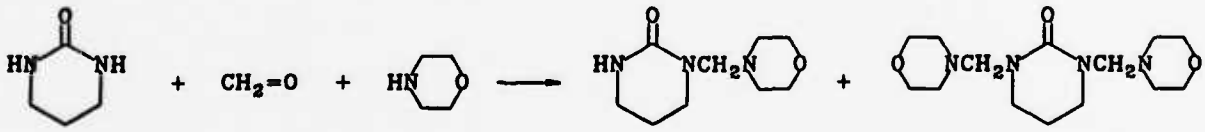


26 27 28



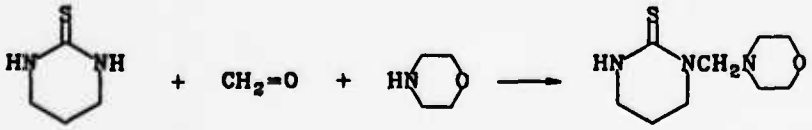
29

Scheme VII



30 31 32

Scheme VIII



33 34

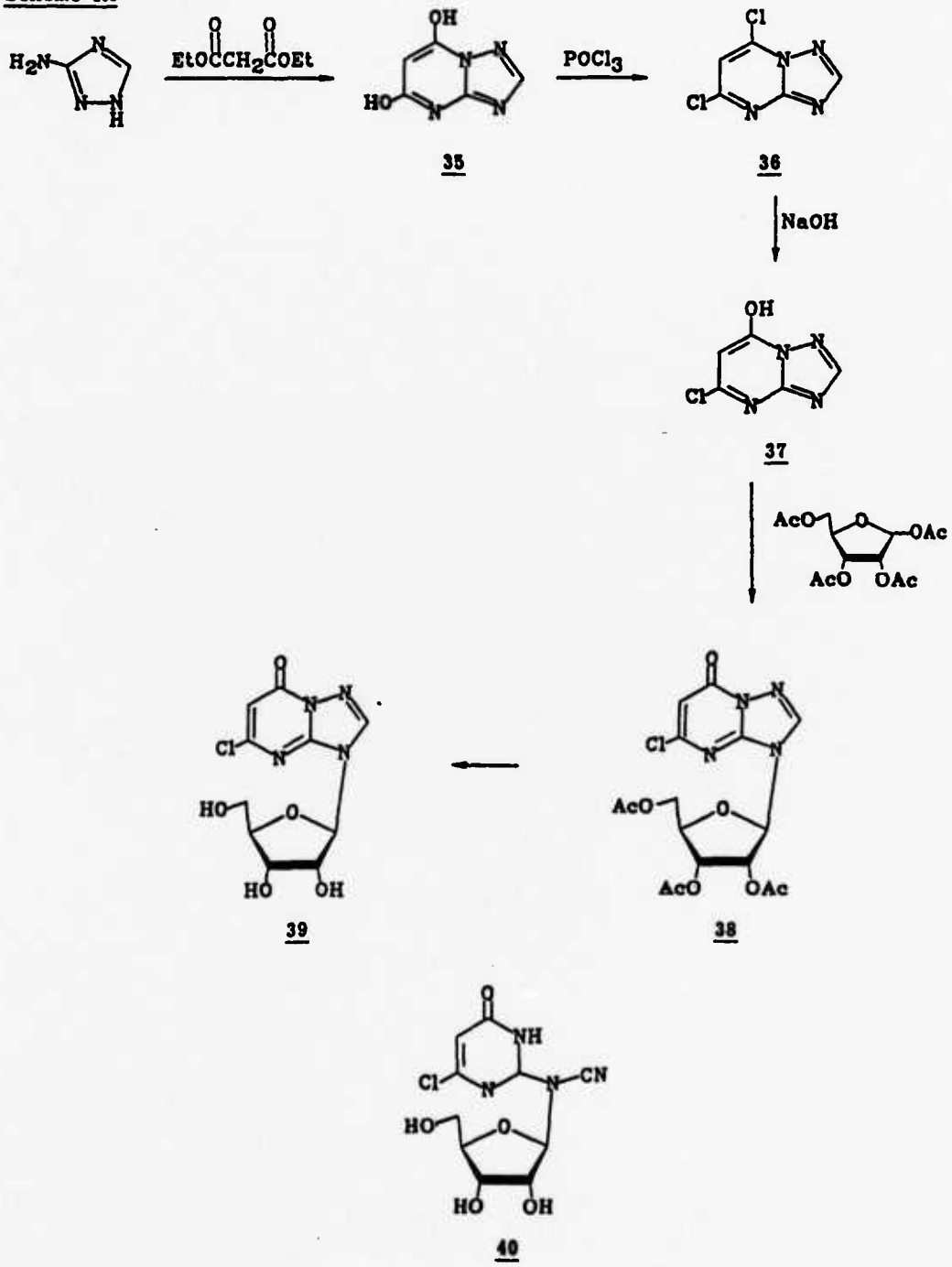
this deblocking by treating **38** with ethanolic ammonia.[12] Thin-layer chromatography seemed to indicate that the reaction was giving the usual mixture of completely and partially deacetylated products, and therefore, the mixture was further treated with ethanolic ammonia until only one product was present. Isolation and characterization of this product showed that it had the correct mass. However, the IR for this compound exhibited two bands at 2177 and 2245 cm^{-1} which were inconsistent for the target structure, and which instead corresponded to the presence of nitriles in the compound. Also, the proton NMR showed only one aromatic proton, not the two different protons expected for a triazolopyrimidine. These observations suggested that our conditions conditions were rigorous enough to have opened the triazole ring to give compound **40**. We then reattempted the less rigorous deblocking of **38** with porcine esterase, and we obtained the properly deblocked desired product **39**. A comparison of this product with the compound mixture obtained from the exhaustive ethanolic ammonia attempts showed that the desired product had been forming in these earlier attempts, but that it had been misidentified as a partially deblocked intermediate. Therefore, this showed that the ethanolic ammonia procedure was an appropriate method, and it was used to prepare larger quantities of **39**. In the repeat synthesis, we determined that the undesired ring opening begins to occur after the deblocking reaction has proceeded for more than 16 h, and that several days were required for complete conversion of **39** to ring opened product **40**. Therefore, by stopping the reaction after 16 h, the desired nucleoside **39** was obtained with only a trace of a partially deprotected product (by TLC, 12:1 chloroform:methanol) which was assumed to be the monoacetylated nucleoside.

As shown in **Scheme X**, our resynthesis of 3-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (AVS-4205) (**47**) gave three other protected triazolotriazole nucleosides in addition to the target compound. These compounds included: 3-amino-1-(2′,3′,5′-tri-*O*-benzoyl-α-D-ribofuranosyl-*s*-triazolo[5,1-*c*]-s-triazole (**44**), 3-imino-2*H*-2-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole (**45**) (the main product isolated), and 3-amino-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole (**46**). 3-Amino-1,2,4-triazole was first nitrated to 3-nitroamino-1,2,4-triazole (**41**) by treatment with fuming nitric acid.[13] Reduction of **41** with zinc dust and acetic acid gave 3-hydrazino-1,2,4-triazole (**42**), which was then treated with cyanogen bromide to give 3-amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (**43**).[14] Coupling **43** with 2,3,5-tri-*O*-benzoyl-D-ribofuranose 1-acetate and $SnCl_4$ gave the mixture of products **44-47** which were isolated by column chromatography. We were unsuccessful in repeated attempts to deprotect **47** with methanolic ammonia to the second requested target **48**. Therefore, target compound **47** and protected nucleosides **44**, **45**, and **46** were all submitted for screening.

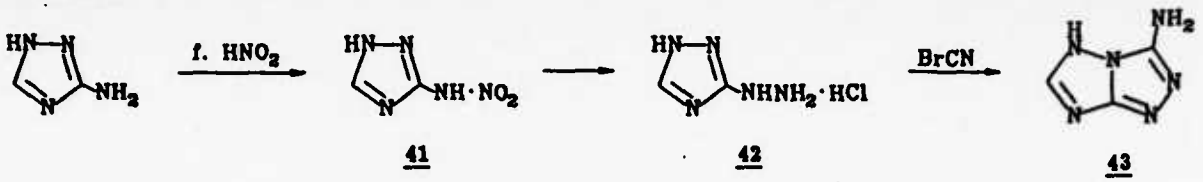
We synthesized 6-amino-2,4-dithiouracil (**50**)[15] by the procedure shown in **Scheme XI**. Commercially available 4-amino-6-hydroxy-2-mercaptopyrimidine (**49**) was dried and then treated with P_2S_5 in pyridine to give the desired product.

Our approach to the synthesis of 6-carboxamidopurine riboside (**56**)[16-18] is shown in **Scheme XII**. 6-Iodopurine (**51**) was first converted to 6-cyanopurine (**52**) by treatment with CuCN in pyridine. 6-Cyanopurine (**52**) should then have been hydrolyzable to 6-carboxamidopurine (**53**) by treatment with sodium hydroxide. However, we were unsuccessful in our early attempts to hydrolyze the 6-cyano compound **52** without consistently obtaining a mixture of both carboxamide **53** and carboxylic acid **54**. After trying many reaction

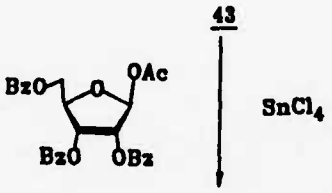
Scheme IX

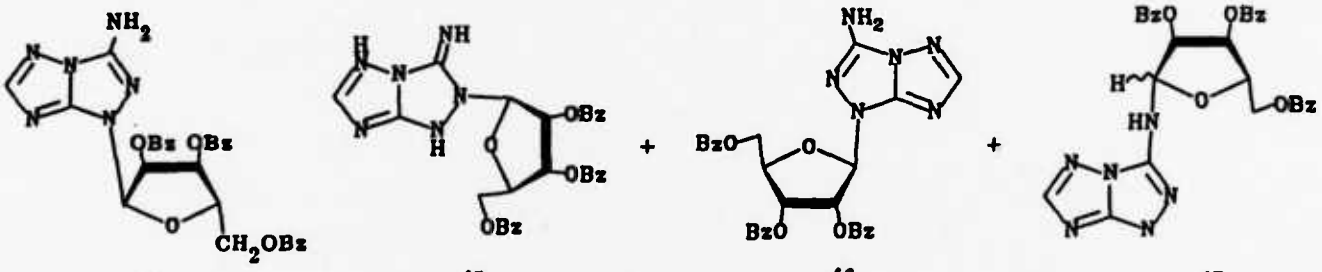


Scheme X

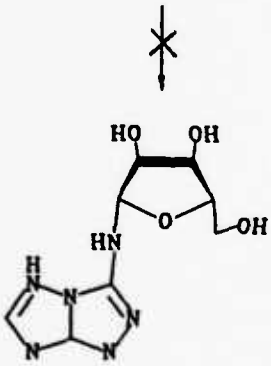


41 42 43





44 45 46 47



48

Scheme XI

49 50

condition alterations, we finally determined that refluxing **52** with 1 equivalent of 2.2 *N* NaOH in an ethanol solution, followed by cooling, the addition of another 0.1 equivalent of base, and then reheating to reflux gave 6-carboxamidopurine (**53**) in good yield. Compound **53** was then coupled with 1,2,3,5-tetra-*O*-acetyl-ribofuranose using $SnCl_4$ as catalyst, according to the procedure of Robins *et al.*,[18] and **55** was obtained. This protected nucleoside analog was then deprotected with MeOH/NaOMe to give the desired nucleoside **56**.

We synthesized 4-thio-6-azauridine (**59**) by the procedure shown in **Scheme XIII**. 2′,3′,5′-Tri-*O*-acetyl-4-thio-6-azauridine (**58**) was first prepared by treating 2′,3′,5′-tri-*O*-acetyl-6-azauridine (**57**) with P_2S_5.[19] The crude thio compound was then deblocked with Dowex 1 (OH^- form) to yield 4-thio-6-azauridine (**59**).

