5-Cyclopropylcarbonyloxy-5-(1-phenylethyl)barbituric Acid (8). Compound 8 was prepared from **3** (3.72 g, 0.015 mol) and cyclopropanecarboxylic acid (20 g, 0.23 mol) in the same way as described for the preparation of compound 4. Obtained was 8 (0.7 g, 14.7%), mp 114–115°. *Anal.* ($C_{16}H_{16}O_5N_2$) C, H, N.

5-*n*-Hexanoyloxy-5-(1-phenylethyl)barbituric Acid (9). To a solution of **3** (2.4 g, 0.01 mol) in pyridine (30 ml) was added hexanoyl chloride (6 g, 0.045 mol) and the mixture was stirred at 75° for 18 hr, then cooled, and poured into ice (150 g) containing HCl (30 ml). The mixture was extracted with EtOAc and the extract was evaporated to give an oil which was chromatographed on silica gel. Elution with C_6H_6–EtOAc (9:1) gave **9** (0.8 g, 23%), an oil. *Anal.* ($C_{18}H_{22}O_5N_2$) C, H, N.

5-(1-Adamantylcarbonyloxy)-5-(1-phenylethyl)barbituric Acid (10). To a mixture of 1-adamantanecarboxylic acid (3.0 g, 0.012 mol) and methanesulfonic acid (10 ml) was added **3** (2.0 g, 0.008 mol). The mixture was stirred at 85° for 0.5 hr, then cooled to 25°, and stirred for 16 hr. The solution was poured into ice-H_2O (300 ml) and the light brown precipitate was removed by filtration and chromatographed on silica gel. Elution with C_6H_6–EtOAc (9:1), followed by crystallization from acetone–hexane (1:1), gave **10** (0.15 g, 4.55%), mp 262–264°. *Anal.* ($C_{23}H_{28}O_5N_2$) C, H, N.

5-Trimethylsilyloxy-5-(1-phenylethyl)barbituric Acid (11). Procedure A. To a solution of **3** (2.5 g, 0.01 mol) in pyridine (25 ml) was added trimethylchlorosilane (1.1 g, 0.01 mol). The solution was stirred at 130° for 16 hr, then cooled, and poured into ice H_2O (200 ml) containing HCl (25 ml). The solution was extracted with EtOAc, the extract was evaporated, and the residue was chromatographed on silica gel. Elution with C_6H_6–EtOAc (4:1) provided pure **11** (1.8 g, 56%), mp 156–159°. *Anal.* ($C_{15}H_{20}O_4N_2Si$) C, H, N, Si.

Procedure B. Compound **3** (5.0 g, 0.02 mol) and *N,O*-bis(trimethylsilyl)acetamide (BSA, 6 g, 0.029 mol) were dissolved in pyridine (5 ml) and stirred 16 hr at 25° in a closed flask. Chromatography on silica gel using C_6H_6–EtOAc (19:1) gave the product which was crystallized from C_6H_6 to give **11** (2.7 g, 42%), mp 156.5–158°.

5-Triethylsilyloxy-5-(1-phenylethyl)barbituric Acid (12). Compound **12** was prepared from **3** (7.5 g, 0.03 mol) and triethylchlorosilane (5 g, 0.033 mol) in the same way as described in procedure A for the preparation of compound **11**. Obtained was **12** (2.6 g, 24%), mp 101–104°. *Anal.* ($C_{18}H_{26}O_4N_2Si$) C, H, N, Si.

5-Triphenylsilyloxy-5-(1-phenylethyl)barbituric Acid (13). Compound **13** was prepared from **3** (3.75 g, 0.015 mol) and triphenylchlorosilane (5.0 g, 0.017 mol) in the same way as described in procedure A for the preparation of compound **11**. Obtained was **13** (3.7 g, 49%), mp 270–273.5°. *Anal.* ($C_{30}H_{26}O_4N_2Si$) C, H, N, Si.

5-Tosyloxy-5-(1-phenylethyl)barbituric Acid (14). Compound **14** was prepared from **3** (2.48 g, 0.01 mol) and tosyl chloride (1.9 g, 0.01 mol) in the same way as described for the preparation of compound **9**. Obtained was **14** (1.98 g, 49%), mp 178–180°. *Anal.* ($C_{19}H_{18}O_6N_2S$) C, H, N, S.

