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AUTHORITY

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SRI-KM-88-061

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

ANNUAL PROGRESS REPORT

John A. Secrist III
Cecil D. Kwong
Charles A. Krauth
Angela G. Ford
Yajnanarayana H. R. Jois
Deborah A. Carter

JANUARY 19, 1988
(For the period 1 December 1986 - 30 November 1987)

Supported by

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

Contract No. DAMD17-86-C-6011

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

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REPORT DOCUMENTATION PAGE

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Synthesis Laboratory for the U. S. Army Medical Research Institute of Infectious Diseases Selection Panel

12. PERSONAL AUTHOR(S) John A. Secrist III; Cecil D. Kwong; Charles A. Krauth, Angela G. Ford; Yajnanarayana H. R. Jois; Deborah A. Carter

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

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. Types of compounds prepared thus far include: 1-benzyloxyadenosines, 9-substituted 1-benzyloxyadenines, 1,2,4,5,3,6-tetraazadiphosphorines, substituted imidazoles, selenadiazoles triazoles, triazolotriazoles, guanidines, pyrazoles, adamantanecarboxamides, adamantylthioureas, adamantylthiosemicarbazides, and chloroquines.

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Mrs. Virginia M. Miller	301/663-7325	SGRD-RMI-S

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Unclassified

18. Continued

adamantylthiosemicarbazides, triazoles, and chloroquines.

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I. Introduction

This report summarizes activities relating to Contract No. DAMD17-86-C-6011, 1 December 1986 through 30 November 1987. The purpose of this contract is to support the synthesis of a wide variety of compounds for evaluation in the U. S. Army Medical Research Institute of Infectious Diseases (USAMRIID) viral testing program. Compounds that are to be made include: 1) known compounds that need to be made in larger quantities for proper evaluation; and 2) new compounds whose structures are determined by rational processes.

During the year covered by this report, most of our efforts were directed toward the synthesis of the new compounds. Our strategy was to select potential lead compounds from the USAMRIID list of active antiviral compounds, and then to propose and synthesize analogs of these compounds. By following this strategy, we were able to provide 99 new compounds for screening. In the later months, we also began synthesizing 8 compounds which were specifically requested by USAMRIID. Two of these compounds were submitted during the last quarter; of those remaining, all except two are in the process of being synthesized or purified. The two compounds not receiving any attention are 4-iminopyrazolo[3,4-d]-1,3-thiazin-6-thione (AVS-000266) and bisdesethylchloroquine. The data sheet supplied with the request for the first compound showed that USAMRIID already had 15 g in stock. We have requested further verification that USAMRIID really needs more of this compound. As for bisdesethylchloroquine, we have attempted to synthesize this compound but have determined that it is unstable in its free base form or as an ammonium sulfate salt. Spectral data indicates that this compound undergoes further reaction during workup and upon sitting even for only a few days at room temperature. Furthermore, the literature preparation for this compound contains a few key inconsistencies, particularly with the analytical data. Based on these observations, we questioned our ability to provide USAMRIID with an analytically pure sample of this compound. When we notified USAMRIID of this problem, especially with respect to whether we should continue with our efforts to make this compound, Dr. Ussery suggested exploring whether a sample of the compound would be available from the Walter Reed Army Institute of Research. Dr. Robert R. Engle of WRAIR informed us that such a sample was available. A copy of the letter was sent to Dr. Ussery by Dr. Engle. We have also received a copy of the procedure used to make this compound. A comparison of their procedure with the one we used revealed only one difference. They isolated the bromide salt instead of the

sulfate salt or the free amine. We will not pursue the synthesis of this compound unless we are requested to do so by Dr. Ussery after the small sample has been evaluated.

Finally, we also submitted five compounds that had been prepared previously at SoRI. These compounds were known to have biological activity and were therefore submitted as potential lead compounds. One of these, ribofuranosyl-6-ethylthiopurine has already been found to have activity against AD2, VV, JE, SF, and YF viruses, and it is an exciting lead compound for further synthetic activity.

II. Personnel

During the year covered by this report, we added two more chemists to our group, thus fulfilling our personnel requirements for this project. In January, Dr. Yajnanarayana H. R. Jois joined our group as a Postdoctoral Fellow, augmenting our efforts with his heterocyclic synthesis experience. Ms. Deborah A. Carter joined us in May following her graduation (M.S. Chemistry) from Auburn University, adding her background in synthetic and medicinal chemistry to our group.

The time charges made during the second year are listed below, and are divided into various categories for ease of understanding:

Name	Hours 1 Dec 86 - 30 Nov 87	Percent of Time
Project Supervision		
Dr. J. A. Secrist III	204.50	11.2
Chemists		
Dr. C. D. Kwong	1820.25	97.3
C. A. Krauth	1714.50	93.7
A. G. Ford	1856.75	99.3
H. R. Y. Jois	1077.25	57.6
D. A. Carter	1249.50	66.8
Analytical Services		
Dr. W. C. Coburn	359.50	20.1
Dr. J. M. Riordan	446.50	23.9
M. C. Kirk	376.00	20.5
C. Richards	395.50	22.1
R. T. Morris	346.75	18.5
S. A. Campbell	27.00	1.5

Name	Hours 1 Dec 86 - 30 Nov 87	Percent of Time
Glassware Technician		
W. Johnson	204.00	11.4
J. Crow	195.25	10.7
A. Jackson	99.00	5.4

III. Compounds Submitted

The compounds that we submitted during the contract year are shown in Tables 1-4. Our SoRI numbers and the USAMRIID numbers are listed for each compound along with the amounts submitted. We can prepare additional quantities of any compounds submitted, if it is warranted.

IV. Chemistry

Our efforts during the second contract year have been directed toward a number of target areas. Some of these areas were carryovers from the first contract year, including: analogs and substitution variants of adenosine/adenine N^1-oxide; tetraazadiphosphorines; selenadiazoles; triazoles and triazolotriazoles; 6-carboxypurines; and 2-substituted imidazole intermediates leading to 8-substituted-3-deazaguanine. New areas that we have pursued include: 5-substituted and 4,5-disubstituted ethyl pyrazole-3-carboxylates; adamantane-containing compounds; and allopurinol (or 4-hydroxypyrazolo[3,4-d]pyrimidine) derivatives. As a result of these efforts, we submitted 99 new targets or intermediates for screening. We have also worked on 8 compounds specifically requested by USAMRIID and submitted 2 of these. Finally, we also submitted 5 compounds which were already available at SoRI. These compounds was known biologically active compounds, and they were submitted to determine if they might also be potential lead compounds for our project. For the year we submitted a total of 106 compounds.

The synthesis of the O-alkylated analogs of adenosine N^1-oxide (1) followed the same general procedure used for the similar compounds produced during the first year of this program. (Since the actual procedures for all of these analogs have proven to be virtually identical, only summarized data will be presented for analogs beyond compound **2e** in the experimental section. As noted in the Experimental Section, compounds **2f-v** were made by following the preparation of 1-(2-cyanobenzyloxy)adenosine, perchlorate salt (**2e**). The precursor for these analogs was the parent compound adenosine N^1-oxide **1**, which was prepared by oxidation of

Table 1

Compounds Submitted from December 1 to February 28, 1987

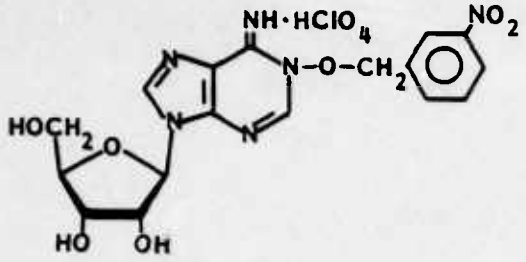
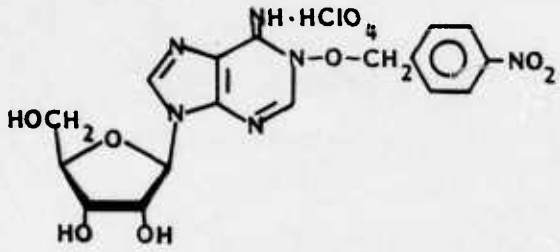
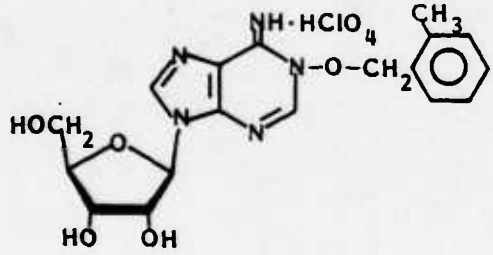
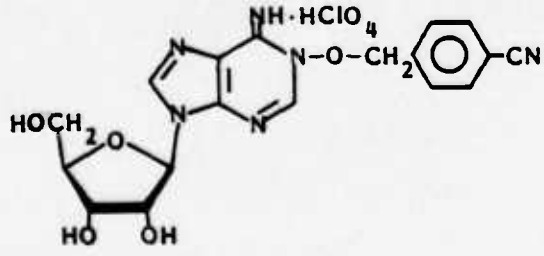
Compound	SoRI No.	AVS No.	Amount Submitted
	6885	002873	1.9 g
	6886	002874	2.0 g
	6887	002875	2.0 g
	6888	002879	2.0 g

Table 1 (Continued)

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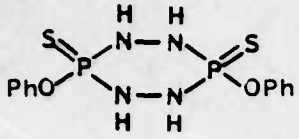
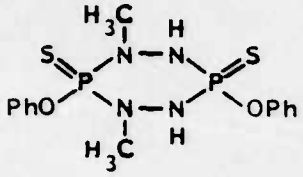
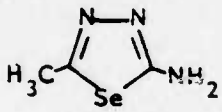
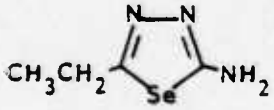
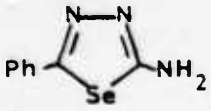
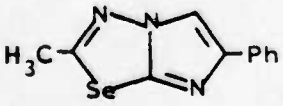
	6854	002739	0.9 g
	6855	002770	2.0 g
	6856	002740	1.5 g
	6862	002772	0.75 g
	6871	002774	0.85 g
	6861	002771	0.8 g

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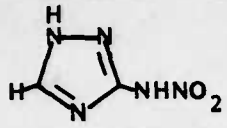
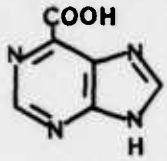
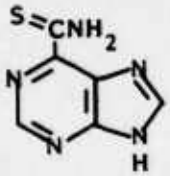
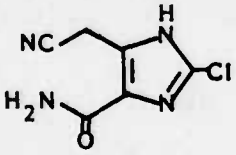
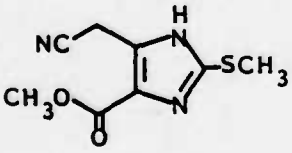
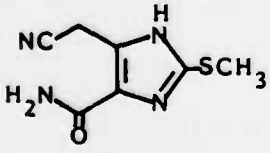
	6881	002787	1.05 g
	6860	002745	1.89 g
	6879	002701	1.6 g
	6842	002566	2.0 g
	6876	001176	1.2 g
	6884	002869	1.53 g

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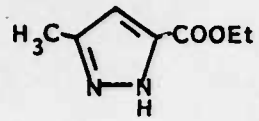
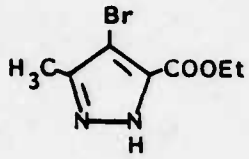
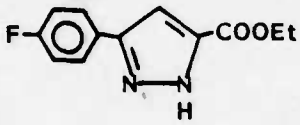
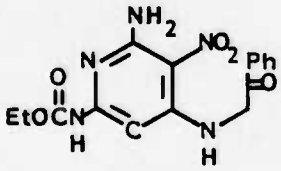
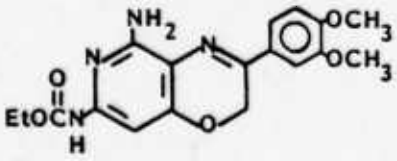
	6889	002876	1.5 g
	6891	002878	1.1 g
	6890	002877	1.5 g
	6053	002872	0.5 g
	6476	002870	0.5 g

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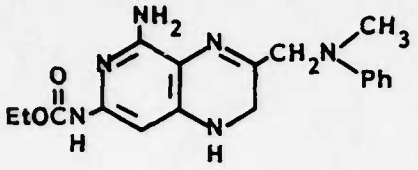
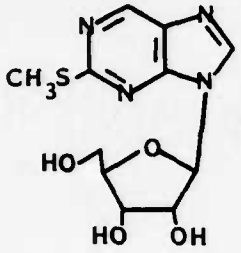
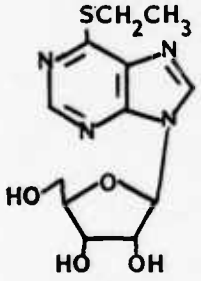
	5261	002871	[illegible]
	915	002293	[illegible]
	1215	002700	[illegible]

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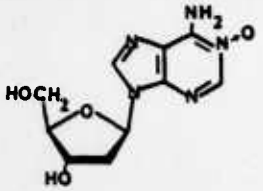
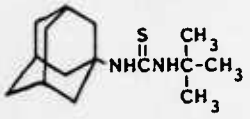
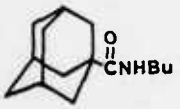
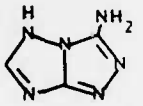
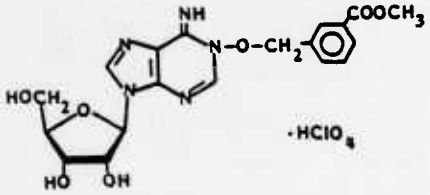
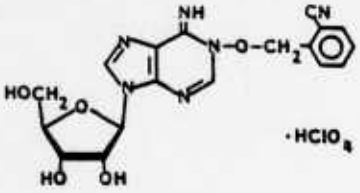
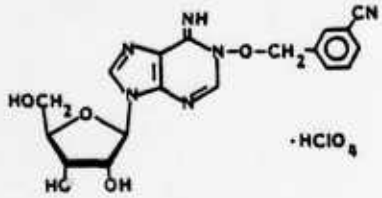
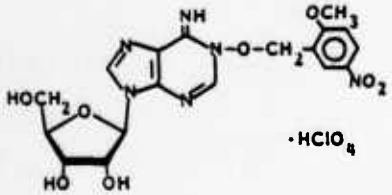
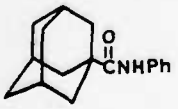
	4305	002995	850 mg
	6892	002885	1.0 g
	6905	002886	0.54 g
	6907	002887	1.53 g
	6908	002888	2.0 g
	6909	002889	2.0 g
	6910	002890	2.0 g
	6911	002891	2.0 g
	6912	002894	1.25 g

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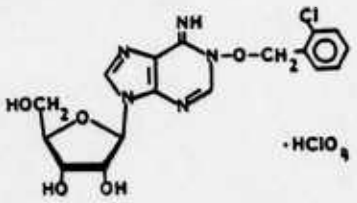
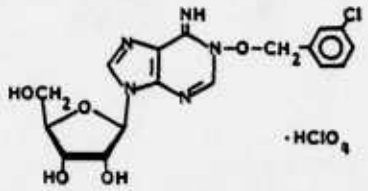
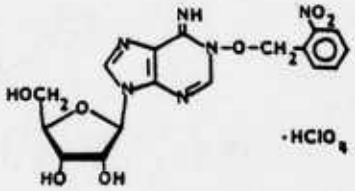
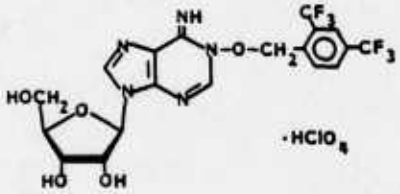
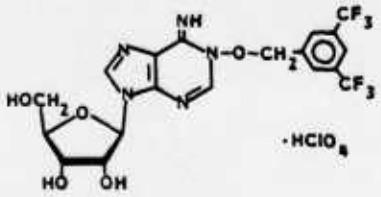
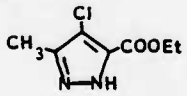
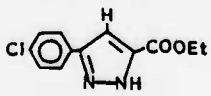
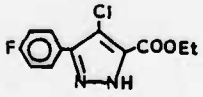
Compound	SoRI No.	AVS No.	Amount Submitted
	6915	002895	2.0 g
	6916	002896	2.0 g
	6925	002908	1.5 g
	6927	002911	1.8 g
	6928	002912	1.5 g
	6929	002913	2.0 g
	6930	002914	0.58 g
	6931	002915	1.2 g
	6932	002916	1.4 g

Table 2 (Continued)

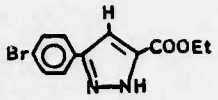
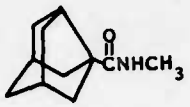
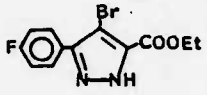
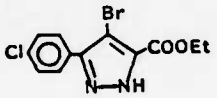
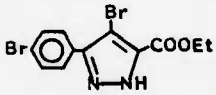
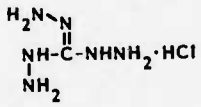
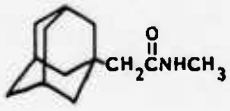
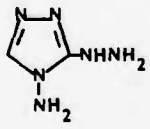
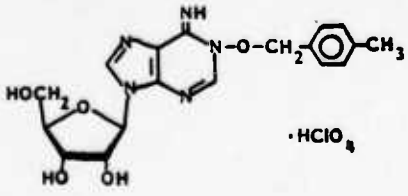
Compound	SoRI No.	AVS No.	Amount Submitted
	6933	002917	1.9 g
	6934	002918	0.73 g
	6943	002957	1.1 g
	6944	002958	1.4 g
	6945	002959	1.7 g
	6946	002960	1.5 g
	6955	002961	1.0 g
	6956	000244	1.5 g
	6957	002994	1.5 g

Table 3

Compounds Submitted from June 1 to August 31, 1987

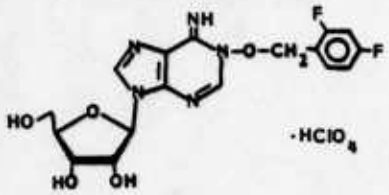
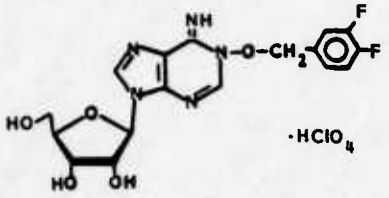
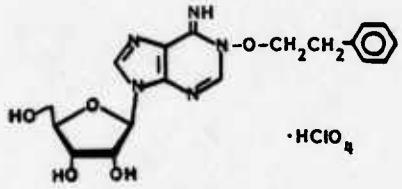
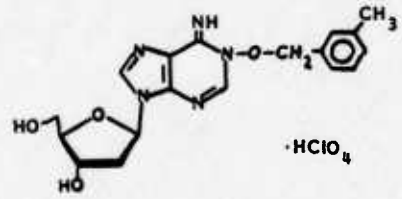
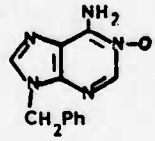
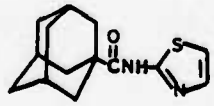
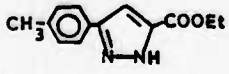
Compound	SoRI No.	AVS No.	Amount Submitted
	6987	003533	1.4 g
	6988	003534	850 mg
	6989	003535	1.8 g
	6990	003536	1.9 g
	6991	003537	1.2 g
	6992	003538	0.62 g
	6995	003546	2.0 g

Table 3 (Continued)

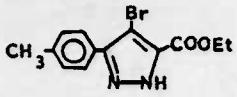
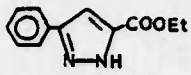
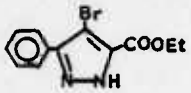
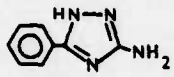
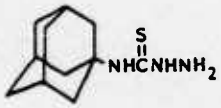
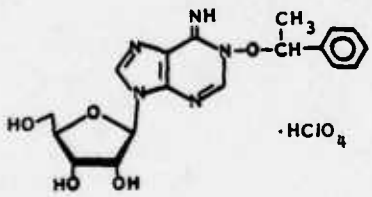
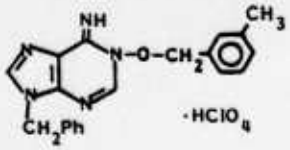
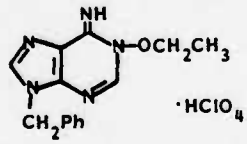
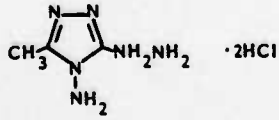
Compound	SoRI No.	AVS No.	Amount Submitted
	6996	003547	1.7 g
	6998	003548	1.8 g
	6999	003549	1.1 g
	7000	003550	1.5 g
	7002	003551	2.0 g
	7008	003607	1.4 g
	7009	003608	1.1 g
	7010	003609	1.0 g
	7017	003610	1.5 g

Table 3 (Continued)

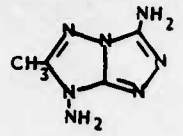
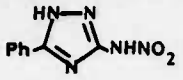
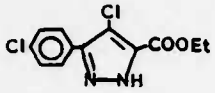
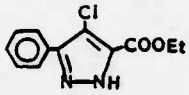
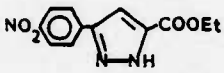
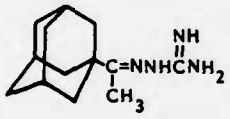
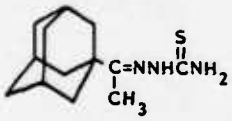
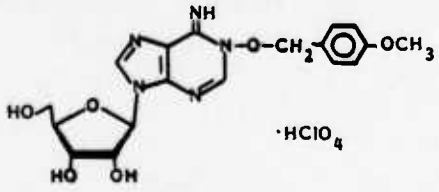
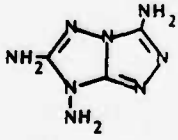
Compound	SoRI No.	AVS No.	Amount Submitted
	7018	003611	1.5 g
	7019	003612	1.5 g
	7020	003613	1.5 g
	7021	003614	0.75 g
	7022	003615	2.0 g
	7023	003677	2.0 g
	7024	003678	2.0 g
	7037	003679	2.0 g
	7038	003680	1.5 g

Table 4

Compounds Submitted from September 1 to November 30, 1987

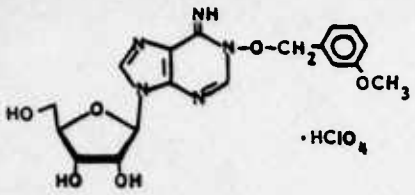
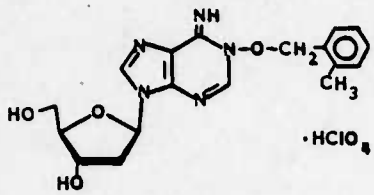
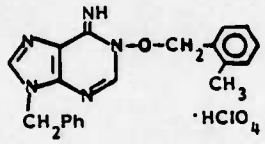
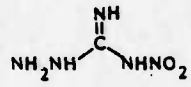
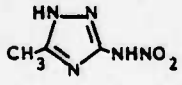
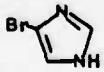
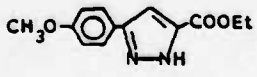
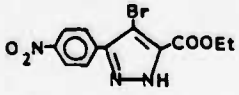
Compound	SoRI No.	AVS No.	Amount Submitted
	7055	003912	2 g
	7056	003913	0.9 g
	7057	003914	0.85 g
	7058	003915	1.6 g
	7059	003916	1.46 g
	7060	003917	3.0 g
	7061	003918	2.0 g
	7062	003919	1.8 g

Table 4 (Continued)

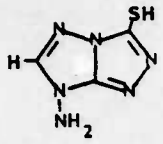
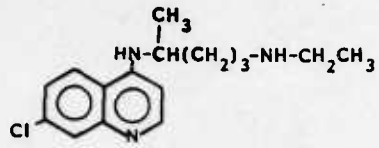
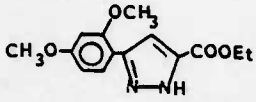
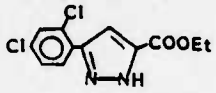
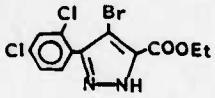
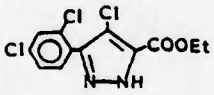
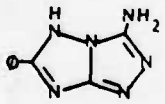
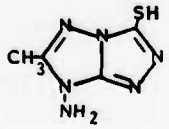
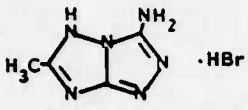
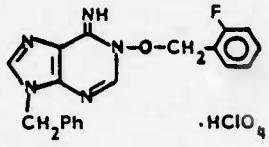
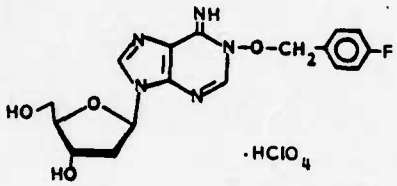
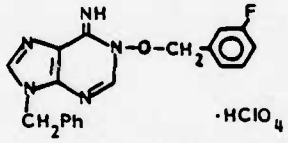
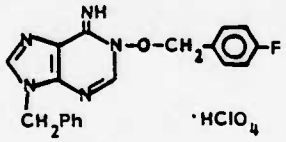
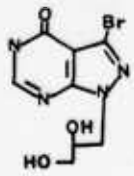
Compound	SoRI No.	AVS No.	Amount Submitted
	7074		1.39 g
	7086	003980	5.26 g
	7091	003996	2.0 g
	7092	003997	2.0 g
	7093	003998	1.5 g
	7094	003999	1.5 g
 ·HBr	7095	004000	1.05 g
	7096	004001	1.15 g

Table 4 (Continued)

Compound	SoRI No.	AVS No.	Amount Submitted
	7097	004002	0.71 g
	7099	004003	1.8 g
	7100	004004	1.5 g
	7101	004005	1.5 g
	7102	004006	1.1 g
	7105	004073	0.554

adenosine with m-chloroperbenzoic acid.[1-3] Compound 1 was alkylated with the appropriately substituted benzyl and alkyl bromides to give the corresponding alkylated N^1-oxyadenosines, and these were then immediately converted to their respective perchlorate salts, as shown in Scheme I. The alkylated N^1-oxyadenosines submitted this year are indicated as 2a-v. (Pertinent data for these compounds and the following N^1-oxyadenine analogs are also given in Table 5.)

We also synthesized N^1-oxyadenine derivatives containing 9-benzyl or 9-(2'-deoxyribose) substituents. Compounds 3a-n were made by following the same general synthetic scheme (shown in Scheme II) employed for the previously mentioned 1-benzyloxyadenosines. Commercially available 2'-deoxyadenosine and synthetic 9-benzyladenine[4,5] were first oxidized with m-chloroperbenzoic acid. They were then alkylated with the appropriately substituted benzyl or alkyl halides, and finally converted to their respective perchlorate salts.

Another area that we continued to pursue from the first program year was the synthesis of congeners of compound 4. We made and submitted compounds 5[6] and 7[7,8] by following the route shown in Scheme III. The main difficulty in preparing these compounds was the separation and purification of the desired products from the mixtures obtained in the reaction sequences. Similar but more severe problems were encountered in our attempts to synthesize compound 6 by the analogous approach also shown in Scheme III. These problems indicated to us that synthesis of compound 6 would probably be long and difficult, and therefore we shifted our efforts to other more fruitful avenues.

We continued to investigate the synthesis of various selenadiazoles and obtained compounds 8a-c by following Scheme IV. We also obtained bicyclic compound 9[9] from aminoselenadiazole[6] 8a, by treatment of this compound with 2-chloroacetophenone. When we tried to make closely related compounds 8d, 8e, and 10 by following the procedures for 8a-c and 9 we obtained at best extremely low yields of the desired products. Furthermore, variations in reaction conditions such as increases in either or both reaction time and temperature as well as modifications in the sequence of addition of reaction components did not improve the yields. Because of these problems, we shifted our interests away from this compound class to other classes with more potential for giving products for screening.