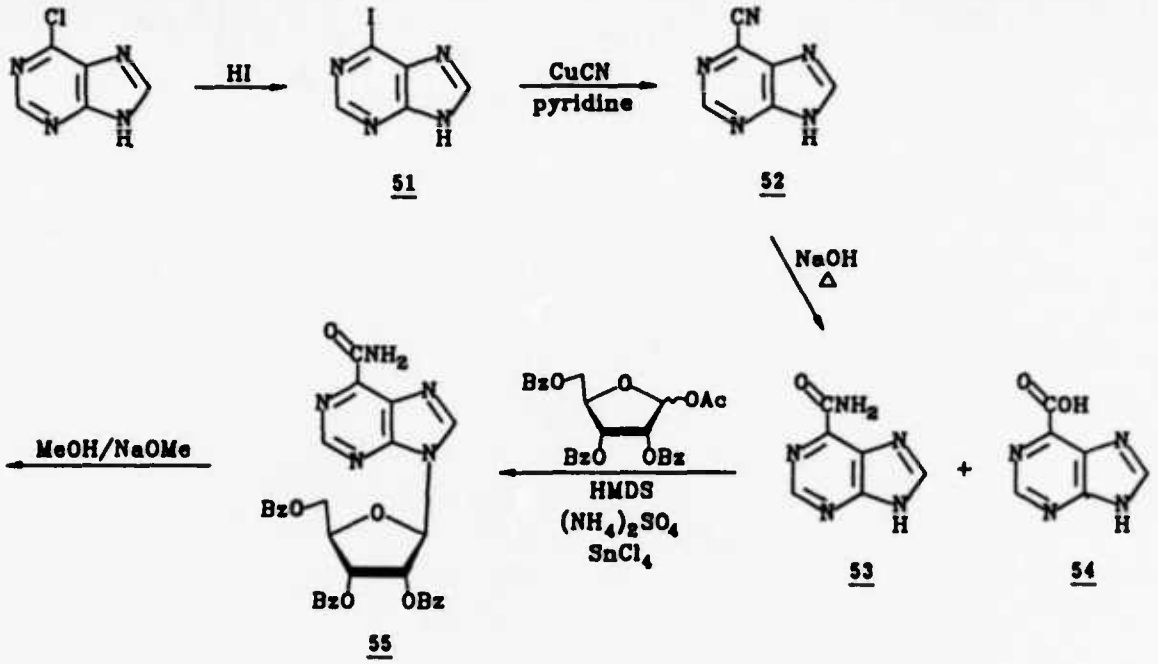
During the twentieth quarter, Dr. Gabrielsen expressed an interest in any SRI compounds which had been shown to be *S*-adenosylhomocysteine hydrolase inhibitors, since compounds with similar activity had been shown to be effective against the *Ebola* virus. We selected the following adenosine derivatives from our nucleoside analog archives: 3-deazaadenosine; arabino-3-deazaadenosine; and carbocyclic 3-deazaadenosine. The syntheses of these compounds are shown in **Schemes XIV-XVII**. However, detailed synthetic procedures will not be provided either here or in the experimental section, because this information is available in the indicated references.

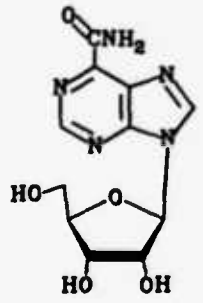
As shown in **Scheme XIV**, 3-deazaadenosine (**63**)[20] was synthesized by the following reaction sequence. The trimethylsilyl derivative of 4,6-dichloroimidazo[4,5-*c*]pyridine (**60**)[21] was generated and then treated with 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose to give **61**. The acetyl protecting groups and the 4-chloro group were simultaneously removed by treatment with ethanolic ammonia. Then, the remaining 6-chloro group of **62** was catalytically reduced to give 3-deazaadenosine (**63**).

Scheme XV shows that arabino-3-deazaadenosine (**67**)[22] was made similarly. 4,6-Dichloroimidazo[4,5-*c*]pyridine (**60**) was reacted with 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (**64**) in 1,2-dichloroethane and 4Å molecular sieves. The resulting protected nucleoside **65** was treated with ethanolic ammonia to aminate the 4-position, and catalytic reduction then removed the benzyl groups while simultaneously removing the remaining 6-chloro group to give the target nucleoside **67**.

The synthesis of carbocyclic 3-deazaadenosine (**82**)[23] required the synthesis of (±)-4β-amino-2α,3α-dihydroxy-1-cyclopentanemethanol (**76**),[24-25] as shown in **Scheme XVI**. Permanganate dihydroxylation of norbornadiene gave diol **68** which was then diacetylated to **69** by treatment with acetic anhydride. Diacetate **69** was then oxidized with sodium permanganate to diacetoxycyclopentanedicarboxylic acid **70**. This compound was converted to anhydride **71** with ethoxyacetylene and to diacetoxycarbamoylcyclopentanecarboxylic acid (**72**) by treatment with ammonia under anhydrous conditions. Hofmann hypobromite reaction of **72** followed by esterication of the carboxyl function, acetylation of the amino and hydroxyl groups to **74**, reduction of the ester with lithium borohydride, and hydrolysis of the resulting **75** gave 4-amino-2,3-dihydroxy-1-cyclopentanemethanol (**76**). Then, as shown in **Scheme XVII**, 4-amino-2,3-dihydroxy-1-cyclopentanemethanol (**76**) was reacted with 2,4-dichloro-3-nitropyridine (**77**) in ethanol with triethylamine. The 3-nitro group of resulting adduct **78** was then reduced to the 3-amino compound **79** with Raney nickel and cyclized by treatment with triethylorthoformate in DMAC with an acid catalyst to give **80**. This intermediate was converted to the final product **82** by displacement of the 4-chloro with hydrazine followed by refluxing with Raney nickel.

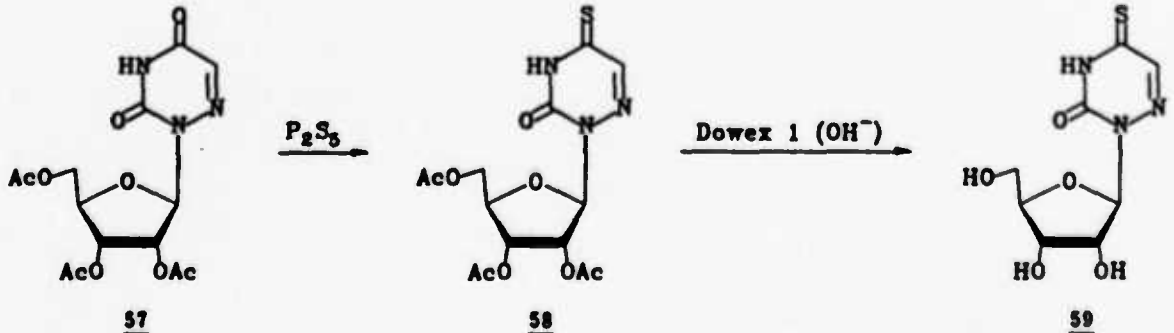
Scheme XII



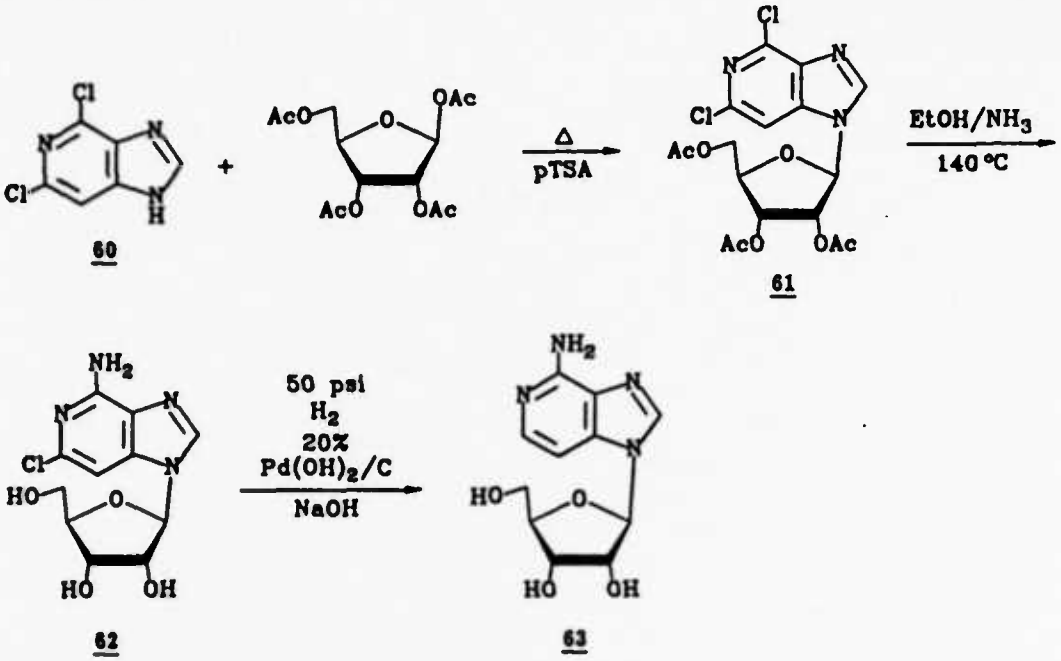


56

Scheme XIII

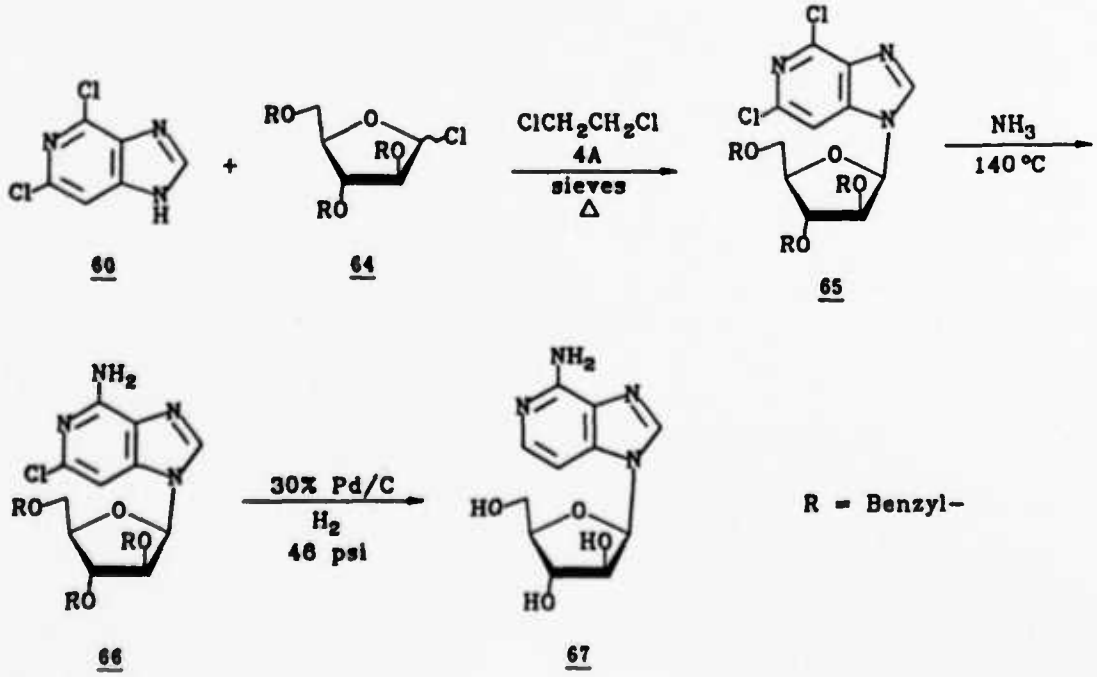


Scheme XIV



60 61 62 63

Scheme XV



60 64 65 66 67

Another group of nucleoside analogs was also selected from our carbocyclic nucleoside archives. These compounds include: carbocyclic 8-azaadenosine; carbocyclic 2′-deoxy-8-azaadenosine; carbocyclic 2′-deoxy-8-azainosine; carbocyclic 2,6-diamino-8-azapurine-2′-deoxyribofuranoside; carbocyclic 2′-deoxy-8-azaguanosine; carbocyclic 2′-deoxy-8-aza-6-thioguanosine; and carbocyclic 2-amino-6-methoxy-8-azapurine-2′-deoxyribofuranoside. (We are also trying to obtain a sample of carbocyclic adenosine for submission in this same screen). All of these compounds were previously prepared for evaluation as potential antitumor agents; they were requested by Dr. Gabrielsen as a result of the recently reported antiviral activity of other carbocyclic nucleoside analogs.[26-30] Their syntheses are given in **Schemes XVIII-XXI**. However, as with the previous group of nucleoside analogs, detailed synthetic procedures will not be provided in the experimental section since these procedures are available in the indicated references.