Diethyl Ethoxymalonate (16). To a solution of sodium (4.6 g, 0.02 mol) in EtOH (300 ml) was added diethyl bromomalonate (47.8 g, 0.2 mol) and the mixture was heated at reflux for 4 hr and then cooled to 25°. NaBr (20 g, 0.196 mol) was removed by filtration and the filtrate was evaporated. The resulting liquid was distilled at 5 mm and the product **16** (28 g, 70%) was collected at 135–140°. *Anal.* ($C_9H_{16}O_5$) C, H.

Diethyl Ethoxy(1-phenylethyl)malonate (17). To a solution of sodium (2.3 g, 0.1 mol) in EtOH (100 ml) was added **16** (20.4 g, 0.1 mol). The mixture was stirred at 25° for 2 hr. 1-Bromoethylbenzene (18.5 g, 0.1 mol) was added and the mixture was stirred at reflux for 6 hr and then cooled to 25°. NaBr (9.1 g, 0.09 mol) was removed by filtration and the filtrate was evaporated. The resulting liquid was distilled at 5 mm and the product **17** (12.4 g, 40%) was collected at 175–180°.

5-Ethoxy-5-(1-phenylethyl)barbituric Acid (15). To a solution of sodium (1.38 g, 0.06 mol) in EtOH (100 ml) was added urea (3.7 g, 0.06 mol). The mixture was stirred until a clear solution was obtained. Compound **17** (6.1 g, 0.02 mol) was added dropwise and the mixture was stirred at reflux for 16 hr and then cooled to 25°. Ice-H_2O (100 ml) was added and the solution was acidified with HCl to pH 2. The precipitate was removed by filtration and washed with H_2O to give **15** (1.3 g, 24%), mp 230–233°. *Anal.* ($C_{14}H_{16}O_4N_2$) C, H, N.

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Analogs of 5'-Deoxy-5'-(methylthio)adenosine†

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Twenty analogs of 5'-deoxy-5'-(methylthio)adenosine have been prepared in which the heterocyclic base, the sugar moiety, and the substituent on sulfur have all been varied. Two principal routes to these compounds were used: (1) displacement of the tosyloxy or chlorine function from $C_{5'}$ of the nucleoside or (2) preparation and reaction of the appropriate sugar with a chloropurine followed by nucleophilic displacement of the chloro group(s) from the resulting nucleosides. Only one of these nucleosides (**51**) showed a significant degree of cytotoxicity and none was active against leukemia L1210 *in vivo*.

S-Adenosyl-L-methionine (SAM), synthesized *in vivo* from adenosine triphosphate and L-methionine by ATP:L-methionine adenosyltransferase,[1] an enzyme that appears to be ubiquitous in both normal and malignant tissues, functions as a methyl group donor for transmethylations[2] and as a propylamine donor for polyamine synthesis.[3,4] In carrying out these transformations, SAM is converted to *S*-adenosyl-L-homocysteine (SAH) and 5'-deoxy-5'-(methylthio)adenosine (MTA), both of which are known to inhibit the transmethylation reactions of SAM *in vitro*.[5-7] Analogs of these compounds could interfere with the biosynthesis of SAM, with methylation by SAM, with the decarboxylation of SAM, or with the propylamine transfer from "decarboxylated SAM" to putrescine to form spermidine; either one of the latter two events would interfere with polyamine synthesis. Transfer of aminoalkyl groups other than aminopropyl would produce unnatural polyamines. Any of these postulated events could have serious consequences for proliferating cells and result in cell death. In addition, metabolism of analogs by SAM-me-