We also continued to make compounds similar to compound 11 with good success during this year. Following Scheme V, we were able to make the nitroaminotriazole 12 (R = H) in good yield by nitration of 3-amino-1,2,4-triazole.[11] This compound was then reduced with activated zinc to give hydrazinotriazole 13 (R

Table 5. Substituted N¹-Oxyadenosine and N¹-Oxyadenines Submitted This Quarter

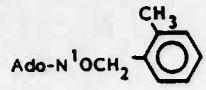
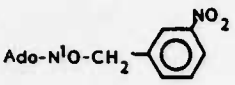
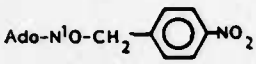
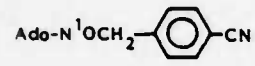
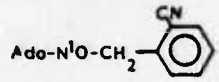
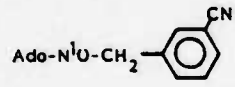
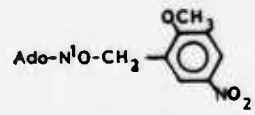
SoRI No.	Product	N¹-Oxide	BrCHR	DMAc	NH_4ClO_4	Yield (%)	M.P. cap	M.F. C, H, N Theory	Found
6887		3.0 g (10.6 mmol)	9.8 g (53 mmol)	60 mL	6.25 g 25 mL H_2O	4.0 g (77%)	122-125 °C dec.	$C_{18}H_{22}ClN_5O_9 \cdot 0.75\ H_2O$ C = 43.12, H = 4.72, N = 13.97	C = 43.18 H = 4.67 N = 14.18
6885		3.0 g (10.6 mmol)	11.4 g (53 mmol)	60 mL	6.25 g 25 mL H_2O	2.1 g (38%)	128-132 °C dec.	$C_{17}H_{19}ClN_6O_{11} \cdot 0.50\ H_2O$ C = 38.68, H = 3.76, N = 15.92	C = 38.64 H = 3.84 N = 15.80
6886		2.5 g (8.83 mmol)	9.5 g (44.2 mmol)	50 mL	5.2 g 20 mL H_2O	3.2 g (70%)	112-122 °C dec.	$C_{17}H_{19}ClN_6O_{11} \cdot 0.50\ H_2O$ C = 38.68, H = 3.76, N = 15.92	C = 38.72 H = 3.78 N = 15.88
6888		2.0 g (7.04 mmol)	4.3 g (21.9 mmol)	40 mL	4.2 g 15 mL H_2O	2.74 g (78%)	112-118 °C dec.	$C_{18}H_{19}ClN_6O_9 \cdot H_2O$ C = 41.83, H = 4.10, N = 16.26	C = 41.60 H = 3.98 N = 16.20
6909		2.5 g (8.83 mmol)	5.19 g (26.5 mmol)	50 mL	5 g 25 mL H_2O	3.5 g (79%)	117-124 °C	$C_{18}H_{19}ClN_6O_9 \cdot 0.25\ H_2O$ C = 42.95, H = 3.90, N = 16.70	C = 42.84 H = 3.92 N = 16.63
6910		2.5 g (8.83 mmol)	5.19 g (26.5 mmol)	50 mL	5 g 25 mL H_2O	3.2 g (73%)	130-135 °C	$C_{18}H_{19}ClN_6O_9 \cdot 0.50\ H_2O$ C = 42.52, H = 3.97, N = 16.55	C = 42.42 H = 3.90 N = 16.48
6911		2.5 g (8.83 mmol)	5.0 g (20.3 mmol)	50 mL	5 g 25 mL H_2O	4.0 g (83%)	200-208 °C	$C_{18}H_{21}ClN_6O_{12}$ C = 39.39, H = 3.86, N = 15.31	C = 39.43 H = 3.86 N = 15.30

Table 5 (Continued)

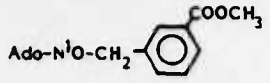
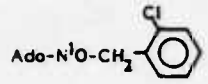
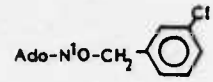
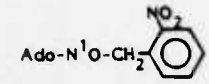
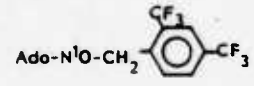
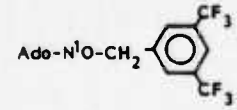
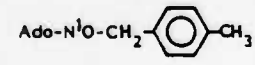
SoRI No.	Product	N'-Oxide	BrCHR	DMAc	NH_4ClO_4	Yield (%)	M.P. cap	M.F. C, H, N Theory	Found
6908		2.5 g (8.83 mmol)	5.0 g (21.8 mmol)	50 mL	5 g 25 mL H_2O	3.6 g (77%)	176-181 °C dec.	$C_{19}H_{22}ClN_5O_{11}\cdot 0.25\ H_2O$ C = 42.55, H = 4.23, N = 13.06	C = 42.54 H = 4.18 N = 13.04
6915		2.5 g (8.83 mmol)	5.0 g (24.3 mmol)	50 mL	5 g 25 mL H_2O	3.6 g (80%)	126-130 °C dec.	$C_{17}H_{19}Cl_2N_5O_9\cdot 0.25\ H_2O$ C = 39.82, H = 3.83, N = 13.66	C = 39.86 H = 3.82 N = 13.79
6916		2.5 g (8.83 mmol)	5.0 g (24.3 mmol)	50 mL	5 g 25 mL H_2O	3.5 g (78%)	140-145 °C dec.	$C_{17}H_{19}Cl_2N_5O_9\cdot 0.50\ H_2O$ C = 39.48, H = 3.90, N = 13.54	C = 39.52 H = 3.80 N = 13.62
6927		2.5 g (8.83 mmol)	5.7 g (26.5 mmol)	50 mL	5 g 25 mL H_2O	2.19 g (47%)	117-124 °C	$C_{17}H_{19}ClN_6O_{11}\cdot H_2O$ C = 38.03, H = 3.92, N = 15.66	C = 38.12 H = 3.78 N = 15.86
6928		2.5 g (8.83 mmol)	5.0 g (16.3 mmol)	50 mL	5 g 25 mL H_2O	1.9 g (35%)	114-119 °C	$C_{19}H_{18}ClF_6N_5O_9$ C = 37.15, H = 3.04, N = 11.40	C = 37.02 H = 3.12 N = 11.38
6929		2.5 g (8.83 mmol)	5.0 g (16.3 mmol)	50 mL	5 g 25 mL H_2O	3.3 g (61%)	113-124 °C	$C_{19}H_{18}ClF_6N_5O_9\cdot 0.75\ H_2O$ C = 36.61, H = 3.15, N = 11.24	C = 36.66 H = 3.09 N = 11.32
6957		2.5 g (8.83 mmol)	4.9 g (26.5 mmol)	50 mL	5 g 25 mL H_2O	1.9 g (44%)	117-122 °C	$C_{18}H_{22}ClN_5O_9\cdot 0.25\ H_2O$ C = 43.91, H = 4.61, N = 14.22	C = 44.06 H = 4.66 N = 14.36

Table 5 (Continued)

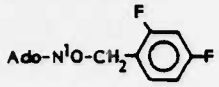
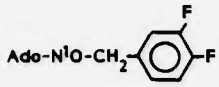
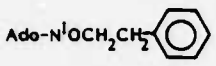
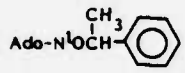
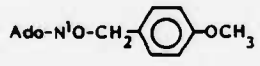
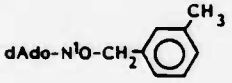
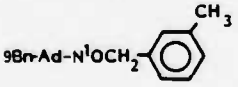
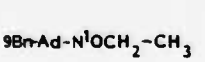
SoRI No.	Product	N¹-Oxide	$BrCH_2R$	DMAc	NH_4ClO_4	Yield (%)	M.P. cap	C, H, N Theory	Found
6987		2.5 g (8.83 mmol)	5 g (24.2 mmol)	50 mL	5 g 25 mL H_2O	1.7 g (38%)	116-130 °C	$C_{17}H_{18}ClF_2N_5O_9 \cdot H_2O$ C = 38.68, H = 3.82, N = 13.27	C = 38.58 H = 3.66 N = 13.40
6988		2.5 g (8.83 mmol)	5 g (24.2 mmol)	50 mL	5 g 25 mL H_2O	1.1 g (24%)	116-122 °C	$C_{17}H_{18}ClF_2N_5O_9 \cdot 0.75H_2O$ C = 39.02, H = 3.76, N = 13.38	C = 38.98 H = 3.60 N = 13.48
6989		2.5 g (8.83 mmol)	4.9 g (26.5 mmol)	50 mL	5 g 25 mL H_2O	2.1 g (49%)	92-100 °C	$C_{18}H_{22}ClN_5O_9 \cdot 0.75H_2O$ C = 43.12, H = 4.72, N = 13.97	C = 42.98 H = 4.64 N = 13.94
7008		2.5 g (8.83 mmol)	5 mL	50 mL	5 g 25 mL H_2O	1.7 g (40%)	128-133 °C	$C_{18}H_{22}ClN_5O_9 \cdot H_2O$ C = 42.74, H = 4.78, N = 13.84	C = 42.66 H = 4.71 N = 13.96
7037		2.5 g (8.83 mmol)	5 mL	50 mL	5 g 25 mL H_2O	2.4 g (55%)	123-129 °C	$C_{18}H_{22}ClN_5O_{10} \cdot H_2O$ C = 41.43, H = 4.64, N = 13.42	C = 41.33 H = 4.68 N = 13.32
6990		2.0 g (7.49 mmol)	5.5 g (30.0 mmol)	40 mL	4 g 20 mL H_2O	2.3 g (66%)	118-122 °C	$C_{18}H_{22}ClN_5O_8 \cdot H_2O$ C = 44.13, H = 4.94, N = 14.30	C = 44.28 H = 4.92 N = 14.44
7009		1.0 g (4.15 mmol)	2.3 g (12.45 mmol)	20 mL	2 g 10 mL H_2O	1.4 g (76%)	199-202 °C	$C_{20}H_{20}ClN_5O_5$ C = 53.88, H = 4.52, N = 15.71	C = 54.04 H = 4.60 N = 15.75
7010		1.0 g (4.15 mmol)	3.32 g (21.3 mmol)	20 mL	2 g 10 mL H_2O	1.3 g (85%)	248-252 °C	$C_{19}H_{16}ClN_5O_5$ C = 45.47, H = 4.36, N = 18.94	C = 45.36 H = 4.43 N = 18.77

Table 5. (continued)

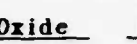
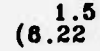
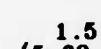
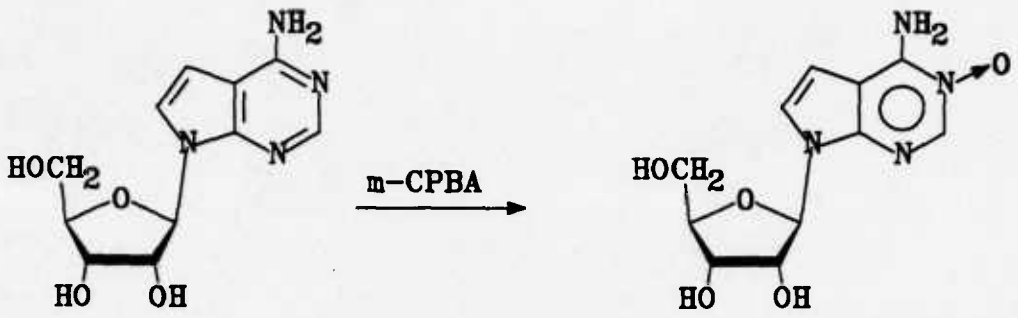
SoRI No.	Product	N1-Oxide	$BrCH_2R$	DMAC	NH_4ClO_4	Yield %	M.P.Cap	C,H,N Theory	Found
7055	Ado-N^1-OCH_2- 	2.5 g (8.83 mmol)	5 g	50 mL	5 g 25 mL H_2O	2.3 g (52%)	109-119°C	$C_{18}H_{22}ClN_5O_{10}$· 1.25 H_2O C=41.07, H=4.50 N=13.31	C=40.66 H=4.60 N=13.32
7056	dAdo-N^1-OCH_2-	1.5 g (5.82 mmol)	3.12 g	30 mL	3 g 15 mL H_2O	1.26 g (47%)	108-118°C	$C_{18}H_{22}ClN_5O_8$· C=44.13, H=4.94, N=14.30	C=44.24 H=4.93 N=14.36
7057	9-Bn-Ad-N^1-OCH_2-	1.5 g (8.22 mmol)	3.45 g	30 mL	3 g 15 mL H_2O	1.2 g (43%)	107-112°C	$C_{20}H_{20}ClN_5O_5$· 0.25 H_2O C=53.34, H=4.59, N=15.55	C=53.40 H=4.56 N=15.53
7065	Ado-N^1-OCH_2-	2.5 g (8.83 mmol)	5 g	50 mL	5 g 25 mL H_2O	3.3 g (77%)	110-116°C	$C_{17}H_{19}ClFN_5O_9$· H_2O C=40.05, H=4.15 N=13.74	C=40.16 H=4.06 N=13.79
7066	Ado-N^1-OCH_2-	2.5 g (8.83 mmol)	5 g	50 mL	5 g 25 mL H_2O	3.3 g (77%)	106-114°C	$C_{17}H_{19}ClFN_5O_9$· H_2O C=40.05, H=4.15 N=13.74	C=40.20 H=4.03 N=13.61
7067	dAdo-N^1-OCH_2-	1.5 g (5.82 mmol)	3.19 g	30 mL	3 g 15 mL H_2O	1.9 g (71%)	88-90°C	$C_{17}H_{19}ClFN_5O_8$· H_2O C=41.35, H=4.29, N=14.18	C=41.28 H=4.30 N=14.20
7068	dAdo-N^1-OCH_2-	1.5 g (5.82 mmol)	3.12 g	30 mL	3 g 15 mL H_2O	1.6 g (60%)	94-98°C	$C_{17}H_{19}ClFN_5O_8$· H_2O C=41.35, H=4.29, N=14.18	C=41.36 H=4.28 N=14.40

Table 5. (continued)

SoRI No.	Product	N^1-Oxide	$BrCH_2R$	DMAC	NH_4ClO_4	Yield %	M.P.,Cap	C,H,N Theory	Found
7089	dAdo-N^1-OCH_2-  -CH_3	1.5 g (5.82 mmol)	3.12 g	30 mL	3 g 15 mL H_2O	1.5 g (57%)	97-105°C	$C_{18}H_{22}ClFN_5O_6 \cdot 0.75\ H_2O$ C=44.54,H=4.88, N=14.43	C=44.40 H=4.89 N=14.45
7099	9-Bn-Ad-N^1-OCH_2- 	1.5 g (6.22 mmol)	3.5 g	30 mL	3 g 15 mL H_2O	2.35 g (84%)	203-205°C	$C_{19}H_{17}ClFN_5O_5$ C=50.73,H=3.81, N=15.57	C=50.77 H=3.88 N=15.51
7100	dAdo-N^1-OCH_2-  -F	1.5 g (5.62 mmol)	3.12 g	30 mL	3 g 15 mL H_2O	1.9 g (71%)	152-156°C	$C_{17}H_{19}ClFN_5O_6 \cdot 0.125\ H_2O$ C=42.71,H=4.06, N=14.65	C=42.58 H=3.96 N=14.88
7101	9-Bn-Ad-N^1-OCH_2-	1.2 g (4.98 mmol)	2.8 g	25 mL	2.5 g 15 mL H_2O	1.95 g (87%)	180-185°C	$C_{19}H_{17}ClFN_5O_5 \cdot 0.25\ H_2O$ C=49.73,H=3.95, N=15.28	C=49.90 H=3.84 N=15.30
7102	9-Bn-Ad-N^1-OCH_2-  -F	1.2 g (4.98 mmol)	2.8 g	25 mL	2.5 g 15 mL H_2O	1.5 g (88%)	200-203°	$C_{19}H_{17}ClFN_5O_5$. C=50.73,H=3.81, N=15.57	C=50.70 H=3.86 N=15.53

Ado = Adenosine. dAdo = 2'-deoxyadenosine. 9-Bn-Ad = 9-benzyladenine.

Scheme I



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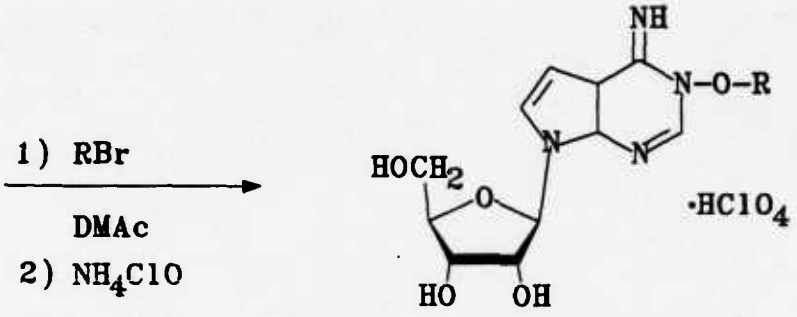
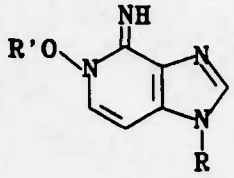


2

R

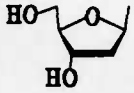
a) 3-nitrobenzyl
b) 4'-nitrobenzyl
c) 2'-methylbenzyl
d) 4'-cyanobenzyl
e) 2'-cyanobenzyl
f) 3'-cyanobenzyl
g) 2'-methoxy-5'-nitrobenzyl
h) 3'-carbomethoxybenzyl
i) 2'-chlorobenzyl
j) 3'-chlorobenzyl
k) 2'-nitrobenzyl
l) 2',4'-bis(trifluoromethyl)benzyl
m) 3'5,'-bis(trifluoromethyl)benzyl
n) 4'-methylbenzyl
o) 2',4'-difluorobenzyl
p) 3',4'-difluorobenzyl
q) 1-phenylethyl
r) 2-phenylethyl
s) 4'-methoxybenzyl
t) 3'-methoxybenzyl
u) 2'-fluorobenzyl
v) 3'-fluorobenzyl

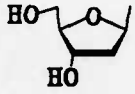
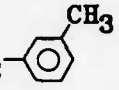
Scheme II

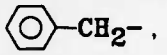


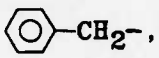
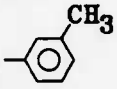
$\cdot HClO_4$

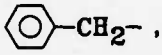
3

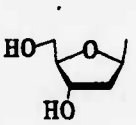
a) R =  , R' = H

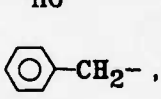
b) R =  , R' = 

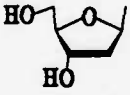
c) R =  , R' = H

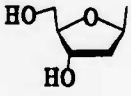
d) R =  , R' = 

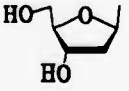
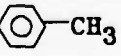
e) R =  , R' = $-CH_2CH_3$

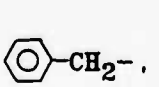
f) R =  , R' = 

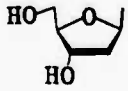
g) R =  , R' = 

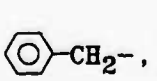
h) R =  , R' = 

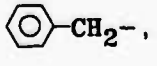
i) R =  , R' = 

j) R =  , R' = 

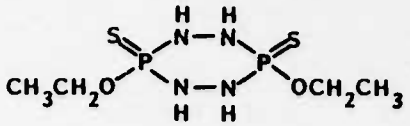
k) R =  , R' = 

l) R =  , R' = 

m) R =  , R' = 

n) R =  , R' = 

Scheme III



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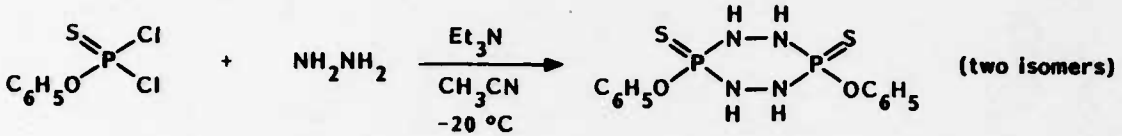
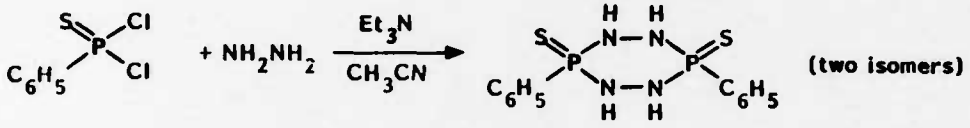


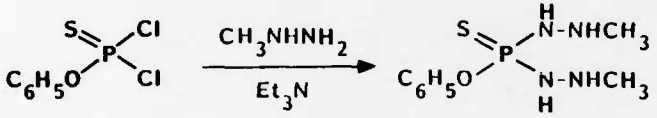
(two isomers)

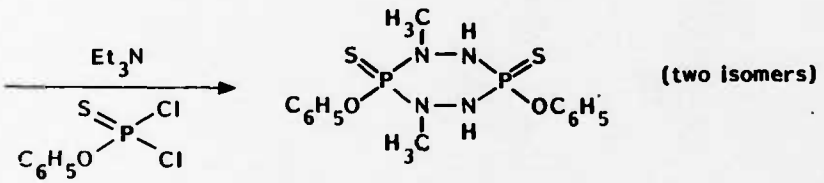
5



(two isomers)

6

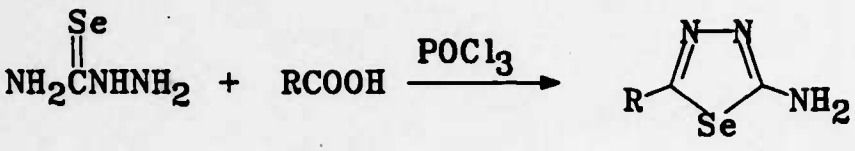




(two isomers)

7

Scheme IV

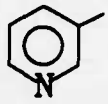


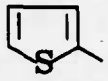
8

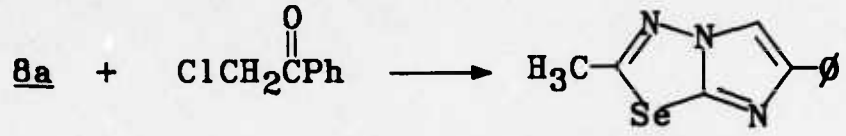
a) R = CH_3

b) R = Et

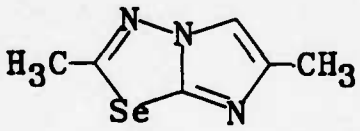
c) R = Ph

d) R = 

e) R = 

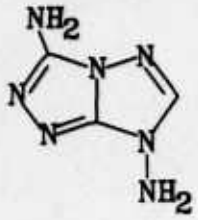


9



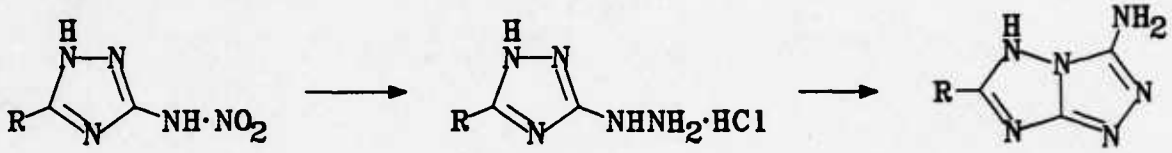
10

Scheme V



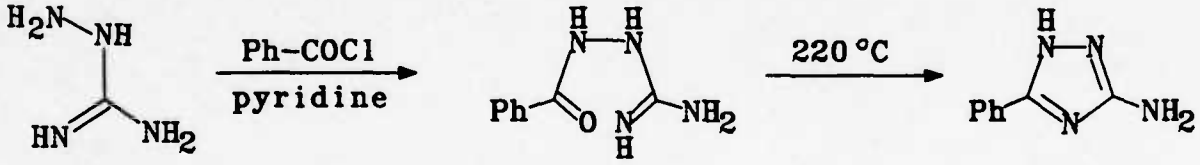
11

(AVS-000245)

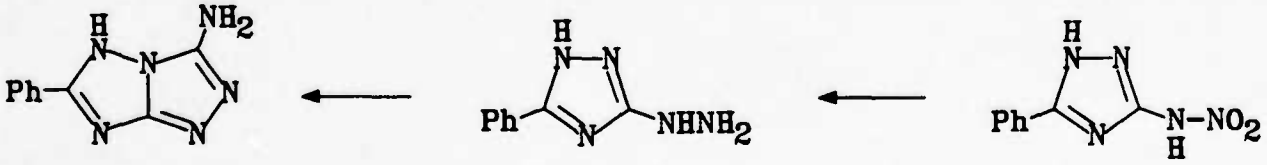


12 13 14

a) R = H
b) R = Ph
c) R = CH_3



15 16



14b 13b 12b

= H),[12] a compound that we were unable to submit because of its instability. We were, however, able to use this compound to synthesize triazolotriazole **14a** as shown in Scheme V, by treatment with cyanogen bromide.[13] We also were able to use the same general procedure to make analogs **14b** and **14c** as shown in Schemes V and VI. For these compounds, the corresponding phenyl and methyl substituted aminotriazoles required synthesis because they were not commercially available.

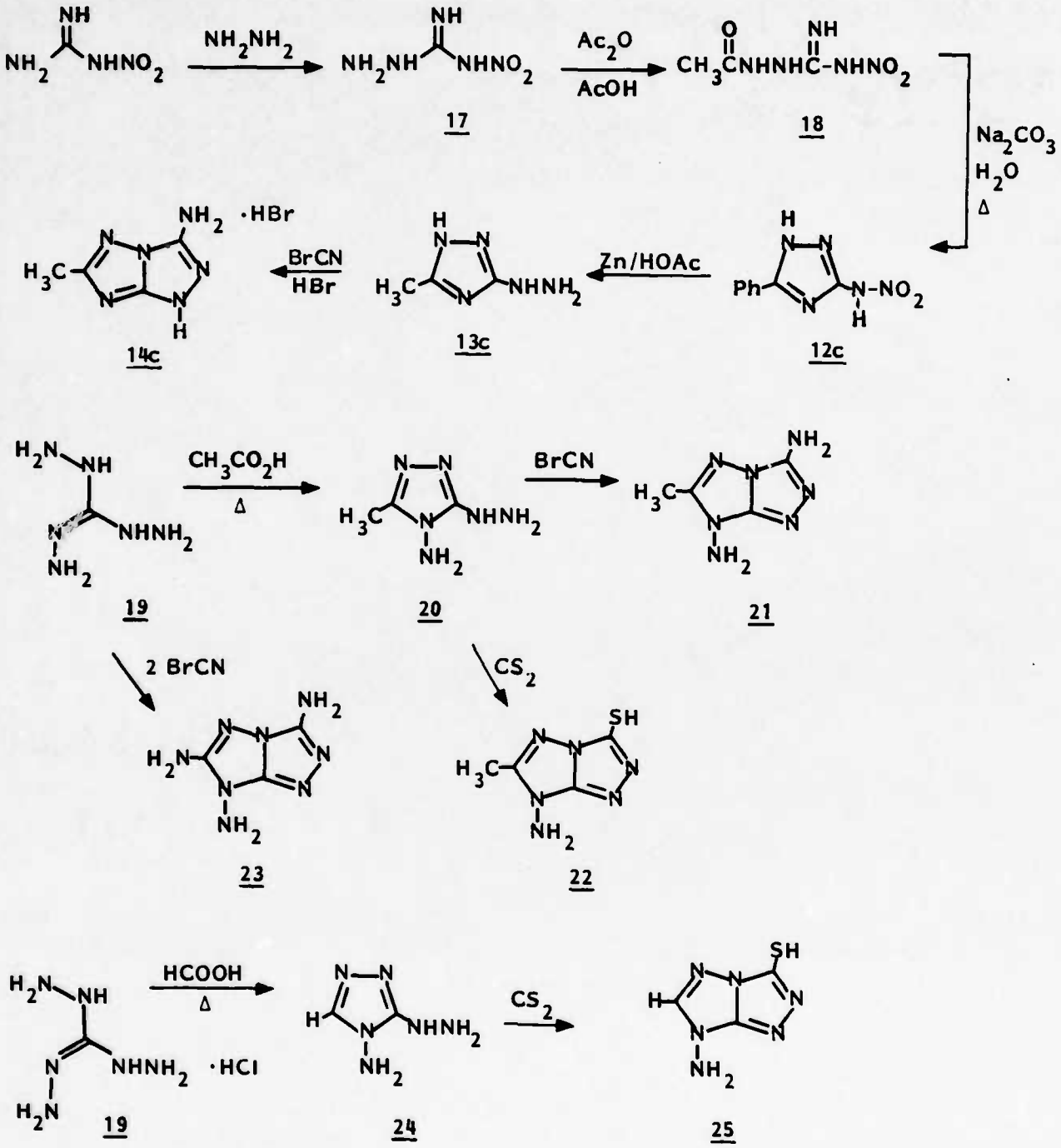
To prepare triazolotriazole **14b**, aminoguanidine was benzoylated (**15**) in pyridine and cyclized at 220 °C[14] to give aminotriazole **16**. This compound was then nitrated to give nitroaminotriazole **12b**.[11] After reduction of the nitroamino compound to the hydrazinotriazole **13b**, cyclization with cyanogen bromide produced triazolotriazole **14b**.[12,13]

We synthesized triazolotriazole **14c** by following a similar approach. Nitroguanidine was treated with hydrazine to give **17**, which was acetylated to **18**, and then cyclized with aqueous sodium carbonate giving nitroaminotriazole **12c**.[15,16] Reduction with zinc/acetic acid followed by treatment with cyanogen bromide gave the desired compound **14c**.[13]

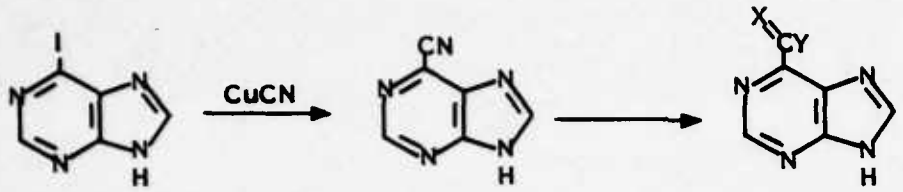
As shown in Scheme VI, bicyclic compounds **21-23** and **25** were made from triaminoguanidine **19**, which was easily obtained by the addition of hydrazine to aminoguanidine. Compound **21** was made via a two-step process: Triaminoguanidine **19** was heated with acetic acid, thus effecting cyclization to triazole **20**,[17] and then further cyclized to triazolotriazole **21** by treatment with cyanogen bromide.[13] Similarly, triazolotriazole **22** was also obtained from triazole **20** by treatment with carbon disulfide. Triazolotriazole **23** was made directly from triaminoguanidine by treatment with two equivalents of cyanogen bromide. The last triazolotriazole made by this approach was triazolotriazole **25**. Triaminoguanidine was heated with formic acid giving triazole **24**, which was then further cyclized by treatment with carbon disulfide to triazolotriazole **25**.

As a result of our efforts to synthesize various related 6-substituted analogs in the purine and 8-azapurine series, we were able to submit purine-6-carboxylic acid **26a** and purine-6-thiocarboxamide **26b**, as shown in Scheme VII.[18] We had hoped to, but were unable to alter these compounds further by incorporating a halogen at either the 2- or 8-positions. Our preliminary investigations into various approaches to these alterations all resulted in complex product mixtures. Similarly, our attempts (shown in Scheme VII) to synthesize purine and 8-azapurine analogs such as **27** and **28** from either 2,6-dichloropurine or 4,6-dichloro-5-nitropyrimidine failed

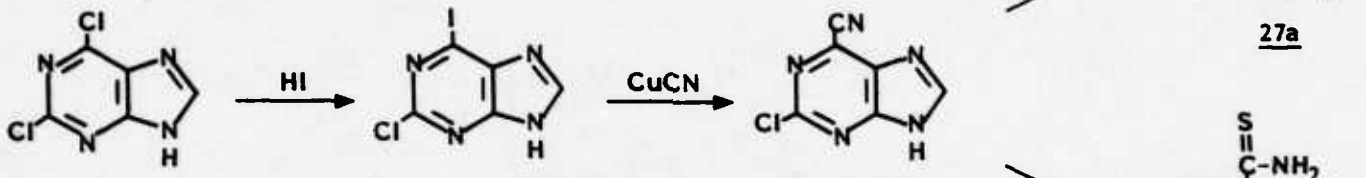
Scheme VI


NH
NH2
NHNO2
NH2NH2
NH2NH
NHNO2
17
Ac2O
AcOH
CH3CNHNHC-NHNO2
18
Na2CO3
H2O
Δ
Ph
N-NO2
12c
Zn/HOAc
H3C
NHNH2
13c
BrCN
HBr
NH2 ·HBr
14c
H2N
NH
NHNH2
NH2
19
CH3CO2H
Δ
20
BrCN
21
2 BrCN
23
CS2
SH
22
HCOOH
Δ
·HCl
24
25

Scheme VII

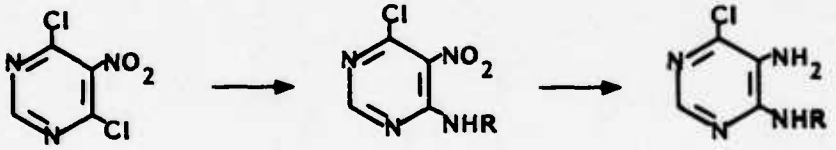


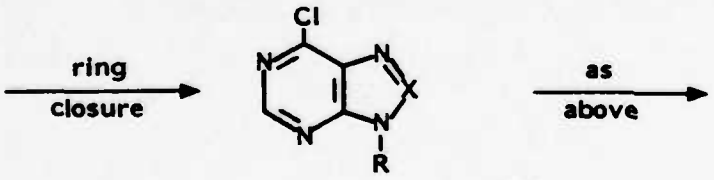
26a: X = O, Y = OH
26b: X = S, Y = NH_2



27a

27b





X = N, C-SH, C-Cl
R = H

28

to give promising results. Although we still felt that these targets merited further attention, we left this area to pursue other more promising target structures.

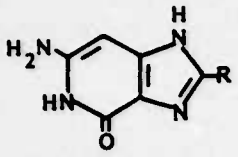
During this year we also continued with our attempts to synthesize 8-substituted 3-deazaguanines 29 following the approach shown in Scheme VIII.[19,20] In our pursuit of 8-chloro-3-deazapurine (29a) we were able to make precursor 30 (submitted last year), but we were not able to cyclize this intermediate even after employing a number of treatment conditions with ammonia. Instead, we obtained low yields of uncyclized amide 31 from all of the reaction attempts, suggesting that the chlorine was deactivating the system toward cyclization.

This year, we also pursued the synthesis of methylthio-substituted 29b by following the same general approach as followed for 29a, as shown in Scheme VIII. Again, we were able to synthesize precursor 32, but as with the analogous chlorine-containing compound, we were not able to cleanly effect cyclization, and the only recoverable product after the cyclization attempt was compound 33. Because of the low number of submittable compounds that we were obtaining, we decided to postpone any more work directed toward 3-deazaguanine analogs.

During the latter part of the first quarter of this year we began directing our efforts toward synthesizing substituted pyrazoles such as 34. This group of compounds was selected based upon the activity of methyl 4-chloro-5-[2,4-dichlorophenyl]pyrazole-3-carboxylate [AVS-000332] against PIC, VEE, and JBE viruses. Following a procedure developed by Knorr et al.[21] we made ethyl 5-methylpyrazole-3-carboxylate (34a) from ethyl 2,4-dioxovalerate and hydrazine. Halogenation at the 4-position using the standard procedure of bromine or chlorine in acetic acid, as shown in Scheme IX, gave 34b and 34c.