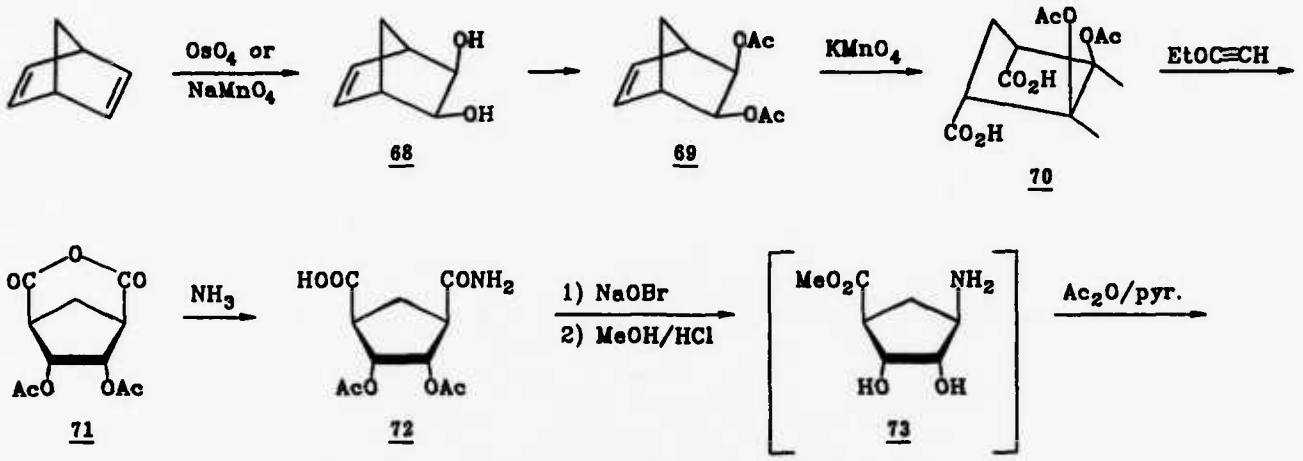
As shown in **Scheme XVIII**, carbocyclic 8-azaadenosine (**84**)[31] was synthesized by reacting previously mentioned (±)-4β-amino-2α,3α-dihydroxy-1-cyclopentanemethanol (**76**)[24,25] with 5-amino-4,6-dichloropyrimidine followed by cyclization with sodium nitrite and HCl and treatment with liquid ammonia at 60 °C.

The synthesis of all of the remaining nucleoside analogs of this group required the synthesis of (±)-*cis*-4-amino-*trans*-2-hydroxycyclopentanemethanol (**93**).[32] As shown in **Scheme XIX**, *exo*-5-norbornen-2-ol acetate was oxidized with sodium permanganate to dicarboxylic acid **86** and then cyclized to anhydride **87** by treatment with acetic anhydride. Treatment of **87** with methanol gave a mixture of monomethylesters **88**, which were then treated with thionyl chloride and ammonia to further convert them to easily separable carbamoylcyclopentanecarboxylates **89** and **90**. Reduction of **89** with lithium borohydride in tetrahydrofuran gave **91**. Hofmann hypobromite conversion of **91** to the methylcarbamate **92** was followed by hydrolysis to (±)-*cis*-4-amino-*trans*-2-hydroxycyclopentanemethanol (**93**).

Scheme XX shows that the synthetic route to carbocyclic 2′-deoxy-8-azaadenosine (**96**) and carbocyclic 2′-deoxy-8-azainosine (**97**)[31] next required the synthesis of **94**, from the reaction of 5-amino-4,6-dichloropyrimidine with **93**. Cyclization of **94** by treatment with sodium nitrite and HCl gave 6-chloropurine nucleoside analog **95**. This intermediate was then either treated with ammonia at 60 °C to give carbocyclic 2′-deoxy-8-azaadenosine (**96**), or it was refluxed with additional HCl to give carbocyclic 2′-deoxy-8-azainosine (**97**).

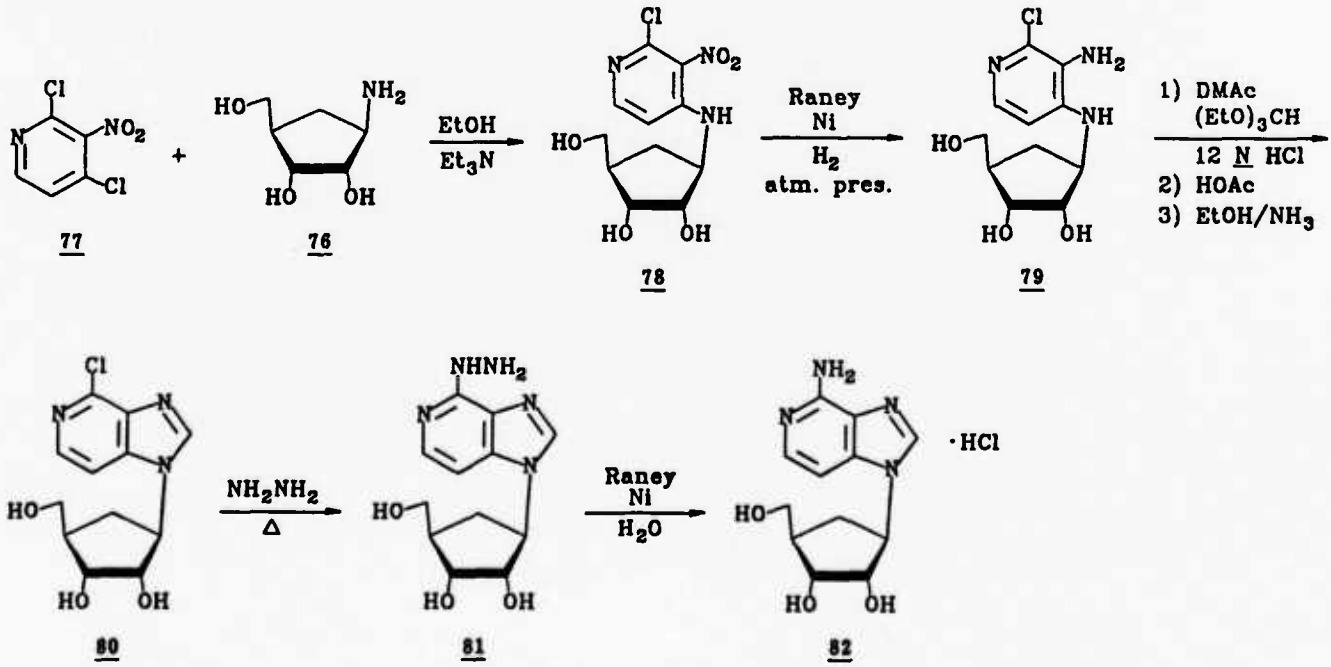
As shown in **Scheme XXI**, carbocyclic 2,6-diamino-8-azapurine-2′-deoxyribofuranoside (**102**),[33,34] carbocyclic 2′-deoxy-8-azaguanosine (**103**),[33,34] carbocyclic 2′-deoxy-8-aza-6-thioguanosine (**104**)[32] and carbocyclic 2-amino-6-methoxy-8-azapurine-2′-deoxyribofuranoside (**105**)[35] were all synthesized from a common intermediate **101**. This intermediate was synthesized by first reacting 2-amino-4,6-dichloropyrimidine with (±)-*cis*-4-amino-*trans*-2-hydroxycyclopentanemethanol (**93**).[32] This compound was then converted to the 5-aminopyrimidine **100** by coupling with 4-chlorobenzenediazonium chloride followed by reduction with zinc in acetic acid. Cyclization with sodium nitrite in aqueous acetic acid then gave intermediate **101** which was easily converted to carbocyclic 2,6-diamino-8-azapurine-2′-deoxyribofuranoside (**102**) and carbocyclic 2′-deoxy-8-azaguanosine (**103**) by treatment with ammonia at 60 °C or dilute aqueous base, respectively. Carbocyclic 2′-deoxy-8-aza-6-thioguanosine (**104**) and carbocyclic 2-amino-6-methoxy-8-azapurine-2′-deoxyribofuranoside (**105**) were similarly obtained by treatment of **101** with H_2S/NaOMe or NaOMe, respectively.

Scheme XVI



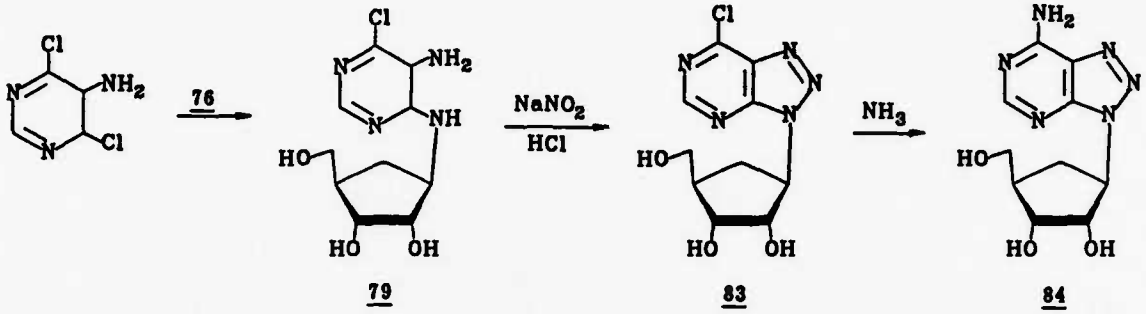
68 69 70 71 72 73 74 75 76

Scheme XVII

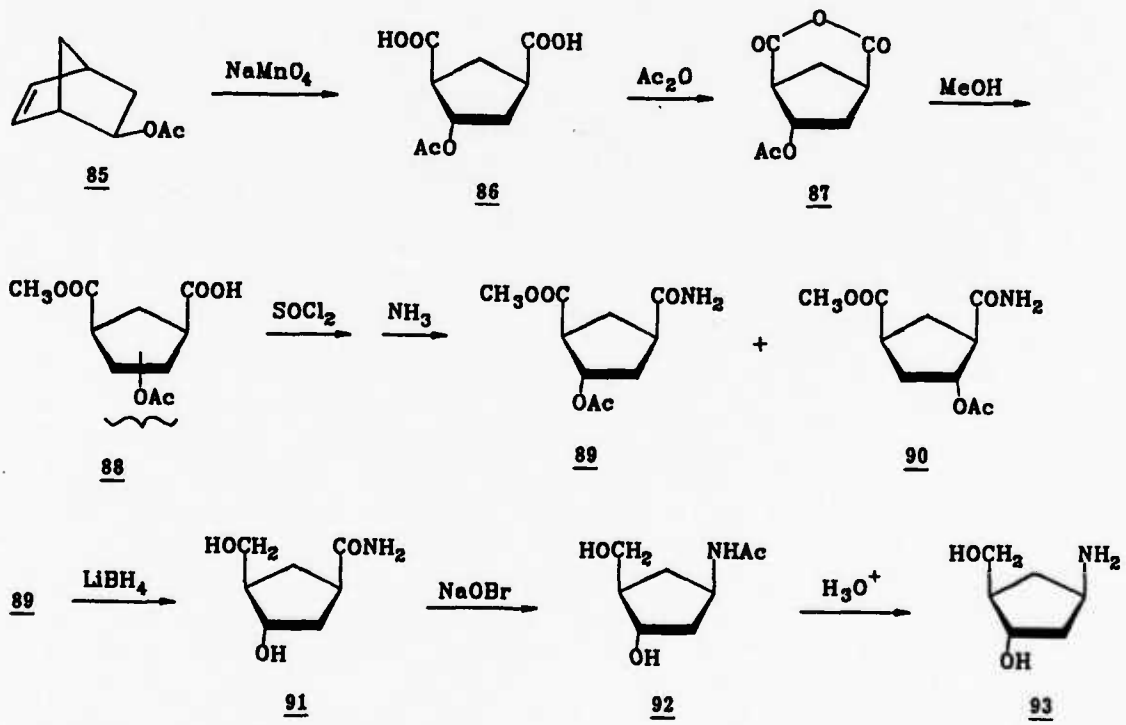


77 76 78 79 80 81 82

Scheme XVIII



Scheme XIX



During this quarter we have also continued with our efforts to synthesize a number of other USAMRIID-requested compounds. Among these are: 6-ethylsulfinylpurine riboside; 9-[(phosphonylmethoxy)ethyl]-2-aminopurine (PMEMAP); 9-[(phosphonylmethoxy)ethyl]-2,6-diaminopurine (PMEDAP); the amidine analog of 6-carboxamidopurine riboside; a 7-*S*-substituted analog of 5-chloro-3-β-D-ribofuranosyl-*s*-triazolopyrimidin-7-one (AVS-0124); 4-amino-5-glucosamino-2-thiouracil; 4-amino-5-mannosamino-2-thiouracil; 2,4-dithio-6-azauridine; 5′-*O*-[[[[2′,3′,4′,6′-tetra-*O*-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2′,3′-isopropylidene-2-thio-6-azauridine; and carbocyclic adenosine.