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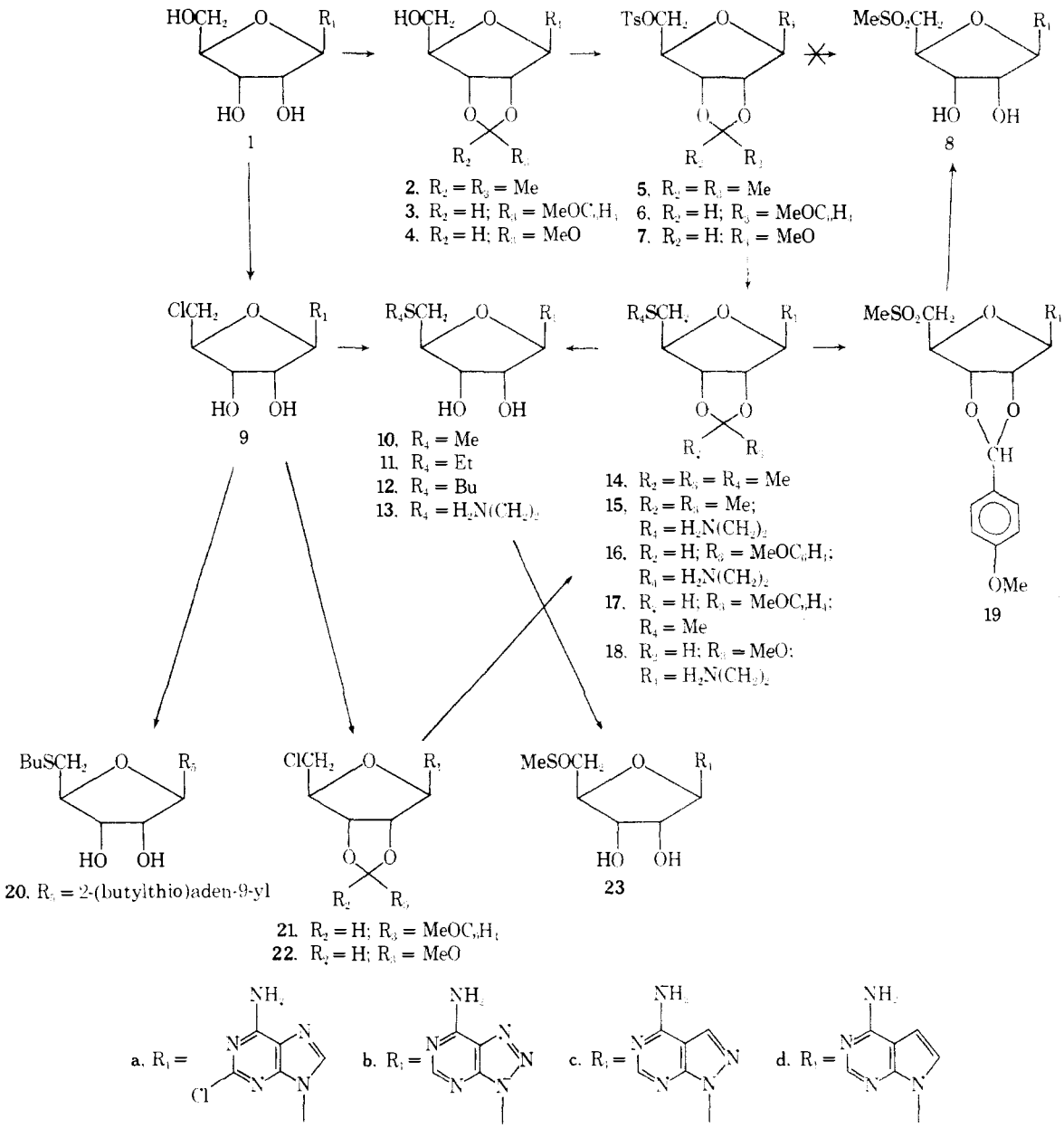
Scheme I



tabolizing enzymes could release cytotoxic purines or purine nucleosides.