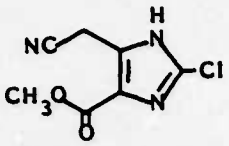
Synthesis of virtually all of the other desired pyrazole analogs (with R = various substituted phenyls) proved to be relatively straightforward. The ethyl 5-substituted-phenyl-2,4-dioxobutyrates were made by condensing the appropriately substituted acetophenones with diethyl oxalate.[22] As with the synthesis of pyrazole 34a these butyrates were treated with hydrazine hydrate to produce the corresponding pyrazoles. These pyrazoles were either submitted as is or after pyrazole ring halogenation with either bromine or chlorine in acetic acid. We encountered problems in our attempts to make the 4-chloro products of ethyl 5-(p-tolyl)pyrazole-3-carboxylate 34o and ethyl 5-(p-methoxyphenyl)pyrazole-3-carboxylate 34t. Similarly, we could not control either the chlorination or bromination of 5-(2',4'-dimethoxyphenyl)pyrazole-3-carboxylate (34v). Chlorination of the activated phenyl rings of 34o, t, v, and bromination of the phenyl ring of 34v were found to compete with the corresponding halogenations of the pyrazoles under our reaction

Scheme VIII

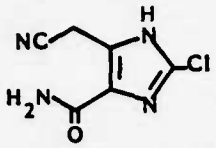


29

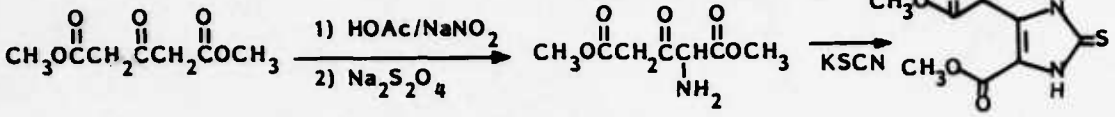
a) R = Cl
b) R = SCH_3

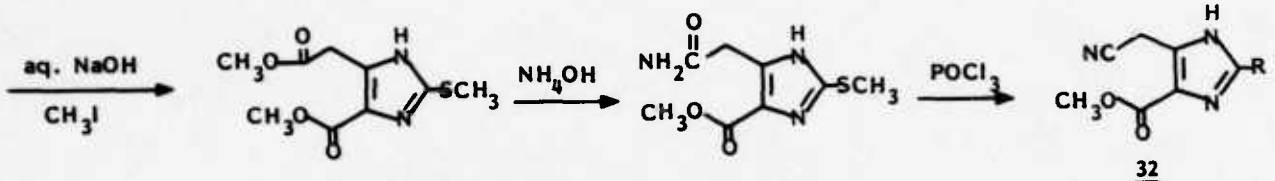


30

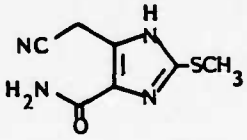


31



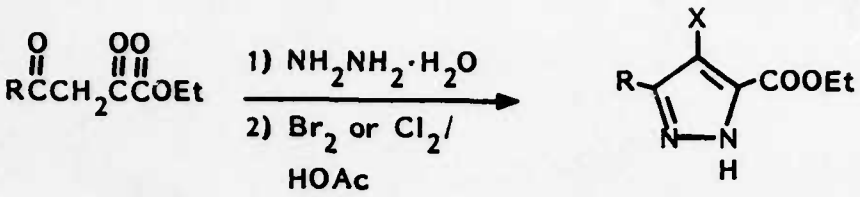


32

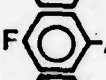


33

Scheme IX



34

a: R = CH_3, X = H
b: R = CH_3, X = Cl
c: R = CH_3, X = Br
d: R =  , X = H
e: R =  , X = Br
f: R =  , X = Cl
g: R =  , X = H
h: R =  , X = Br
i: R =  , X = H
j: R =  , X = Br
k: R =  , X = Cl
l: R =  , X = H
m: R =  , X = Br
n: R =  , X = Cl

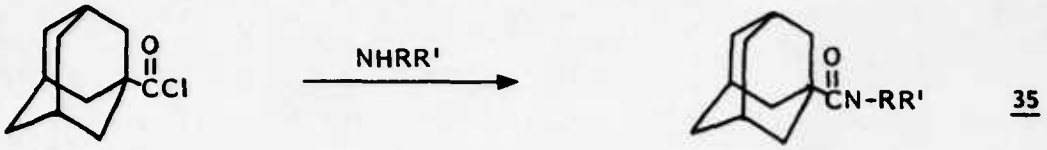
o: R =  , X = H
p: R =  , X = Br
q: R =  , X = H
r: R =  , X = Br
s: R =  , X = Cl
t: R =  , X = H
u: R =  , X = Br
v: R =  , X = H
w: R =  , X = H
x: R =  , X = Br
y: R =  , X = Cl

conditions, and as a result, we routinely obtained mixtures of polychlorinated (or polybrominated) products. Furthermore, we were unable to find a chromatographic system that enabled us to separate these compounds; therefore, in the interest of efficient use of time, no additional effort was expended on these specific compounds. We were also unable to obtain one other target pyrazole, 5-(p-bromophenyl)-4-chloropyrazole-3-carboxylate. Our attempts to obtain this compound by chlorinating 5-(p-bromophenyl)-3-carboxylate (**34g**) resulted in the unexpected formation of 5-(p-chlorophenyl)-4-chloropyrazole-3-carboxylate (**34k**), even after reaction times as short as 1 h.

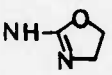
During this year, we also synthesized a number of adamantane-containing compounds. Since the methylamide of 1-adamantanecarboxylic acid had been shown to be active in the USAMRIID screen, our work was first directed toward producing similar amides of 1-adamantanecarboxylic acid and 1-adamantaneacetic acid. As shown in Scheme X, we made the dimethyl- and n-butylamides (**35a** and **35b**, respectively) and the anilide **35c** of 1-adamantanecarboxylic acid starting with commercially available 1-adamantanecarboxylic acid chloride. We similarly made the methyl, dimethyl and n-butyl amides and the anilide of 1-adamantaneacetic acid **36a-d** and the methylamide of 1-noradamantanecarboxylic acid **37** by first generating the acid chloride by standard preparative procedures and then adding the requisite amines. Unfortunately, only **35a-c** and **37** were submitted, because we were unable to purify the other amides to the necessary analytical purity. Another 1-adamantanecarboxamide derivative that we synthesized was amide **35d**. As with amides **35a-c**, we made this amide by adding 2-aminothiazole to adamantane carbonyl chloride. Interestingly, when we tried to make amide **35e** by virtually the same procedure, we did not obtain the desired product, but instead recovered mainly starting material. We also pursued alkylated 1-adamantamines such as mono- and dimethyladamantylamine and trimethyladamantylammonium iodide (**38**, **39**). After numerous attempts with different reaction conditions we obtained only mixtures of all methylated forms under a number of reaction conditions. Therefore, we dropped this class and began pursuing the adamantane-containing compounds shown in Scheme XI.

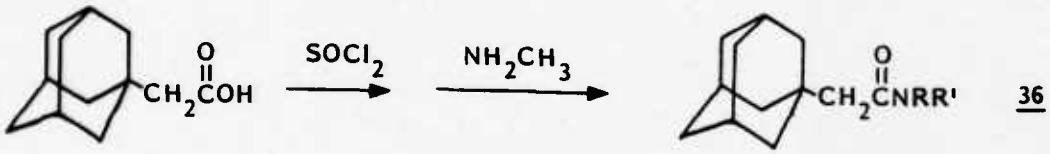
One of these compounds was an adamantyl thiourea, because members of this compound class had been reported to have antiviral activity against the PR8 strain of influenza comparable to that of 1-aminoadamantane hydrochloride.[23] We made one analog of this class, 1-adamantyl-3-t-butylthiourea **40**, by adding adamantamine to t-butyl isothiocyanate.

Scheme X



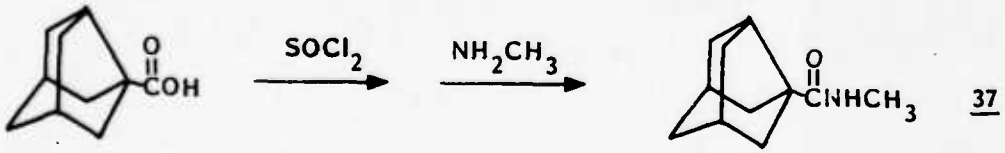
35

a: R = R' = CH_3
b: R = n-Bu, R' = H
c: R = $PhCH_2$-, R' = H
d: R = NH-  , R' = H
e: R = NH-  , R' = H



36

a: R = CH_3, R' = H
b: R = R' = CH_3
c: R = n-Bu, R' = H
d: R = $PhCH_2$, R' = H



37

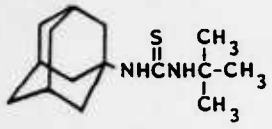
Scheme XI

38

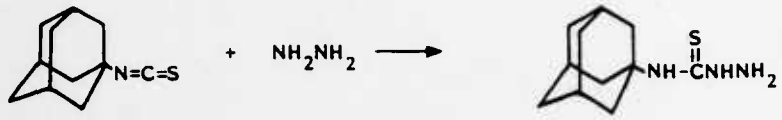
39

a: R = CH_3, R' = H

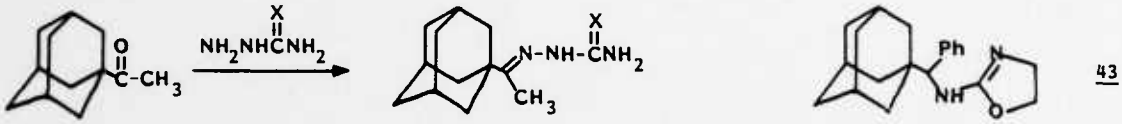
b: R = R' = CH_3



40



41



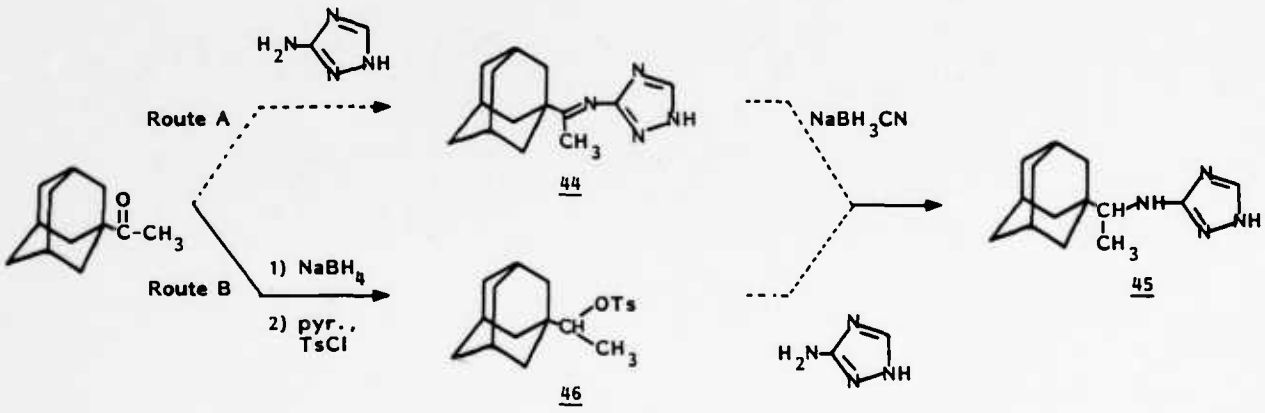
42

43

a: X = NH

b: X = S

c: X = O



44

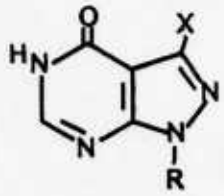
We also synthesized adamantyl thiosemicarbazide (**41**)[21] by the addition of hydrazine to adamantyl isothiocyanate, and we made hydrazone **42a** and thiosemicarbazone **42b**[25] by the addition of aminoguanidine and thiosemicarbazide, respectively, to adamantyl methyl ketone. Interestingly, we were not able to synthesize the analogous semicarbazone **42c** by following the same general procedure. Another adamantane-containing compound class that we pursued was analogs of compound **43**. Unfortunately, our efforts to synthesize compounds from adamantyl methyl ketone were unsuccessful by either of our proposed routes. Route A was halted because we could not get 3-aminotriazole to add to the adamantyl methyl ketone. Route B was stopped because we were unable to form a tosylate from 1-adamantyl-1-ethanol with any success. We found that tosylation of this compound was very slow, and that any tosylate that formed rapidly eliminated; as a result of this we obtained only starting material and low yields of 1-vinyladamantane.

The final target class that we pursued was based on allopurinol (4-hydroxypyrazolo[3,4-d]pyrimidine). The USAMRIID list of active antiviral compounds showed a number of active pyrazolopyrimidine compounds. Because most of these were the usual ribosylated forms, we felt that this immediately pointed out the need for analogs with altered sugar moieties such as those shown in Scheme XII. Thus far, we have submitted one of our target compounds, (**47a**). This compound was made by condensing bromoallopurinol with glycidol,[26] a reaction which proceeded cleanly and gave a reasonable yield. When we tried to repeat the same general procedure with allopurinol, we routinely obtained mixtures of products that were alkylated at any or all of the possible sites, instead of just the desired product **47b**. We have encountered similar problems with our attempts to attach the other altered sugar moieties to either bromoallopurinol or allopurinol. We have recently tried phase-transfer catalysts to effect this attachment and have been getting more promising results.

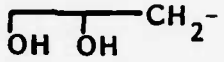
During this year, specific requests for quantities of the following compounds were made: 5-chloro-3-β-D-ribofuranosyl)-s-triazolo[1,5-a]pyrimidin-7-one; 1-β-D-ribofuranosylimidazo[1,2-b]pyrazole-7-carbonitrile; 3(5)-nitro-5(3)-bromo-1,2,4-triazole; 4(5)-bromo-1H(3H)-imidazole; 4-iminopyrazolo[3,4-d]-1,3-thiazin-6-thione; 3-bromo-1-β-D-ribofuranosylpyrazolo[3,4-d]pyrimidin-4-one; bisdesethyl chloroquine; desethyl chloroquine; and 3-bromo-1-β-D-ribofuranosylpyrazolo[3,4-d]pyrimidin-4-one (**47c**). The status of these compounds is as follows:

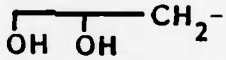
(1) The 4(5)-bromo-1H(3H)-imidazole (**48**)[27] has been made and submitted (Scheme XIII).

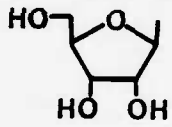
Scheme XII



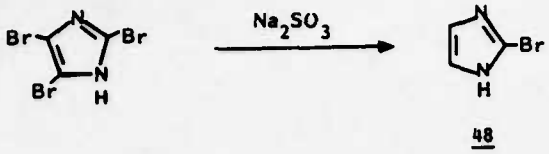
47

a: X = Br, R = 

b: X = H, R = 

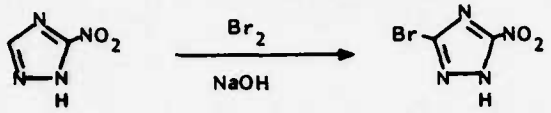
c: X = H, R = 

Scheme XIII



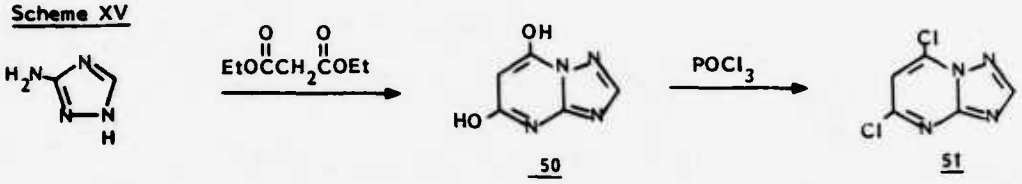
48

Scheme XIV

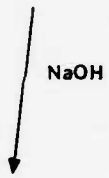


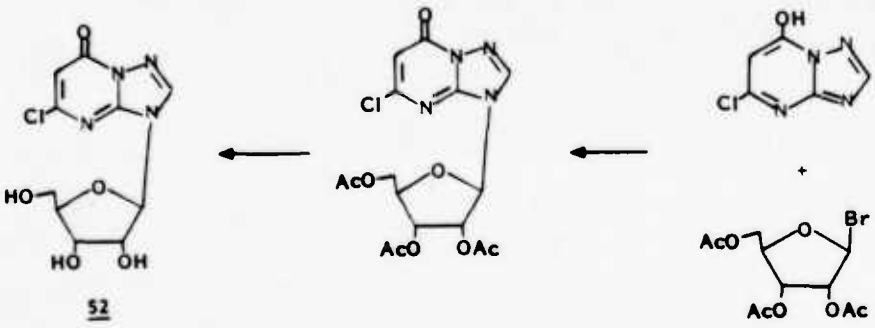
49

Scheme XV



50 51





52

(2) The 3(5)-nitro-5(3)-bromo-1,2,4-triazole (49) has been made, but we are finding it difficult to purify (Scheme XIV).

(3) In our efforts to synthesize 5-chloro-3-β-D-ribofuranosyl-S-triazolo[1,5-a]pyrimidin-7-one (52), we have synthesized 5-triazolo[1,5-a]pyrimidin-5,7-dione (50) but we have encountered unexpected difficulties in our attempts to convert 50 to 5,7-dichloro-S-triazolo[1,5-a]pyrimidine (51) (Scheme XV).

(4) We have made imidazo[1,2-b]pyrazole-7-carbonitrile (53) and soon should be coupling it with the necessary sugar intermediate to get the 1-β-D-ribofuranosylated form (54) (Scheme XVI).

(5) 4-Iminopyrazolo[3,4-d]-1,3-thiazin-6-thione 55 (Scheme XVII) is the compound that your records show that you have 15 g in stock. As per Dr. Ussery, we will not be preparing any of this compound unless we receive an additional request.

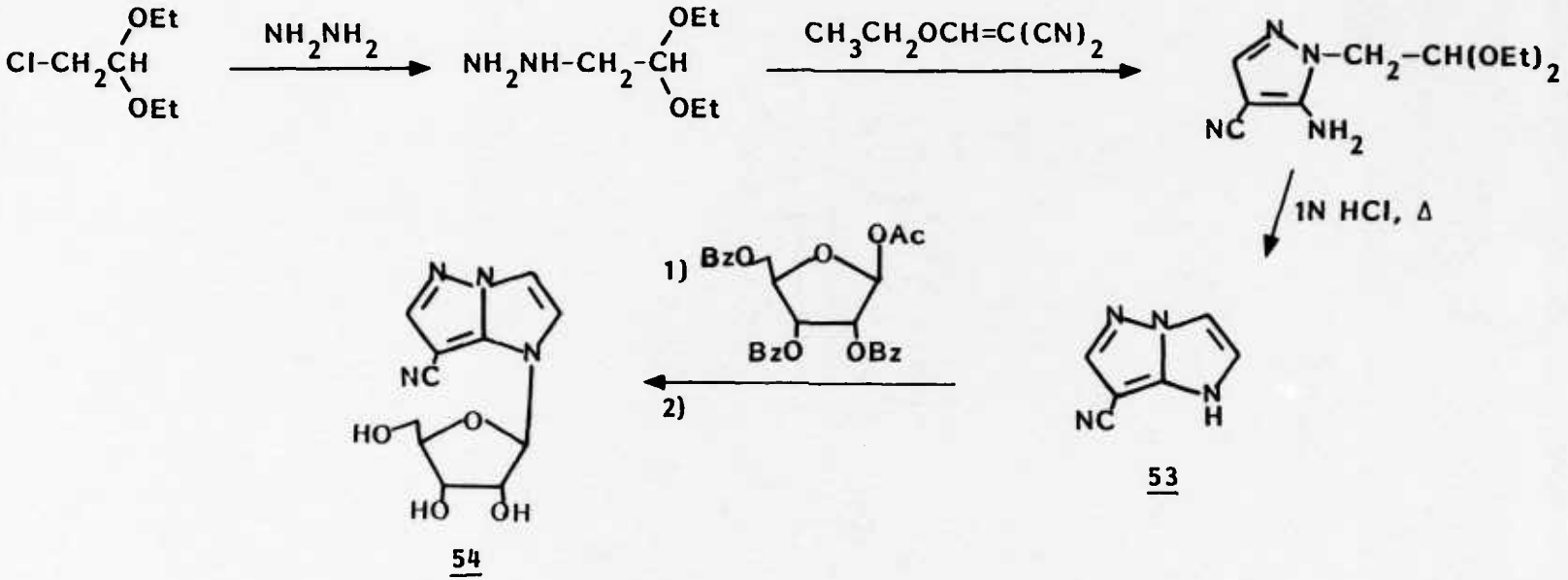
(6) We prepared bisdesethyl chloroquine 58a but found it to be highly unstable (Scheme XVIII). We determined via MS during our attempts to purify the product mixture that bisdesethylchloroquine intramolecularly cyclizes to 4-(2'-methyl-1'-pyrrolidyl)-7-chloroquinoline (59). We await notification from you as to whether we should continue to try to make this compound, depending upon the results with the material supplied by Walter Reed.

(7) We made and submitted desethyl chloroquine (58b),[28,29] and determined that this compound was both more easily obtained and much more stable than the bisdesethyl chloroquine (58a). During the synthesis of this compound and bisdesethyl chloroquine we developed a new, more efficient synthesis of the side chain precursor, 4-aminopentanol 56. Instead of forming the oxime of 5-hydroxypentan-2-one and catalytically reducing it (with Raney nickel or palladium on carbon with pressure), we treated 5-hydroxypentan-2-one with $NaBH_3CN$ and ammonium acetate in ethanol. This provided the amino alcohol in one step.

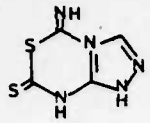
(8) We have made and are purifying the 3-bromo-1-β-D-ribofuranosyl-pyrazolo[3,4-d]pyrimidin-4-one (47c) (Scheme XIX).

As we mentioned earlier, we also submitted compounds that were either intermediates or targets from past projects at SoRI. In an effort to identify new lead compounds for the USAMRIID antiviral program, we chose compounds that were available in sufficient quantity, and that might be made again in larger quantity if their activities warranted it. Compounds that fell into this category are shown in

Scheme XVI

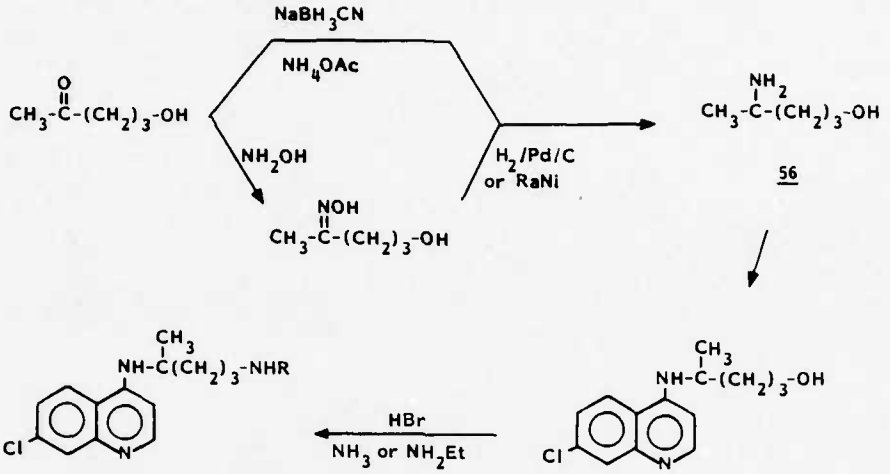

Cl-CH2CH(OEt)2
NH2NH2
NH2NH-CH2-CH(OEt)2
CH3CH2OCH=C(CN)2
N-CH2-CH(OEt)2
NC
NH2
1N HCl, Δ
1) BzO
OAc
BzO
OBz
2)
NC
N
H
HO
OH
53
54

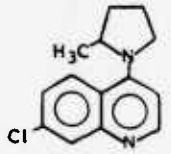
Scheme XVII



55

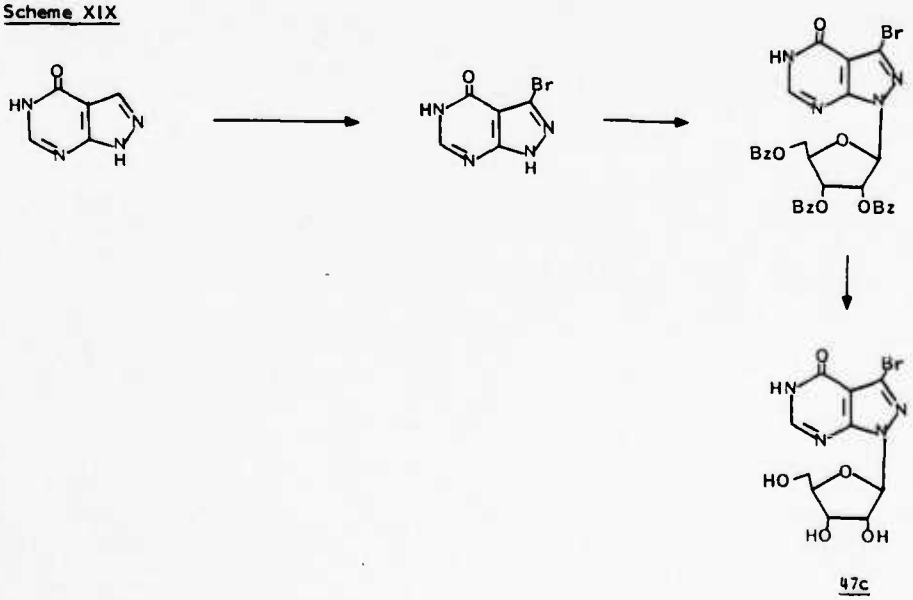
Scheme XVIII





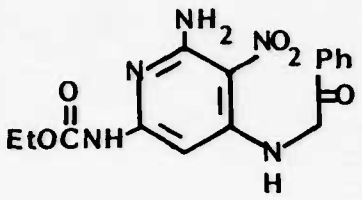
59

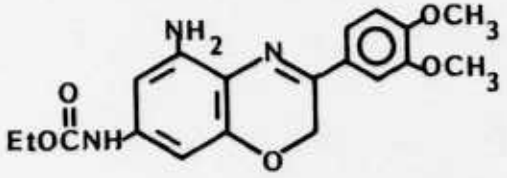
Scheme XIX

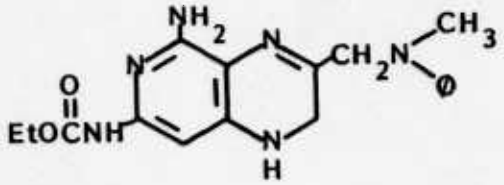


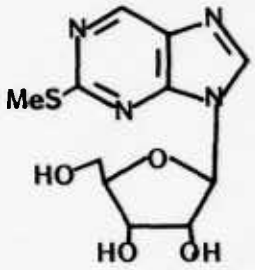
47c

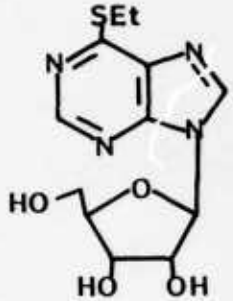
Scheme XX. SoRI Compounds Submitted as Potential Lead Compounds











Scheme XX. One of these compounds, 9-β-D-ribofuranosyl-6-ethylthiopurine, has already been shown to have activity against a number of viruses in the screen.

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 temeperature 20 °C), as indicated. Infrared data were obtained with a Nicolet 10-MX spectrometer. In most cases only strong or medium peaks in the 1800-600 cm^{-1} range were reported. UV absorption spectra were determined in the appropriate pH 1 (0.1 N HCl), pH 7 buffer, and pH 13 (0.1 N NaOH) solutions with a Cary 17 spectrophotometer or a Perkin Elmer Model Lambda 9 UV/VIS/NIR spectrophotometer. Melting point data was obtained with a Mel-Temp Capillary Melting point apparatus, and all melting points were uncorrected. Elemental analysis data were obtained either from an in-house Perkin Elmer Model 240 Elemental Analyzer or from Atlantic Microlab of Atlanta, Georgia.

1-(3-Nitrobenzyloxy)adenosine, Perchloric Acid Salt (2a). In a 100 mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate drying tube was placed 3.0 g (10.6 mmol) of adenosine-N^1-oxide (1), 60 mL of (molecular sieve (4A)-dried) N,N-dimethyl acetamide (DMAC), and 9.8 g (53.0 mmol) of 3-nitrobenzyl bromide. The mixture was stirred at room temperature. Since solution was not complete after 20 min, 2.0 mL more DMAC was added. Solution was achieved within 10 min and the light yellow solution was stirred for 2 h. The reaction mixture was poured with stirring into 800 mL of molecular sieve dried ether. The mixture was stirred until the gum stuck to the walls of the flask leaving a nearly clear liquid phase which was decanted. The gummy residue was washed with 400 mL of ether, decanted, recovered with 400 mL of ether and ground to a powder. The powder was allowed to settle, the ether was decanted, and the residue was dried in a stream of argon. The residue was dissolved in 25 mL of H_2O and added with stirring to a warm solution of 5 g (42.6 mmol) of ammonium perchlorate dissolved in 25 mL of H_2O. The product crystallized upon scratching and chilling. Two recrystallizations from H_2O yielded 2.1 g (38%); UV λ_{max} 259 nm (19,400) at pH 1; 259 (19,100) at pH 7; 258 (17,560) at pH 13; MS (FAB) *m/e* 419 (M + 1); IR 1691, 1620, 1533, 1511, 1352, 1225, 1090 broad, 900, 790, 625 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ

3.60, 3.71 (2 m, 2, $J_{4',5'a} = J_{4',5'b} = 3.9$ Hz, $J_{5'a,5'b} = 12.0$ Hz, CH_2-5'), 4.01 (apparent q, 1, H-4'), 4.18 (apparent t, 1, $J_{3',4'} = 3.7$ Hz, H-3'), 4.51 (apparent t, 1, $J_{2',3'} = 4.8$ Hz, H-2'), 5.04-5.16 (br s, 1, 5'-OH), 5.26-5.40 (br s, 1, 3'-OH), 5.55 (s, 2, OCH_2Ar), 5.54-5.68 (br s, 1, 2'-OH), 5.97 (d, 1, $J_{1',2'} = 5.4$ Hz, H-1'), 7.80 (t, 1, H-Ar5), 8.17 (d, 1, H-Ar6), 8.35 (m, 1, H- Ar4), 8.67 (s, 1, H-Ar2), 8.83 (s, 1, H-8), 9.17 (s, 1, H-2), 9.8-10.5 (br s, 2, $H\text{-}\overset{\oplus}{N}H_2$); ^{13}C NMR ($Me_2SO$-$d_6$) δ 60.88 (C-5'), 69.99 (C-3'), 74.49 (C-2'), 80.11 (C-OCH_2Ar), 85.92 (C-4'), 87.79 (C-1'), 119.42 (C-5), 124.40 (Ar-C5), 125.45 (Ar-C4), 129.95 (Ar-C2), 134.13 (Ar-C6), 137.25 (Ar-C1), 142.87 (C-8), 144.95 (C-2), 145.24 (C-4), 147.64 (Ar-C3), 148.31 (C-6).