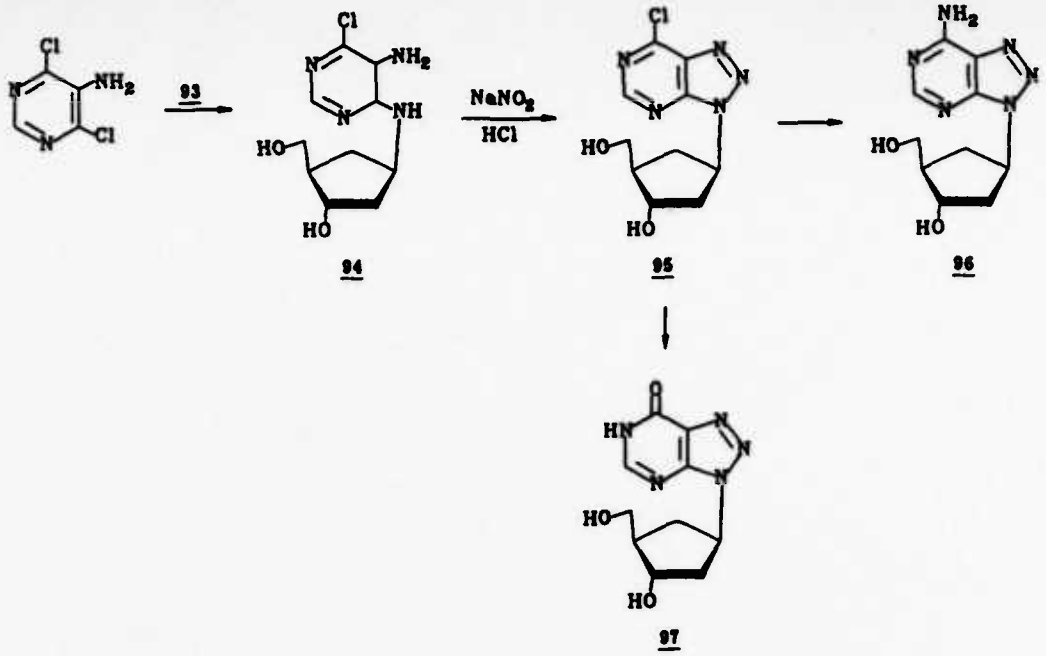
We synthesized 6-ethylsulfinylpurine riboside (**106**) by the route shown in **Scheme XXII**. This analog and potential metabolite of 6-ethylthiopurine riboside (AVS-2700) (**24**) was made by oxidizing 6-ethylthiopurine riboside with *m*-chloroperbenzoic acid.[6] Analytical data for the product showed that our product was contaminated with sulfonyl analog **25**, a compound previously submitted and already described in this report. Our attempts to purify this product chromatographically were not successful, and therefore, Dr. Gabrielsen decided that further pursuit of this compound was not necessary unless activity was found with previously submitted sulfonyl analog **25**.

In earlier reports, we indicated that we had developed reasonable syntheses for 9-[(phosphonylmethoxy)ethyl]-2-aminopurine (PMEMAP, **110a**) and 9-[(phosphonylmethoxy)ethyl]-2,6-diaminopurine (PMEDAP, **110c**).[4,5] As shown in **Scheme XXIII**, these compounds were made with the same sidechain precursor **14** that had been used to synthesize PMEG **18**. Sidechain precursor **14** was reacted with 2,6-dichloropurine in DMF and K_2CO_3 at 80-90 °C to give **108**. The desired protected acyclo nucleosides were obtained by the catalytic reduction of **108** to **109a** or with sodium azide to give **109b** followed by catalytic reduction to **109c**. Deprotection of these phosphonate esters with bromotrimethylsilane gave the desired PMEMAP **109a** and PMEDAP **109c**. Unfortunately, as with other analogs containing the ribavirin triazolecarboxamide, the purification of these compounds was very difficult, and our investigations of a number of purification methods were slow to find a reasonable and consistent method for purifying these compounds to analytical purity. As a result of these difficulties, Dr. Gabrielsen directed us not to pursue these compounds any further until the activities of PMEA and PMEG have been determined.

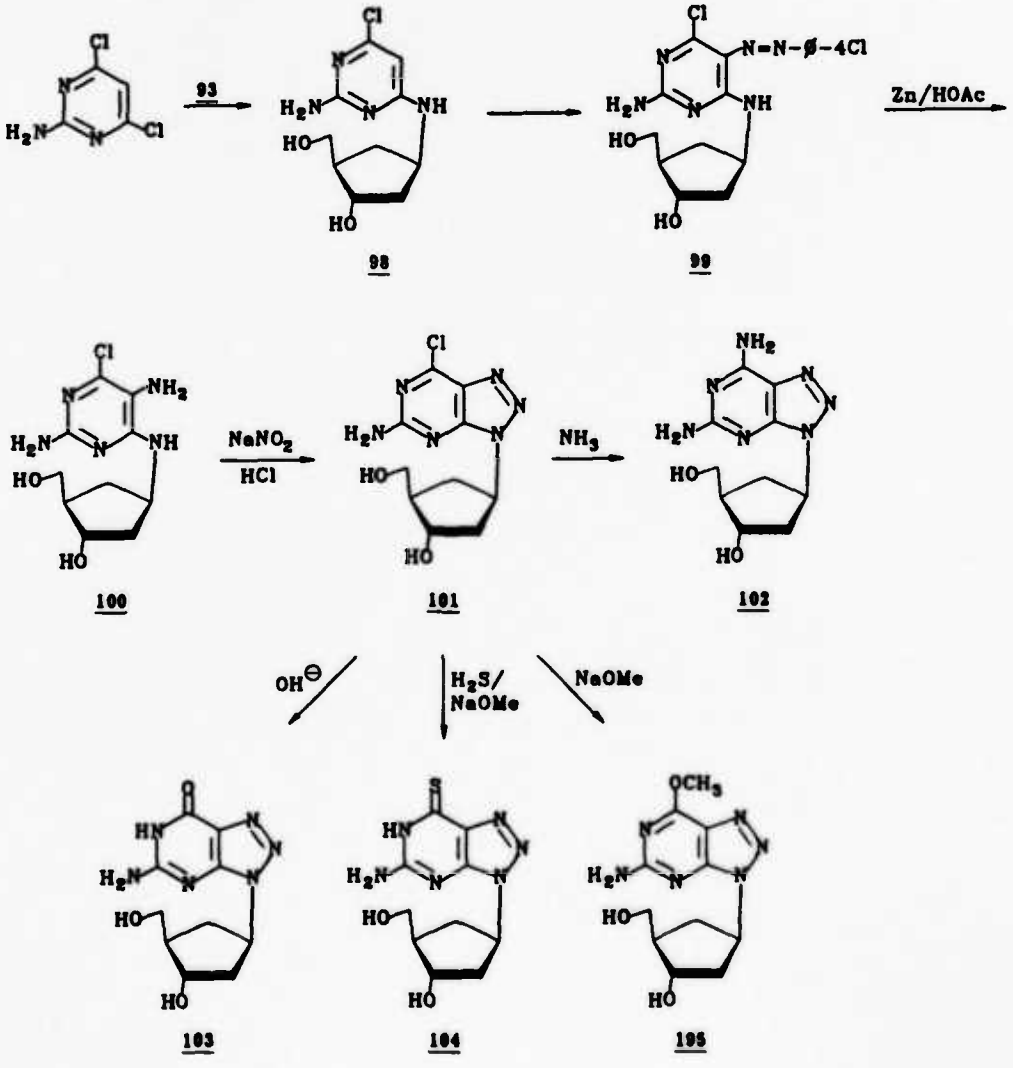
The other compounds that have not been pursued any further are two low priority compounds: the amidine analog of 6-carboxamidopurine riboside and the 7-*S*-substituted analog of 5-chloro-3-β-D-ribofuranosyl-*s*-triazolopyrimidin-7-one (AVS-0124). Because this project was in its final quarters, Dr. Gabrielsen concurred with us that our remaining time should be directed toward the remaining higher priority compounds. Our work on these compounds is described in the following sections.

We have continued with our attempts to synthesize 4-amino-5-glucosamino-2-thiouracil (**112**) by the route shown in **Scheme XXIV**. Our approach was patterned after a synthesis for 4-amino-5-*N*-glucosylaminouracil[33] in which this related compound was obtained simply by heating 4,5-diaminouracil with glucose in methanol. In our first attempt, we substituted 4,5-diamino-2-thiouracil (**111**) for the 4,5-diaminouracil, and we obtained what appeared to be a low yield of product (according to mass spectrometric data). Therefore, the reaction was repeated with altered reaction conditions to try to improve this yield. Both longer reaction times and either additional or different solvents were investigated. (Our solvent investigation

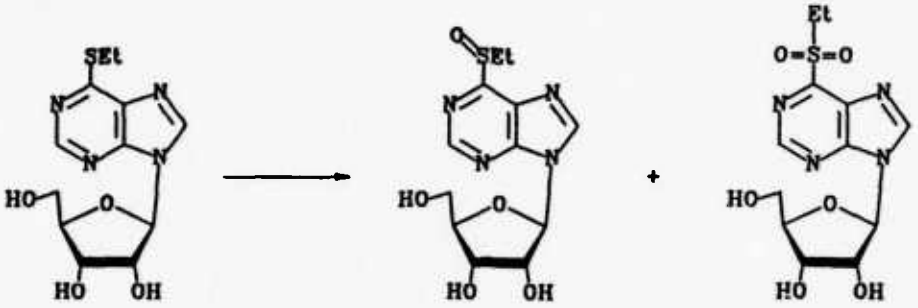
Scheme XX



Scheme XXI

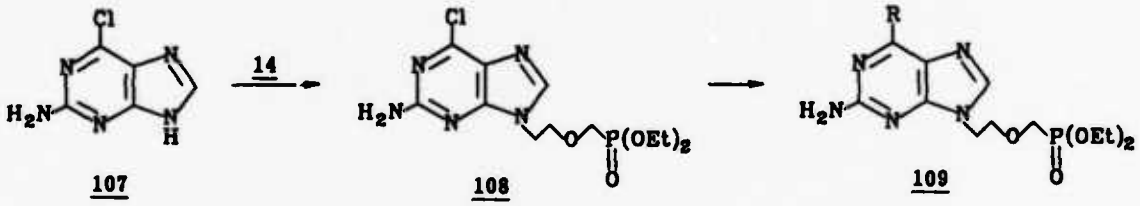


Scheme XXII



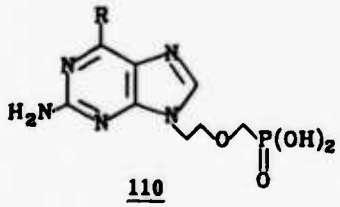
24 106 25

Scheme XXIII



107 108 109

a) R = H
b) R = N_3
c) R = NH_2
d) R = OH



110

a) R = H
b) R = NH_2
c) R = OH

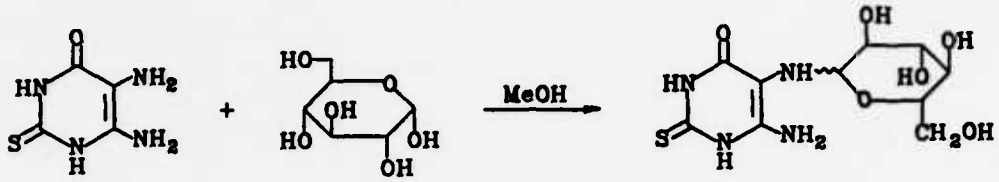
resulted from our observation that the 4,5-diamino-2-thiouracil was not especially soluble in methanol.) No appreciable increase in yield was obtained with all of these modifications. Perhaps the most promising of these changes was our attempted *N*-glycosylation using DMSO as the solvent which resulted once again in our obtaining a product with the expected MS (FAB) of 321 (M + 1). However, the elemental analysis for this product was unacceptable even after numerous recrystallizations. Therefore, we are continuing to modify the reaction conditions in our pursuit of the *N*-glucosamino compound, and we do not plan to begin work on the mannosyl analog until the necessary reaction conditions have been determined for the glucosyl derivative.