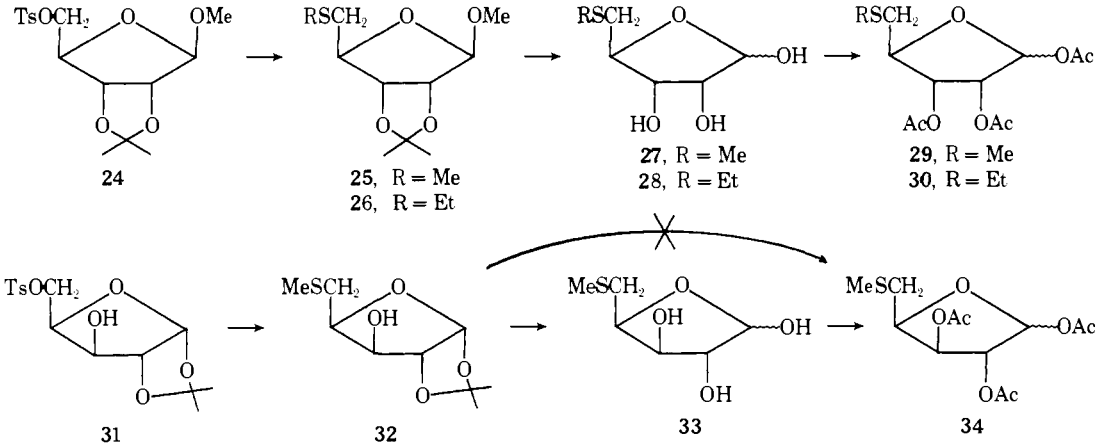
Until now, most of the analogs of MTA or SAH that have been synthesized are derivatives of adenosine,[5-12] although analogs of SAH containing 2-fluoroadenine,[6] guanine,[11] and hypoxanthine[5] have been prepared as well as a derivative of 2,8-dichloropurine.[8] Only one analog, 2′,5′-dideoxy-5′-(methylthio)adenosine, containing a carbohydrate other than ribose has been prepared.[10] In the present work we undertook to study the effect of changes in all three parts of the molecule—the purine, the sugar, and the S substituent—on biologic activity.

Chemistry. Two complementary methods have been used for the preparation of 5′-(alkylthio)-5′-deoxyribonucleosides of purines: (1) displacement of a halo or tosyloxy group from the 5′ position of the ribonucleoside;[6,9-12] (2) preparation of the appropriate 5-(alkylthio)-5-deoxyribofuranose and reaction of it with a purine or metal derivative thereof.[8] At the onset it appeared that some of the nucleosides we desired to prepare could be made more expediently by method 1, others by 2, while still others with equal facility by either method. We decided to investigate first the preparation of 2-chloro-5′-deoxy-5′-(methylthio)adenosine (**10a**) by both methods. Tosylation of 2-chloro-2′,3′-*O*-isopropylideneadenosine (**2a**) was carried out at low temperature to give a good yield of pure product **5a**. Displacement of the tosyloxy group by sodium methyl mercaptide to give **14a** proceeded smoothly, and removal of the isopropylidene group under mild conditions gave the desired **10a** (Scheme I).

An attempt to prepare methyl 5-deoxy-2,3-*O*-isopropylidene-5-(methylthio)ribofuranoside (**25**) by the displacement of the *p*-nitrobenzenesulfonyloxy group of methyl 2,3-*O*-isopropylidene-5-*O*-(*p*-nitrobenzenesulfonyl)ribofuranoside was unsuccessful because cleavage of the carbon-sulfur bond occurred, rather than the carbon-oxygen bond, to give methyl-*p*-nitrophenyl sulfide.‡ 1,2,3-Tri-*O*-acetyl-5-deoxy-5-(methylthio)ribofuranose (**29**) was then prepared by a literature procedure[8] and fused with 2,6-dichloropurine (**35**),[14] in the absence of acid catalyst, to give an 80% yield of 9-[2,3-di-*O*-acetyl-5-deoxy-5-(methyl-

‡Previously, the displacement of the *p*-nitrobenzenesulfonyloxy group of this sugar by cyanide was found to take place readily in the normal manner.[13]

Scheme II



thio)-β-D-ribofuranosyl]-2,6-dichloropurine (**37a**). Treatment of 37a with methanolic ammonia[14] gave a 57% yield of **10a** containing some of the corresponding 6-methoxy compound that could be removed by chromatography. Having assessed the utility of both methods for the preparation of **10a**, we proceeded to prepare a variety of analogs of 5′-deoxy-5′-(methylthio)adenosine by application of the more appropriate route to each particular case. The 5′-chloro-5′-deoxy derivatives of 2-chloroadenosine, 8-azaadenosine, 4-amino-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine, and tubercidin (**9a–d**) were prepared for use in method 1 by the thionyl chloride–hexamethylphosphoramide method.[12] Also prepared for this work were 2-chloro-2′,3′-*O*-anisylidene-5′-*O*-tosyladenosine (**6a**), 7-amino-3-(2,3-*O*-isopropylidene-5-*O*-tosyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (**5b**), 7-amino-3-(2,3-*O*-anisylidene-5-*O*-tosyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (**6b**), 7-amino-3-(2,3-*O*-methoxymethylidene-5-*O*-tosyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (7b), and the 2′,3′-*O*-anisylidene and 2′,3′-*O*-methoxymethylidene derivatives of 2,5′-dichloroadenosine. The 5′-chloro-5′-deoxy derivatives **9c** and **9d** proved to be excellent intermediates for the preparation of 4-amino-1-[5-deoxy-5-(ethylthio)-β-D-ribofuranosyl]pyrazolo[3,4-*d*]pyrimidine (**11c**) and 4-amino-7-[5-(butylthio)-5-deoxy-β-D-ribofuranosyl]pyrrolo[2,3-*d*]pyrimidine (**12d**). However, when an attempt was made to prepare 5′-(butylthio)-2-chloro-5′-deoxyadenosine (**12a**) by the reaction of **9a** with butyl mercaptan in dilute sodium hydroxide, both chlorines of **9a** reacted to give in good yield 2,5′-bis(butylthio)-5′-deoxyadenosine (**20**). The desired **12a** could be prepared, however, by carrying out the reaction in dimethylacetamide with potassium carbonate.