1-(4-Nitrobenzyloxy)adenosine, Perchloric Acid Salt (2b). In a 100 mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate drying tube was placed 2.5 g (8.83 mmol) of adenosine-N^1-oxide (1), 50 mL of molecular sieve (4A) dried N,N-dimethyl acetamide (DMAC), and 9.5 g (44.2 mmol) of 4-nitrobenzyl bromide. The mixture was stirred at room temperature. Since solution was not complete after 20 min, 2.0 mL more DMAC was added. Solution was achieved within 10 min and the light, yellow solution was stirred for 2 h. The reaction mixture was poured with stirring into 800 mL of molecular sieve dried ether. The mixture was stirred until the gum stuck to the walls of the flask leaving a nearly clear liquid phase which was decanted. The gummy residue was washed with 400 mL of ether, decanted, recovered with 400 mL of ether and ground to a powder. The powder was allowed to settle, the ether was decanted, and the residue was dried in a stream of argon. The residue was dissolved in 25 mL of H_2O and added with stirring to a warm solution of 5 g (42.6 mmol) of ammonium perchlorate dissolved in 25 mL of H_2O. The product crystallized upon scratching and chilling. One recrystallization from H_2O yielded 3.2 g (70%); UV λ_{max} 260 nm (22,270) at pH 1; 260 (21,970) at pH 7; 265 (18,550) at pH 13 (slowly decreased); MS (FAB) *m/e* 419 (M + 1); IR 1686, 1524, 1348, 1220, 1090 broad, 854, 750, 625 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.57, 3.70 (2 m, 2, $J_{4',5'a} = 4.0$ Hz, $J_{4',5'b} = 3.9$ Hz, $J_{5'a,5'b} = 12.0$ Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent q, 1, $J_{3',4'} = 3.7$ Hz, H-3'), 4.50 (apparent q, 1, $J_{2',3'} = 4.9$ Hz, H-2'), 5.09 (t, 1, $J_{5',5'\text{-}OH} = 5.3$ Hz, 5'-OH), 5.34 (d, 1, $J_{3',3'\text{-}OH} = 5.2$ Hz, 3'-OH), 5.55 (s, 2, OCH_2Ar), 5.60 (d, 1, $J_{2',2'\text{-}OH} = 6.1$ Hz, 2'-OH), 5.95 (d, 1, $J_{1',2'} = 5.4$ Hz, H-1'), 7.97 (d, 2, Ar-H-2,6), 8.34 (d, 2, Ar-H-3,5), 8.83 (s, 1, H-8), 9.11 (s, 1, H-2), 9.8-10.5 (broad, 2, $H\text{-}\overset{\oplus}{N}H_2$); ^{13}C NMR ($Me_2SO$-$d_6$) δ 60.87 (C-5'), 69.97 (C-3'), 74.53 (C-2'), 80.03 (C-OCH_2Ar), 85.89 (C-4'), 87.84 (C-1'), 119.43 (C-5), 123.38 (Ar-C-3,5), 131.38 (Ar-C-2,6), 139.45 (Ar-C1), 142.88 (C-8), 144.76 (C-2), 145.24 (C-4), 148.01 (Ar-C4), 148.33 (C-6).

1-(2-Methylbenzyloxy)adenosine, Perchloric Acid Salt (2c). In a 100 mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate drying tube was placed 2.5 g (8.83 mmol) of adenosine-$\underline{N}^1$-oxide (1), 50 mL of molecular sieve (4A) dried N,N-dimethyl acetamide (DMAC), and 9.8 g (44.2 mmol) of 2-methylbenzyl bromide. The mixture was stirred at room temperature. Since solution was not complete after 20 min, 2.0 mL more DMAC was added. Solution was achieved within 10 min and the light, yellow solution was stirred for 2 h. The reaction mixture was poured with stirring into 800 mL of molecular sieve dried ether. The mixture was stirred until the gum stuck to the walls of the flask leaving a nearly clear liquid phase which was decanted. The gummy residue was washed with 400 mL of ether, decanted, recovered with 400 mL of ether and ground to a powder. The powder was allowed to settle, the ether was decanted, and the residue was dried in a stream of argon. The residue was dissolved in 25 mL of H_2O and added with stirring to a warm solution of 5 g (42.6 mmol) of ammonium perchlorate dissovled in 25 mL of H_2O. The product crystallized upon scratching and chilling. One recrystallization from H_2O yielded 4.0 g (77%); UV λ_{max} 259 nm (13,420) at pH 1; 259 (13,260) at pH 7; 258 (13,210) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR 1687, 1510, 1415, 1225, 1127, 1083, 916, 880, 767, 690, 623 cm^{-1}; ^1H NMR (Me_2SO-$\underline{d}_6$) δ 2.47 (s, 3, CH_3), 3.57, 3.68 (2 m, 2, $\underline{J}_{4',5'a}$ = 3.9 Hz, $\underline{J}_{4',5'b}$ = 4.0 Hz, $\underline{J}_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.15 (apparent t, 1, $\underline{J}_{3',4'}$ = 3.8 Hz, H-3'), 4.43-4.53 (br s, 1, $\underline{J}_{2',3'}$ = 4.9 Hz, H-2'), 4.98-5.14 (br s, 1, 5'-OH), 5.24-5.38 (br s, 1, 3'-OH), 5.46 (s, 2, $OC\underline{H}_2Ar$), 5.54-5.64 (br s, 1, 2'-OH), 5.92 (d, 1, $\underline{J}_{1',2'}$ = 5.4 Hz, H-1'), 7.20-7.50 (m, 4, H-Ar), 8.61 (s, 1, H-2), 8.83 (s, 1, H-8), 9.70-9.88 (br s, 1, $H\text{-}\overset{\oplus}{N}H_2$), 10.38-10.54 (br s, 1, $H\text{-}\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-$\underline{d}_6$) δ 18.64 (CH_3), 60.83 (C-5'), 69.92 (C-3'), 74.46 (C-2'), 79.56 (C-$OC\underline{H}_2Ar$), 85.83 (C-4'), 87.74 (C-1'), 119.84 (C-5), 125.84 (Ar-C3), 129.93 (Ar-C6), 130.45 (Ar-C4), 131.34 (Ar-C2), 138.13 (Ar-C1), 142.84 (C-8), 144.40 (C-2), 145.17 (C-4), 148.32 (C-6).

1-(4-Cyanobenzyloxy)adenosine, Perchloric Acid Salt (2d). In a 100 mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate drying tube was placed 2.0 g (7.04 mmol) of adenosine-$\underline{N}^1$-oxide (1), 40 mL of molecular sieve (4A) dried N,N-dimethyl acetamide (DMAC), and 4.3 g (21.9 mmol) of 4-cyanobenzyl bromide. The mixture was stirred at room temperature. Since solution was not complete after 20 min, 2.0 mL more DMAC was added. Solution was achieved within 10 min and the light, yellow solution was stirred for 2 h. The reaction mixture was poured with stirring into 800 mL of molecular sieve dried ether. The mixture was stirred until the gum stuck to the walls of the flask leaving a nearly clear liquid phase which was decanted. The gummy residue was washed with 400 mL

of ether, decanted, recovered with 400 mL of ether and ground to a powder. The powder was allowed to settle, the ether was decanted, and the residue was dried in a stream of argon. The residue was dissolved in 25 mL of H_2O and added with stirring to a warm solution of 5 g (42.6 mmol) of ammonium perchlorate dissolved in 25 mL of H_2O. The product crystallized upon scratching and chilling. One recrystallization from H_2O yielded 2.7 g (78%); UV λ_{max} 259 nm (13,800) at pH 1; 259 (13,620) at pH 7; 258 (sh) at pH 13; MS (FAB) *m/e* 399 (M + 1); IR 2240, 1687, 1510, 1420, 1385, 1225, 1215, 1075 broad, 825, 621 cm^{-1}; ^1H NMR (Me_2SO-$\underline{d}_6$) δ 3.61, 3.73 (2 m, 2, $\underline{J}_{4',5'a}$ = 3.9 Hz, $\underline{J}_{4',5'b}$ = 5.6 Hz, $\underline{J}_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 4.02 (apparent q, 1, H-4'), 4.19 (apparent q, 1, $\underline{J}_{3',4'}$ = 3.7 Hz, H-3'), 4.51 (apparent q, 1, $\underline{J}_{2',3'}$ = 4.8 Hz, H-2'), 5.11 (t, 1, $\underline{J}_{5',5'\text{-OH}}$ = 5.3 Hz, 5'-OH), 5.35 (apparent d, 1, $\underline{J}_{3',3'\text{-OH}}$ = 5.2 Hz, 3'-OH), 5.51 (s, 2, $OC\underline{H}_2Ar$), 5.62 (apparent d, 1, $\underline{J}_{2',2'\text{-OH}}$ = 6.1 Hz, 2'-OH), 5.97 (apparent d, 1, $\underline{J}_{1',2'}$ = 5.4 Hz, H-1'), 7.90 (d, 2, Ar-H-3,5), 7.99 (d, 2, Ar-H-2,6), 8.83 (s, 1, H-8), 9.10 (s, 1, H-2), 9.7-10.6 (broad, 2, H-$\overset{\oplus}{N}H_2$; ^{13}C NMR (Me_2SO-$\underline{d}_6$) δ 60.84 (C-5'), 69.94 (C-3'), 74.51 (C-2'), 80.44 (C-$OC\underline{H}_2Ar$), 85.85 (C-4'), 87.83 (C-1'), 112.16 (Ar-C4), 118.38 (C-C≡N), 119.39 (C-5), 131.03 (Ar-C-2,6), 132.26 (Ar-C-3,5), 137.43 (Ar-C1), 142.85 (C-8), 144.71 (C-2), 145.21 (C-4), 148.29 (C-6).

1-(2-Cyanobenzyloxy)adenosine, Perchloric Acid Salt (2e). In a 100-mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate drying tube was placed 2.5 g (8.83 mmol) of adenosine-$\underline{N}^1$-oxide (1), 50 mL of molecular sieve (4A) dried $\underline{N}$,$\underline{N}$-dimethylacetamide (DMAC), and 5.2 g (26.5 mmol) of α-bromo-$\underline{o}$-cyanotoluene. The mixture was stirred at room temperature. The reaction was stirred for 2 h after complete solution was achieved. The reaction solution was poured into 300-500 mL of anhydrous ether with slight swirling. After the product stuck to the walls of the flask the supernatant was decanted. The gummy residue was washed with 400 mL ether, decanted, again covered with 400 mL of ether and ground to a powder. The powder was allowed to settle, the ether was decanted, and the residue was dried in a stream of argon. The residue was dissolved in 25 mL of H_2O and added with stirring to a warm solution of 5 g (42.6 mmol) of ammonium perchlorate dissolved in 25 mL of H_2O. The product crystallized upon scratching and chilling. One recrystallization from H_2O and drying at 78 °C for 16 h over phosphorus pentoxide yielded 3.5 g (79%); UV λ_{max} 260 nm (12,700) at pH 1; 259 (12,560) at pH 7; 257 (12,160) at pH 13; MS (FAB) *m/e* 399 (M + 1); IR 2250, 1684, 1505, 1222, 1100 (broad), 772, and 623 cm^{-1}; ^1H NMR (Me_2SO-$\underline{d}_6$) δ 3.59, 3.68 (2 m, 2, $\underline{J}_{4',5'a}$ = 3.8 Hz, $\underline{J}_{4',5'b}$ = 3.9 Hz, $\underline{J}_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $\underline{J}_{3',4'}$ = 3.5 Hz, H-3'),

4.49 (apparent t, 1, $J_{2',3'}$ = 4.8 Hz, H-2'), 5.0 (br s, 1, 5'-OH), 5.33 (br s, 1, 3'-OH), 5.60 (br, 1, 2'-OH), 5.60 (s, 2, O$\underline{CH_2}$Ar), 5.94 (apparent d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.70 (t, 1, Ar-H, 4), 7.87, 7.90 (2 m, 2, Ar-H, 3,5), 7.99 (d, 1, Ar-H, 6), 8.81 (s, 1, H-2), 8.83 (s, 1, H-8), 9.8-10.6 (br, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-$\underline{d_6}$) δ 60.81 (C-5'), 69.89 (C-3'), 74.44 (C-2'), 78.56 (C-O$\underline{CH_2}$Ar), 85.83 (C-4'), 87.74 (C-1'), 112.53 (Ar-C-2), 117.12 (C-C$\equiv$N), 119.58 (C-5), 130.50, 131.71, 133.20, 133.38 (Ar-C-3,4,5,6), 135.16 (Ar-C-1), 142.81 (C-8), 144.23 (C-2), 145.16 (C-4), 148.38 (C-6).

1-(3-Cyanobenzyloxy)adenosine, Perchloric Acid Salt (2f). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was used. One recrystallization from H_2O and drying at 78 °C for 16 h over phosphorus pentoxide yielded 3.2 g (73%); UV λ_{max} 259 nm (13,500) at pH 1; 259 (12,900) at pH 7; 257 (12,980) at pH 13; MS (FAB) *m/e* 399 (M + 1); IR 2230, 1694, 1510, 1235, 1215, 1090 (broad), 892, 690, 655, 640, and 623 cm^{-1}; ^{1}H NMR (Me_2SO-$\underline{d_6}$) δ 3.59, 3.69 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.8 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 4.00 (apparent q, 1, H- 4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.7 Hz, H-3'), 4.50 (apparent t, 1, $J_{2',3'}$ = 4.7 Hz, H-2'), 5.12 (br, 1, 5'-OH), 5.34 (br, 1, 3'-OH), 5.45 (s, 2, O$\underline{CH_2}$Ar), 5.60 (br, 1, 2'-OH), 5.96 (apparent d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.69 (t, 1, Ar-H-5), 7.96, 8.02 (2 m, 2, Ar-H-4,6), 8.25 (s, 1, Ar- H-2), 8.83 (s, 1, H-8), 9.13 (s, 1, H-2), 9.78, 10.45 (br, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-$\underline{d_6}$) δ 60.87 (C-5'), 69.97 (C-3'), 74.50 (C-2'), 80.26 (C-O$\underline{CH_2}$Ar), 85.90 (C-4'), 87.82 (C-1'), 111.44 (Ar-C-3), 118.31 (C-C$\equiv$N), 119.41 (C-5), 129.64 (Ar-C-5), 133.18 (Ar-C-4), 133.60 (Ar-C-1), 134.32 (Ar-C-2), 135.33 (Ar-C-6), 142.87 (C-8), 144.84 (C-2), 145.25 (C-4), 148.28 (C-6).

1-(2-Methoxy-5-nitrobenzyloxy)adenosine, Perchloric Acid Salt (2g). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. One recrystallization from H_2O and drying at 78 °C over phosphorus pentoxide yielded 4.0 g (83%); UV λ_{max} 259 nm (14,550) and 310 (10,620) at pH 1; 259 (14,510) and 310 (10,870) at pH 7; 311 (11,800) at pH 13; MS (FAB) *m/e* 449 (M + 1); IR 1681, 1595, 1510, 1500, 1490, 1332, 1261, 1212, 1127, 1090 (broad), 1036, 900, 640, and 620 cm^{-1}; ^{1}H NMR (Me_2SO-$\underline{d_6}$) δ 3.59, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.5 Hz, $J_{4',5'b}$ = 3.5 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.86 (s, 3, CH_3OAr), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 4.0 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.1 Hz, H-2'), 5.09 (apparent t, 1, $J_{5',5'\text{-OH}}$ = 4.9 Hz, 5'-OH), 5.33 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 5.0 Hz, 3'-OH), 5.50 (s, 2, O$\underline{CH_2}$Ar), 5.59 (apparent d, 1, $J_{2',2'\text{-OH}}$ = 6.0 Hz, 2'-OH), 5.95 (d, 1, $J_{1',2'}$ = 5.34 Hz, H-1'), 7.31 (d, 1, Ar-H-3), 8.40 (apparent q, 1, Ar-H-4),8.56 (d, 1, Ar-H-6), 8.84 (s, 2, H-2,8), 9.74, 10.35 (br, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-$\underline{d_6}$) δ 56.78 (C-ArO$\underline{C}H_3$), 60.86 (C-5'), 69.96 (C-3'), 74.59 (C-2'), 75.61 (C-O$\underline{CH_2}$Ar), 85.89 (C-4'),

87.89 (C-1'), 111.80 (Ar-C-3), 119.35 (C-5), 121.12 (Ar-C-1), 127.77, 128.24 (Ar-C-6,4), 140.31 (Ar-C-5), 142.93 (C-8), 144.52 (C-2), 145.25 (C-4), 148.39 (C-6), 163.21 (Ar-C-2).

1-(3-Methoxycarbonylbenzyloxy)adenosine, Perchloric Acid Salt (2h). The procedure used for 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. The product crystallized upon addition of the NH_4ClO_4 solution and was redissolved with heat, filtered and chilled. The white product was collected and dried at 78 °C for 20 h over phosphorus pentoxide; yield, 3.6 g (77%); UV λ_{max} 259 nm (12,670) at pH 1; 259 (12,670) at pH 7; 257 (13,410) at pH 13; MS (FAB) *m/e* 432 (M + 1); IR 1710, 1684, 1435, 1315, 1294, 1214, 1100 (broad), 895, 765, and 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.69 (2 m, 2, $J_{4',5'a}$ = 3.7 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.1 Hz, CH_2-5'), 3.89 (s, 3, $ArCO_2\underline{CH_3}$), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.7 Hz, H-3'), 4.50 (apparent t, 1, $J_{2',3'}$ = 4.8 Hz, H-2'), 5.10, 5.34, 5.61 (br, 3, 5',3',2'-OH), 5.49 (s, 2, $O\underline{CH_2}Ar$), 5.96 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.64 (t, 1, Ar-H-5), 7.99, 8.06 (d, 2, Ar-H-6,4), 8.33 (s, 1, Ar-H-2), 8.83 (s, 1, H-8), 9.03 (s, 1, H-2), 9.82, 10.44 (br, 2, $H\text{-}\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 52.21 C-$ArCO_2\underline{CH_3}$), 60.88 (C-5'), 69.99 (C-3'), 74.56 (C-2'), 81.02 (C-$O\underline{C}H_2Ar$), 85.90 (C-4'), 87.87 (C-1'), 119.38 (C-5), 128.94 (Ar-C-5), 129.81 (Ar-C-3), 130.32, 131.40, 135.49 (Ar-C-6,4,2), 132.78 (Ar-C-1), 142.87 (C-8), 144.88 (C-2), 145.23 (C-4), 148.33 (C-6), 165.80 (C-$Ar\underline{C}O_2CH_3$).

1-(2-Chlorobenzyloxy)adenosine, Perchloric Acid Salt (2i). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was repeated. One recrystallization from H_2O and drying at 78 °C over phosphorus pentoxide for 16 h provided a pure specimen; yield 3.6 g (80%); UV λ_{max} 260 nm (12,690) at pH 1; 259 (12,550) at pH 7; 258 (12,510) at pH 13; MS (FAB) *m/e* 408 (M + 1); IR 1689, 1509, 1220, 1100 (broad), 931, 860, 774, 769, 645, 640, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 4.0 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.6 Hz, H-2'), 5.09 (br s, 1, 5'-OH), 5.31 (br s, 1, 3'-OH), 5.54 (s, 2, $O\underline{CH_2}Ar$), 5.60 (br s, 1, 2'-OH), 5.93 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.42-7.78 (m, 4, H-Ar), 8.70 (s, 1, H-2), 8.83 (s, 1, H-8), 9.82, 10.48 (2 br s, 2, $H\text{-}\overset{\oplus}{N}H_2$; ^{13}C NMR (Me_2SO-d_6) δ 60.82 (C-5'), 69.91 (C-3'), 74.45 (C-2'), 78.14 (C-$O\underline{C}H_2Ar$), 85.84 (C-4'), 87.71 (C-1'), 119.44 (C-5), 127.42, 129.50, 131.70 (Ar-C-3,4,5), 129.99 (Ar-C-2), 132.94 (Ar-C-6), 134.02 (Ar-C-1), 142.84 (C-8), 144.33 (C-2), 145.19 (C-4), 148.39 (C-6).

1-(3-Chlorobenzyloxy)adenosine, Perchloric Acid Salt (2j). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. One recrystallization from H_2O with drying at 78 °C over phosphorus pentoxide for 16 h yielded

3.5 g (78%); UV λ_{max} 259 nm (12,910) at pH 1; 259 (12,560) at pH 7; 258 (12,560) at pH 13; MS (FAB) *m/e* 408 (M + 1); IR 1694, 1620, 1575, 1510, 1430, 1415, 1380, 1220, 1075 (broad), 885, 785, 685, 622 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.69 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4,5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.17 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.50 (apparent t, 1, $J_{2',3'}$ = 4.7 Hz, H-2'), 5.09 (br, 1, 5'-OH), 5.33 (br, 1, 3'-OH), 5.40 (s, 2, O$\underline{CH_2}$Ar), 5.60 (br, 1, 2'-OH), 5.96 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.48-7.88 (m, 4, H-Ar), 8.82 (s, 1, H-8), 9.10 (s, 1, H- 2), 9.78, 10.44 (2 br, 1, H-$\overset{\oplus}{N}H_2$; ^{13}C NMR (Me_2SO-d_6) δ 60.85 (C-5'), 69.95 (C-3'), 74.46 (C-2'), 80.63 (C-O$\underline{CH_2}$Ar), 85.87 (C-4'), 87.78 (C-1'), 119.34 (C-5), 129.23, 129.54, 130.41 (Ar-C-2,4,6), 130.24 (Ar-C-5), 133.00 (Ar-C-3), 134.32 (Ar-C-1), 142.84 (C-8), 144.82 (C-2), 145.20 (C-4), 148.26 (C-6).

1-(2-Nitrobenzyloxy)adenosine, Perchloric Acid Salt (2k). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. Two recrystallizations from H_2O with drying at 78 °C over phosphorus pentoxide for 18 h yielded 2.1 g (47%); UV λ_{max} 259 nm (18,170) at pH 1; 259 (18,090) at pH 7; 257 (16,890) at pH 13; MS (FAB) *m/e* 419 (M + 1); IR 1685, 1538, 1530, 1510, 1347, 1105 (broad), 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.7 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.1 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.08 (br s, 1, 5'-OH), 5.32 (br s, 1, 3'-OH), 5.60 (br s, 1, 2'-OH), 5.76 (s, 2, O$\underline{CH_2}$Ar), 5.95 (d, 1, $J_{1',2'}$ = 5.35 Hz, H-1'), 7.75 (m, 1, Ar-H-4), 7.90 (m, 1, Ar-H-5), 7.99 (apparent d, 1, Ar-H-3), 8.22 (apparent d, 1, Ar-H-6), 8.83 (s, 1, H-8), 8.94 (s, 1, H-2), 9.80, 10.46 (br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.83 (C-5'), 69.92 (C-3'), 74.46 (C-2'), 77.01 (C-O$\underline{CH_2}$Ar), 85.84 (C-4'), 87.77 (C-1'), 119.54 (C-5), 124.81 (Ar-C-3), 128.32 (Ar-C-1), 130.29 (Ar-C-4), 131.11 (Ar-C-5), 134.03 (Ar-C-6), 142.79 (C-8), 144.45 (C-2), 145.21 (C-4), 147.54 (Ar-C-2), 148.36 (C-6).

1-[2,4-Bis(trifluoromethyl)benzyloxy]adenosine, Perchloric Acid Salt (2l). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was repeated. The product was dissolved in water and came back out as a gel twice. The gel was dried at room temperature and finally at 78 °C for 14 h over phosphorus pentoxide; yield, 1.9 g (35%); UV λ_{max} 259 nm (13,240) at pH 1; 259 (12,710) at pH 7; 257 (12,090) at pH 13; MS (FAB) *m/e* 510 (M + 1); IR 1684, 1348, 1304, 1281, 1123 (broad), 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.60, 3.69 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.6 Hz, $J_{5'a,5'b}$ = 12.3 Hz, CH_2-5'), 4.00 (apparent q, 1, H- 4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.50 (apparent t, 1, $J_{2',3'}$ = 5.0 Hz, H-2'), 5.09 (br s, 1, 5'-OH), 5.33 (br s, 1, 3'-OH), 5.60 (br s, 1, 2'-OH), 5.71 (s, 2, O$\underline{CH_2}$Ar), 5.93 (apparent d, 1, H-1'), 8.15 (m, 2, Ar-H-3,6), 8.77 (apparent d, 1, Ar-H-5), 8.84 (s, 1,

H-8), 8.91 (s, 1, H-2), 9.84, 10.48 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.94 (C-5'), 70.04 (C-3'), 74.58 (C-2'), 76.36 (C-O$\underline{C}H_2$Ar), 85.99 (C-4'), 87.81 (C-1'), 119.77 (C-5), 123.08, 123.14, 123.21 (2 C-CF_3, Ar-C-3), 128.04, 129.71, 130.03, 132.35 (Ar-C-2,4,5,6), 135.91 (Ar-C-1), 142.86 (C-8), 144.53 (C-2), 145.31 (C-4), 148.53 (C-6).

1-[3,5-Bis(trifluoromethyl)benzyloxy]adenosine, Perchloric Acid Salt (2m). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was used. The product was dissolved in H_2O and twice came back as a gel which was dried to an amorphous powder at 78 °C for 14 h over phosphorus pentoxide; yield, 3.3 g (61%); UV λ_{max} 259 nm (12,600) at pH 1; 259 (12,280) at pH 7; 257 (12,100) at pH 13; MS (FAB) *m/e* 510 (M + 1); IR 1684, 1366, 1282, 1129 (broad), 684, and 624 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.61, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 11.9 Hz, CH_2-5'), 4.01 (apparent q, 1, H-4'), 4.18 (apparent t, 1, $J_{3',4'}$ = 3.8 Hz, H-3'), 4.52 (apparent t, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.08 (br s, 1, 5'-OH), 5.34 (br s, 1, 3'-OH), 5.59 (br s, 1, 2'-OH), 5.56 (s, 2, O$\underline{C}H_2$Ar), 5.98 (apparent d, 1, $J_{1',2'}$ = 5.41 Hz, H-1'), 8.26 (s, 1, Ar-H-4), 8.52 (s, 1, Ar-H-6), 8.84 (s, 1, H-8), 9.30 (s, 1, H-2), 9.84, 10.51 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 61.02 (C-5'), 70.15 (C-3'), 74.62 (C-2'), 79.74 (C-O$\underline{C}H_2$Ar), 86.08 (C-4'), 87.96 (C-1'), 119.55 (C-5), 123.21 (Ar-C-4), 123.23 (2 C-CF_3), 130.35 (Ar-C-3,5), 131.74 (Ar-C-2,6), 135.37 (Ar-C-1), 143.04 (C-8), 145.14 (C-2), 145.41 (C-4), 148.39 (C-6).

1-(4-Methylbenzyloxy)adenosine, Perchloric Acid Salt (2n). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. One recrystallization from H_2O and drying overnight at 78 °C over phosphorus pentoxide yielded 1.9 g (44%); UV λ_{max} 259 nm (12,900) at pH 1; 259 (12,600) at pH 7; 258 (12,510) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR 1679, 1505, 1425, 1220, 1100 (broad), 855, 623 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.34 (s, 3, H-Ar$\underline{C}H_3$), 3.59, 3.67 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.8 Hz, H-2'), 5.09, 5.32, 5.59 (3 br, 3,5',3',2'-OH), 5.37 (s, 2, O$\underline{C}H_2$Ar), 5.94 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.26 (d, 2, Ar-H-3,5), 7.54 (d, 2, Ar-H-2,6), 8.81 (s, 1, H-8), 8.92 (s, 1, H-2), 9.73, 10.39 (br, 2, H-$\overset{\oplus}{N}H_2$).

1-(2,4-Difluorobenzyloxy)adenosine, Perchloric Acid Salt (2o). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. After two recrystallizations from H_2O and drying at 78 °C for 5 h over phosphorus pentoxide, a pure specimen was obtained, yield 1.7 g (38%); UV λ_{max} 259 nm (13,500) at pH 1; 259 (13,300) at pH 7; 257 (13,000) at pH 13; MS (FAB) *m/e* 410 (M + 1); IR 1690, 1620, 1508, 1100 (broad), and 624 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.58, 3.70 (2 m,

2, $J_{4',5'a}$ = 3.7 Hz, $J_{4,5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.1 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.16 (apparent s, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.48 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.09, 5.33 (2 apparent s, 2, OH-5',3'), 5.47 (s, 2, O$\underline{CH_2}$Ar), 5.60 (apparent d, 1, OH-2'), 5.94 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.22, 7.39 (2 m, 2, Ar-H-3,5), 7.76 (q, 1, Ar-H-6), 8.81 (s, 2, H-8,2), 9.79, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-$\underline{d_6}$) δ 60.86 (C-5'), 69.95 (C-3'), 74.36 (C-O$\underline{CH_2}$Ar), 74.48 (C-2'), 85.89 (C-4'), 87.73 (C-1'), 104.24 (Ar-C-3), 111.85 (Ar-C-5), 117.00 (Ar-C-1), 119.39 (C-5), 134.60 (Ar-C-6), 142.87 (C-8), 144.55 (C-2), 145.25 (C-4), 148.41 (C-6), 161.55, 163.47 (Ar-C-2,4).

1-(3,4-Difluorobenzyloxy)adenosine, Perchloric Acid Salt (2p). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. Two recrystallizations from H_2O and drying at 78 °C for 5 h over phosphorus pentoxide yielded, 1.1 g (24%); UV λ_{max} 259 nm (13,000) at pH 1; 259 (13,400) at pH 7; 258 (12,900) at pH 13; MS (FAB) *m/e* 410 (M + 1); IR 1687, 1522, 1440, 1294, 1100 (broad), and 624 cm^{-1}; ^{1}H NMR (Me_2SO-$\underline{d_6}$) δ 3.59, 3.69 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 3.7 Hz, $J_{5'a,5'b}$ = 12.1 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.17 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.50 (br s, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.10, 5.35, 5.60 (3 br s, 3, OH-5',3',2'), 5.38 (s, 2, O$\underline{CH_2}$Ar), 5.95 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.55, 7.88 (2 m, 3, Ar-H-2,5,6), 8.82 (s, 1, H-8), 9.03 (s, 1, H-2), 9.76, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

1-(2-Phenylethyloxy)adenosine, Perchloric Acid Salt (2q). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was adapted by heating the reaction at 45 °C for 18 h. After two recrystallizations from H_2O and drying at 56 °C for 20 h *in vacuo* over phosphorus pentoxide analytically pure material was obtained, yield 2.1 g (49%); UV λ_{max} 259 nm (12,100) at pH 1; 259 nm (13,000) at pH 7; 257 nm (12,700) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR 1691, 1505, 1225, 1100 broad, 760, 705, 625 cm^{-1}; ^{1}H NMR (Me_2SO-$\underline{d_6}$) δ 3.23 (t, 2, $OCH_2\underline{CH_2}Ar$), 3.58, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.8 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.15 (apparent q, 1, $J_{3',4'}$ = 3.7 Hz, H-3'), 4.48 (apparent q, 1, $J_{2',3'}$ = 5.01 Hz, H-2'), 4.60 (t, 2, O$\underline{CH_2}CH_2Ar$), 5.09 (apparent t, 1, OH-5'), 5.34 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 5.0 Hz, OH-3'), 5.60 (apparent d, 1, $J_{2',2'\text{-OH}}$ = 6.0 Hz, OH-2'), 5.94 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.25, 7.36 (2 m, 5, Ar-H), 8.08 (s, 1, H-8), 9.06 (s, 1, H-2), 9.65, 10.39 (br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-$\underline{d_6}$) δ 32.91 ($OCH_2\underline{CH_2}Ar$), 60.83 (C-5'), 69.91 (C-3'), 74.46 (C-2'), 80.41 (O$\underline{CH_2}CH_2Ar$), 85.82 (C-4'), 87.80 (C-1'), 119.37 (C-5), 126.55 (Ar-C-4), 128.40 (Ar-C-2,6), 128.78 (Ar-C-3,5), 136.08 (Ar-C-1), 142.75 (C-8), 144.45 (C-2), 145.21 (C-4), 148.21 (C-6).