We have also been attempting to synthesize 2,4-dithio-6-azauridine (114, R = H). Since this compound has not been previously reported, we have been evaluating a number of thiation reactions, including P_2S_5 and Lawessen's reagent.[34-37] Of these methods, the most promising route seems to be the conversion of 2-thio-6-azauridine (113, R = H) to its 2′,3′,5′-triacetate (113, R = Ac) followed by the treatment of this triacetate with P_2S_5, as shown in **Scheme XXV**. Unfortunately, this reaction appears not to proceed to 100% conversion, or that if it does, the desired product may be unstable, and it may be decomposing to the monothio nucleoside triacetate. Therefore, our current strategy is to allow the reaction to proceed to its completion point and to isolate the desired product from the unreacted material.

We had originally hoped to synthesize 1-β-D-ribofuranosyl-6-amino-2,4-dithiouridine (117) by the direct ribosylation of previously submitted 6-amino-2,4-dithiouridine with 1,2,3,5-*O*-ribofuranose tetraacetate, as shown in **Scheme XXVI**. This was not a reported method in the literature, but it seemed worth pursuing since this route would have been short and since 6-amino-2,4-dithiouridine (115) was immediately available. Early attempts to do this with HMDS/TMSCl were not successful, and therefore, we have begun investigating other literature routes to 6-aminopyrimidine nucleosides.[38,39] As shown in **Scheme XXVII**, our current approach begins with 2′,3′-isopropylidine-5-iodouridine (118). This compound will be cyclized by refluxing with sodium ethoxide in ethanol, and the resulting cyclonucleoside 119 will be treated with NH_3/NH_4Cl to give 2′,3′-isopropylidine-6-aminouridine (120). Compound 120 will then be 5′-*O*-tosylated and cyclized by treatment with potassium-*t*-butoxide to give the 2,5′-anhydro compound 121. Treatment with H_2S to give the 2′,3′-isopropylidine-2-thio-6-aminouridine (122) followed by P_2S_5 should then give the desired 1-β-D-ribofuranosyl-6-amino-2,4-dithiouridine (117).

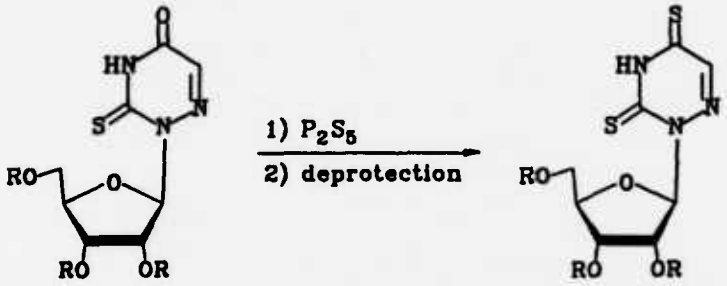
Our approach to the synthesis of 5′-*O*-[[[[(2′′,3′′,4′′,6′′-tetra-*O*-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2′,3′-*O*-isopropylidene-2-thio-6-azauridine (124) closely follows the literature synthesis for 5′-*O*-[[[[(2′′,3′′,4′′,6′′-tetra-*O*-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2′,3′-*O*-isopropylideneuridine[40] and is shown in **Scheme XXVIII**. We synthesized the required 2′,3′-*O*-isopropylidene-2-thio-6-azauridine (123) by treatment of 2-thio-6-azauridine with copper sulfate, acetone, and sulfuric acid.[41] Target compound 124 should then have been obtained by the coupling sequence of adding the 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose to chlorosulfonyl isocyanate in methylene chloride at -20 to -15 °C, followed by the addition of 2′,3′-*O*-isopropylidene-2-thio-6-azauridine (123) in a solution of acetonitrile and pyridine. Thus far, we have not been able to isolate or even detect by MS the desired product (expected MS(FAB) M + 1 = 946), even after repeated attempts. We have obtained a mixture of products which contain the expected by-products 125 and 126, as well as a high molecular weight product with a MS(FAB) M + 1 of 1013, whose

Scheme XXIV



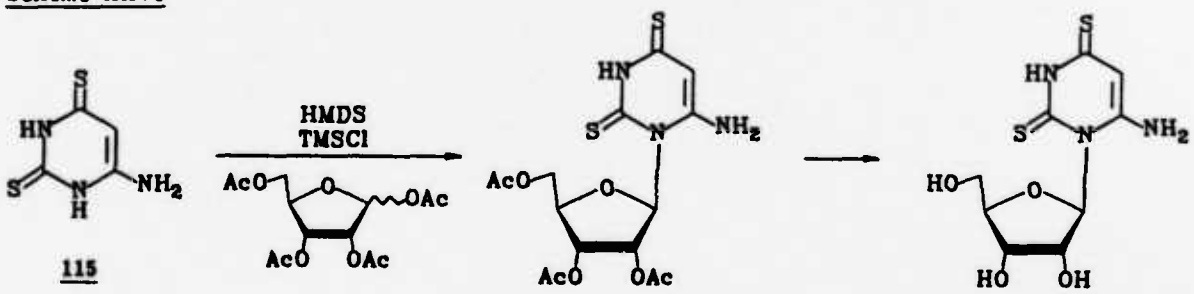
111 112

Scheme XXV



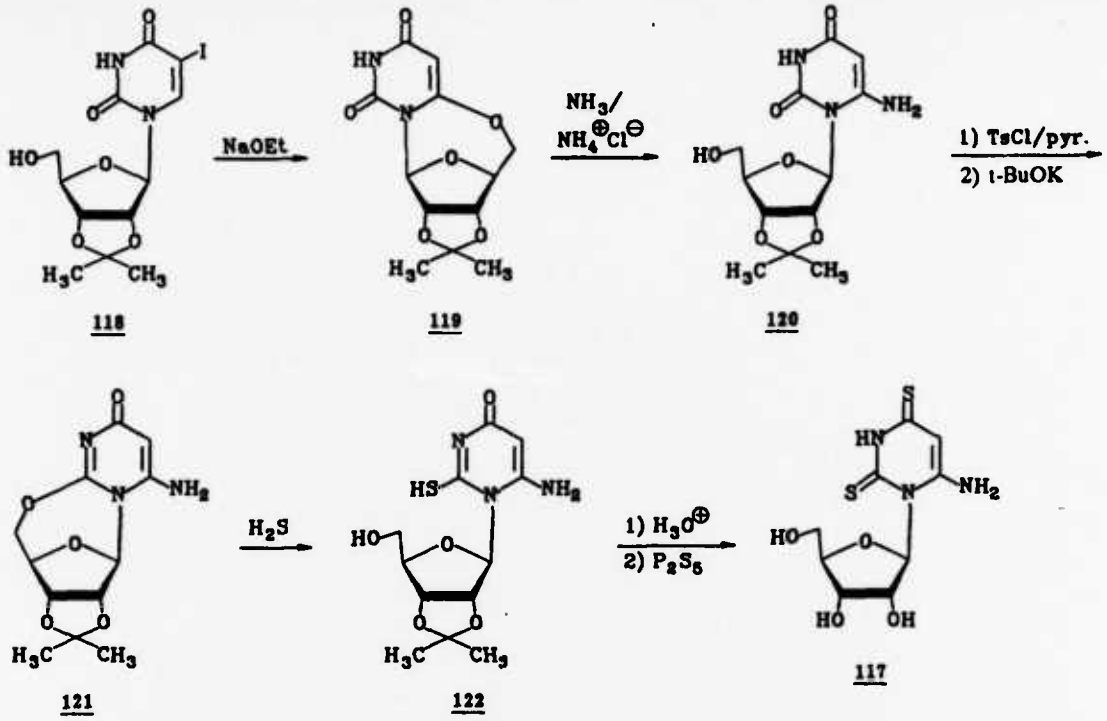
113 (R = H, Ac) 114

Scheme XXVI



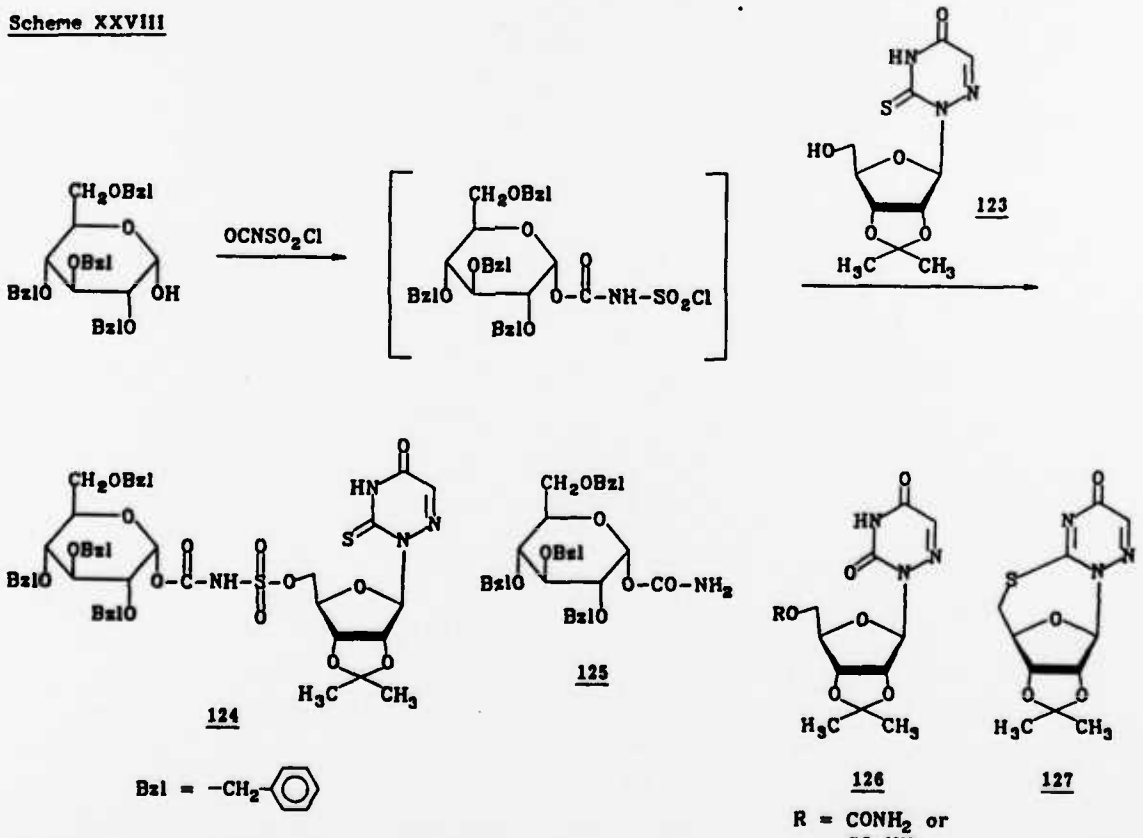
115 116 117

Scheme XXVII



118 119 120 121 122 117

Scheme XXVIII



123 124 125 126 127

R = $CONH_2$ or SO_2NH_2

structure has not been elucidated. A cursory attempt to duplicate the literature procedure with 2′,3′-*O*-isopropylideneuridine has led to our isolation of what appears by MS to be 5′-*O*-[[[[(2″,3″,4″,6″-tetra-*O*-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2′,3′-*O*-isopropylideneuridine, and this shows that our reagents and technique are adequate. We currently feel that our inability to isolate the target compound is due to the 2-thio group's interfering with the final coupling reaction. The molecular ion for the cyclonucleoside (MS (FAB) M + 1 = 284) is prominent in the mass spectrum, and this suggests that the 2-thione is participating in an intermolecular cyclization by displacement of the 5′-*O*-sulfonate linkage to give the cyclonucleoside **127**. We are now trying to determine reaction condition modifications that may allow us to prevent this cyclization from occurring. We have informed Dr. Gabrielsen of this situation, and we have suggested the 6-azauridine analog as an alternate target if we are unable to overcome this problem. Dr. Gabrielsen has agreed with this suggestion as a last resort.

In the final stages of this project, we will also be pursuing one final compound, carbocyclic adenosine.[25] Thus far, we have been trying to obtain this compound from our compound archives. However, if this cannot be done, and if there is a sufficient amount of time, we will pursue the synthesis of this compound by the preparation in the literature.

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 (δ) 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 either a Cary 17 spectrometer 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 with an in-house Perkin Elmer Model 240 Elemental Analyzer or from Atlantic Microlab of Atlanta, Georgia.