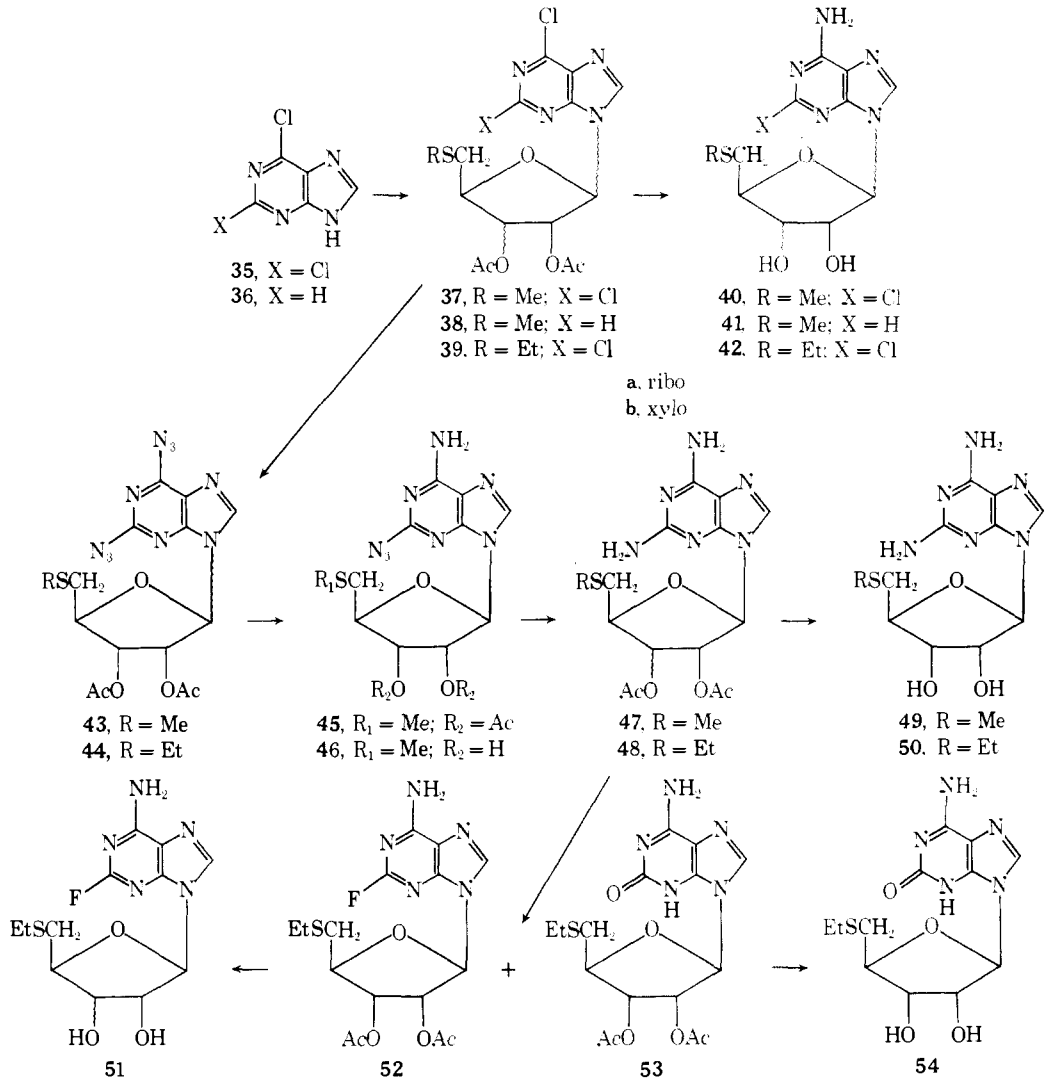
7-Amino-3-[5-deoxy-5-(methylthio)-β-D-ribofuranosyl]-*v*-triazolo[4,5-*d*]pyrimidine (**10b**) was prepared from **5b** *via* **14b** and directly from **9b**. Oxidation of **10b** with 30% hydrogen peroxide gave 7-amino-3-[5-deoxy-5-(methylsulfinyl)-β-D-ribofuranosyl]-*v*-triazolo[4,5-*d*]pyrimidine (**23b**). An attempt to prepare the sulfone **8b** by prolonged oxidation with hydrogen peroxide resulted in extensive glycosyl cleavage. If the protected nucleoside **19b** was used, glycosyl cleavage was minimal, although the anisylidene group was lost during the course of the reaction giving **8b**. Later we found that **8b** could be prepared in high yield directly from **10b** by rapid oxidation with neutral potassium permanganate (Scheme II).