1-(1-Phenylethoxy)adenosine, Perchloric Acid Salt (2r). The general procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. However, because it took 1 h for the N^1-oxide to go into solution the reaction mixture was stirred for 4 h before it was worked up. Also, since crystallization did not occur upon chilling and scratching, small spots were frozen on the flask with dry ice and scratched. After crystals had grown, the flask was stored overnight in the refrigerator. The product was collected, washed with ice H_2O and dried at 56 °C for 6 h over phosphorus pentoxide, yield, 1.7 g (40%); UV λ_{max} 259 nm (12,400) at pH 1; 259 (12,500) at pH 7; 258 (12,900) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR 1691, 1510, 1430, 1400, 1325, 1225, 1100 broad, 875, 720, 705, 635, 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.80 (d, 3, CH_3), 3.55, 3.65 (2 m, 2, CH_2-5'), 3.95 (apparent q, 1, H-4'), 4.12 (apparent t, 1, H-2'), 5.07, 5.31, 5.68 (3 apparent s, 3, OH-5',3'-2'), 5.71 (apparent q, 1, OCHAr), 5.90 (m, 1, H-1'), 7.42, 7.59 (2 m, 5, Ar-H), 8.77 (apparent t, 2, H-8,2), 9.53, 10.32 (br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 18.61 (C-CH_3), 60.80 (C-5'), 69.88 (C-3'), 74.39 (C-2'), 85.83 (C-4'), 87.65 (C-1'), 88.60 (C-OCHAr), 118.97 (C-5), 128.49, 128.54 (Ar-C-2,3,5,6), 129.85 (Ar-C-4), 136.05 (Ar-C-1), 142.83 (C-8), 144.72 (C-2), 144.89 (C-4), 148.61 (C-6).

1-(4-Methoxybenzyloxy)adenosine, Perchloric Acid Salt (2s). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was used. The hydrobromide was treated with 50 mL H_2O and only partially dissolved. The mixture was added to the warm solution of NH_4ClO_4. As the lumps were ground while trying to effect solution, product began to crystallize. The mixture was chilled in an ice bath, and the lumps were pulverized as much as possible. After 1 h in the ice bath, the precipitate was collected. The product was dissolved in 300 mL hot EtOH, cooled, treated with silica gel to remove salts, filtered through a silica gel plug, and diluted with hexane. The white product was collected, washed with hexane, and dried at 56 °C for 5 h over phosphorus pentoxide, yield, 2.4 g (55%); UV λ_{max} 258 nm (13,900) at pH 1; 259 (12,100) at pH 7; 259 (11,400) at pH 13; MS (FAB) *m/e* 404 (M + 1); IR 1684, 1610, 1516, 1252, 1229, 1180, 1100 broad, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.70 (2 m, 2, CH_2-5'), 3.79 (s, 3, OCH_3), 3.99 (apparent q, 1, H-4'), 4.16 (apparent q, 1, H-3'), 4.49 (apparent q, 1, H-2'), 5.09 (apparent t, 1, OH-5'), 5.33 (apparent d, 1, OH-3'), 5.35 (s, 2, OCH_2Ar), 5.60 (d, 1, OH-2'), 6.93 (d, 1, H-1'), 6.99 (d, 2, Ar-H-3,5), 7.69 (d, 2, Ar-H-2,6), 8.80 (s, 1, H-8), 8.87 (s, 1, H-2), 10.02 (br s, 2, H-$\overset{\oplus}{N}H_2$).

1-(3-Methoxybenzyloxy)adenosine, Perchloric Acid Salt (2t). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. The crude product was collected after only 1 h of chilling in an ice bath, 4.0 g (90%) yield. After one

reprecipitation from hot EtOH with hexane, the crude product (3.4 g) was dissolved in 200 mL hot EtOH, treated with a small amount of silica gel, filtered through a layer of silica gel, diluted with hexane, the product was collected by filtration, washed with hexane and dried at 56 °C for 5 h over phosphorus pentoxide, yield 2.3 g (52%); UV λ_{max} 260 nm (13,200) at pH 1; 260 (12,700) at pH 7; 258 (13,100) at pH 13; MS (FAB) *m/e* 404 (M + 1); IR 1683, 1605, 1510, 1495, 1435, 1100 (broad), 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.56, 3.68 (2 m, 2, CH_2-5'), 3.78 (s, 3, OCH_3), 3.98 (apparent q, 1, H-4'), 4.14 (apparent q, 1, H-3'), 4.47 (apparent q, 1, H-2'), 5.07 (apparent t, 1, OH-5'), 5.31 (apparent d, 1, OH-3'), 5.36 (s, 2, OCH_2Ar), 5.59 (apparent d, 1, OH-2'), 5.92 (d, 1, H-1'), 7.03 (m, 1, Ar-H-4), 7.19 (d, 1, Ar-H-6), 7.28 (apparent t, 1, Ar-H-2), 7.37 (t, 1, Ar-H-5), 8.76 (s, 1, H-8), 8.88 (s, 1, H-2), 9.95 (br s, 2, H-$\overset{\oplus}{N}H_2$).

1-(2-Fluorobenzyloxy)adenosine, Perchloric Acid Salt (2u). The procedure for 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. After one recrystallization from H_2O and drying at 78 °C for 14 h over phosphorus pentoxide, a pure specimen was obtained, yield 3.3 g (77%); UV λ_{max} 259 nm (13,400) at pH 1; 259 (13,100) at pH 7; 257 (12,500) at pH 13; MS (FAB) *m/e* 392 (M + 1); IR 1686, 1515, 1415, 1227, 1100 (broad), 770, 622 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.69 (2 m, 2, CH_2-5'), 3.99 (apparent q, H-4'), 4.15 (apparent t, 1, H-3'), 4.48 (apparent s, 1, H-2'), 5.09, 5.33 (2 br s, 2, OH-5,'3'), 5.52 (s, 2, OCH_2Ar), 5.60 (br s, 1, OH-2'), 5.94 (d, 1, H-1'), 7.30, 7.56, 7.69 (3 m, 4, Ar-H), 8.79 (s, 1, H-2), 8.82 (s, 1, H-8), 9.78, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

1-(3-Fluorobenzyloxy)adenosine, Perchloric Acid Salt (2v). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. One recrystallization from H_2O and drying at 78 °C for 14 h over phosphorus pentoxide yielded, 3.3 g (77%); UV λ_{max} 259 nm (13,700) at pH 1; 259 (13,700) at pH 7; 258 (13,100) at pH 13; MS (FAB) *m/e* 392 (M + 1); IR 1684, 1507, 1100 (broad), 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.69 (2 m, 2, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, H-3'), 4.49 (apparent t, 1, H-2'), 5.43 (s, 2, OCH_2Ar), 5.97 (d, 1, H-1'), 7.34, 7.52, 7.63 (3 m, 4, Ar-H), 8.83 (s, 1, H-8), 9.05 (s, 1, H-2), 9.78, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

2'-Deoxyadenosine-N^1-oxide (3a). The procedure for the preparation of adenosine-N^1-oxide[1,2] was used. The 2'-deoxyadenosine monohydrate (1.0 g, 3.72 mmol) was stirred in 100 mL of methanol at room temperature. It went into solution quickly and 1.0 g (4.63 mmol) of m-chloroperoxybenzoic acid (MCPBA) was added in several portions. After 3/4 of the MCPBA was added a white precipitate began to form. Because thin layer chromatography after 5 h indicated the presence

of starting material, another small portion MCPBA was added and the reaction was stirred overnight. The reaction mixture was poured into 1.5 L of ethyl acetate and stirred 2 h. The product was collected by filtration, washed with ethyl acetate, and dried over phosphorus pentoxide, yield, 1.0 g (100%); mp 219-221 °C cap (dec); UV λ_{max} 258 nm (12,520) at pH 1; 261 (8,490) at pH 7; 268 (8,600) at pH 13; MS (FAB) *m/e* 268 (M + 1); IR 1680, 1499, 1355, 1233, 1213, 1091, 1075, 1070, 1025 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.32 (m, 1, $J_{2'a,3'}$ = 3.6 Hz, $J_{1',2'a}$ = 6.2 Hz, H-2'a), 2.70 (m, 1, $J_{2'b,3'}$ = 5.9 HZ, $J_{1',2'b}$ = 7.2 Hz, $J_{2'a,2'b}$ = 13.3 Hz, H-2'b), 3.52, 3.60 (2 m, 2, $J_{5'a,5'b}$ = 11.8 Hz, CH_2-5'), 3.87 (apparent q, 1, $J_{4',5'a}$ = $J_{4',5'b}$ = 4.7 Hz, H-4'), 4.41 (apparent q, 1, $J_{3',4'}$ = 2.7 Hz, $J_{2'a,3'}$ = 3.6 Hz, $J_{2'b,3'}$ = 5.9 Hz, H-3'), 4.98 (apparent t, 1, $J_{5',5'\text{-OH}}$ = 5.0 Hz, 5'-OH), 5.38 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 3.8 Hz, 3'-OH), 6.33 (t, 1, $J_{1',2'a}$ = 6.2 Hz, $J_{1',2'b}$ = 7.2 Hz, H-1'), 8.51 (s, 1, H-2), 8.63 (s, 1, H-8). *Anal.* Calcd for $C_{10}H_{13}N_5O_4 \cdot 0.40H_2O$: C, 43.76; H, 5.07; N, 25.52. Found: C, 43.83; H, 5.06; N, 25.28.

2'-Deoxy-1-(3-methylbenzyloxy)adenosine, Perchloric Acid Salt (3b). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was repeated. After two recrystallizations from water and drying at 78 °C for 5 h over phosphorus pentoxide 2.3 g (66%) was obtained; UV λ_{max} 260 nm (13,300) at pH 1; 259 (13,300) at pH 7; 258 (13,400) at pH 13; MS (FAB) *m/e* 372 (M + 1); IR 1691, 1507, 1425, 1218, 1100 broad, 933, 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.35 (s, 3, $\underline{CH_3}Ar$), 2.39, 2.65 (2 m, 2, CH_2-2'), 3.54, 3.61 (2 m, 2, CH_2-5'), 3.92 (apparent q, 1, H-4'), 4.42 (m, 1, H-3'), 4.97 (br s, 1, OH-5'), 5.37 (s, 2, $O\underline{CH_2}Ar$), 5.39 (m, 1, OH-3'), 6.38 (t, 1, H-1'), 7.28, 7.34, 7.43, 7.49 (m, 4, Ar-H-2,4,5,6), 8.76 (s, 1, H-8), 8.93 (s, 1, H-2), 9.74, 10.37 (2 br s, 2, H-$\overset{\oplus}{N}H_2$; ^{13}C NMR (Me_2SO-d_6) δ 20.78 (C-$\underline{CH_3}Ar$), 39.84 (C-2'), 61.20 (C-5'), 70.26 (C-3'), 81.74 (C-$O\underline{CH_2}Ar$), 84.02 (C-1'), 88.20 (C-4'), 119.31 (C-5), 127.72, 128.30, 130.30, 131.23, 131.87, 137.71 (Ar-C-1,2,3,4,5,6), 142.86 (C-8), 144.59 (C-4), 144.83 (C-2), 148.24 (C-6).

9-Benzyladenine-N^1-oxide (3c). The procedure for the preparation of adenosine-N^1-oxide[1,2] was used. 9-Benzyladenine[4,5] (2.0 g, 8.89 mmol) was stirred in 160 mL of methanol at room temperature. m-Chloroperoxybenzoic acid (MCPBA) (1.84 g, 10.7 mmol) was added in several portions. Since thin-layer chromatography (TLC) showed the presence of starting material, three additional (unweighed) portions were added and the mixture was stirred overnight. The reaction mixture was poured into 500 mL of ethyl acetate and stirred 2 h. The white product was collected, washed with ethyl acetate, and dried; crude yield, 1.3 g (62%).

This material was combined with 700 mg from a later batch of the N^1-oxide and recrystallized from 450-mL of hot EtOH. An analytical sample was obtained by

drying the product at 78 °C for 5 h over phosphorus pentoxide; yield, 1.7 g; mp 270-272 °C dec (cap); UV λ_{max} 259 (13,000) at pH 1; 262 (9,100), 233 (46,100) at pH 7; 308 (4,400), 269 (8,700), 232 (26,300) at pH 13; MS (EI) *m/e* 241 (M), 225 (M-O); IR 1669 broad, 1503, 1490, 1410, 1361, 1330, 1263, 1235, 1221, 1160, 1140, 713, 695 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.40 (s, 2, $\underline{CH_2}Ar$), 7.33 (m, 5, Ar), 8.43 (s, 1, H-2), 8.63 (s, 1, H-8). *Anal.* Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.74; H, 4.64; N, 28.98.

9-Benzyl-1-(3-methylbenzyloxy)adenine, Perchloric Acid Salt (3d). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was used. Since the reaction appeared slower than previous efforts it was stirred for 4.5 h after solution was complete. The hydrobromide was not soluble in H_2O so the NH_4ClO_4 and the hydrobromide were dissolved in a mixture of 175 mL of H_2O and 75 mL EtOH with heat. The solution was filtered, chilled and the product collected, washed with H_2O and dried at 78 °C for 6 h over phosphorus pentoxide; yield, 1.4 g (76%); UV λ_{max} 261 nm (13,500) at pH 1; 261 (13,300) at pH 7; 259 (13,600) at pH 13; MS (FAB) *m/e* 346 (M + 1); IR 1695, 1575, 1375, 1100 broad, 795, 765, 729, 645, 640, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.33 (s, 3, $\underline{CH_3}Ar$), 5.37, 5.50 (s, 4, $\underline{CH_2}Ar$), 7.35 (m, 9, Ar-H), 8.71, 8.89 (s, 2, H-8,2), 9.68, 10.34 (br s, 2, H-$\overset{\oplus}{N}H_2$).

9-Benzyl-1-ethoxyadenine, Perchloric Acid Salt (3e). In a 50-mL round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube was suspended 1 g (4.15 mmol) of 9-benzyladenine-N^1-oxide in 20 mL of dry dimethylacetamide and 3.3 g (21.3 mmol) of ethyl iodide was added. The reaction was very slow - incomplete solution after 9 h. After the reaction was stirred 72 h, the hydroiodide was precipitated by the addition of ether and unreacted ethyl iodide was washed away with ether. The hydroiodide and a NH_4ClO_4 solution (2 g/10 mL H_2O) were mixed in about 30 mL H_2O and enough EtOH was added to the hot mixture to effect solution. The hot solution was filtered, chilled, the product was collected, washed with H_2O, and dried at 78 °C for 5 h over phosphorus pentoxide; yield, 1.3 g (85%); UV λ_{max} 261 nm (12,500) at pH 1; 260 (12,700) at pH 7; 258 (13,100) at pH 13; MS (FAB) *m/e* 270 (M + 1); IR 1701, 1620, 1515, 1455, 1425, 1415, 1225, 1100 broad, 1000, 735, 707, 650, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.43 (t, 3, $OCH_2\underline{CH_3}$), 4.42 (q, 2, $O\underline{CH_2}CH_3$), 5.51 (s, 2, $\underline{CH_2}Ar$), 7.38 (m, 5, Ar-H), 8.71 (s, 1, H-8), 9.11 (s, 1, H-2), 9.56, 10.28 (br s, 2, H-$\overset{\oplus}{N}H_2$).

2'-Deoxy-1-(2-methylbenzyloxy)adenosine, Perchloric Acid Salt (3f). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was used. One recrystallization of the crude product from H_2O and drying at 78 °C overnight with phosphorus pentoxide yielded, 1.26 g (47%); UV λ_{max} 259 nm (13,400) at pH 1; 259

(13,100) at pH 7; 258 (13,100) at pH 13; MS (FAB) *m/e* 372 (M + 1); IR 1684, 1505, 1220, 1100 (broad), 765, 750, 635, 625 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.37, 2.64 (2 m, 2, CH_2-2'), 2.47 (s, 3, $\underline{CH_3}Ar$), 3.52, 3.61 (2 m, 2, CH_2-5'), 3.90 (apparent q, 1, H-4'), 4.41 (m, 1, H-3'), 4.95 (br s, 1, OH-5'), 5.39 (br s, 1, OH-3'), 5.46 (s, 2, $O\underline{CH_2}Ar$), 6.38 (t, 1, H-1'), 7.24, 7.36, 7.45 (3 m, 4, H-Ar), 8.59 (s, 1, H-2), 8.78 (s, 1, H-8), 9.76, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

9-Benzyl-1-(2-methylbenzyloxy)adenine, Perchloric Acid Salt (3g). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. Since solution did not occur even after 4 h, the reaction mixture was warmed to 50 °C for 2 h, and this gave a clear solution during the first hour. The reaction mixture was stirred at room temperature overnight then poured into 500 mL of anhydrous ether. The ether was decanted and the residue washed with 2 x 500 mL ether, and dried in a stream of nitrogen. The residue was treated with 75 mL of H_2O and 50 mL of ethanol. Most of the sample dissolved. A warm solution of 3 g NH_4ClO_4 in 20 mL of warm H_2O was added and the mixture was warmed to achieve complete solution. After the solution was filtered, it was chilled and scratched to induce crystallization. The product was collected, washed with H_2O, and dried. The crude product was recrystallized from 100 mL H_2O-50 mL EtOH, and dried at 78°C for 5 h over phosphorus pentoxide, yield, 1.2 g (43%); UV λ_{max} 262 nm (13,500) at pH 1; 261 (13,400) at pH 7; 259 (13,600) at pH 13; MS (FAB) *m/e* 346 (M + 1); IR 1691, 1514, 1220, 1100 (broad), 764, 725, 706, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.45 (s, 3, CH_3Ar), 5.45, 5.50 (2 s, 4, $O\underline{CH_2}Ar$, $N\underline{CH_2}Ar$), 7.71-7.46 (m, 9, H-Ar), 8.57 (s, 1, H-2), 8.72 (s, 1, H-8), 9.73, 10.40 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

2'-Deoxy-1-(2-fluorobenzyloxy)adenosine, Perchloric Acid Salt (3h). The procedure for the preparation of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. One recrystallization from H_2O and drying at 78 °C over phosphorus pentoxide for 8 h yielded, 1.9 g (71%); UV λ_{max} 259 nm (13,700) at pH 1; 259 (13,600) at pH 7; and 258 (13,300) at pH 13; MS (FAB) *m/e* 376 (M + 1); IR 1680, 1645, 1508, 1240, 1220, 1205, 1100 (broad), 990, 944, 930, 915, 875, 870, 765, 622 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.39, 2.65 (2 m, 2, CH_2-2'), 3.53, 3.61 (2 m, 2, CH_2-5'), 3.91 (apparent q, 1, H-4'), 4.42 (apparent s, 1, H-3'), 4.97 (br s, 1, OH-5'), 5.39 (apparent s, 1, OH-3'), 5.50 (s, 2, $O\underline{CH_2}Ar$), 6.37 (t, 1, H-1'), 7.30, 7.56, 7.69 (3 m, 4, H-Ar), 8.77 (2 apparent s, 2, H-8,2), 9.76 10.42 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

2'-Deoxy-1-(3-fluorobenzyloxy)adenosine, Perchloric Acid Salt (3i). The procedure of 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was repeated. One recrystallization from H_2O and drying at 56 °C over phosphorus pentoxide for 5 h yielded 1.6 g (60%); UV λ_{max} 259 nm (13,700) at pH 1; 259 (13,500) at pH 7; 258

(13,100) at pH 13; MS (FAB) *m/e* 376 (M + 1); IR 1690, 1505, 1425, 1260, 1225, 1100 (broad), 932, 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.39, 2.65 (2 m, 2, CH_2-2'), 3.54, 3.61 (2 m, 2, CH_2-5'), 3.91 (apparent q, 1, H-4'), 4.42 (m, 1, H-3'), 4.97 (m, 1, OH-5'), 5.41 (s, 2, $O\underline{CH_2}Ar$), 5.41 (m, 1, OH-3'), 6.39 (t, 1, H-1'), 7.32, 7.50, 7.62 (3 m, 4, H-Ar), 8.78 (s, 1, H-8), 9.03 (s, 1, H-2) 9.76, 10.40 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

2'-Deoxy-1-(4-methylbenzyloxy)adenosine, Perchloric Acid Salt (3j). The procedure for 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was followed. One recrystallization from H_2O and drying at 78°C for 8 h over phosphorus pentoxide yielded, 1.5 g (57%); UV λ_{max} 259 nm (13,300) at pH 1; 259 (13,300) at pH 7; 258 (13,300) at pH 13; MS (FAB) *m/e* 372 (M + 1); IR 1692, 1505, 1425, 1380, 1220, 1100 (broad), 931, 855, 815, 641, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.34 (s, 3, CH_3Ar), 2.39, 2.64 (2 m, 2, CH_2-2'), 3.53, 3.61 (2 m, 2, CH_2-5'), 3.91 (apparent q, 1, H-4'), 4.42 (br m, 1, H-3'), 4.97 (br s, 1, OH-5'), 5.36 (s, 2, $O\underline{CH_2}Ar$), 6.37 (t, 1, H-1'), 7.26, 7.53 (2 d, 4, H-Ar), 8.76 (s, 1, H-8), 8.89 (s, 1, H-2), 9.70, 10.36 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

9-Benzyl-1-(3-fluorobenzyloxy)adenine, Perchloric Acid Salt (3k). The procedure of 9-benzyl-1-(2-fluorobenzyloxy)adenine, perchloric acid salt was followed. A pure sample was obtained without recrystallization, yield 1.95 g (87%); UV λm_{ax} 262 nm (13,700) at pH 1; 261 (13,900) at pH 7, 259 (13,900) at pH 13; MS (FAB) *m/e* 350 (M + 1); IR 1692, 1672, 1510, 1456, 1100 (broad), 713, 702, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.40 (s, 2, $O\underline{CH_2}Ar$), 5.50 (s, 2, N $\underline{CH_2}Ar$), 7.30-7.61 (3 m, 9, H-Ar), 8.72 (s, 1, H-8), 8.98 (s, 1, H-2), 9.71, 10.38 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

2'-Deoxy-1-(4-fluorobenzyloxy)adenosine, Perchloric Acid Salt (3l). The procedure for 1-(2-cyanobenzyloxy)adenosine, perchloric acid salt was repeated. After one recrystallization from H_2O and drying at 78°C for 5 h over phosphorus pentoxide 1.9 g (71%) was obtained; UV λ_{max} 259 nm (13,000) at pH 1; 259 (12,900) at pH 7; 258 (12,900) at pH 13; MS (FAB) *m/e* 376 (M + 1); IR 1683, 1514, 1508, 1385, 1229, 1218, 1100 (broad), 925, 622 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.38, 2.65 (2 m, 2, CH_2-2'), 3.53, 3.61 (2 m, 2, CH_2-5'), 3.91 (apparent 1, H-4'), 4.42 (m, 1, H-3'), 4.97 (br s, 1, OH-5'), 5.39 (s, 2, $O\underline{CH_2}Ar$), 6.38 (t, 1, H-1'), 7.30 (m, 2, Ar-H-3,5), 7.74 (m, 2, Ar-H-2,6), 8.77 (s, 1, H-8), 8.98 (s, 1, H-2), 9.72, 10.39 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

9-Benzyl-1-(2-fluorobenzyloxy)adenine, Perchloric Acid Salt (3m). The 9-benzyladenine-N^1-oxide (1.5 g, 6.22 mmol) was suspended with stirring in 30 mL dimethylacetamide (DMAC) in a 50 mL round-bottom flask protected with a Drierite filled drying tube. The 2-fluorobenzylbromide (3.5 g, 18.7 mmol) was added and complete solution required 6 h. The reaction was stirred overnight, and then

poured into ~500 mL ether, resulting in the formation of a very fluffy white solid. Since only about half of the ether could be decanted, the decanted ether was replaced with fresh ether and shaken. After the precipitate settled, the ether was decanted again, and this operation was repeated 2 more times. The fluffy product was collected by filtration, washed with ether, then dissolved in 200 mL of EtOH-H_2O (1:1). A solution of 3 g (25.5 mmol) of ammonium perchlorate in 15 mL warm H_2O was added, the mixture was warmed to dissolve the fluffy precipitate, filtered, chilled, and scratched to facilitate crystallization. The product was collected, washed with H_2O and dried at 78 °C overnight with phosphorus pent- oxide, yield, 2.35 g (84%); UV λ_{max} 261 nm (13,800) at pH 1; 261 (13,800) at pH 7; 259 (14,000) at pH 13; MS (FAB) *m/e* 350 (M + 1); IR 1684, 1620, 1580, 1514, 1490, 1455, 1415, 1100 (broad), 754, 697, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.49 (s, 4, OCH_2Ar, $N\text{-}CH_2Ar$), 7.25-7.70 (m, 9, Ar-H), 8.70 (s, 1, H-8), 8.74 (s, 1, H-2), 9.73, 10.39 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

9-Benzyl-1-(4-fluorobenzyloxy)adenine, Perchloric Acid Salt (3n). The procedure of 9-benzyl-1-(2-fluorobenzyloxy)adenine, perchloric acid salt was followed. A pure sample was obtained without recrystallization, yield, 1.5 g (68%); UV λ_{max} 261 nm (13,000) at pH 1; 261 (13,000) at pH 7; 259 (13,500) at pH 13; MS (FAB) *m/e* 350 (M + 1); IR 1692, 1615, 1600, 1575, 1513, 1495, 1425, 1355, 1228, 1162, 1100 (broad), 860, 845, 725, 710, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.39 (s, 2, $O\underline{CH_2}Ar$), 5.51 (s, 2, $N\text{-}\underline{CH_2}Ar$), 7.34, 7.73 (2 m, 9, H-Ar), 8.72 (s, 1, H-8), 8.95 (s, 1, H-2), 9.70, 10.36 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

3,6-Diphenoxyhexahydro-1,2,4,5,3,6-tetrazadiphosphorine 3,6-Disulfide[6] (5). In an oven-dried 500 mL round-bottomed 3-necked flask equipped with an addition funnel, drying tube, mechanical stirrer, and a thermometer was placed 250 mL of acetonitrile (dried over molecular sieves), 4.7 g (46.6 mmol) of triethylamine, and 0.50 g (15.5 mmol) of anhydrous hydrazine. The reaction was protected from atmospheric moisture with an argon atmosphere. The reaction solution was chilled to -20 °C and a solution of 3.3 g (0.016 mol) of phenyl dichloridothiophosphate in 20 mL of acetonitrile (molecular sieve) was added dropwise over 3 h with good stirring. The temperature was maintained at -20 to -15 °C during the addition and for one-half h more. The reaction was then stirred for 1 h at -10 °C and at room temperature overnight. After the reaction mixture was evaporated, the gummy white solid was treated with ~30 mL of ethyl acetate. The insoluble portion was removed by filtration and the filtrate evaporated to a glass, 3.0 g (56%). The glass was dissolved in ~10 mL of warm methanol, filtered, cooled, and the filtrate slowly diluted with water. As crystallization occurred more water was slowly added until a

heavy precipitate had formed. The mixture was chilled and the product collected and dried: 2.2 g (41%); mp 174-177 °C cap cloudy melt, 184-186 °C clear melt.

The crude product was recrystallized from 15 mL methanol by adding 15 mL water. The product was collected, washed with water, and dried: 1.9 g (35%). The product was passed through a 50-g flash column of silica gel using 3:1 carbon tetrachloride/tetrahydrofuran. After two recrystallizations from ethyl acetate-hexane, an analytical sample was obtained, dried *in vacuo* over phosphorus pentoxide at 78 °C for 3 h: yield 1.1 g (20%); mp 193-200 °C cap; MS (EI) *m/e* 372 (M), 279 (372 - OPh); IR 1590, 1488, 1196, 1160, 932, 901, 768, 703, 694, 686 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.21, 7.37 (2 m, 10, Ar); 7.76, 7.88 (2 d, 4, NH). *Anal.* Calcd for $C_{12}H_{14}N_4O_2P_2S_2$: C, 38.71; H, 3.79; N, 15.05. Found: C, 38.75; H, 3.89; N, 14.80.

1,5-Dimethyl-3,6-diphenoxyhexahydro-1,2,4,5,3,6-tetrazadiphosphorine 3,6-Disulfide[7,8] (7). In an oven dried apparatus consisting of a 1 L three-necked round-bottomed flask equipped with two addition funnels, a magnetic stirring bar, a reflux condenser, and a calcium sulfate drying tube was placed 12.2 g (0.121 mol) of triethylamine and 300 mL of molecular sieve (4A) dried ether. The reaction was conducted in an argon atmosphere. The triethylamine solution was heated to gentle reflux and solutions of 13.5 g (55 mmol) of phenyl 2,2'-dimethylphosphorodihydrazidothioate in 75 mL of dry ether and 12.5 g (55 mmol) of phenyldichlorothiophosphate in 75 mL of dry ether were added dropwise, simultaneously, over 3 h with good stirring. The reaction mixture was refluxed an additional 2 h before it was cooled and the precipitated triethylamine hydrochloride was removed by filtration. The filter cake was washed with ether and the filtrate (and washings) was evaporated at reduced pressure. The crude product was treated with 3:1 carbon tetrachloride/tetrahydrofuran and passed through a flash column of 500 g of silica gel. The appropriate fractions, as indicated by TLC, were combined and evaporated.

Since TLC indicated some product was not dissolved and passed through the flash column, the residue was treated with 250 mL of ethyl acetate. The ethyl acetate solution was added to 50 g of silica gel and evaporated *in vacuo*. The silica gel was placed on top of a 200 g silica gel column and developed with 3:1 carbon tetrachloride/tetrahydrofuran. The fractions containing the product were combined, evaporated, and combined with the product fraction from the previous column by solution in toluene. The solution was filtered, cooled, and slowly diluted with hexane. Crystallization was induced by scratching. The product was collected, washed with hexane, and dried: yield 2.6 g (12%); mp 150-160 °C cap; MS (EI) *m/e* 400 (M), 307 (400 - OPh); IR 1585, 1488, 1196, 1160, 1020, 938, 929, 905, 787, 768,

760, 690, 674 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.99 (apparent q, 6, CH_3 of 1,4-Me_2 II), 3.19 (apparent q, 6, CH_3 of 2,4-Me_2 I), 7.20 (m, 10, Ar), 7.40 (m, 10, Ar), 8.35 (d, 2, NH of 1,4-Me_2 II), 8.42 (d, 2, NH of 2,4-Me_2 I). *Anal.* Calcd for $C_{14}H_{18}N_4O_2P_2S_2 \cdot 0.010C_7H_8$: C, 42.63; H, 4.70; N, 13.53. Found: C, 42.56; H, 4.63; N, 13.55.

2-Amino-5-methyl-1,3,4-selenadiazole[9] (8a). To a well stirred suspension of 5.5 g (39.9 mmol) of aminoselenosemicarbazide[10] in 40 mL of acetic acid and protected from atmospheric moisture by an argon atmosphere and a calcium sulfate drying tube was added 9.1 g (59.8 mmol) of phosphorus oxychloride over 20 min. The reaction mixture was stirred 1 h at room temperature and refluxed gently for 1 h. The reaction was then cooled and evaporated to dryness. The residue was suspended in 100 mL of water, made acidic with 10 mL of concentrated hydrochloric acid, and heated at reflux for 2 h. The reaction mixture was chilled in an ice bath and made basic with sodium hydroxide (6N). The precipitate was collected, washed with water and dried. The residue was dissolved in 180 mL hot ethanol, filtered, and diluted with ~250 mL of hexane. The product was collected, washed with hexane and dried: yield 3.4 g (53%); mp 227-228 °C cap dec; MS (EI) *m/e* 163 (M); IR 1640, 1537, 1526, 1511, 1504, 1328, 1172 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.45 (s, 3, CH_3), 7.10 (s, 2, NH_2). *Anal.* Calcd for $C_3H_5N_3Se$: C, 22.23; H, 3.11; N, 25.93. Found: C, 22.56; H, 3.12; N, 26.00.

2-Amino-5-ethyl-1,3,4-selenadiazole (8b). The 2-amino-5-ethyl-1,3,4-selenadiazole was prepared from 2.4 g (17.4 mmol) of aminoselenosemicarbazide, 20 mL of propionic acid, and 4.0 g (26.1 mmol) of phosphorus oxychloride by the procedure previously described for the 5-methyl derivative: yield 833 mg (27%); mp 201-202 °C cap, shiny platelets; MS (EI) *m/e* 177 (M); IR 1632, 1517, 1501, 1326, 1010 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.21 (t, 3, $C\underline{H}_3CH_2$), 2.80 (q, 2, $C\underline{H}_2CH_3$), 7.13 (s, 2, NH_2). *Anal.* Calcd for $C_4H_7N_3Se$: C, 27.28; H, 4.01; N, 23.86. Found: C, 27.43; H, 4.12; N, 24.00.