4-(4′-Hydroxy-1′-methylbutylamino)-7-chloroquinoline (3). A mixture of 4,7-dichloroquinoline (10.3 g, 0.05 mol) and 4-amino-1-pentanol (10.7 g, 0.1 mol) was cautiously heated to 145 °C under dry conditions while stirring in a 500-mL round-bottomed flask. The temperature and stirring were maintained for 4 h. The mixture was cooled to below 100 °C before ice water (100 mL) was added. After overnight stirring, the resulting white solid was filtered, washed with water, and dried to give 10.4 g of a white solid. MS (EI) *m/e* 264 (M). The product was then used without further purification.

4-(4′-Ethylamino-1′-methylbutylamino)-7-chloroquinoline (4). Concentrated sulfuric acid (4.6 mL) and 4-(4′-hydroxy-1′-methylbutylamino)-7-chloroquinoline (10 g, 0.038 mol) were cautiously added with cooling and stirring to 48% hydrobromic acid (21.5 mL). The solution was heated to boiling as rapidly as possible

in an Erlenmeyer flask. The mixture was simmered gently until the formation of turbidity denoted the separation of a second phase (5-10 minutes). Heating was immediately discontinued, the solution was cooled in an ice bath, and water (40 mL) was added. The solution was extracted with chloroform several times (400 mL total volume). The chloroform extracts were combined, dried with $MgSO_4$, and transferred to the flask to be used for the final step. Solvent was then removed under reduced pressure with warming. Anhydrous ethylamine (65 mL) was then added to the ice bath-cooled flask. The flask was then sealed with a stopper and secured with tape. Cooling was continued, and the flask was swirled until the salt dissolved. The mixture was allowed to stand for 42 h. The ethylamine was then removed by evaporation with gentle heating. The residue was taken up in 150 mL of water containing 50 g calcium carbonate. The solution was extracted several times with chloroform. Solvent was removed, and to the residue, ethanol and then water were added in equal portions (100 mL each) to induce turbidity. The solution was adjusted to pH 8-8.2 using 6*N* HCl. Water (100 mL) was added, and the solution was extracted with ether. An aqueous solution containing 10 g of KOH was added, and the mixture was extracted with chloroform. Drying with $MgSO_4$ followed by evaporation, distillation (at 175 °C, 0.03 mmHg), and chromatography (silica gel, $CHCl_3$-MeOH, 9:1) gave 2.5 g of an off-white solid; mp 97-99 °C; MS (EI) *m/e* 292 (M); IR (KBr) 2965, 2934, 1612, 1576, 1540, 1455, 1381, 1366, 1331, 802 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.37 (m, 2, H-2,5), 7.77 (d, 1, H-8), 7.42 (m, 1, H-6), 6.94 (d, 1, -NH-), 6.49 (d, 1, H-3), 3.70 (t, 1, CH), 2.48 (m, 4, -CH_2NCH_2-), 1.70 (m, 1, H-2′), 1.52 (m, 3, H-2′, 3′), 1.22 (d, 3, CH_3), 0.97 (t, 3, -CH_2CH_3). *Anal.* Calcd. for $C_{16}H_{22}N_3Cl$: C, 65.85; H, 7.60; N, 14.40. Found: C, 65.60; H, 7.62; N, 14.35.

1,2,4-Triazole-3-carboxamide, 1-β-D-Ribofuranosyl-5′-triphosphate, Disodium salt, With Water and Disodium Pyrophosphate (7). Ribavirin (671 mg, 2.53 mmol) was added to a cold (0 °C) stirred solution of phosphorus oxychloride (0.76 ml, 8.19 mmol) in trimethylphosphate (10 mL). The reaction suspension was stirred at 0 °C for 2 h before complete dissolution occurred. This solution was treated with a solution of bis-tri-*n*-butylammonium pyrophosphate (8.69 g, 15.86 mmol) and tributylamine (3.2 mL, 13.45 mmol) in 15 mL of DMF. This reaction solution was stirred at 0 °C for 20 min, and was then poured into 350 mL of ice water. The pH was adjusted to 8 with triethylamine before the solution was lyophilized, and the residue was washed with ether and dried. The solid was dissolved in water, applied to an activated carbon-Celite-sand column, and eluted with EtOH-H_2O-concentrated NH_4OH (10:10:1). The fractions containing the desired triphosphate were combined and freeze-dried. This solid was dissolved in water and passed through a column of Bio-Rad Ag 50W-X4 (50 mL), Na+ form(100-200 mesh). The fractions containing the nucleotide were collected and lyophilized. Yield 308 mg. MS (FAB) *m/e* 483 (M + 1); IR (KBr) 3100-3600 (broad), 1690, 1255, 1095, 985, 890 cm^{-1}. ^{13}P NMR (1.6 mL Hepes Buffer, pH 7.4, containing 0.4 mL D_2O and 0.05 mL EDTA, 150 mg/10 mL, with H_3PO_4 as external reference): δ 21.2 (t), 10.3 (dt), 6.0 (d). *Anal.* Calcd. for $C_8H_{13}N_4O_{14}Na_2P_3 \cdot H_2O \cdot Na_2H_2P_2O_7$: C, 10.13; H, 1.81; N, 5.90. Found: C, 10.31; H, 1.94; N, 5.87.

9-[2-(Diethylphosphonylmethoxy)ethyl]-2-amino-6-chloropurine (16). To a heterogeneous mixture of 2-amino-6-chloropurine (5 g, 29 mmol) and K_2CO_3 (6 g, 43 mmol) in DMF (80 mL) was added 2-(diethylphosphonylmethoxy)ethyl-1-tosylate (8.75 g, 23 mmol). The reaction mixture was stirred at room temperature under argon for 72 h, and then the reaction was heated at 60 °C for 4 h. The reaction mixture was filtered,

and the filtrate was evaporated *in vacuo* to a gummy yellow residue. The semisolid residue was suspended in 600 mL of 30% *n*-propyl alcohol in $CHCl_3$. The mixture was filtered and the filtrate was concentrated to give a dark yellow viscous residue (14 g). Purification by column chromatography on silica gel, eluting with a gradient of 5→10→14→16% MeOH in $CHCl_3$, yielded pale yellow crystals (7.8 g). MS (FAB) *m/e* 349 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 1.15 (t, 6, CH_2CH_3), 3.82-3.88 (m, 4, NCH_2CH_2O-, CH_2P), 3.92 (m, 4, OCH_2CH_3), 4.25 (m, 2, NCH_2), 6.91 (s, 2, NH_2), 8.1 (s, 1, =CH-).

Methyl 1-[2-(Diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxylate (19). Methyl 1,2,4-triazole-3-carboxylate (3.81 g, 0.075 mol), 2-(diethylphosphonylmethoxy)ethane-1-tosylate (6.3 g, 0.083 mol), and anhydrous potassium carbonate (5.6 g, 0.04 mol) were added to 150 mL dry DMF under argon. The mixture was stirred at room temperature with periodic checking by TLC ($CHCl_3$:MeOH, 9:1). After 2 days, the reaction seemed to stall, and therefore the mixture was heated at 90 °C for two 8 hr installments. The reaction mixture was then cooled to room temperature and filtered to remove insoluble materials. The DMF was then evaporated and the resulting semisolid sludge was chromatographed on silica gel ($CHCl_3$-MeOH, 9:1). Among the isolated products were the desired intermediate (R_f = 0.5), a structural isomer (R_f = 0.6), and a product (R_f = 0.45) whose MS corresponded to the decarboxylated analog, diethylphosphonylmethoxylethyl-1,2,4-triazole with the actual site of alkylation not being determined. Only a small amount of (19) was rigorously purified for structure verification. We have provided analytical data for (19) which was isolated as a light golden oil. For the conversion of the carboxylic ester to the carboxamide, the mixture of products was used. Separation of the decarboxylated analog (21) from the resulting amide (22) was much easier than from the corresponding ester (19). MS (FAB) *m/e* 321 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 8.68 (s, 1, triazole H), 4.48 (t, 2, J = 5 Hz, NCH_2), 3.98 (apparent q, 4, J = 8 Hz, OCH_2CH_3), 3.92 (m, 2, CH_2P), 3.36 (s, m, 5, OCH_3, NCH_2CH_2), 1.18 (t, 6, J = 7 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{10}H_{19}N_4O_5P \cdot 0.5H_2O$: C, 38.10; H, 6.39; N, 17.77. Found: C, 37.97; H, 6.16; N, 18.16.

1-[2-(Diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide (22). The mixture of products (0.75 g) containing 19 and 20 from the previous reaction were added to concentrated ammonium hydroxide (50 mL) and stirred overnight at room temperature. The solvent was then removed under vacuum and the resulting viscous light yellow oily residue was chromatographed (silica gel, $CHCl_3$-MeOH, 9:1) to separate the mixture of products, carboxamide (22) (0.6 g, R_f = 0.25) and the decarboxylated triazole analog (20) (0.1 g, R_f = 0.45), both as almost colorless, viscous oils. MS (FAB) *m/e* 303 (M + 1); IR (KBr) 3315, 3184, 1685, 1479, 1291, 1238, 1121, 1047, 1026, 974 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 8.56 (s, 1, triazole H), 7.74, 7.54 (2 br s, 2, NH_2), 4.42 (t, 2, J = 5 Hz, NCH_2CH_2-), 3.97 (apparent q, 4, J = 7 Hz, -OCH_2CH_3), 3.96-3.88 (m, 2, NCH_2CH_2O), 3.35 (d, 2, J = 8 Hz, CH_2P), 1.17 (t, 3, J = 8 Hz, -OCH_2CH_2); IR (KBr) 3412, 1688, 1476, 1291, 1236, 1122, 1048, 1026, 975, 349 cm^{-1}. *Anal.* Calcd. for $C_{10}H_{19}N_3O_5P \cdot 0.5H_2O$: C, 38.10; H, 6.39; N, 17.77. Found: C, 38.05; H, 6.39; N, 17.91.

1-[2-(Phosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxylamide(23). The1-[2-(diethylphosphonylmethoxy)-ethyl]-1,2,4-triazole-3-carboxamide (22) was dissolved in anhydrous acetonitrile under an inert atmosphere (N_2). Bromotrimethylsilane (3.0 mL, 3.5 g, 0.___ mol) was then added dropwise with stirring at room temperature. The mixture was stirred for 14 h, and then the solvent and volatile reactants were removed under vacuum to

give a golden oil. The oil was further vacuumed overnight before an aqueous acetone solution (10 mL, 1:9) was added. Since no precipitation could be induced, the solvents were removed under vacuum. The residue was then dissolved in MeOH. After 3 days at room temperature, a small amount of white solid precipitated. After another day, the solid was collected, washed with MeOH (2 X 5 mL), and dried to give 95 mg of analytically pure **23**; mp 167-9 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.68 (s, 1, triazole H), 7.76, 7.04 (2 br s, 2, NH_2), 4.42 (t, 2, J=5 Hz, NCH_2CH_2), 3.90 (t, 2, J = 5 Hz, NCH_2CH_2), 3.60 (d, 2, J = 9 Hz, CH_2P). *Anal.* Calcd. for $C_6H_{11}N_4O_5P \cdot 0.2H_2O$: C, 28.41; H, 4.52; N, 22.08. Found: C, 28.69; H, 4.54; N, 21.79.

Compound **23** could be isolated in better yield after its conversion to its ammonium salt by the following procedure. Dilute ammonium hydroxide was added to 47 mg of the mixture containing **23**. The solution was then filtered and evaporated under vacuum, giving a hygroscopic foam. When allowed to absorb moisture from the air, 27 mg of the hydrated ammonium salt was isolated as a white solid. *Anal.* Calcd. For $C_6H_{11}N_4O_5P \cdot 2.5\ NH_3 \cdot 1HBr \cdot 2H_2O$: C, 17.59; H, 5.78; N, 22.22. Found: C, 17.22; H, 5.45; N, 22.08.