Preparation of the 2-aminoethylthio analogs **13a,b** presented a more difficult problem because of the nature of the target nucleosides. Although 2,5′-dichloro-5′-deoxyadenosine (**9a**) will react with 2-aminoethanethiol, the reaction was relatively sluggish—a result of the lower reactivity of this thiol as compared to the alkylthiols and of the 5′-chloro group compared to the 5′-tosyloxy function. The main difficulty, however, lay in the purification of **13a**. The solution to this problem was the use of **5a** which gave a nucleoside (**15a**) that could be extracted into chloroform and freed of excess thiol and other impurities. Removal of the isopropylidene group from pure **15a** then gave a nucleoside that could be isolated pure as its sulfate salt. This approach failed with the anisylidene derivative **16a** because of the instability of the anisylidene blocking group to the extraction procedure using cold dilute sulfuric acid. In the case of the *v*-triazolo[4,5-*d*]pyrimidine derivatives, the situation was quite different. The isopropylidene derivative **15b** could be obtained pure, but all attempts to remove the isopropylidene group resulted in extensive glycosyl cleavage. Apparently 2′,3′-alkylidene blocking groups are more stable to acid when attached to the ribonucleoside of the *v*-triazolo[4,5-*d*]pyrimidine than when attached to ribonucleoside of 2-chloroadenine. In this case, the anisylidene group proved ideal since **16b** was not deprotected by the cold acid extraction but was sufficiently acid sensitive to be removed without extensive glycosyl cleavage.

We next turned our attention to nucleosides best prepared by method 2. 1,2,3-Tri-*O*-acetyl-5-deoxy-5-(ethylthio)ribofuranose (**30**), prepared from **24** by the sequence shown, and 2,6-dichloropurine were fused without catalyst to give 9-[2-di-*O*-acetyl-5-deoxy-5-(ethylthio)-β-D-ribofuranosyl]-2,6-dichloropurine (**39a**). Reaction of **39a** with ethanolic ammonia gave 2-chloro-5′-deoxy-5-(ethylthio)adenosine (**42a**) contaminated with a small amount of a second nucleoside identified by its spectra and chromatographic travel as 2-chloro-5′-deoxy-5′-(ethylsufinyl)adenosine. Both **37a** (see above) and **39a** were converted to the diazido compounds **43** and **44**. The catalytic reduction of **43** was slow and initially incomplete; after treatment with methanolic ammonia, 2-azido-5′-deoxy-5′-(methylthio)adenosine (**46**) was isolated and identified. Further reduction of **46** then gave 2-amino-5′-(methylthio)adenosine (**49**), which was also prepared *via* **47** by lengthy reduction of **43**. In the same manner, **44** was converted to **48** and deacetylated to give **50**. Compound **48** was also subjected to the modified Scheimann reaction[15] producing **52** and **53**. Treatment of these nucleosides with ethanolic ammonia gave 5′-deoxy-5′-(ethylthio)-2-fluoroadenosine (**51**) and a lesser amount of 5′-deoxy-5′-(ethylthio)isoguanosine (**54**). (Scheme III).