2-Amino-5-phenyl-1,3,4-selenadiazole (8c). The 2-amino-5-phenyl-1,3,4-selenadiazole was prepared from 3.0 g (21.7 mmol) of the aminoselenosemicarbazide, 2.65 g (21.7 mmol) of benzoic acid, and 8.3 g (54.3 mmol) of phosphorus oxychloride by the procedure previously described for the 5-methyl derivative. The thick paste was mixed with a mechanical stirrer. An analytical sample was obtained by recrystallizing the crude product from EtOH-H_2O: yield 950 mg (40%); mp 241-242 °C cap dec; MS (EI) *m/e* 225 (M), 183 (225 - N=C-NH_2), 122 (225 - PhC=N), 103 (PhC=N); IR 1630, 1507, 1473, 1255, 1040, 759, 692, 657 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.43 (m, 3, Ar-H-3',4',5'), 7.55 (s, 2, NH_2), 7.72 (apparent q, 2, Ar-H-

2',6'). *Anal.* Calcd for $C_8H_7N_3Se$: C, 42.87; H, 3.15; N, 18.75. Found: C, 43.05; H, 3.28; N, 18.94.

2-Methyl-6-phenylimidazo[2,1-b]-1,3,4-selenadiazole[9] (9). The procedure of Lalezari and Shafiee was used with only slight modification. A mixture of 1.8 g (11.1 mmol) of 2-amino-5-methyl-1,3,4-selenadiazole, 1.7 g (11.1 mmol) of 2-chloroacetaphenone in 25 mL of 95% EtOH was refluxed gently. After 6 h reflux, TLC showed only a partial reaction. Triethylamine, 1 mL (7.2 mmol), was added and the reaction thinned in a few min. A second portion of Et_3N, 1 mL (7.2 mmol), was added and a brown solution was obtained. Heating was discontinued after 24 h even though some starting material remained. The reaction was evaporated to a gummy-yellow solid. The residue was dissolved in 50 mL of hot EtOH, filtered, cooled, and scratched to induce crystallization. The product was collected, washed with a little EtOH, and dried: yield 1.1 g (38%); mp 153-156 °C. An analytical sample was obtained by recrystallization from 10-15 mL hot EtOH: yield 875 mg (30%); mp 154-156 °C cap; MS (EI) *m/e* 263 (M), 222 (263 - $CH_3C{\equiv}N$), 195 (263 - $CH_3C{\equiv}N{-}N{=}CH$); IR 1605, 1545, 1535, 1460, 1437, 1168, 740, 690, 680 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.75 (s, 3, CH_3), 7.26 (t, 1, 4' of Ph); 7.39 (t, 2, Ar-H-3',5'), 7.80 (d, 2, Ar-H-2',6'), 8.05 (s, 1, 5-CH). *Anal.* Calcd for $C_{11}H_9N_3Se$: C, 50.39; H, 3.46; N, 16.03. Found: C, 50.48; H, 3.60; N, 16.02.

3-Nitroamino-1,2,4-triazole[11] (12a). Fuming nitric acid (d 1.52, 35 mL) was added slowly over 15 min to 3-amino-1,2,4-triazole (8.5 g, powder) at 0 °C with vigorous stirring. The reaction mixture was stirred further for 30 min at 10-20 °C and quenched by pouring it into ice-water. The solid was filtered and vacuum dried to afford pure product (10.1 g), mp 215-217 °C (dec) (lit. mp 215-217 °C); MS (EI) *m/e* 129 (M). UV λ_{max} (H_2O) 206 (550), 283 (1300); IR (KBr) 3490, 3450 (sh), 3260 (NH_2, $NHNO_2$, NH), 3150-2750 (C-H), 1580, 1540 (C=N), 1430, 1330, 1290, 1250, 1140, 1075, 1065, 1060, 1000, 965, 905 cm^{-1}; ^1H NMR (Me_2SO- d_6) δ 14.4-13.8 (br s, 1, NH, D_2O exchangeable), 8.5 (s, 1, C-H), 3.7-3.1 (br s, 1, $NHNO_2$, D_2O exchangeable). *Anal.* Calcd for $C_2H_5N_5O_2$ $0.5H_2O$): C, 17.39; H, 2.92; N, 50.73. Found: C, 17.66; H, 2.97; N, 51.17.

3-Nitroamino-5-phenyl-1,2,4-triazole (12b). Fuming nitric acid (d 1.52, 9.7 mL) was added slowly over 15 min to compound **16** (4.45 g) at 0 °C. The reaction mixture was stirred further for 30 min at 10-20 °C and quenched by pouring it into ice-water. The solid was filtered, dried, and crystallized from water (4.85 g), mp 183-185 °C (dec); MS (EI) *m/e* 205 (M); IR (KBr) 3420, 3100, 2975 (broad, NH, $NHNO_2$, C-H), 1617 (C=N), 1601, 1583 (aromatic), 1553, 1514, 1486, 1425, 1305, 1229 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 14.6-14.2 (bs, 1, NH), 8.05-7.9 (m, 2, o-Ph-H), 7.6-7.55

(m, 3, m- and p-Ph-H), 7.7-7.2 (broad, 1, $NHNO_2$); ^{13}C NMR (Me_2SO-d_6) 153.2 (C-3), 148.4 (C-5), 131.1 (C-4'), 129.1 (C-3' and C-5'), 126.0 (C-2' and C-6'), 125.0 (C-1'). *Anal.* Calcd for $C_8H_7N_5O_2 \cdot 0.2H_2O$: C, 46.02; H, 3.57; N, 33.55. Found: C, 45.96; H, 3.58; N, 33.62.

3-Methyl-5-nitroamino-1,2,4-triazole[16] (12c). A solution of 1-acetamido-3-nitroguanidine (18.7 g) and sodium carbonate (13 g) in water (180 mL) was heated for 25 min. It was then cooled, acidified with conc. HCl, and refrigerated overnight. The product was filtered, washed with cold water, and dried (22 g). A portion was recrystallized from water, mp 203-205 °C (dec.), MS (EI) 143 (M); IR (KBr) 3450, 3205, 3075 (NH), 2972, 2850 (CH), 1614 (C=N), 1572, 1496, 1445, 1380, 1370, 1338, 1300, 1248, 1100, 1090, 1025, 1010, 994 cm^{-1}. ^1H NMR (Me_2SO-d_6) δ 14.0-13.4 (NH), 3.6-3.1 (NH), 2.3 (s, 3H, CH_3); ^{13}C NMR (Me_2SO-d_6) δ 152.5 (C-5), 147.7 (C-3), 11.0 (CH_3) ppm. *Anal.* Calcd for $C_3H_5N_5O_2 \cdot 0.5H_2O$: C, 23.68; H, 3.98; N, 46.05. Found: C, 23.77; H, 3.85; N, 46.11.

3-Hydrazino-1,2,4-triazole hydrochloride[12] (13a). 3-Nitroamino-1,2,4-triazole (10 g) and activated zinc dust (20 g) were moistened with water and ground to a paste. The paste was suspended in water (50 mL) at 10 °C and treated with 50% aqueous acetic acid (100 mL) over 2 h, the temperature being maintained at 10-20 °C. The mixture was stirred at 20 °C for an additional 4 h, heated to 60 °C for 1 h, and allowed to cool. The excess of zinc was filtered and the filtrate saturated with hydrogen sulfide (2 h). After removal of zinc sulfide the filtrate and washings were treated with 10 N hydrochloric acid. Evaporation of the solvent and boiled with chloroform (5-10 mL, 30 min). Desired product (5.23 g) separated upon addition of absolute ethanol (25 mL). MS (EI) *m/e* 99 (M); IR (KBr) 3340, 3300-2700 (NH, $NHNH_2$ and C-H), 1650 (broad, C=N), 1580, 1530, 1360, 1300, 1275, 1215, 1130, 1060, 1030, 950 cm^{-1}. (This compound was not stable to storage and was used as is for the next step.)

3-Amino-5H-s-triazolo[5,1-c]-s-triazole (14a). A solution of 3-hydrazino-s-triazole hydrochloride (4.4 g) and cyanogen bromide (3.43 g) in aqueous methanol (132 mL, 85%) was refluxed for 48 h. The solvent was removed by evaporation, the solid residue was dissolved in water (12 mL), and the solution was neutralized with sodium acetate, giving a solid precipitate. The product was crystallized from water (2.4 g), mp 260 °C (dec) (lit.[13] 260 °C). MS (EI) *m/e* 124 (M); IR (KBr) 3340, 3190, 3150-2600 (broad, NH, NH_2, and C-H), 1660, 1630, 1600 (C=N), 1510, 1460, 1400, 1375, 1275, 1245, 1190, 1180, 1160, 1030, 980, 905 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.05 (s, 1, NH, D_2O exchangeable), 7.95 (s, 1, C-H), 6.5 (s, 2, NH_2, D_2O

exchangeable). *Anal.* Calcd for $C_3H_4N_6$: C, 29.03; H, 3.25; N, 67.72. Found: C, 28.92; H, 3.29; N, 67.96.

3-Amino-6-phenyl-5H-s-triazolo[5,1-c]-s-triazole, hydrobromide[11,12,13] **(14b)**: 3-Nitroamino-5-phenyl-1,2,4-triazole (8.61 g) and activated zinc dust (10.77 g) were moistened with water and ground to a paste. The paste was suspended in water (27 mL) at 10 °C and treated with 50% aqueous acetic acid (54 mL) over 2 h, while maintaining the temperature between 10-20 °C. The mixture was stirred at 20°C for an additional 4 h, heated to 60 °C for 1 h, and allowed to cool. The excess zinc was removed by filtration and the filtrate saturated with hydrogen sulfide for 2h. After removal of zinc sulfide, the filtrate and washings were treated with 10 N HCl. The hydrazino compound obtained (4.1 g) was refluxed with cyanogen bromide (1.87 g) in 85% aqueous methanol (72 mL) for 48 h. The solvent was removed by evaporation, and the solid residue was dissolved in water and neutralized with sodium acetate, giving a solid precipitate. The product was recrystallized from water and treated with one equivalent of hydrobromic acid, giving a pure product, 1.45 g, mp 263-265 °C dec.); MS (*m/e*) 200 (M); IR (KBr) 3450-2400 (broad, NH, NH_2, CH, HBr), 1698, 1672, 1600, 1535, 1500, 1475, 1445, 1435, 1375, 1290 cm^{-1}. ^1H NMR (Me_2SO-d_6): δ 12.0-9.0 (broad, NH, NH_2 and H^+), 8.2-8.0 (m, 2, ortho-Ar-H), 7.75-7.60 (m, 3, p- and m-Ar-H); ^{13}C NMR (Me_2SO-d_6): δ 160.4 (C-6), 150.7 (C-8), 141.2 (C-3), 131.7 (C-4'), 129.1 (C-3' and C-5'), 126.6 (C-2' and C-6') and 126.4 (C-1'). *Anal.* Calcd for $C_9H_8N_6 \cdot HBr$: C, 38.45; H, 3.23; N, 29.90. Found: 38.35; H, 3.57; N, 29.63%.

3-Amino-6-methyl-5H-s-triazolo[5,1-c]-s-triazole, hydrobromide[12,13] **(14c)**. 3-Methyl-5-nitroamino-1,2,4-triazole (5.37 g) and activated zinc dust (9.6 g) were moistened with water and ground to a paste. The paste was suspended in water (24 mL) at 10 °C and treated with 50% aqueous acetic acid (48 mL) over 2 h, while maintaining the temperature between 10-20 °C. The mixture was stirred at 20 °C for an additional 4 h, heated to 60° for 1 h, and allowed to cool. The excess zinc was removed by filtration and the filtrate saturated with hydrogen sulfide (2 h). After removal of zinc sulfide, the filtrate and washings were treated with 10 N HCl. 3-Methyl-5-hydrazino-1,2,4-triazole hydrochloride (4.7 g) was obtained by evaporation of the solvent. This compound was treated with cyanogen bromide (3.33 g) in 85% aqueous methanol (128 mL) and was refluxed for 48 h. The solvent was removed by evaporation, and the solid residue was dissolved in water and neutralized with sodium acetate, giving a solid precipitate. The product was crystallized from water (560 mg) and treated with one equivalent of hydrobromic acid, giving a pure product, 0.75 g, 256-261 °C (dec.); MS (EI) 138 (M); IR (KBr)

3270, 3228, 3187 (NH, NH_2), 3082 (C-H), 1701, 1665, 1610, 1570, 1500, 1430, 1390, 1363, 1346, 1165 cm^{-1}. ^1H NMR (Me_2SO-d_6) δ 13.3-12.0 (bs, 1, NH), 9.1-7.8 (bs, 2, NH_2) and 2.5 (s, 3, CH_3); ^{13}C NMR (MeSO-d_6) δ 159.2 (C-6), 148.9 (C-8), 140.8 (C-3) and 12.8 (CH_3). *Anal.* Calcd. for $C_4H_6N_6 \cdot HBr$: C, 21.93; H, 3.22; N, 38.37. Found: C, 22.16; H, 3.39; N, 38.39.

Benzamidoguanidine (15). Freshly distilled benzoyl chloride (30 mL) was added dropwise to a well stirred solution of aminoguanidine hydrogen carbonate (30 g) in dry pyridine (250 mL) at 0 °C. The reaction mixture was further stirred at room temperature for 12 h, and the solvent removed under reduced pressure. The residue was treated with water (250 mL) and made strongly alkaline with 10 N sodium hydroxide. The solid was filtered and dried (10.46 g), mp 180-182 °C; MS (EI) *m/e* 178 (M).

3-Amino-5-phenyl-1,2,4-triazole (16). Benzamidoguanidine (15) (22.38 g) was heated in an oil bath at 220 °C for 5 min. The residue was crystallized from water, giving colorless silky needles (18 g), mp 183-185 °C (dec); MS (EI) *m/e* 160 (M); IR (KBr) 3350 (NH_2), 3250-2800 (NH, CH), 1665, 1640 (C=N), 1610, 1600, 1580 (aromatic), 1535, 1525, 1495, 1465, 1445, 1430, 1400 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.1-12.0 (s, 1, NH), 7.9 (d, 2, Ph-H ortho protons), 7.5-7.3 (m, 3, m- and p-Ph-H), 6.2-5.9 (bs, 2, NH_2); ^{13}C NMR (Me_2SO-d_6) 153.5 (C-3), 150.1 (C-5), 130.7 (C-4'), 129.1 (C-3' and C-5'), 126.2 (C-1'), 125.9 (C-2' and C-6'). *Anal.* Calcd for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 60.07; H, 5.40; N, 35.02.

Nitroaminoguanidine[15] (17). Into a two liter flask equipped with a stirrer, dropping funnel, and thermometer was placed 52 g (0.5 mol) of nitroguanidine and one liter of distilled water at 60-65 °C. To the well agitated slurry was added dropwise, 32 g (0.55 mol) of 87% hydrazine monohydrate in 500 mL of water over one hour. The temperature was maintained at 55-60 °C for an additional 15 min, and then it was cooled to below 45 °C and neutralized with conc. HCl. The solution obtained from the reaction was refrigerated overnight, and the resulting solid product was filtered and dried, 26.9 g, mp 170-172 °C; MS (FAB) 120 (M + 1); IR (KBr) 3432, 3400, 3322, 3220 (NH,NH_2), 1669, 1618, 1580, 1510, 1410, 1356, 1294, 1171 cm^{-1}. *Anal.* Calcd for $CH_5N_5O_2$: C, 10.08; H, 4.23; N, 58.82. Found: C, 10·17; H, 4·25; N, 58·73.

1-Acetamido-3-nitroguanidine[16] (18). A solution of nitroaminoguanidine (31 g), glacial acetic acid (78 mL), and acetic anhydride (26 mL) was heated for 2 hour at 85-90 °C, cooled, and diluted with large excess of diethyl ether. The resulting precipitate was filtered and washed with ether. The yield of dried product was 24.7 g. A portion was recrystallized from water, mp 187-189 °C; MS (FAB) 162 (M + 1);

IR (KBr) 3387, 3242 (broad), 3075, 3025 (NH), 2925 (CH), 1702 (CO), 1635 (C=N), 1587, 1525, 1425, 1390, 1373, 1300 (broad), 1197, 1040 cm^{-1}. ^1H NMR (Me_2SO-d_6) δ 9.95-8.1 (broad, 4, NH) and 1.9 (s, 3, CH_3); ^{13}C NMR (Me_2SO-d_6): δ 169.5 (C=O), 161.0 (C=NH) and 20.7 (CH_3). *Anal.* Calcd. for $C_3H_7N_5O_3$: C, 22.36; H, 4.38; N, 43.47. Found: C, 22.42; H, 4.42; N, 43.11.

Triaminoguanidine Hydrochloride (19). Aminoguanidine bicarbonate (34 g) was suspended in 2 N HCl (63 mL), and conc. HCl was added with stirring until acidification was complete. The mixture was filtered, and the filtrate was concentrated, giving a residue which was dissolved in 125 mL boiling ethanol and heated with 32 mL of hydrazine hydrate for 4-5 h on a water bath. The reaction mixture was cooled, and the resulting precipitate was filtered and washed with methanol. It was crystallized from 2% HCl in ethanol, 11.1 g, mp 228-229 °C (dec) (lit.[17] 231 °C (dec)). MS (EI) *m/e* 104 (M); IR (KBr) 3400-2200 ($NHNH_2$, NH_2, HCl), 2060, 1940, 1810, 1680 (C=N), 1480, 1090 cm^{-1}. *Anal.* Calcd for CH_8N_6. HCl: C, 8.54; H, 6.45; N, 59.79. Found: C, 8.78; H, 6.42; N, 59.73.

4-Amino-3-hydrazino-5-methyl-s-triazole dihydrochloride[17] (20). Triaminoguanidine hydrochloride (14.0 g) was refluxed with acetic acid (20 mL) for 2.5 h. The solution was cooled, conc. HCl (70 mL) was added, and the mixture was warmed on a water bath for 30 min. The reaction mixture was cooled and allowed to stand for several hours at 0 °C and then the solid was filtered and crystallized from water (16.41 g), mp 218-220 °C (dec); MS (EI) *m/e* 128 (M); IR (KBr) 3400-2300 (broad, NH_2, $NHNH_2$, HCl, C-H), 1651, 1635, 1610 (C=N); ^1H NMR (Me_2SO-d_6) δ 9.5-6.0 (broad, NH_2, $NHNH_2$, H^+), 2.5 (s, CH_3); ^{13}C NMR (D_2O, dioxane as internal reference) δ 153.6 (C-5), 153.5 (C-3), 9.4 (CH_3). [Note: Compound (22) was found to decompose in dimethyl sulfoxide to 4-amino-5-methyl-1,2,4-triazole]. *Anal.* Calcd for $C_3H_8N_6 \cdot 2HCl$: C, 17.91; H, 5.01; N, 41.80. Found: C, 17.80; H, 5.02; N, 41.32.

3,7-Diamino-6-methyl-7H-s-triazolo[5,1-c]-s-triazole[13] (21). A solution of 22 (9.23 g) and cyanogen bromide (6.7 g) in aqueous methanol (235 mL, 85%) was refluxed for 48 h. The solvent was removed by evaporation, the solid residue was dissolved in water, and the solution was neutralized with sodium acetate. A precipitate was obtained which was filtered and crystallized from water (4.4 g), mp 260-265 °C (dec); MS (EI) *m/e* 153 (M^+); IR (KBr) 3301, 3195, 3109 (N-NH_2, C-NH_2, C-H), 1644, 1631 (C=N), 1580, 1554, 1390, 1360 cm^{-1}; ^1H NMR (D_2O + DSS) δ 2.45 (s, CH_3); ^{13}C NMR (Me_2SO-d_6) δ 159.849 (C-6), 148.9 (C-8), 142.1 (C-3), 10.6 (CH_3). *Anal.* Calcd for $C_4H_7N_7$: C, 31.37; H, 4.61; N, 64.03. Found: C, 31.39; H, 4.69; N, 64.08.

7-Amino-6-methyl-7H-s-triazolo[5,1-c]-s-triazole-3-thiol[13] **(22).** A solution of 4-amino-3-hydrazino-5-methyl-s-triazole dihydrochloride (6.2 g) and potassium hydroxide (5.4 g) in 70% aqueous ethanol (150 mL) was refluxed with carbon disulfide (25 mL) for 30 h. The solvent was removed and the residue was dissolved in water (25 mL). The solution was acidified (pH 3) by addition of conc. HCl. The pale yellow solid obtained was filtered and recrystallized from water, 2.0 g; mp 203-205 °C (dec.); MS (EI) *m/e* 170 (M); IR (KBr) 3425 (H_2O), 3259, 3237, 3151, 3098, 3015, 2985, 2945, 2900, 2790, 1645, 1619, 1555, 1513, 1455, 1443, 1405, 1325, 1289, 1255, 1185, 1014 cm^{-1}; ^1H NMR (Me_2SO-d_6); δ 13.5 (s, 1, SH), 6.3-5.5 (bs, 2, NH_2) and 2.4 (s, 3, CH_3); ^{13}C NMR (Me_2SO-d_6): δ 159.4 (C-6), 154.8 (C-3), 149.5 (C-8) and 10·5 (CH_3). *Anal.* Calcd for $C_4H_6N_6S·H_2O$: C, 25.52; H, 4.28; N, 44.66. Found: C, 25.59; H, 4.30; N, 44.70.

3,6,7-Triamino-7H-s-triazolo[5,1-c]-s-triazole[13] **(23).** A solution of triaminoguanidine hydrochloride (14.06 g, 0.1 mol) and cyanogen bromide (21.2 g, 0.2 mol) in aqueous methanol (405 mL, 85%) was refluxed for 48 h. The solvent was removed by evaporation, and the resulting solid was taken up in water and neutralized with sodium acetate. The precipitate was filtered and crystallized from water (8.08 g), mp 285-288 °C (dec); MS (EI) *m/e* 154 (M); IR (KBr) 3402, 3257, 3222, 3168, 3114 (N-NH_2, C-NH_2), 1691, 1679, 1647, 1615, 1518 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 160.0 (C-6), 147.2 (C-8), 141.0 (C-3). *Anal.* Calcd for $C_3H_6N_8·HBr$: C, 15.33; H, 3.00; N, 47.68. Found: C, 15.54; H, 3.05; N, 48.07.

4-Amino-3-hydrazino-s-triazole dihydrochloride[17] **(24).** Triaminoguanidine hydrochloride (21.74 g) was heated at reflux with 85% formic acid (32 mL) for 30 min. The solution was cooled, conc. HCl (120 mL) was added, and the mixture was warmed for 30 min. The reaction mixture was cooled and allowed to stand overnight at 0 °C. The resulting solid was filtered and crystallized from water, 29 g; mp 215-217 °C; MS (EI) *m/e* 114 (M); IR (KBr) 3350 (NH_2), 3300-2050 (broad, $NHNH_2$, 2 HCl, CH), 2000, 1645, 1600, 1525, 1510, 1430, 1315, 1210, 1060 cm^{-1}; ^{13}C NMR (80% H_2O, 20% D_2O, dioxane as internal reference): δ 153.3 (C-3) and 143.5 (C-5). [Note: Compound 24 was found to decompose in dimethyl sulfoxide to 4-amino-1,2,4-triazole.] *Anal.* Calcd for $C_2H_6N_6·2HCl$: C, 12.84; H, 4.31; N, 44.94. Found: C, 12.95; H, 4.33; N, 44.76.

7-amino-7H-s-triazolo[5,1-c]-s-triazole-3-thiol[13] **(25).** A solution of 4-amino-3-hydrazino-s-triazole dihydrochloride (5.5 g) and potassium hydroxide (5.4 g) in 70% aqueous ethanol (150 mL) was refluxed with carbon disulfide (25 mL) for 30 h. The solvent was removed and the residue was dissolved in water (25 mL). The solution was acidified (pH 3) by addition of conc. HCl. The pale yellow solid obtained was

filtered and recrystallized from water, 1.7 g; mp 165-166 °C (dec.); MS (EI) *m/e* 156 (M); IR (KBr) 3240, 3220, 3155, 3135, 3112, 3010, 2940, 2911, 2860, 2810, 2750, 1636, 1607, 1493, 1430, 1387, 1330, 1275, 1240, 1215, 1155, 1075, 1030, 997 cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 13.6 (s, 1, SH), 8.7 (s, 1, CH), 6.3-6.1 (br s, 2, NH_2); ^{13}C NMR (Me_2SO-d_6): δ 155.5 (C-3), 151.0 (C-6), 148.9 (C-8). *Anal.* Calcd for $C_3H_4N_6S$: C, 23.07; H, 2.58; N, 53.82. Found: C, 23.11; H, 2.69; N, 53.37.

6-Purinecarboxylic acid[18] (26a). To 2.5 g (0.017 mol) of 6-cyanopurine was added 16.7 mL of 2 N sodium hydroxide, and the mixture was refluxed for 1 h. The resulting clear solution was cooled and acidified to pH 2 with concentrated hydrochloric acid. The precipitate was filtered off, washed with water, and dried *in vacuo* to give a powdery yellow solid (1.89 g); mp 193-194 °C; IR (KBr) 3400, 2800, 1721, 1481, 1433, 1392, 1301, 1230, 1205, 1169, 928, 758 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 13.42 (br s, 1, 6-H), 9.11 (s, 1, 2-H), 8.80 (s, 1, 8-H). *Anal.* Calcd for $C_6H_4N_4O_2$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.23; H, 3.33; N, 30.47.

Purine-6-thiocarboxamide[18] (26b). Hydrogen sulfide was passed through a solution of 1.75 g (0.012 mol) of 6-cyanopurine in approximately 40 mL ethanolic ammonia (temperature kept at 0 °C) for 4 h and was left stirring at room temperature overnight. The mixture was evaporated to dryness yielding 1.6 g of a powdery yellow solid; mp 300 °C; IR (KBr) 3353, 3260, 3145, 3125, 3114, 3082, 3064, 3059, 1600, 1398 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.74 (br s, 1, NH), 10.35 (d, 1, NH_2), 9.03 (s, 1, 8-H), 8.74 (s, 1, 4-H); MS (EI) *m/e* 179 (M). *Anal.* Calcd for $C_6H_5N_5S$: C, 40.21; H, 2.81; N, 39.08. Found: C, 40.01; H, 3.14; N, 38.95.

4-Cyanomethyl-2-chloroimidazole-5-carboxamide[19,20] (31). Methyl 4-cyanomethyl-2-chloroimidazole-5-carboxylate (7.0 g, 0.035 mol) was slowly added to liquid ammonia in a cooled (-78 °C) glass liner of a stainless steel bomb. The bomb was sealed, allowed to slowly warm to room temperature, and heated at 110 °C for 21 days. Then, the bomb was cooled to room temperature and the ammonia was slowly removed by evaporation at atmospheric pressure followed by vacuum. The resulting brown solid was then Soxhlet-extracted with ether, giving 3.3 g of an insoluble light brown solid (found to be starting material) and 7.1 g of a light yellow solid (from the ether extract), which was the desired product; mp 233-235 °C; MS (EI) 199 (M), 201 (M + 2); ^1H NMR ($CDCl_3$) δ 13.56 (br s, 1, -N<u>H</u>-), 7.42 (br s, 2 H, -N<u>H</u>$_2$), 4.28 (s, 3 H, -C<u>H</u>$_2$CN); IR (KBr) 3393, 3207, 2267, 1669, 1600, 1500, 1425, 1408, 1379, 1250, 625 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + HCl) δ 162.2 (C=O), 129.9 (C-2), 129.1 (C-4), 128.5 (C-5), 117.1 (CN), 14.7 ($-CH_2$). *Anal.* Calcd for $C_6H_5ClN_4O$: C, 39.03; H, 2.73; N, 30.37. Found: C, 39.12; H, 2.92; N, 30.18.

Methyl 4(5)-Cyanomethyl-2-methylthioimidazole-5(4)-carboxylate[19,20] **(32).** Methyl 4(5)-carboximidomethyl-2-methylthioimidazole-5(4)-carboxylate (6.4 g, 0.028 mol) was added to 125 mL freshly distilled phosphorus oxychloride. The mixture was refluxed for 3 h before it was cooled to room temperature and then evaporated to dryness, under vacuum. After most of the $POCl_3$ had been removed, the reaction flask was cooled in a dry ice/acetone bath at -78 °C. Water/ice (300 mL) was slowly added with swirling, and then the reaction mixture was allowed to warm to room temperature. The pH was adjusted to 7-8 with slow addition of NH_4OH, and then the mixture was extracted with ether (~1 L), dried and evaporated. A dark blue solid was obtained (6.3 g) which was chromatographed (in 10:1 $CHCl_3$/MeOH, silica gel) to give 1.53 g of the desired product as a light yellow solid; mp 117-118 °C. An additional 2.1 g of this material was later obtained from a second chromatographic effort with a 1:1 ethyl acetate/pet. ether solvent system. MS (EI) 211 (M); ^{1}H NMR (Me_2SO-d_6) δ 4.22 (s, 2, -C$\underline{H}_2$CN), 3.82 (s, 3-OC$\underline{H}_3$), 2.60 (s, 3, -SC$\underline{H}_3$); IR (KBr) 3255, 2266, 1712, 1593, 1488, 1439, 1431, 1357, 1308, 1251, 1098; ^{13}C NMR (Me_2SO-d_6 + HCl) δ 159.3 (C=O), 146.1 (C-2), 135.1 (C-5), 121.6 (C-4), 116.8 (C≡N), 51.8 (-OCH_3), 15.9 (-CH_2), 14.5 (-SCH_3). *Anal.* Calcd for $C_8H_9N_3O_2S$: C, 45.50; H, 4.29; N, 19.89. Found: C, 45.50; H, 4.36; N, 19.66.

4-Cyanomethyl-2-methylthioimidazole-5(4)-carboxamide[19,20] **(33).** Methyl 4-cyanomethyl-2-methylthioimidazole-5(4)-carboxylate (3.4 g, 0.16 mol) was slowly added to a cooled (-78 °C) glass liner for a bomb, filled with 50 mL liquid ammonia. The bomb was capped, sealed, and allowed to slowly warm to room temperature before significant heat was applied to heat the bomb to 110 °C. After 21 days, the bomb was cooled to room temperature, the ammonia allowed to slowly evaporate, and the residual dark brown goo kept under vacuum for ~2 h. Column chromatography with silica gel and a 10:1 $CHCl_3$/MeOH solvent system gave a brown solid which was recrystallized from ethyl acetate to give the desired product as a lighter brown solid 1.59 g; mp 146-147 °C). MS (EI) 196 (M); ^{1}H NMR (Me_2SO-d_6) δ 17.76 (br s, 1, -N$\underline{H}$-), 7.30 (br s, 2, -N$\underline{H}_2$), 4.22 (s, 2, -C$\underline{H}_2$CN), 2.60 (s, 3, -SCH_3); IR (KBr) 3200, 1654, 1603, 1492, 1396, 2260 (CN) cm^{-1}. *Anal.* Calcd for $C_7H_8N_4OS$: C, 42.85; H, 4.11; N, 28.55. Found: C, 42.74; H, 4.33; N, 28.29.

Ethyl 5-Methylpyrazole-3-carboxylate[21] **(34a).** (Following the molar proportions of the reference, but using hydrazine hydrate instead of hydrazine sulfate and NaOH.) Ethyl 2,4-dioxovalerate (20 g, 0.127 mol) was added to 100 mL water. The solution was cooled in an ice-water bath while hydrazine monohydrate (6.54 g, 0.108 mol) was slowly added with stirring. After the hydrazine addition was complete, stirring was continued and the solution was allowed to come to room temperature.