6-Ethylsulfonyl-9-β-D-ribofuranosylpurine (25). A stirred solution of 6-ethylthiopurine riboside (1.57 g, 5.03 mmol) in 200 mL of acetone was treated with *m*-chloroperoxybenzoic acid (2.71 g, 15.72 mmol). The reaction was stirred at room temperature for 5 h. The solvent was removed under reduced pressure, and the residue was stirred with ether (50 mL). The ether was decanted from the solid, and the ether washing was repeated several times. This crude solid product was purified on a silica gel column by eluting with chloroform:methanol (7:1, v/v). The combined product fractions were evaporated to give a glassy hygroscopic solid that was dissolved in water and lyophilized to give a hygroscopic solid that was dried *in vacuo*: Yield 770 mg (45 %); mp ~65 °C; UV λ_{max} 279 nm (ε 8,800) at pH 1, 279 (8,800) at pH 7; 254 (12,160), 309 (1,524) at pH 13; MS (FAB) *m/e* 345 (M + 1); IR (KBr) 1590, 1563, 1495, 1395, 1355, 1205, 1130, 1080, 1045, 725 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.40 (t, 3, SCH_2CH_3), 3.62 (2 m, 2, CH_2-5′), 3.76 (q, 2, SCH_2CH_3), 4.01 (app. q, 1, H-4′), 4.22 (q, 1, H-3′), 4.62 (q, 1, H-2′), 5.10 (t, 1, OH-5′), 5.26 (d, 1, OH-3′), 5.60 (d, 1, OH-2′), 6.11 (d, 1, H-1′), 9.14 (s, 1, H-8). *Anal.* Calcd. for $C_{12}H_{16}N_4O_6S \cdot 0.15EtOH \cdot 0.2H_2O$: C, 41.63; H, 4.91; N, 15.79. Found: C, 41.77; H, 5.27; N, 15.80.

3-Acetamido-7-amino-6-methyl-7*H*-*S*-triazolo-[5,1-c]-*S*-triazole (29). 3,7-Diamino-6-methyl-7*H*-*S*-triazolo-[5,1-*c*]-*S*-triazole (2.7 g, 0.018 mol) and acetic anhydride were combined and stirred for 72 h at room temperature. The resulting white solid was filtered and rinsed with ether, yielding 2.4 g; mp 240-241 °C; MS (EI) *m/e* 195 (M); IR (KBr) 3104, 2761, 1709, 1635, 1617, 1579, 1558, 1373, 1273, 1250 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 10.46 (s, 1, NH), 6.06 (s, 2, NH_2), 2.38 (s, 3, CH_3), 2.06 (s, 3, $COCH_3$). ^{13}C NMR (Me_2SO-d_6) δ 169.3 (C=O), 157.9 (C-6), 152.5 (C-8), 134.3 (C-3), 22.2 (O=CCH_3), 10.4 (CH_3-6). *Anal.* Calcd. for $C_6H_9N_7O \cdot 0.1H_2O$: C, 36.91; H, 4.65; N, 50.24. Found: C, 36.93; H, 4.87; N, 49.65.

1-Morpholinomethyltetrahydro-2(1*H*)-pyrimidinone (31). Tetrahydro-2(1*H*)-pyrimidinethione (10.8 g, 0.1 mol), 37.7% formalin (8.9 mL, 0.1 mol), and morpholine (8.7 g, 0.1 mol) were added to methanol (250 mL) and heated at 60 °C for 4 h. The reaction mixture was cooled, and the solvent was removed under vacuum. The resulting residue was washed with ether and recrystallized from ethyl acetate, ethanol, and three more times from ethyl acetate to give the desired product as colorless plates (2.5 g). TLC (silica gel, chloroform:methanol, iodine chamber) showed that the mother liquors still contained the desired product.

However, no more effort was directed toward the isolation and purification of additional product; mp 143-145 °C; MS (FAB) *m/e* 200 (M + 1); IR (KBr) 3225, 2938, 2926, 2871, 2855, 2820, 1660, 1647, 1514, 1460, 1445, 1426, 1397, 1302, 1285, 1278, 1220, 1207, 1189, 1167, 1128, 1116, 862, 770 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.22 (br s, 1, NH), 3.88 (s, 2, NCH_2N), 3.54 (m, 4, -OCH_2-), 3.24 (m, 2, pyrm NCH_2), 3.10 (m, 2, -$NHCH_2$-), 2.36 (m, 4, morph NCH_2), 1.76 (m, 2, pyrm -$CH_2CH_2CH_2$-); ^{13}C NMR (Me_2SO-d_6) δ 155.35 (C=O), 67.79 (NCH_2N), 66.05 (-OCH_2-), 50.51 (morph -$NHCH_2$-), 44.82 (pyrm -NCH_2-), 39.61 (pyrm -$NHCH_2$-), 21.91 (pyrm -$CH_2CH_2CH_2$-). *Anal.* Calcd for $C_9H_{17}N_3O_5$: C, 54.30; H, 8.60; N, 21.10. Found: C, 54.07; H, 8.88; N, 20.92.

1,3-Bis-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinone (32). A solution of 37.7% formalin (8.9 g, 0.1 mol), morpholine (8.7 g, 0.1 mol), and tetrahydro-2(1*H*)-pyrimidinone (10 g) was refluxed in 250 mL MeOH for 2 h. The solvent was then evaporated under reduced pressure, the residue washed with dry ether and boiled with ethyl acetate. The undissolved material was filtered, and crude monomorpholinomethylated product was obtained from the ethyl acetate. The bis-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinoine was obtained from the mother liquid after evaporation and column chromatography (silica gel, CH_3OH-MeOH, 9:1, iodine) followed by recrystallization from ethyl acetate. Yield, 0.6 g; mp 120-122 °C (reported 121-123 °C); MS (FAB) *m/e* 299 (M + 1); ^1H NMR (Me_2SO-d_6) δ 3.94 (s, 4, -NCH_2N-), 3.55 (m, 8, -OCH_2-), 3.32 (m, 4, pyrm NCH_2), 2.38 (m, 8, morph NCH_2), 1.84 (m, 2, pyrm -$CH_2CH_2CH_2$-); IR (KBr) 2933, 2913, 2867, 2851, 2818, 1645, 1632, 1497, 1459, 1438, 1430, 1291, 1276, 1211, 1202, 1118, 1111, 1003, 921, 864, 757 cm^{-1}; *Anal.* Calcd. for $C_{14}H_{26}N_4O_3$: C, 56.35; H, 8.78; N, 18.78. Found: C, 56.69; H, 8.92; N, 18.87.

1-Morpholinomethyl-tetrahydro-2(1*H*)-pyrimidinethione (34). Tetrahydro-2(1*H*)-pyrimidinethione (5.8 g, 0.05 mol), 37.7% formalin (9.2 mL, 0.11 mol), and morpholine (9 g, 0.104 mol) were added to methanol (60 mL) and refluxed for 2 h. Removal of the solvent and crystallization from ethanol (x 3) gave two crops of colorless needles (1.2 g and 1.7 g). Only the former of these was found to be analytically pure; mp 160-162 °C (reported, 156-158 °C); MS (FAB) *m/e* 216 (M + 1); IR (KBr) 3346, 2950, 2919, 2871, 2863, 2818, 2802, 1535, 1510, 1357, 1285, 1266, 1202, 1170, 1109, 1002, 861, 851 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.98 (br s, 1, NH), 4.50 (s, 2, CH_2), 3.54 (m, 4, -OCH_2-), 3.31 (m, 2, pyrm NCH_2), 3.10 (m, 2, -$NHCH_2$-), 2.48 (m, 4, morph NCH_2), 1.32 (m, 2, pyrm -$CH_2CH_2CH_2$-). *Anal.* Calcd. for $C_9H_{17}N_3O_5$: C, 50.20; H, 7.96; N, 19.52. Found: C, 50.17; H, 8.03; N, 19.62.

5-Chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (39). 5-Chloro-3-(2′,3′,5′-tri-*O*-acetyl-β-*D*-ribofuranosyl)-*s*-triazolo-[1,5-*a*]pyrimidin-7-one (38) (300 mg) was suspended in a solution of 10 mL acetone and 90 mL 0.1 *M* NH_4HCO_3 with good stirring and heating at 35-37 °C. Porcine esterase (0.1 mL) was added and the mixture was stirred for 3 days. Since the reaction was incomplete, another 0.1 mL more esterase was added and the heating was continued for 4 more hours. The reaction mixture was evaporated to dryness *in vacuo* and azeotroped with EtOH/benzene. The sample was purified by passing it through a 50 g silica gel flash chromatography column, eluting with chloroform-methanol (12:1). The appropriate fractions were combined and evaporated. This residue (~100 mg) was dissolved in hot EtOH, cooled, scratched to induce crystallization, and stored in the freezer. The product was collected and dried, yielding 52 mg (24%).

Retreatment of a faster eluting fraction with esterase followed by the same workup led to the isolation of an additional 52 mg (24%) of product.

Ethanolic ammonia deblocking: Into a stainless steel bomb were placed 250 mg (**38**) and ~50 mL of saturated NH_3/EtOH. The reaction was stirred at room temperature overnight and then evaporated. The residue was then chromatographed on a 50 g flash chromatography column and eluted with chloroform-methanol (12:1). The product (60 mg) was combined with the two products from the esterase deblocking and was blended, yielding 164 mg of the desired product; mp 167-169 °C cap.; UV λ_{max} 283 nm (12,500) at pH 1, pH 7, and pH 13; MS (FAB) *m/e* 303 (M + 1); IR 1710, 1689, 1669, 1586, 1548, 1512, 1502, 1103, 1095, 1070 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.60, 3.74 (2 m, 2, CH_2-5′), 3.98 (m, 1, H-4′), 4.17 (apparent q, 1, H-3′), 4.42 (apparent q, 1, H-2′), 5.19 (t, 1, OH-5′), 5.24 (d, 1, OH-3′), 5.69 (d, 1, OH-2′), 5.77 (d, 1, H-1′), 6.26 (s, 1, H-6), 9.19 (s, 1, H-2).

2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyltriazolotriazoles (44-47). 3-Amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole[13,14] (**43**, 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 until 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 were dried and concentrated. Thin-layer chromatographic analysis of this crude product (silica gel, chloroform-methanol, 9:1 v/v) showed four products with R_f values of 0.45, 0.81, and 0.9 along with unchanged and 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 three products were separated and further purified by repeating the silica gel column chromatography. A fourth product was isolated from the chromatographic purification of the fraction containing compound **44**, when the solvent system was changed to cyclohexane-ethyl acetate (1:1). Structures of these compounds were assigned on the basis of spectral data as follows:

3-Amino-1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole (44). The above cited compound with R_f 0.85, yield 238 mg; mp 83-86°C; MS (FAB) *m/e* 569 (M + 1); IR (KBr) 3425, 3335 (NH_2), 3175, 3065 (CH), 1727 (C=O), 1653 (C=N), 1602, 1569 (aromatic), 1452, 1317, 1268, 1176, 1165, 1110, 1069, 1025, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07 (m, 2, ortho H's), [7.84 (m, ortho H's) and 7.83 (s, H-6)](2), 7.56-7.21 (m, 9, meta and para H's), 6.45 (d, 1, $J_{1',2'}$ = 5.5 Hz, H-1′), 5.98 (t, 1, $J_{2',3'}$ = 6.5 Hz, H-2′), 5.37 (m, 1, H-4′), 4.91 (br s, 2, NH_2), 4.81 (dd, 1, $J_{4',5'a}$ = 3.3 Hz, $J_{5'a,5'b}$ = 12.3 Hz, H-5′a), 4.65 (dd, 1, $J_{4',5'b}$ = 3.8 Hz, H-5′b); ^{13}C NMR ($CDCl_3$) δ 166.1, 165.4 and 164.8 (C=O), 158.42 (C-6, $^1J_{CH}$ = 206.7 Hz), 155.93 (C-8, $^3J_{C\text{-}8,H\text{-}6}$ = 9.9 Hz, $^3J_{C\text{-}8,H\text{-}1'}$ = 3.5 Hz), 139.85 (C-3), 133.41, 133.39, 133.29, 129.70, 129.67, 129.66, 129.38, 128.89, 128.50, 128.37, 128.26 (aromatic), 87.24 (C-1′, $^1J_{C,H}$ = 168.0 Hz), 81.54 (C-4′), 71.39 (C-2′), 70.97 (C-3′), 63.85 (C-5′). *Anal.* Calcd. for $C_{29}H_{24}N_6O_7 \cdot 0.2C_6H_{12}$: C, 61.96; H, 4.55; N, 14.36. Found: C, 61.73; H, 4.54; N, 14.17.