Reaction of 1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranoside (**31**)[16] with sodium methyl mercaptide gave 5-deoxy-1,2-*O*-isopropylidene-5-(methylthio)-α-D-xylofuranoside (**32**), but acetolysis of **32** failed to give a usable

Scheme III

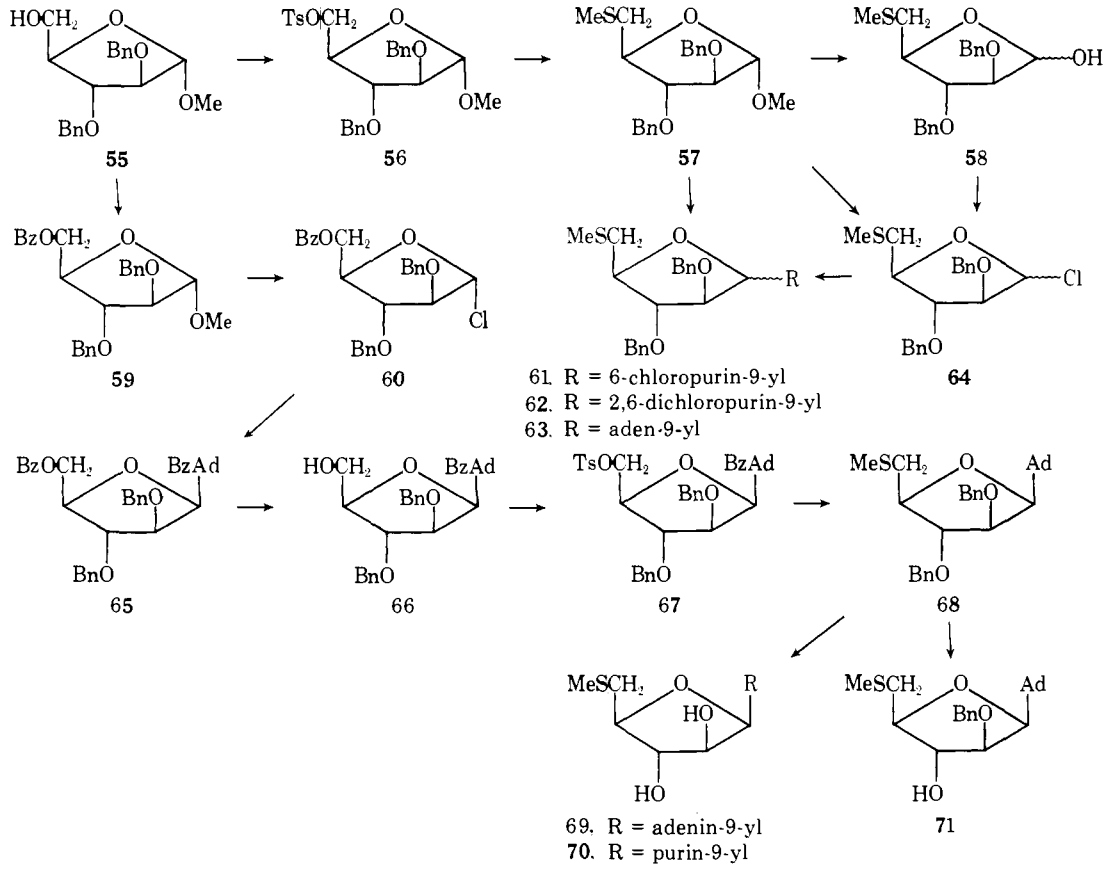


sugar. Acid hydrolysis of **32** gave **33**, which could be acetylated to 1,2,3-tri-*O*-acetyl-5-deoxy-5-(methylthio)-D-xylofuranose (**34**). Fusion of **34** with 2,6-dichloropurine (**35**) without acid catalyst gave a mixture of anomeric xylofuranosides (**37b**) that were difficult to separate. Consequently, they were treated with methanolic ammonia to convert them to the 2-chloroadenines (**40b**), which could be separated chromatographically and identified. An 18% yield of β-**40b** and a 6% yield of α-**40b** were obtained (3β:1α). Fusion of **34** with 6-chloropurine (**36**) gave essentially the same results—a 22% yield of β-**41b** and a 6.8% yield of α-**41b**.