After about 45 min, a light yellow solid began precipitating. Stirring at room temperature was continued for another 3.25 h before the solid was filtered (14.9 g). The solid was added to 40 mL ether, heated, and stirred. Insoluble solid was filtered. The ether solution was concentrated to about 250 mL before pet. ether was added until the solution became cloudy. Cooling overnight yielded the desired product, a white solid. Further concentration of the mother liquor solution followed by pet. ether addition yielded more of this solid (final yield 9.4 g, mp 63-64 °C); MS (EI) 154 (M); ^{1}H NMR ($\underline{d_6}$-acetone) δ 6.53 (s, 1, vinyl $\underline{H}$), 4.28 (q, $\underline{J}$ = 7.5 Hz, 2, $CH_3\underline{CH_2}O$), 2.30 (s, 3, CH_3-), 1.30 (t, $\underline{J}$ = 7.75 Hz, 3 H, -$\underline{CH_2}CH_3$); IR (KBr) 3224, 1722, 1420, 1227, 1175, 1097, 1029, 995, 781 cm^{-1}; ^{13}C NMR (Me_2SO-$\underline{d_6}$, mixture of tautomers) δ 162.3 (C=O), 143.3 (C-5), 139.7 (C-3), 106.4 (C-4), 60.0 (-O$\underline{CH_2}CH_3$), 14.2 (-OCH$_2\underline{CH_3}$), 10.2 (C-1'). *Anal.* Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.53; N, 18.17. Found: C, 54.31; H, 6.88; N, 17.84.

Ethyl 4-Bromo-5-methylpyrazole-3-carboxylate (34b). 5-Methyl pyrazole-3-carboxylic acid, ethyl ester (1.54 g, 0.01 mol) was dissolved in 60 mL of glacial acetic acid. The solution was cooled in an ice water bath before bromine (1.6 g, 0.01 mol) was slowly added with stirring. The solution was stirred at 0 °C for 1 h. A white solid formed which partially dissolved while the reaction mixture was allowed to warm to room temperature. The solution was poured over 200 mL ice water. Sodium bicarbonate was slowly added to the solution until all of the acetic acid had been neutralized. The mixture was then extracted with 300 mL ether. The ether was dried and evaporated to a light yellow solid. Since the odor of HOAc persisted, even after 24 h under vacuum, the solid material was again added to a $NaHCO_3$ solution and extracted with ether. Drying and concentration gave a 1.4 g of the desired product as a light yellow solid (mp 80-81 °C). MS (EI) 232, 234 (M, M + 2); ^{1}H NMR (Me_2SO-$\underline{d_6}$) δ 11.2 (br s, 1, NH), 4.36 (q, $\underline{J}$ = 7 Hz, 2, -O$\underline{CH_2}CH_3$), 2.30 (s, 3, -CH_3), 1.35 (t, $\underline{J}$ = 7 Hz, 3, -OCH$_2\underline{CH_3}$); IR (KBr) 3180, 3080, 2972, 2952, 2857, 1731, 1451, 1267, 1175, 1086 cm^{-1}. ^{13}C NMR (Me_2SO + CF_3COOD) δ 160.1 (C=O), 141.8 (C-5), 137.3 (C-3), 95.0 (C-4), 60.3 (-OCH_2), 14.1 (-OCH$_2\underline{CH_3}$), 10.1 (C-1'). *Anal.* Calcd for $C_7H_9N_2O_2Br$: C, 36.07; H, 3.89; N, 12.04. Found: C, 36.15; H, 4.14; N, 12.08.

Ethyl 5-Methyl-4-chloropyrazole-3-carboxylate (34c). Ethyl 5-methylpyrazole-3-carboxylate (3.4 g, 0.022 mol) was dissolved in glacial acetic acid (25 mL) at room temperature. Chlorine (scrubbed with conc. H_2SO_4) was bubbled through the glacial acetic solution. After 1 h, a white solid precipitated. Stirring was continued until the solid had gone back into solution, and the whole was stirred for a total of about 4 h. The reaction mixture was poured over ~200 mL of ice and water and

neutralized with aqueous bicarbonate solution. The resulting off-white solid was filtered, dried, and recrystallized from ether. Chromatography with silica gel and $CHCl_3$ gave 0.8 g of pure compound as well as some slightly impure product (~1.1 g), mp 95-6 °C; MS (EI) 188 (M); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) 13.85, 13.58 (s, 1, NH), 4.29 (q, J = 7.2 Hz, 12, -OCH_2), 2.23 (s, 3 H, -CH_3), 1.30 (t, J = 7 Hz, 3 H, -OCH_2CH_3). IR (KBr) 3092, 2981, 2961, 2932, 2866, 1733, 1458, 1266, 1176, 1107 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 160.0 (C=O), 140.1 (C-5), 135.7 (C-3), 109.6 (C-4), 60.4 (-OCH_2), 14.1 (-OCH_2CH_3), 9.2 (C-11).

Ethyl 5-(p-Fluorophenyl)pyrazole-3-carboxylate (34d). Ethyl 4-(p-fluorophenyl)-2,4-dioxobutyrate (13 g, 0.055 mol) was added to 50 mL water and hydrazine monohydrate (2.7 g, 0.054 mol) was slowly added with stirring. After 30 min at room temperature, the solution was heated to 50-60 °C for 3 h, and then kept at room temperature overnight. The solid was then filtered, dried, and added to 600 mL MeOH. The insoluble solid was removed, and the methanol solution was concentrated to 20% original volume. The resulting light yellow solid (4.2 g) was isolated by filtration and was found to be the desired product. Another 6.1 g of the desired product was obtained by further concentration etc., of the methanolic solution (yield 16.3 g, mp 145-146 °C). MS (EI) 234 (M); ^{1}H NMR (d_6 acetone) δ 7.03-8.05 (m, 5, and pyrazole arom. protons), 4.33 (q, J = 7 Hz, 2, -OCH_2CH_3), 2.82 (br s, 1, NH), 1.36 (t, J = 7 Hz, 3 H, -OCH_2CH_3); IR (KBr) 3135, 1726, 1509, 1276, 1246, 1190, 1166, 995, 841, 779 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 163.7 (C=O or C-4'), 160.4, 160.5 (C=O or C-4'), 146.5 (C-5), 139.6 (C-3), 127.4, 127.5 (C-2'), 127.3 (C-1'), 115.6, 115.9 (C-3'), 105.2 (C-4), 60.5 (-OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{11}N_2O_2$: C, 61.53; H, 4.73; N, 11.96. Found: C, 61.51; H, 5.05; N, 12.00.

Ethyl 5-(p-Fluorophenyl)-4-bromopyrazole-3-carboxylate (34e). Ethyl 5-(p-fluorophenyl)pyrazole carboxylate (2.34 g, 0.1 mol) was added to 60 mL glacial acetic acid. Bromine (1.6 g, 0.1 mol) was then added, and the reaction mixture was stirred for 4 h. The acetic acid was removed under vacuum before water was added. Aqueous sodium bicarbonate was added until the solution was neutral. Ether extraction, drying, and partial solvent evaporation yielded two crops of solids (the first white and the second a light orange). Neither of these were pure by MS, and therefore they were combined with the mother liquor and the whole chromatographed (silica gel, $CHCl_3$:MeOH 9.5:1) giving 1.5 g of a white solid, mp 176-8 °C; MS (EI) 312 (M); ^{1}H NMR (Me_2SO-d_6) δ 14.35 (s, 1, NH), 7.80 (m, 2, Ph-H), 7.36 (m, 2, Ph-H), 4.34 (q, J = 7 Hz, 2, -OCH_2CH_3), 1.34 (t, J = 7 Hz, 3, -OCH_2CH_3); IR (KBr) 2989, 1735, 1505, 1413, 1235, 1191 1164, 1048, 973 cm^{-1}; ^{13}C

NMR data; (Me_2SO-d_6 + CF_3COOD) δ 164.1, 160.8 (C-4'), 159.5 (C=O), 144.7 (C-3), 136.8 (C-5), 130.1, 130.0 (C-2'), 126.0 (C-1'), 115.8, 115.5 (C-3'), 94.2 (C-4), 60.9 (-OCH_2-), 14.2 (-OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{10}N_2O_2BrF$: C, 46.03; H, 3.22; N, 8.97. Found: C, 46.39; H, 3.27; N, 9.03.

Ethyl 5-(p-Fluorophenyl)-4-chloropyrazole-3-carboxylate (34f). Ethyl-5-(p-fluorophenyl)pyrazole carboxylate (2.34 g, 0.1 mol) was dissolved in 60 mL glacial acetic acid. Chlorine gas (scrubbed with conc. H_2SO_4) was bubbled through the reaction mixture for a total of 18 h before the reaction mixture was poured over ice-water. The resulting yellow solid (~2.9 g) was recrystallized from hot ether, giving a light yellow solid which was further washed with room temperature ether. A white solid was obtained (1.6 g, mp 176-8 °C); MS (EI) 268 (M) ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.45 and 14.20 (s, 1, NH), 7.84, 7.38 (m, 4, Ph-H's), 4.36 (br s, 2, -OCH_2CH_3), 1.34 (m, 3, -OCH_2CH_3); IR (KBr) 2991, 1736, 1505, 1416, 1236, 1192, 1165, 1058, 974, 842 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 164.0, 160.8 (C-4'), 159.3 (C=O), 142.9 (C=3), 135.1 (C-5), 129.6, 129.5 (C-2'), 125.6 (C-1'), 116.0, 115.7 (C-3'), 109.1 (C-4), 60.9 (-OCH_2-CH_3), 14.2 ((-OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{10}N_2O_2ClF$: C, 53.73; H, 3.76; N, 10.44. Found: C, 53.60; H, 3.83; N, 10.30.

Ethyl 5-(p-Bromophenyl)pyrazole-3-carboxylate (34g). Ethyl 5-(p-bromophenyl)-2,4-dioxybutyrate (10.2 g, 0.034 mol) was mixed with 75 mL water. Hydrazine hydrate (1.65 g, 0.033 mol) was added slowly with stirring. The mixture was heated at 40-50 °C for 4 h and stirred at room temperature overnight. The resulting solid was vacuum filtered and added to ~400 mL MeOH. All undissolved solids were removed by filtration, and the filtrate was reduced to ~20% of the original volume. A small portion was isolated and dried, giving a solid with a broad melting point. This solid was recombined with the MeOH mother liquor and the whole was evaporated to dryness and chromatographed (silica gel, 9.5:1, $CHCl_3$:MeOH), giving 6.3 g of a light orange solid. Some of the orange solid (2.5 g) was then recrystallized from hot methanol giving 2.0 g of a light yellow solid; mp 128-9 °C; MS (EI) 294 (M); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.1, 13.98 (s, 1, -NH), 7.81, 7.64 (s, 4, Ph-H), 7.34, 7.26 (m, 3, pyr-H), 4.32 (m, 2, -OCH_2CH_3), 1.34 (t, J = 9 Hz, 3 H, -OCH_2CH_3); IR (KBr) 3294, 1696, 1444, 1303, 1277, 1028, 1012, 956, 829, 774 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 160.3 (C=O), 146.4 (C-3), 139.2 (C-5), 131.8 (C-2'), 129.9 (C-1'), 127.3 (C-3'), 121.3 (C-4'), 105.5 (C-4), 60.5 (-OCH_2-), 14.2 (-OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{11}N_2O_2Br$: C, 48.83; H, 3.76; N, 9.49. Found: C, 48.86; H, 3.93; N, 9.37.

Ethyl 5-(p-Bromophenyl)-4-bromopyrazole-3-carboxylate (34h). Ethyl 5-(p-bromophenyl)pyrazole-3-carboxylate (2.0 g, 0.0068 mol) was dissolved in 25 mL glacial acetic acid. Bromine (1.62 g, 0.01 mol) was added and the mixture was stirred for 20 h. The reaction was worked up by pouring over 40 mL ice and water. The resulting white solid was washed with aqueous sodium bicarbonate and recrystallized from EtOH, giving a total of 1.7 g of product, mp 187-9 °C; MS (EI) 372 (M); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.56, 14.28 (s, 1, NH), 7.79, 7.21 (m, 4, Ph-H), 4.35 (m, 2, $-OCH_2CH_3$), 1.33 (m, 3, $-OCH_2CH_3$); IR (KBr) 3125, 2975, 1730, 1480, 1464, 1240, 1193, 1046, 1008, 968, 962, 841 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) 159.3 (C=O), 144.7 (C-3), 136.5 (C-5), 131.6 (C-2'), 129.6 (C-3'), 128.8 (C-1'), 122.3 (C-4'), 92.4 (C-4), 60.9 ($-OCH_2-$), 14.1 ($-OCH_2CH_3$). *Anal.* Calcd for $C_{12}H_{10}N_2O_2Br_2$: C, 38.53; H, 2.69; N, 7.49. Found: C, 38.90; H, 2.85; N, 7.44.

Ethyl 5-(p-Chlorophenyl)pyrazole-3-carboxylate (34l). Ethyl 5-(p-chlorophenyl)-2,4-dioxobutyrate (13.9 g, 0.055 mol) was mixed with water (75 mL). Hydrazine monohydrate (2.7 g, 0.054 mol) was then slowly added with stirring. After overnight stirring at room temperature, the resulting yellowish solid was vacuum filtered. The solid material was added to hot ether and the whole was heated to ~40 °C. The solution was cooled, the ether-insoluble material was filtered, and the ether solution was then evaporated to dryness giving 4.2 g of a orange-colored solid. Since an NMR of the crude product showed that starting material was still present, the solids were recombined and added to water (78 mL) and hydrazine hydrate (~2.0 g). The reaction mixture was then heated at 40-50 °C for 4 h, cooled, and filtered giving a light orange solid. The solid was added to hot MeOH (600 mL). MeOH-insoluble was filtered off and the MeOH was concentrated to ~20% volume giving 8.5 g of a yellowish solid. Because this material had an unacceptably broad melting point (138-146 °C), it was filtered through silica gel with $CHCl_3$ giving light yellowish-brown flakes (6.9 g, mp 148-50 °C). A smaller fraction (2.5 g) was then chromatographed (silica gel, $CHCl_3$:MeOH, 9.5:1) giving 1.6 g of an off-white solid which melted in two stages (128-30 °C partially and 146-8 °C). Re-melting the melted material occurred only at the higher 146-8 °C range. MS (EI) 250, 252 (M, M + 2); ^{1}H NMR (Me_2SO-d_6) δ 14.06 (s, 1, NH), 7.89 (m, 2, Ph-H's), 7.51 (m, 2, Ph-H's), 7.30 (s, 1, pyr-H), 4.34 (q, 2, $-OCH_2CH_3$, 1.34 (t, 3, $-OCH_2CH_3$); IR (KBr) 3294, 1697, 1444, 1303, 1285, 1278, 1093, 1016, 956, 832 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 160.3 (C=O), 146.4 (C-3), 139.3 (C-5), 132.8 (C-4'), 129.6 (C-1'), 128.8 (C-3'), 127.0 (C-2'), 105.5 (C-4), 60.5 ($-OCH_2-$), 14.2 ($-OCH_2CH_3$). *Anal.* Calcd for $C_{12}H_{11}N_2O_2Cl$): C, 57.49; H, 4.42; N, 11.17. Found: C, 57.45; H, 4.71; N, 11.35.

Ethyl 5-(p-Chlorophenyl)-4-bromopyrazole-3-carboxylate (34j). Ethyl 5-(p-chlorophenyl)pyrazole carboxylate (1.9 g, 0.0076 mol) was dissolved in 25 mL glacial acetic acid. Bromine (1.3 g, 0.008 mol) was then added and the reaction mixture was stirred for 2 days. The mixture was then added to 400 mL ice and water and was neutralized with $NaHCO_3$ (added slowly). Ether extraction, drying, and solvent evaporation followed by recrystallization from ether gave a white solid; 1.6 g; mp 195-7 °C; MS (EI) 268 (M); ^{1}H NMR (Me_2SO-d_6) δ 14.42 (s, 1, NH), 7.30 (d, J = 8 Hz, 2, Ph-H), 7.60 (d, J = 8 Hz, 2, Ph-H), 4.35 (q, J = 7 Hz, 2, -OCH_2CH_3); IR (KBr) 2985, 2922, 1735, 1492, 1237, 1192, 1095, 1048, 973, 837 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 159.4 (C=O), 144.5 (C-3'), 136 (C-5'), 133.8 (C-4'), 129.4 (C-2'), 128.7 (C-3'), 128.5 (C-1'), 94.5 (C-4), 60.9 (-OCH_2-), 14.1 (-OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{10}N_2O_2BrCl$: C, 43.73; H, 3.06; N, 8.50. Found: C, 43.88; H, 3.15; N, 8.60.

Ethyl 5-(p-Chlorophenyl)-4-chloropyrazole-3-carboxylate (34k). Ethyl 5-(p-chlorophenyl)pyrazole-3-carboxylate (2.1 g, 0.084 mol) was dissolved in glacial acetic acid (~25 mL). Chlorine (scrubbed through conc. H_2SO_4) was slowly bubbled through the HOAc solution with stirring for three days. The reaction mixture was poured over 400 mL ice-water, stirred, and neutralized with the slow addition of $NaHCO_3$. Ether extraction gave a crude product which was chromatographed (silica gel, ether:petroleum ether, 2:3) to give 1.5 g of a white solid; mp 194-195 °C; MS (EI) *m/e* 284 (M); ^{1}H NMR (Me_2SO-d_6, tautomeric mixture) δ 14.52, 14.38 (s, 1, NH), 7.39, 7.30 (m, 2, Ph-H), 7.66, 7.58 (m, 2, Ph-H), 4.38 (m, 2, -OCH_2CH_3), 1.36 (m, 3, -OCH_2CH_3); IR (KBr) 3175, 2987, 1736, 1486, 1413, 1239, 1193, 1096, 1058, 973, 964, 836 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 159.1 (C=O), 142.9 (C-5), 134.9 (C-3), 133.7 (C-4'), 128.9 (C-2',3'), 128.2 (C-1'), 109.5 (C-4), 60.9 (-OCH_2), 14.2 (-CH_2CH_3). *Anal.* Calcd for $C_{12}H_{10}N_2O_2Cl_2$: C, 50.55; H, 3.54; N, 9.82. Found: C, 50.17; N, 3.64; N, 9.79.

Ethyl 5-Phenylpyrazole-3-carboxylate (34l). Ethyl 5-phenyl-2,4-dioxobutyrate (10.7 g, 0.049 mol) was mixed with 100 mL water. Hydrazine hydrate (2.45 g, 0.049 mol) was slowly added with stirring, and the mixture was stirred overnight at room temperature. The resulting yellow powdery precipitate was filtered, dried, dissolved in ether, extracted with water, dried, and evaporated to dryness giving 9.7 g crude product. TLC in silica gel (9.5:1, $CHCl_3$:MeOH) showed one main component. Recrystallization of 2.5 g crude product gave 2.0 g of a white solid; mp 129-130 °C; MS (EI) *m/e* 216 (M); ^{1}H NMR (Me_2SO-d_6) δ 13.99 (s, 1, NH), 7.87 (m, 2, Ph-H), 7.48 (m, 2, Ph-H), 7.39 (m, 1, Ph-H), 7.26 (s, 1, 4-H), 4.32 (q, J_{AB} = 6.6 Hz, 2,-OCH_2CH_3), 1.34 (t, J = 6.6 Hz, 3, -OCH_2CH_3); IR (KBr) 1725, 1419, 1277, 1240, 1192, 1138, 1023, 1000, 760 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + 1 drop TFA) δ 160.9 (C=O),

146.9 (C-5), 140.2 (C-3), 130.5 (C-1'), 129.0 (C-3'), 128.3 (C-4'), 125.4 (C-2'), 105.2 (C-4), 60.5 (-$CH_2\underline{C}H_3$). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.57; H, 5.77; N, 13.14.

Ethyl 5-Phenyl-4-bromopyrazole-3-carboxylate (34m). Ethyl 5-phenylpyrazole-3-carboxylate (2.0 g, 0.0093 mol) was dissolved in glacial acetic acid (50 mL). Bromine (1.48 g, 0.0093 mol) was added, and the reaction mixture was stirred for 40 h at room temperature. It was then poured over 158 mL of ice and water. The resulting white gummy solid was filtered, washed with 500 mL aqueous $NaHCO_3$, and again filtered to dryness. The crude white solid was then chromatographed (silica gel, ether:petroleum ether, 2:3) and recrystallized from ether giving 1.2 g white solid; mp 129-131 °C; MS (EI) *m/e* 295 (M); ^{1}H NMR (Me_2SO-$\underline{d}_6$, mixture of tautomers) δ 14.48, 14.25 (s, 1, NH), 7.76 (m, 2, Ph-$\underline{H}$), 7.20 (m, 3, Ph-$\underline{H}$), 4.34 (m, 2, -O$\underline{C}H_2CH_3$), 1.35 (t, $\underline{J}$ = 7 Hz, 3, -$OCH_2\underline{C}H_3$); IR (KBr) 2973, 2929, 1736, 1457, 1236, 1193, 1051, 972, 764, 688 cm^{-1}; ^{13}C NMR (Me_2SO-$\underline{d}_6$ + 1 drop TFA) δ 159.8 (C=O), 145.0 (C-5), 137.4 (C-3), 129.4 (C-1'), 128.9 (C-4'), 128.7 (C-3'), 127.8 (C-2'), 94.1 (C-4), 60.8 (-O$\underline{C}H_2$), 14.2 ($OCH_2\underline{C}H_3$). *Anal.* Calcd for $C_{12}H_{11}N_2O_2Br$: C, 48.93; H, 3.76; N, 9.49. Found: C, 48.68; H, 3.97; N, 9.73.

Ethyl 5-Phenyl-4-chloropyrazole-3-carboxylate (34n). Ethyl 5-phenylpyrazole-3-carboxylate (1.4 g, 0.0064 mol) was dissolved in glacial acetic acid (50 mL). Chlorine (scrubbed with conc. H_2SO_4) was bubbled through the solution, and the reaction mixture was stirred for 2 h at room temperature. It was then poured over ~400 mL ice-water, the solution was neutralized with $NaHCO_3$, and the resulting light yellow flaky solid was filtered and dried. The solid was then dissolved in ether and insoluble material was removed by filtration. The ether solution was evaporated to dryness and the resulting gummy solid was chromatographed (silica gel, ether:petroleum ether, 2:3) giving 0.8 g of a fluffy white solid; mp 115-116 °C; MS (EI) *m/e* 250 (M); ^{1}H NMR (Me_2SO-$\underline{d}_6$, mixture of tautomers) δ 14.44, 14.20 (s, 1, NH), 7.80, 7.50 (m, 5, Ph-$\underline{H}$), 4.35 (m, 2, -O$\underline{C}H_2CH_3$), 1.33 (m, 3, -$OCH_2\underline{C}H_3$); IR (KBr, cm^{-1}) 3250, 2985, 1723, 1709, 1276, 1181, 1162, 1055, 843, 771, 691, 685; ^{13}C NMR (Me_2SO-$\underline{d}_6$ + 1 drop TFA) δ 159.8 (C=O), 143.6 (C-5), 135.9 (C-3), 129.2 (C-1'), 129.1 (C-4'), 129.0 (C-3'), 127.5 (C-2'), 61.0 (C-4), 39.5 (-O$\underline{C}H_2$), 14.2 (-$CH_2\underline{C}H_3$). *Anal.* Calcd for $C_{12}H_{18}N_2O_2Cl$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.45; H, 4.64; N, 11.44.

Ethyl 5-(p-Tolyl)pyrazole-3-carboxylate (34o). Ethyl 5-(p-tolyl)-2,4-dioxobutyrate (13.9 g, 0.059 mol) was mixed with ~100 mL water. Hydrazine hydrate (3.0 g, 0.059 mol) was slowly added with stirring, and then the mixture was stirred overnight at room temperature. The resulting light yellow powdery precipitate was

filtered and dried, giving 10.4 g of crude product. TLC in silica gel (ether:petroleum ether, 2:2) showed only a slight amount of impurities present. The solid (2.2 g) was chromatographed with silica gel (ether:petroleum ether, 2:3) giving 2.1 g of the desired product as a white solid; mp 144-145 °C; MS (EI) *m/e* 230 (M); ^{1}H NMR (Me_2SO-d_6) δ 13.91 (s, 1, NH), 7.76 (m, 2, Ph-H), 7.28 (m, 2, Ph-H), 7.20 (s, 1, 4-H), 4.32 (q, J = 8.4 Hz, 2, OCH_2CH_3), 2.36 (s, 3, Ph-CH_3), 1.44 (t, J = 8.4 Hz, 3, -OCH_2CH_3); IR (KBr) 3140, 1724, 1487, 1413, 1272, 1242, 1131, 994, 986, 817, 783 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + 1 drop TFA) δ 160.9 (C=O), 146.5 (C-5), 140.5 (C-3), 137.7 (C-4'), 129.5 (C-3'), 127.4 (C-1'), 125.3 (C-2'), 104.7 (C-4), 60.4 (-OCH_2), 20.8 (Ph-CH_3), 14.2 (-CH_2CH_3). *Anal.* Calcd for $C_{15}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.50; H, 6.14; N, 12.38.

Ethyl 5-(p-Nitrophenyl)pyrazole-3-carboxylate (34q). Ethyl 5-(p-nitrophenyl)-2,4-dioxobutyrate (10.6 g, 0.04 mol) was mixed with 200 mL H_2O. Hydrazine hydrate (2 g, 0.04 mol) was slowly added with stirring, and the mixture was stirred overnight at room temperature. The resulting yellow powdery solid was filtered and dried giving 7.2 g crude product. Chromatography (silica gel, ether:petroleum ether, 1:2) of 4 g yielded 2.6 g of pure product; mp 210-212 °C; MS (EI) *m/e* 261 (M); ^{1}H NMR (Me_2SO-d_6) δ 14.35 (s, 1, NH), 8.31 (d, J = 8.4 Hz, 2, Ph-H), 8.16 (d, J = 8.4 Hz, 2, Ph-H), 7.52 (s, 1, 4-H), 4.34 (q, J = 7 Hz, 2, -OCH_2CH_3), 1.35 (t, J = 7 Hz, 3, -OCH_2CH_3); IR (KBr) 3180, 1735, 1722, 1607, 1523, 1514, 1338, 1286, 1258, 1203, 1154, 854, 755 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 159.8 (C=O), 158.7 (C-4'), 146.8 (C-5), 138.3 (C-3), 137.7 (C-1'), 126.2 (C-2'), 124.1 (C-3'), 107.0 (C-4), 60.9 (-OCH_2), 14.2 (-CH_2CH_3). *Anal.* Calcd for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09. Found: C, 54.99; H, 4.36; N, 16.36.

Ethyl 5-(p-Nitrophenyl)-4-bromopyrazole-3-carboxylate (34r). Ethyl 5-(p-nitrophenyl)pyrazole-3-carboxylate (2.1 g, 0.008 mol) was dissolved in glacial acetic acid (25 mL). Bromine (1.27 g, 0.007 mol) was added to the solution, and the mixture was stirred overnight at room temperature. An aliquot of the reaction mixture was then poured over ice and water and the resulting solid was filtered and dried. An additional 0.001 mol of bromine was added and the mixture was stirred over a second night. The reaction mixture was poured over ice and water (~400 mL), and the resulting slurry was neutralized with sodium bicarbonate. The slurry was filtered giving a light brown solid which was added to another ~300 mL H_2O and refiltered giving a white solid (1.9 g); mp 173-4 °C; MS (EI) *m/e* 339 (M); ^{1}H NMR (Me_2SO-d_6) δ 14.70 (s, 1, NH), 8.36 (d, J = ~9 Hz, 2, Ph-H), 8.10 (d, J = ~9 Hz, 2, Ph-H), 4.36 (q, J = ~6 Hz, 2, -OCH_2CH_3), 1.46 (t, J = ~8.5 Hz, 3, -OCH_2CH_3); IR (KBr) 33.6, 3110, 1734, 1689, 1603, 1517, 1347, 1236, 1215, 1044, 958, 855 cm^{-1};

^{13}C NMR (Me_2SO-d_6) δ 159.4 (C=O), 147.9 (C-4'), 145.6 (C-5), 137.4 (C-1'), 136.1 (C-3), 129.0 (C-2'), 124.2 (C-3'), 96.1 (C-4'), 61.7 (-CH_2), 14.3 (-CH_3). *Anal.* Calcd for $C_{12}H_{10}N_3O_4Br$: C, 42.37; H, 2.96; N, 12.35. Found: C, 41.95; H, 3.06; N, 12.66.

Ethyl 4-(p-nitrophenyl)-4-chloropyrazole-3-carboxylate (34s). Ethyl 5-(p-nitrophenyl)pyrazole-3-carboxylate (2.3 g, 0.0088 mol) was dissolved in glacial acetic acid. Chlorine gas, scrubbed through H_2SO_4, was bubbled through the median mixture overnight. The mixture was then poured over ice, giving a light yellow solid. Sodium bicarbonate was slowly added until no more solid appeared to be precipitating from the solution. The solid was filtered, dried, chromatographed, (silica gel, ether:pet:ether, 2:3), and recrystallized, giving 1.7 g of a pure white solid (as well as a second crystal fraction consisting of 0.2 g of a slightly impure product); mp 177-8 °C), MS (EI) 295 (M); ^1H NMR (Me_2SO-d_6) + 1 drop CH_3COOD) δ 14.36 (s, 1, NH), 8.36 (m, 2, Ph-H), 8.15 (m, 2, Ph-H), 4.40 (q, J = 7.5 Hz, 2,-OCH_2CH_3), 1.36 (m, 3, -OCH_2CH_3); IR (KBr) 3355, 1751, 1698, 1517, 1389, 1348, 1296, 1262, 1225, 830 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + 1 drop CF_3COOD) δ 158.7 (C=O), 147.4 (C-4'), 143.2 (C-5), 136.3 (C-1'), 134.2 (C-2'), 128.2 (C-2'), 124.1 (C-3'), 110.9 (C-4), 61.3 (-CH_2), 14.2 (-CH_3). *Anal.* Calcd for $C_{12}H_{10}ClN_3O_4$: C, 48.75; H, 3.51; N, 14.21. Found: C, 48.90; H, 3.54; N, 14.09.

Ethyl 5-(p-methoxyphenyl)pyrazole-3-carboxylate (34t). Ethyl 4-(p-methoxyphenyl)-2,4-dioxobutyrate (10.0 g, 0.04 mol) was mixed with 75 mL water. Hydrazine hydrate (2 g, 0.04 mol) was slowly added, and the mixture was stirred overnight at room temperature. The resulting yellow solid was filtered and washed with water. Four grams of the crude product was chromatographed (silica gel, ether:pet ether, 2:3) giving 3.1 g pure product as an off white solid; mp 142-3 °C; MS (EI) 246 (M); ^1H NMR (Me_2SO-d_6, mixture of tautomers) δ 13.84 (s, 1, NH), 7.77 (m, z, Ph-H), 7.14 (s, 1, pyraz-H), 7.02 (m, 2, Ph-H), 4.30 (m, 2, - OCH_2CH_3), 3.80 (s, 3, -OCH_3), 1.32 (t, J = ~7.8 Hz, 3), -OCH_2CH_3); IR (KBr) 3284, 3196, 1705, 1452, 1443, 1269, 1247, 1175, 1026, 956, 826 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + CF_3COOD), δ 161.4 (C=O), 160.0 (C-4'), 146.8 (C-5), 140.9 (C-3), 127.2 (C-2'), 123.3 (C-1'), 114.7 (C-3'), 104.6 (C-4), 60.7 (CH_2), 55.3 (-OCH_3), 14.4 (-CH_2CH_3); *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.40; H, 5.91; N, 11.46.