3-Imino-2*H*-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole (45). The above cited compound with R_f 0.45, yield 9.46 g (30 %); mp 125-127 °C; MS (FAB) *m/e* 569 (M + 1); UV λ_{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 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, H-6, and benzoyl), 6.35 (d, 1, $J_{1',2'}$ = 1.7 Hz, H-1′), 6.25 (dd, 1, $J_{2',3'}$ = 5.2 Hz, H-2′), 6.19 (dd, 1, $J_{3',4'}$ = 6.8 Hz, H-3′), 4.92-4.82 (m, 1, $J_{4',5'a}$ = 5.2 Hz, $J_{4',5'b}$ = 3.6 Hz, H-4′), 4.82-4.77 (d, 1, H-5′b), 4.74-4.65 (dd, 1, $J_{5'a,5'b}$ = 12.1 Hz, H-5′a); ^{13}C NMR ($CDCl_3$) δ 166.3, 165.2, 165.1 (C=O), 160.3 (C-6, $^1J_{C\text{-}6,H}$ = 202.6 Hz), 160.1 (C-8, $J_{C\text{-}8,H}$ = 4.4 Hz), 138.3 (C-3), 133.7, 133.4, 133.0, 129.7, 129.64, 129.6, 129.2, 128.6, 128.43, 128.4, 128.39 (aromatic carbons), 88.8 (C-1′, $^1J_{C\text{-}1',H}$ = 167.8 Hz), 80.4 (C-4′), 75.3 (C-2′), 71.7 (C-3′), 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-Amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole (46). The above cited compound with R_f 0.9, yield 2.34 g (7.3 %); mp 86-87°C; MS (FAB) *m/e* 569 (M + 1); UV λ_{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, H-6 and benzoyl), 6.31 (d, 1, $J_{1',2'}$ = 3.86 Hz, H-1′), 6.28 (dd, 1, $J_{2',3'}$ = 5.32 Hz, H-2′), 6.15 (dd, 1, $J_{3',4'}$ = 5.31 Hz, H-3′), 4.88-4.5 (m, 3, H-4′,5′); ^{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, 129.6, 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′); *Anal.* Calcd. for $C_{29}H_{24}N_6O_7 \cdot 0.33H_2O$: C, 60.62; H, 4.33; N, 14.63. Found: C, 60.81; H, 4.36; N, 14.27. (The CHN data was obtained from a subsequent batch of compound **46** that was identical by TLC, mp, and all other spectral data.)

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (47). The above cited compound with R_f 0.81, yield 7.5 g (23%); mp 189-192 °C; MS (FAB) *m/e* 569 (M + 1); UV λ_{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, H-5), 8.67 (broad d, 1, NH), 8.1-7.83, 7.8-7.3 (m, 16, H-6 and benzoyl), 6.39-6.32 (m, H-1′ of α-isomer), 5.97-5.77 (m, 3, H-1′,2′,3′), 4.8-4.5 (m, 3, H-4′,5′); ^{13}C NMR (Me_2SO-d_6) showed a 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.

4-Amino-2,6-dithiouracil (50). To a solution of 4-amino-6-hydroxy-2-mercaptopyrimidine (**49**, predried, 5 g, 31 mmol) and anhydrous pyridine (150 mL) was added P_2S_5 (15 g, 67.4 mmol). The mixture was heated under argon at reflux for 3 h, during which a red-orange solution formed. The pyridine was removed under pressure to give a crude solid. Water (75 mL) was added carefully and the aqueous mixture was refluxed for 4 h or until all H_2S(g) had been given off. The reaction mixture was filtered and the remaining precipitate was taken up in NH_4OH-H_2O (1:1) and boiled until a clear solution formed. The solution was cooled to room temperature and treated with decolorizing carbon. The solution was filtered through celite, and the filtrate was taken to pH 2 with 1 *M* HCl which caused the precipitation of yellow crystals. Recrystallization

with DMF-water (1:9) yielded 3.1 g; mp >280 °C; MS (FAB) *m/e* 160 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 5.8 (s, 1, vinyl H), 6.9 (br s, 2, NH_2), 12.18 (s, 1, SH), 12.38 (s, 1, SH); IR 1642.2, 1607.2, 1571.9, 1555.4, 1188.9, 1101.6, 1059.8, 820.4, 802.6, 689.8 cm^{-1}. *Anal.* Calcd. for $C_4H_5N_3S$: C, 30.17; H, 3.16; N, 26.39. Found: C, 30.17; H, 3.49; N, 26.39.

6-Carboxamidopurine (53).[16-17] (The 6-carboxamidopurine was prepared by a modification of the referenced procedure by Hitchings and Mackay.) Into a 100-mL round-bottomed flask equipped with a magnetic stirring bar and condenser were placed 6-cyanopurine (**52**, 4.6 g, 31.7 mmol) and EtOH (enough to allow good stirring). Then, 14.4 mL of 2.2 *N* NaOH was added, and the mixture was heated at reflux for 1 h. Since thin-layer chromatographic (TLC) monitoring of an aliquot from this mixture showed the presence of starting material, another 0.5 mL of 2.2 *N* NaOH was added, the heating was continued, and a heavy precipitate quickly formed. (In repetitions of this work, we found that in some cases, no precipitation occurred. With these cases, we suggest that 0.5 mL portions of the NaOH solution should be added at 5 min. intervals until precipitation occurs.) Since a TLC of this product showed only a trace of starting material, the EtOH was removed at reduced pressure, the residue was suspended in H_2O, chilled, and acidified to pH 6-7 with dilute HCl. The product was collected by filtration, washed well with cold H_2O, and dried *in vacuo* over phosphorus pentoxide; yield, 3.9 g (75%); IR (KBr) 1709, 1691, 1570, 1473, 1393, 607 cm^{-1}; MS (FAB) *m/e* 164 (M + 1). This material was used in the subsequent coupling reaction without further purification.

6-Carboxamido-9-β-D-ribofuranosylpurine, 2′,3′,5′-tribenzoate (55).[18] Into a 100-mL round-bottomed flask equipped with a reflux condenser, magnetic stirring bar, and a drying tube was placed 6-carboxamidopurine (**53**, 500 mg, 3.07 mmol), hexamethyl disilazane (HMDS, 30 mL), and $(NH_4)_2SO_4$ (10 mg). The mixture was heated at gentle reflux in an argon atmosphere for 18 h before excess HMDS was removed *in vacuo*. The residue was dissolved in dry 1,2-dichloroethane (30 mL), and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (1.6 g, 3.07 mmol) and anhydrous $SnCl_4$ (1.1 g, 4.3 mmol) were added. The reaction mixture was protected from moisture, covered with an argon atmosphere, and stirred at room temperature for 24 h. The mixture was poured into a cold mixture of 5% aqueous $NaHCO_3$ and $CHCl_3$ (1:1) and stirred for 2 h. The resulting emulsion was further separated by removing any separated water and $CHCl_3$ portions and treating the remaining emulsion with more $CHCl_3$ until the emulsion was broken. The $CHCl_3$ layer was washed with brine, dried with $MgSO_4$, filtered, and evaporated. The crude product was chromatographed with a 200 g silica gel flash column (using 99:1 $CHCl_3$-MeOH as eluent), and the appropriate fractions were combined and evaporated; yield, 1.1 g; MS (FAB) *m/e* 608 (M + 1), 445 (sugar), 164 (B + 2H). The TLC showed a single spot when developed in 98:2 $CHCl_3$-MeOH.

6-Carboxamido-9-β-D-ribofuranosylpurine (56).[16-18] Into a 1-L round-bottomed flask was suspended 2′,3′,5′-tribenzoyl-6-carboxamido-9-β-D-ribofuranosylpurine (**55**, 11 g, 18.1 mmol) in 600 mL absolute EtOH with good stirring. A solution of sodium methoxide in EtOH was added slowly over 45 min to adjust the mixture to pH 8-9 (monitored by pH paper). After 3 h , a TLC aliquot monitoring indicated complete deblocking had occurred, and the reaction was quenched by the addition of 1 mL of glacial acetic acid. The reaction mixture was evaporated, and the residue was suspended in ether, collected by filtration, washed with ether, and dried, giving a crude yield of 5.2 g. This crude product was purified by silica gel flash

chromatography (eluted with 2:1 $CHCl_3$:MeOH). Since the product still contained an appreciable amount of sodium acetate, it was dissolved in 75 mL of water, treated with ~0.5 mL of mixed-bed resin (AG 501X8D) for 5 min, filtered, and the filtrate was freeze-dried; yield, 2.0 g; mp 110-116 °C cap; $UV_{\lambda max}$ 280 nm (7,960) at pH 1; 282 (7,870) at pH 7; 287 (10,750) at pH 13; IR (KBr) 1690, 1585, 1500, 1415, 1335, 1210, 1125, 1085, 1060, 645 cm^{-1}; MS (FAB) *m/e* 296 (M + 1); ^1H NMR (Me_2SO-d_6) δ 3.59, 3.71 (2 m, 2, H-5′), 3.99 (q, 1, H-4′), 4.20 (t, 1, H-3′), 4.61 (t, 1, H-2′), 5.20, 5.36, 5.65 (3 br s, 3, OH-5′,3′,2′), 6.08 (d, 1, H-1′), 8.05, 8.35 (2 br s, 2, $CONH_2$), 8.99 (s, 1, H-2), 9.03 (s, 1, H-8). *Anal.* Calcd. For $C_{11}H_{13}N_5O_5 \cdot 0.7H_2O \cdot 0.25NaOAc$: C, 42.06; H, 4.73; N, 21.33. Found: C, 42.10; H, 4.60; N, 21.33.

6-Aza-4-thiouridine, 2′,3′,5′-Triacetate (58).[19] Into a 100-mL round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and drying tube was added with stirring, 5 g (13.5 mmol) of 6-azauridine, 2′,3′,5′-triacetate (57), and dry pyridine (50 mL). Phosphorus pentasulfide (2.1 g, 4.7 mmol) was then added quickly, the system was flushed with argon, and the reaction was heated at gentle reflux for 3 h. The reaction was then cooled, and the solution was decanted from the dark gum and evaporated at reduced pressure. The residue was dried *in vacuo* over P_2O_5 to remove pyridine. The residue was taken up in EtOH, treated with charcoal, filtered, and evaporated. The dark residue was dissolved in $CHCl_3$, washed with water, dried filtered, and evaporated. A portion of the product was purified by flash chromatography on 100 g of silica gel, using $CHCl_3$ as the eluate. The product was isolated as an orange foam, yield 580 mg; $UV_{\lambda max}$ 325 nm (14,400), 242 (6,10) at pH 1; 335 (13,000), 247 (7,700) at pH 7; 335 (13,300), 247 (7,300) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR (KBr) 1748, 1729, 1580, 1375, 1200 (broad), 1132, 1100, 1074, 1047 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.11 (m, 9, $COCH_3$), 4.17, 4.39 (2 m, 2, H-5′), 4.40 (m, 1, H-4′), 5.43 (t, 1, H-3′), 5.66 (q, 1, H-2′), 6.25 (d, 1, H-1′); 7.67 (s, 1, H-5), 10.40 (s, 1, NH). *Anal.* Calcd. For $C_{14}H_{17}N_3O_8S \cdot 0.1EtOH \cdot 0.1H_2O$: C, 43.31; H, 4.56; N, 10.67. Found: C, 43.26; H, 4.80; N, 10.66.

6-Aza-4-thiouridine (59).[19] A solution of 6-aza-4-thiouridine, 2′,3′,5′-triacetate (58, 1 g, 2.58 mmol) was dissolved in 50 mL of MeOH and slowly passed through a column of Dowex 1 resin (OH^-form). The column was washed with about 300 mL of MeOH and the product was eluted using 5% HOAc in MeOH. The appropriate fractions were combined, evaporated, the residual HOAc removed by evaporation of water (2 x 50 mL), followed by evaporation of 50 mL EtOH/benzene. The product was purified by chromatography through a flash column of 100 g of silica gel with 7:1 $CHCl_3$-MeOH. The appropriate fractions were combined, evaporated, and the residue was washed with ether (2 x 30 mL) and dried at 56 °C over phosphorus pentoxide; yield, 140 mg; mp 104-115 °C dec.; UV λmax 328 nm (13,700), 243 (5,600) at pH 1; 334 (12,600), 247 (7,000) at pH 7; 336 (12,700), 247 (7,100) at pH 13; MS (FAB) *m/e* 262 (M + 1); IR (KBr) 1704, 1575, 1283, 1050 (broad), 990, 590 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.39, 3.50 (2 m, 2, H-5′), 3.80 (app. q, 1, H-4′), 4.02 (app. q, 1, H-3′), 4.24 (app. q, 1, H-2′), 4.65 (t, 1, OH-5′), 5.04 (d, 1, OH-3′), 5.30 (d, 1, OH-2′), 5.84 (d, 1, H-1′), 7.75 (s, 1, H-5), 13.7 (br s, 1, NH). *Anal.* Calcd. For $C_8H_{11}N_3O_5S \cdot 0.3H_2O \cdot 0.07Et_2O$: C, 36.58; H, 4.56; N, 15.46. Found: C, 36.63; H, 4.84; N, 15.38.

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