Ethyl 5-(p-methoxyphenyl)-4-bromopyrazole-3-carboxylate (34u). Ethyl 5-(p-methoxyphenyl)pyrazole-3-carboxylate (2.0 g, 0.0087 mol) was dissolved in 50 mL glacial acetic acid. Bromine (1.39 g, 0.0087 mol) was added and the whole stirred for 2 h. The reaction mixture was poured over ice water and neutralized with sodium bicarbonate. The resulting white solid was filtered and recrystallized from ethanol, giving fine white needles (1.5 g); mp 148-9 °C; MS (EI) 324 (M); ^1H NMR

(Me_2SO-$\underline{d}_6$) δ 14.16 (br s, 1, NH); 7.70 (m, 2, Ph-H); 7.09 (m, 2, Ph-H); 4.34 (q, J = ~7.2 Hz, 2, -OC$\underline{H}_2CH_3$); 3.82 (s, 3, -OCH_3); 1,33 (t, $\underline{J}$ = ~7.2 Hz, 3, -OCH_2CH_3); 3.82 (s, 3, -OCH_3); 1.33 (t, $\underline{J}$ = ~7.2 Hz, 3, -$OCH_2C\underline{H}_3$); IR (KBr) 3109, 3067, 2971, 1720, 1611, 1511, 1420, 1277, 1257, 1197, 1180, 1045, 843, 828 cm^{-1}; ^{13}C NMR (Me_2SO-$\underline{d}_6$) δ 160.0 (C=O), 159.8 (C-4'), 144.2 (C-5), 137.7 (C-3), 129.1 (C-2'), 121.2 (C-1'), 114.1 (C-3'), 93.3 (C-4), 60.6 (-OCH_2), 55.3 (-OC$\underline{H}_3$) 14.1 (-$CH_2\underline{C}H_3$). *Anal.* Calcd for $C_{13}H_{13}BrN_2O_3$: C, 48.02; H, 4.03; N, 8.45. Found: C, 47.76; H, 4.05; N, 8.63.

Ethyl 5-(2',4'-dimethoxyphenyl)pyrazole-3-carboxylate (34v). Ethyl 4-(2',4'-dimethoxyphenyl)-2,4-dioxobutyrate (16.3 g, 0.058 mol) was added to 300 mL H_2O. Hydrazine hydrate (2.9 g, 0.058 mol) was added slowly with stirring, and the reaction mixture was stirred overnight at room temperature. The resulting yellow solid was filtered and dried giving 15.8 g crude product. Three grams of the crude product was chromatographed (silica gel, ether:pet ether, 2:3) giving 2.3 g of a yellow granular solid; mp 102-3 °C; MS (EI) 276 (M); ^1H NMR (Me_2SO-$\underline{d}_6$) mixture of tautomers, δ 13.90, 13.41 (s, 1, N$\underline{H}$); 7.85, 7.65 (m, 1, Ph-H); 7.13, 7.02 (m, s, 1, Ph-H); 6.68, 6.62 (m, 1, Ph-H); 4.29 (m, 2, -OC$\underline{H}_2CH_3$); 3.90 (s, 3, -OCH_2); 3.82 (s, 3,-OC$\underline{H}_3$); 1.31 (t, 3, -$OCH_2C\underline{H}_3$); IR (KBr) 3346, 3138, 1712, 1615, 1587, 1302, 1258, 1250, 1209, 1146, 1029, 997 cm^{-1}; ^{13}C NMR (Me_2SO-$\underline{d}_6$ + CH_3COOD) δ 161.7 (C=O), 160.9 (C-4'), 157.2 (C-2'), 141.8 (C-5), 141.4 (C-3), 128.7 (C-5'), 110.9 (C-1'), 106.5 (C-4), 105.6 (C-5'), 98.8 (C-3'), 60.2 (-OCH_2-), 55.6 (-OCH_3), 55.3 (-OCH_3), 14.3 (-$OCH_2\underline{C}H_3$). *Anal.* Calcd for $C_{14}H_{16}N_2O_4$; C, 60.86; H, 5.83; N, 10.14. Found: C, 60.77; H, 5.97; N, 10.05.

Ethyl 5-(2,'4'-dichlorophenyl)pyrazole-3-carboxylate (34w). Ethyl 4-(2',4'-dichlorophenyl)-2,4-dioxobutyrate (28.9 g, 0.035 mol) was added to ~100 mL H_2O. Hydrazine hydrate (1.73 g, 0.035 mol) was slowly added with swirling, and the reaction mixture was stirred overnight at room temperature. The resulting yellow solid (22.5 g) was filtered and dried. Although thin layer chromatography showed this crude product was essentially pure, 4 g of the crude was chromatographed (silica gel, ether:pet:ether, 2:3) giving 3.0 g of a light yellow solid; mp 127-8 °C; MS (EI) 284 (M); ^1H NMR (Me_2SO-$\underline{d}_6$) mixture of tautomers, δ 14.35, 13.96 (s, 1, NH); 7.83, 7.73, 7.54 (m, 3, Ph-H); 7.37, 7.10 (s, 1, pyraz.-H); 4.34 (m, 2,-OC$\underline{H}_2CH_3$); 1.33 (t, 3, -$OCH_2C\underline{H}_3$); IR (KBr) 1728, 1474, 1263, 1240, 1205, 1139, 1026, 1000, 802, 776 cm^{-1}; ^{13}C NMR (Me_2SO-$\underline{d}_6$ + CF_3COOD) δ 160.2 (C=O), 144.2 (C-5), 138.2 (C-3), 133.8 (C-4'), 132.2 (C-2'), 131.7 (C-6'), 129.9 (C-3'), 129.0 (C-1'), 127.7 (C-5'), 109.0 (C-4), 60.8 (-OCH_2), 14.3 (-$OCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{12}H_{10}Cl_2N_2O_2$: C, 5055; H, 3.54; N, 9.82. Found: 50.47; H, 3.69; N, 9.71.

Ethyl 5-(2',4'-dichlorophenyl)-4-bromopyrazole-3-carboxylate (34x). Ethyl 5-(2',4'-dichlorophenyl)-4-bromopyrazole-3-carboxylate (2.0 g, 0.007 mol) was dissolved in glacial acetic acid (25 mL). Bromine (1.12 g, 0.007 mol) was added to the solution, and the mixture was stirred overnight at room temperature. After work up (by pouring into ice water acid, and neutralizing with bicarbonate solution) the reaction mixture was found to still contain starting material. The solid was dissolved in glacial acetic acid again, more bromine (~1 g) was added, and the mixture was stirred at room temperature for two days. The reaction mixture was poured over ice water, and the mixture neutralized with sodium bicarbonate giving a gummy yellow solid which was isolated, dried, and filtered through ~40 g silica gel with ether giving a white powder (1.6 g); mp 119-20 °C; MS (EI) 362 (M); ^{1}H NMR (Me_2SO-d_6) mixture of tautomers, δ 14.62, 14.35 (s, 1, NH); 7.84, 7.56 (m, 3, Ph-H); 4.38 (s, 2, -OCH_2CH_3; 1.36 (m, 3, -OCH_2CH_3); IR (KBr) 3303, 1711, 1474, 1467, 1250, 1101, 1041, 966, 829, 806 cm^{-1}; ^{13}C NMR (MeSO-d_6) δ 159.3 (C=O), 144.3 (C-5), 135.8 (C-3), 135.3 (C-4'), 134.5 (C-2'), 133.7 (C-6'), 129.4 (C-3') 128.0 (C-1'), 127.6 (C-5'), 97.4 (C-4), 61.0 (-OCH_2), 14.2 (-OCH_2CH_3). *Anal.* Calcd for $C_{12}H_9BrCl_2N_2O_2$: C, 39.59; H, 2.49; N, 7.70. Found: C, 39.57; H, 2.56; N, 7.69.

Ethyl 5-(2',4'-dichlorophenyl)-4-chloropyrazole-3-carboxylate (34y). Ethyl 5-(2',4'-dichlorophenyl)pyrazole-3-carboxylate (2.1 g, 0.008 mol) was dissolved in glacial acetic acid. Chlorine gas (scrubbed with conc. sulfuric acid) was bubbled through the solution for 4 h. The reaction mixture was poured over ice water, and the resulting solution was neutralized with bicarbonate and extracted with ether. Drying and evaporation resulted in 2.4 g of a viscous, pale yellow oil which was chromatographed (silica gel, ether:pet ether, 2:3) to give 2.0 g of a colorless viscous oil. The oil was redissolved in ether, petroleum ether was added, and after sitting overnight, a white solid precipitated from the solution. The precipitate was isolated as a white granular solid (1.4 g); mp 127.8 °C; ^{1}H NMR (Me_2SO-d_6) mixture of tautomers, δ 14.62, 14.36 (s, 1, NH); 7.82-7.59 (br s, 3, Ph-H); 4.40 (m, 2,-OCH_2CH_3); 1.37 (t, 3, -OCH_2CH_3); IR (KBr) 3301, 1713, 1471, 1252, 1101, 1077, 1046, 968, 831, 805 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 159.1 (C=O), 142.5 (C-5), 135.4 (C-4'), 134.4 (C-2'), 134.1 (C-3), 133.6 (C-6'), 129.4 (C-3'), 127.6 (C-5'), 127.3 (C-1'), 111.8 (C-4), 61.0 (-OCH_2-), 14.2 (-OCH_2CH_3). *Anal.* Calcd for $C_{12}H_9Cl_3N_2O_2$: C, 45.10; J, 2.84; N, 8.77. Found: C, 45.07; H, 3.03; N, 8.79.

N,N-Dimethyl-1-adamantanecarboxamide (35a). 1-Adamantanecarboxylic acid chloride (2.0 g, 0.01 mol) was added to a solution containing approximately 20 mL benzene and 20 mL dimethylamine. The solution was heated in a hot water bath, with stirring, for 2 min. The solution was extracted with H_2O (10 mL), 5% HCl (10

mL), 5% NaOH (10 mL), and H_2O (10 mL), respectively. The benzene was evaporated to dryness to yield 1.5 g of white crystals; mp 164-167 °C; MS (EI) *m/e* 207 (M); IR (KBr) 2971, 2944, 2902, 2848, 1614, 1492, 1451, 1379, 1343, 1161 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.96 (s, 1, $-NCH_3$) 1.96 (s, 1, 1,5,7-H), 1.92 (s, 1, H-2,4,9-H) 1.66 (s, 1, H-6,8,10-H); ^{13}C NMR (Me_2SO-d_6) δ 175.2 (C-O), 40.8 (C-3), 38.3 (C-6,7,10), 38.0 (CH_3NCH_3), 36.1 (C-2,4,9), 27.9 (C-1,10). *Anal.* Calcd for $C_{13}H_{21}NO$ $0.2H_2O$: C, 74.03; H, 10.23; N, 6.64. Found: C, 74.18; H, 10.01; N, 6.24.

N-n-Butyl-1-adamantanecarboxamide (35b). 1-Adamantanecarboxylic acid chloride (1.0 g, 0.005 mol) was added to a solution containing approximately 10 mL benzene and 10 mL n-butylamine. The solution was heated in a hot water bath, with swirling, for 2 min. The solution was then extracted with H_2O (5 mL), 5% HCl (10 mL), 5% NaOH (10 mL), and again with H_2O (5 mL), respectively. The benzene was evaporated to dryness to yield 0.54 g of white crystals; mp 85-87 °C; MS (EI) *m/e* 235 (M); IR (KBr) 3314, 2927, 2916, 2901, 2891, 2871, 2849, 1632, 1557, 1283 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.86 (t, 1, CH_3), 1.24 (m, 1, CH_2CH_3), 1.36 (m, 1 H, ($CH_2CH_2CH_2$), 1.64 (s, 2, H-4,6,10), 1.72 (d, 2, H-2,8,9), 1.96 (s, 1, H-3,5,7), 3.02 (m, 1, $NHCH_2$), 7.28 (s, 1, NH); ^{13}C NMR (Me_2SO-d_6) δ 39.67 (C-1), 38.71 (C-4,6,10), 38.04 ($NHCH_2$), 36.13 (C-2,8,9), 31.28 ($CH_2CH_2CH_2$), 19.43 (CH_2CH_3), 13.66 (CH_3). *Anal.* Calcd for $C_{15}H_{25}NO$: C, 76.54; H. 10.70; N, 5.95. Found: C, 76.59; H, 10.73; N, 5.94.

1-Adamantanecarboxanilide (35c). 1-Adamantanecarboxylic acid chloride (1.5 g, 0.008 mol) was added to a solution that contained approximately 10 mL benzene and 5 mL aniline. The solution was heated in a hot water bath for two min with swirling. The solution was then extracted with H_2O (5 mL), 5% HCl (10 mL), 5% NaOH (10 mL), and again with H_2O (5 mL), respectively. The benzene was evaporated to dryness to yield 1.3 g of white crystals. To insure the removal of any acid present, the solid was dissolved in ether, and re-extracted with a saturated sodium bicarbonate solution. The ether extract was evaporated to dryness to yield 1.25 g white crystals; mp 190-192 °C; MS (EI) *m/e* 255 (M); IR (KBr) 3285, 2915, 2899, 2848, 1652, 1645, 1597, 1538, 1439, 1310, 757 cm^{-1}; ^1H NMR (Me_2SO- d_6) δ 1.70 (s, 2, H-4,6,10), 1.91 (d, 2, H-2,8,9), 2.02 (s, 1, H-3,5,7), 7.02 (t, 1, Ph-4H), 7.28 (t, 1, Ph-3,5H), 7.66 (d, 1, Ph-2,6H), 9.09 (s, 1, NH); ^{13}C NMR (Me_2SO-d_6) 175.74 (C=O), 139.23 (NHC), 128.21 (Ph=C3,5), 122.93 (Ph-C3,5), 120.08 (Ph-C2,6), 40.81 (C-1), 38.22 (C-4,9), 35.95 (C-2,8,10), 27.62 (C-3,5,7). *Anal.* Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.84; H, 8.32; N, 5.44.

N-(2-Thiazolo)-1-adamantylcarboxamide (35d). To 1-adamantanecarboxylic acid chloride (1 g, 0.005 mol) was added 2-aminothiazole (2 g, 0.02 mol) in approximately

30 mL benzene. The solution was warmed in a hot water bath for 2 min. The benzene solution was then extracted successively with 5-10 mL H_2O, 10 mL 5% HCl, 10 mL 5% NaOH, and again with 5-10 mL H_2O. The benzene was evaporated yielding a white solid which was recrystallized from hot ethanol (0.62 g), mp 198-200 °C; MS (FAB) *m/e* 263 (M + 1); IR (KBr) 3246, 2915, 2906, 2850, 1650, 1542, 1313, 1278, 1268, and 1154 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.69 (s, 1, O=C-NH), 7.48 (d, 1, J = 3.8 Hz, thiazole 4-H), 7.19 (d, 1, J = 3.8 Hz, thiazole 5-H), 2.06 (s, 3, H-3,5,7), 1.95 (s, 4, H-2,8,9), 1.70 (s, 6, H-4,6,10); ^{13}C NMR (Me_2SO-d_6) δ 176.78 (O=C-NH), 158.5 (thiazole C-2), 137.3 (thiazole C-4), 113.1 (thiazole C-5), 40.4 (C-1), 37.5 (C-2), 35.7 (C-4), 27.5 (C-3). *Anal.* Calcd for $C_{14}H_{18}N_2OS$: C, 64.09; H, 6.91; N, 10.68. Found: C, 63.97; H, 7.11; N, 10.98.

N-Methyl-1-adamantaeacetamide (36a). Thionyl chloride (0.44 mL, 0.006 mol) was added to 1 g (0.005 mol) of 1-adamantaneacetic acid and the mixture was heated gently, with stirring, for several hours. After bringing the mixture to room temperature, the aniline (5 mL, 0.05 mol) in approximately 10 mL ether was added. The solution was again heated gently over a hot water bath, cooled to room temperature, and let stir over the weekend. The mixture was extracted with H_2O (10 mL), 5% HCl (10 mL), 5% NaOH (10 mL), and again with H_2O (10 mL). The ether layer was then evaporated to dryness to yield 1.0 g of white crystals, mp 113-116 °C; MS (EI) *m/e* 207 (M); IR (KBr) 3272, 2926, 2901, 2847, 1653, 1636, 1562, 1451, 1409, 1339 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.57 (br s, 1, NH), 2.54 (d, 3, J = 6 Hz, CH_3), 1.91 (br s, 2, H-3,5,7), 1.81 (s, 1, CH_2), 1.59 (m, 12, H-1,2,4,6,8,9,10); ^{13}C NMR (Me_2SO-d_6) δ 170.1 (C=O), 50.0 (CH_2), 42.1 (C-2,8,9), 36.4 (C-4,6,10), 32.1 (C-1), 28.0 (C-3,5,7), 25.3 (CH_3). *Anal.* Calcd for $C_{13}H_{21}NO \cdot 0.5H_2O$: C, 72.18; H, 10.25; N, 6.48. Found: C, 72.15; H, 9.95; N, 6.40.

N-Methyl-1-noradamantanecarboxamide (37). Thionyl chloride (0.51 mL, 0.007 mol) was added to 3-adamantanecarboxylic acid (1.0 g) with stirring. The mixture was heated gently for approximately 2-3 hours. The mixture was let cool to room temperature, then about 0.5 mL methylamine in 10 mL ether was added slowly with stirring. The mixture was let stir overnight at room temperature. Additional ether was added and the mixture was extracted with H_2O (10 mL), 5% HCl (10 mL), 5% NaOH (10 mL), and again with H_2O (10 mL). The ether layer was then evaporated to dryness to yield 0.73 g of white crystals, mp 160-163 °C; MS (EI) *m/e* 179 (M); IR (KBr) 3335, 2929, 2867, 2849, 1631, 1630, 1540, 1461, 1406, 1311, 1293 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.42 (s, 1, NH), 2.59 (d, 2, J = 6 Hz, CH_3), 2.50 (t, 1, J = 3 Hz, 7-H), 2.22 (s, 1, H-3,5), 1.87 (dd, 1, J = 12 Hz, H-2,8), 1.68 (dd, 2, J = 6 Hz, H-6,9), 1.52 (dd, 2, J = 6 Hz, 4-H); ^{13}C NMR (Me_2SO-d_6) δ 54.2 (C-1), 46.7 (C-6,9),

43.1 (C-2,8), 42.4 (C-7), 36.9 ($\underline{C}H_3$), 34.2 (C-4), 25.9 (C-3,5). *Anal.* Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.82. Found: C, 73.65; H, 9.61; N, 7.73.

1-Adamantyl, 3-t-Butylthiourea (40). Adamantamine (1 g, 6.6 mmol) was dissolved in 15 mL hexane. Insoluble material was filtered out and then t-butyl isothiocyanate (0.84 mL, 6.6 mmol) was added. After stirring for 2 h, solvent was removed yielding 1.32 g of a white solid, mp 133-135 °C; ^{1}H NMR ($CDCl_3$) δ 5.8 (br s, 1, NH), 5.6 (br s, 1, NH), 2.15 (s, 9, CH, CH_2), 1.7 (s, 4, CH_2), 1.45 (s, 9, t-butyl); ^{13}C NMR ($CDCl_3$) δ 179.5 (s, 1, thiourea C), 54.2, 53.2 (2 s, 2, C-NH), 42.2 (s, 3, adamantyl C), 36.2 (s, 3, adamantyl C), 29.5 (s, 3, adamantyl C), 29.4 (s, 3, t-butyl $\underline{C}H_3$). IR (KBr) 3274, 2907, 1537, 1391, 1356, 1324, 1310, 1299, 1201 cm^{-1}. *Anal.* Calcd for $C_{15}H_{26}N_2S$: C, 67.64; H, 9.84; N, 10.52. Found: C, 67.67; H, 10.11; N, 10.25.

1-Adamantylthiosemicarbazide (41). 1-Adamantylisothiocyanate (11.3 g, 0.059 mol) and hydrazine (1.89 mL, 0.059 mol) were combined in THF and the reaction mixture heated at reflux for approximately 2 h. The white solid that precipitated out was filtered, washed with ether, and dried, yield 15.69 g, mp 199-200 °C. MS (EI) *m/e* 225 (M); IR (KBr) 3287, 3197, 2913, 2893, 2855, 2848, 1530, 1361, 1236, and 805 cm^{-1}; ^{1}H NMR (Me_2SO-$\underline{d}_6$) δ 8.36 (s, 1, S=C-N$\underline{H}$-NH_2 or -N$\underline{H}_2$-C=S), 7.41 (s, 1, S=C-N$\underline{H}$-NH_2 or -N$\underline{H}$-C=S), 4.50 (s, 2, S=C-NH-N$\underline{H}_2$), 2.26 (d, 3, C2,8,9-H), 2.01 (s, 2, H-3,5,7), 1.52 (s, 3, H-4,6,10); ^{13}C NMR (Me_2SO-$\underline{d}_6$) δ 179.0 (NH-$\underline{C}$=S), 51.9 (C-1), 41.3 (C-2), 35.9 (C-4), 29.0 (C-3). *Anal.* Calcd for $C_{11}H_{19}N_3S$: C, 58.63; H, 8.50; N, 18.65. Found: C, 58.95; H, 8.90; N, 18.76.

2-[1-(1-Adamantyl)ethylidene]hydrazinecarboximidamide Hydrochloride (42a). To a mixture of 1-adamantylmethyl ketone (1.78 g, 10 mmol) and aminoguanidine bicarbonate (1.36 g, 10 mmol) in 10 mL of methanol was added 1 mL concentrated HCl. After heating at reflux for 1.25 h, the reaction mixture was reduced by approximately two-thirds and then refrigerated overnight, resulting in the formation of a white solid. The solid was filtered, washed with ether, and dried; mp 210-212 °C; MS (EI) *m/e* 234 (M); IR (KBr) 3396, 3388, 3379, 3370, 3358, 2924, 2904, 1672, 1661, cm^{-1}; ^{1}H NMR (Me_2SO-$\underline{d}_6$) δ 10.86 (s, 1, -N$\underline{H}$), 7.53 (br s, 4, N$\underline{H}_2$, H$^+$), 1.99 (s, 3, H-3,5,7), 1.85 (s, 3, N=C-C$\underline{H}_3$), 1.73 (d, 3, H-2,8,9), 1.67 (m, 6, H-4,6,10); ^{13}C NMR (Me_2SO-$\underline{d}_6$) δ 162.7 (HN-$\underline{C}$-NH_2), 156.1 (N=$\underline{C}$-CH_3), 39.9 (C-1), 38.7 (C-2,8,9), 36.1 (C-4,6,10), 27.6 (C-3,5,7), 12.4 (N=C-$\underline{C}H_3$). *Anal.* Calcd for $C_{13}H_{23}N_4Cl{\cdot}0.75H_2O$: C, 54.92; H, 8.68; N, 19.71. Found: C, 54.83; H, 8.57; N, 19.90.

2-[1-(1-Adamantyl)ethylidene]hydrazinecarbothioamide (42b). To a mixture of 1-adamantylmethyl ketone (0.89 g, 5 mmol) and thiosemicarbazide (0.45 g, 5 mmol) in

6 mL methanol was added 0.25 mL concentrated HCl, and the reaction mixture heated at reflux for 1 h. The mixture was allowed to cool at room temperature and stand overnight. The white solid that separated was filtered off, washed with ethanol, and dried, yielding 0.92 g of crystals, mp 206-207 °C; MS (EI) *m/e* 251 (M); IR (KBr) 3411, 2917, 2899, 2845, 1591, 1492, 1449, 1426, 1082, 527 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.82 (s, 1, NHOC=S), 8.09 (s, 1, S=C-NH_2), 7.30 (s, 1, S=CNH), 1.98 (s, 3, H-3,5,7), 1.84 (s, 3, N=C-CH_3), 1.71 (d, 6, H-2,7,8), 1.67 (s, 6, H-4,6,10); ^{13}C NMR (Me_2SO-d_6) δ 178.7 (NHOC-NH_2), 159.3 (NH=CC-CH_3), 39.9 (C-1), 38.7 (C-2,8,9), 36.1 (C-4,6,10), 27.6 (C-3,5,7), 12.4 (NH=C-CH_3). *Anal.* Calcd for $C_{13}H_{21}N_3S$: C, 62.21; H, 8.42; N, 16.72. Found: C, 62.12; H, 8.68; N, 17.01.

3-Bromo-N-1-(2',3'-dihydroxypropyl)pyrazolo[3,4-d]pyrimidin-4(5H)-one (47a).[26] In a 250 mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate tube was placed a mixture of 3-bromopyrazolo[3,4-d]pyrimidine (5 g, 25 mmol), glycidol (1.73 g, 23 mmol), a trace of anhydrous potassium carbonate, and DMF (100 mL). The mixture was stirred at 60 °C for 24 h. After cooling to room temperature the undissolved material was filtered by suction and the solution was evaporated by reduced pressure. The resulting orange syrup was recrystallized from ethanol and applied to a cation exchange column with 50% MeOH and 50% H_2O as the eluting solvents. The eluant was concentrated, recrystallized from ethanol, and dried to yield 600 mg (9%); mp 230-232 °C; MS (EI) *m/e* 289 (M + 1); ^1H NMR (Me_2SO-d_6) δ 3.48 (m, 2, H-4',5'), 3.98 (m, 1, H-3'), 4.46 (m, 2, H-1',2'), 4.75 (s, 1, -C-OH), 4.95 (d, 1, C-OH), 8.2 (d, 1, J_6 = 29.77, H-7), 12.49 (s, 1, -N-H); IR 3292, 3287, 2884, 1690, 1609, 1541, 1392, 1074, 1032, 786 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 50.8 (C-1'), 69.8 (C-2'), 63.6 (C-3'), 104.3 (C-4), 120.2 (C-3), 148.7 (C-7), 153.1 (C-5), 156.3 (C-8). *Anal.* Calcd for $C_8H_{10}N_4O_3Br$: C, 33.20; H, 3.13; N, 19.38. Found: C, 33.08; H, 3.45; N, 18.90.

3-Bromo-1,2,4-triazole (48)·2[27] Sodium sulfite 33 g (0.26 mol) in approximately 200 mL water and 2,4,5-tribromoimidazole 8 g (0.026 mol) were refluxed for 3½ hours, cooled, and refrigerated overnight. Completeness of reaction checked with TLC (silica gel in ethyl acetate, developed in iodine.) The reaction mixture was extracted with ether (5 x 250 mL), dried over sodium sulfate, filtered, and evaporated to dryness, yielding 3 g of a pale yellow solid, mp 118-119 °C; MS (EI) 302 (M); ^1H NMR (Me_2SO-d_6) δ 12.44 (br s, 1, N2-H), 7.64 (s, 1, C1-H), 7.25 (d, 1, J = 1.2 Hz, C4-H); IR (KBr) 2817, 2811, 2590, 1297, 1189, 1069, 961, 821, 755, 619 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 135.7 (C, $^3J_{CH}$ = 8.3 Hz, $^1J_{CH}$ = 210.6 Hz), 115.6 (C4, $^3J_{CH}$ = 3.0 Hz, $^1J_{CH}$ = 196.3 Hz), 113.2 (C5, $^3J_{CH}$ = 9.4 Hz, $^1J_{CH}$ = 13.8 Hz). *Anal.* Calcd

for $C_3H_3N_2Br \cdot 0.1H_2O$: C, 24.22; H, 2.17; N, 18.83. Found: C, 24.06; H, 1.97; N, 18.64.

4-Amino-1-pentanol (56). The preparation of endo-norbornyl-amine[28] was followed. A solution of 3-acetyl-1-propanol (51 mL), ammonium acetate (385 g) and sodium cyano borohydride (22 g) in absolute methanol (1.5 L) was stirred 48 h at 25 °C. Concentrated HCl was added until pH <2 and methanol was removed *in vacuo*. The residue was taken up in a minimum amount of water and extracted with ether (3 x 150 mL). The aqueous solution was brought to pH >10 with solid KOH, and extracted with chloroform (5 x 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give fairly pure product (47 g). The product was further purified by distillation (30 g); bp 124°/26 mm [lit.[27] bp 117-119 °C/25 mm]; IR (neat + a drop chloroform) 3342, 3277, 3219 (NH_2, OH), 2955, 2930, 2865 (CH), 1595, 1450, 1375, 1061 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.3-3.4 (t, 2, CH_2OH), 3.0-2.6 (m, 4, CH, OH, NH_2), 1.5-1.35 (m), 1.35-1.2 (m) (4, CH_2CH_2), 1.0-0.9 (d, 3, CH_3); ^{13}C NMR (Me_2SO-d_6) δ 60.9 (C-1), 46.1 (C-4), 36.1 (C-3), 29.4 (C-2) and 23.7 (C-5).

4-(4'-Hydroxy-1'-methylbutylamino)-7-chloroquinoline[29] (57): A mixture of 4,7-dichloroquinoline (22.3 g) and 4-amino-1-pentanol (23.2 g) was cautiously heated to 145 ± 2 °C with stirring in a 1L round bottom flask under dry conditions. The constant temperature and stirring was maintained for 4 h. The mixture was then cooled to below 100 °C, ice-water (200 mL) was added, and the reaction was stirred overnight. The solid obtained was filtered, washed with water and dried, 32.5 g, MS (EI) *m/e* 264 (M). This compound was used in the next step without further purification.

4-(4'-Ethylamino-1'-methylbutylamino)-7-chloroquinoline[29] (58): To 70 mL of 48% hydrobromic acid was cautiously added with cooling and stirring, 15 mL of concentrated sulfuric acid, carbinol 57 (32 g) was dissolved in the acid mixture and the resulting solution 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 (usually about 5-10 min. of heating was required). Heating was discontinued at once (longer heating appeared to destroy the product), the mixture was allowed to cool to 50 °C, and 100 mL of water was added. The dense, viscous lower layer was taken up in chloroform, and the aqueous layer was extracted with chloroform several times. The chloroform extracts were combined, dried ($MgSO_4$), and transferred to the flask to be used for the final step. Solvent was removed under reduced pressure with gentle warming, and the resulting viscous liquid was evenly distributed over the walls. The flask was then cooled in an ice-bath, and 200 mL of anhydrous ethylamine was added. The flask was sealed with a

stopper wired on tightly, and the mixture was cooled and shaken until all of the salt dissolved. The solution was then stirred for 42 h at room temperature. Excess ethylamine was removed by distillation and the residue was taken up in 300 mL of water containing 100 g of potassium carbonate. The aqueous layer was extracted several times with chloroform, and the organic layers were pooled and concentrated. The residual liquid was taken up in an equal volume of alcohol, and water was added to incipient turbidity. Then, 6 N HCl was added until pH was between 8-8.2. The solution was further diluted with 600 mL of water and extracted thoroughly with ether to remove the by-product. The aqueous solution, upon treatment with 30 g of potassium hydroxide yielded crude product, which was removed by extraction with chloroform. The solvent was removed and distilled to give the pure product, 8.23 g, bp 175-180 °C (0.03 mm) [lit.[7] bp 173-175 °C 0.05 mm]. The distillate slowly solidified to a pale yellow solid, mp 100-102 °C; MS (EI) *m/e* 291 (M); IR (KBr) 3274 (broad, NH, NH), 2964 (CH), 2930, 2820, 1612, 1575, 1540 (aromatic), 1490, 1454, 1424, 1381, 1366, 1331, 1280, 1255, 1205, 1150, 1130, 1080 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.45-8.35 (d, 2, C_2-H and C_5-H), 7.85-7.80 (d, 1, C_8-H), 7.5-7.4 (dd, 1, C_6-H), 7.05-6.90 (d, 1, N_1,-H), 6.50-6.45 (d, 1, C_3-H), 3.8-3.6 (m, 1, CH), 2.6-2.4 (m, 5, CH_2NHCH_2), 1.8-1.4 (m, 4, CH_2CH_2), 1.3-1.2 (d, 3, $CHCH_3$), 1.05-0.95 (t, 3, $CHCH_3$); ^{13}C NMR (Me_2SO-d_6): δ 151.6 (C-2), 149.3 (C-4 or C-8a), 149.1 (C-4 or C-8a), 133.1 (C-7), 127.3 (C-6 or C-8), 124.1 (C-5), 123.5 (C-6 or C-8), 117.3 (C-4a), 98.5 (C-3), 49.0 (C-4'), 47.5 (C-1'), 43.4 ($\underline{C}H_2CH_3$), 33.3 (C-2' or C-3'), 26.2 (C-2' or C-3') 19.6 ($CH\underline{C}H_3$), 15.0 ($CH_2\underline{C}H_3$). *Anal.* Calcd for $C_{16}H_{22}N_3Cl$: C, 65.85; H, 7.60; N, 14.40. Found: C, 65.62; H, 7.69; N, 14.33.

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