The preparation of the arabino analog of 5′-deoxy-5′-(methylthio)adenosine presented another problem. The 5′-*O*-tosyl derivative of 9-β-D-arabinofuranosyladenine has been prepared,[17] and we were able to prepare 9-(5-chloro-5-deoxy-β-D-arabinofuranosyl)adenine by the thionyl chloride procedure. However, previous attempts to displace the 5′-*O*-tosyloxy group of 9-(5-*O*-tosyl-β-D-arabinofuranosyl)adenine resulted in formation of the 2,5-anhydro nucleoside,[17,18] and we found this to be the case with either the tosyl or the chloro derivatives. Further, a number of attempts to block the hydroxyls at C-2 and C-3 of these derivatives were unsuccessful. We then turned our attention to the preparation of a suitably blocked arabinofuranose to react with a purine. Tosylation of methyl 2,3-di-*O*-benzyl-α-D-arabinofuranoside (**55**)[19] proceeded smoothly to give **56**, which was converted to methyl 2,3-di-*O*-benzyl-5-deoxy-5-(methylthio)-α-D-arabinofuranoside (**57**) by the action of sodium methyl mercaptide in methanol. Fusion of **57** with 6-chloropurine (**36**) and with *N*-nonanoyladenine using *p*-toluenesulfonic acid as catalyst failed to produce a significant yield of nucleoside but was successful with 2,6-dichloropurine (**35**). Unfortunately, a 20% yield of α-**62** and only a 10% yield of β-**62** were produced. Initial attempts to convert the methyl glycoside **57** to the chloro sugar **64** under a variety of conditions gave poor results; much decomposition occurred, but **57** could be hydrolyzed in aqueous trifluoroacetic acid to **58** which gave **64** on treatment with ethereal hydrogen chloride. Later it was found that **57** and **59** could be converted smoothly to the chloro sugars **64** and **60** directly by treatment with ethereal hydrogen chloride for 6–7 days at refrigerator temperature. Conversion of **57** to **64** was followed by tlc and by reaction of **64** with methanol which gave the β-anomer of **57**. A comparison of the pmr spectra of this anomeric pair (see Experimental Section) revealed the first observed exception to the empirical rule that the signal from the anomeric proton of cis glycoside occurs downfield from that of the corresponding trans glycoside.[20,21] This rule, which has proven useful in establishing the identity of anomeric purine and pyrimidine nucleosides, must now be viewed with caution, although, hopefully, exceptions to it may be rare.

Reaction of **64** with *N*-nonanoyladenine in benzene at 55° for 4 days using Linde AW-500 molecular seive as the

Scheme IV



acid acceptor gave a 26% yield of nucleosidic material, which after treatment with sodium methoxide was shown to be a mixture of anomers (1β:2α) of 9-[2,3-di-*O*-benzyl-5-deoxy-5-(methylthio)-D-arabinofuranosyl]adenine (**63**). When the reaction was carried out in ethylene chloride at 55° for 10 days using Linde 4A molecular seive, the anomeric mixture was more favorable—3β:2α, but still not satisfactory for preparative work. Consequently, **55** was benzoylated to give **59**, which was converted to the chloro sugar **60** by treatment first with hydrogen chloride in acetic acid and with ethereal hydrogen chloride (see above). Reaction of **60** with *N*-nonanoyladenine in refluxing benzene for 3 days using Linde AW-500 molecular seive gave a low yield of nucleosides, which were shown by pmr to be a 3β:1α anomeric mixture of 9-(5-*O*-benzoyl-2,3-di-*O*-benzyl-D-arabinofuranosyl)-*N*-nonanoyladenine, but reaction of **60** with *N*-benzoyladenine for 12 days at 60° in ethylene chloride using Linde 4A molecular seive gave a reasonable yield of anomerically pure **65**, which was *O*-debenzoylated to **66** with sodium hydroxide in pyridine. Treatment of **66** with tosyl chloride in pyridine gave **67**, which was allowed to react with sodium methyl mercaptide in methanol to give the methylthio compound **68**. Catalytic hydrogenolysis of **68** was slow and resulted in the removal of the 3-*O*-benzyl group only giving **71**, whereas initial attempts to remove the benzyl groups with sodium in liquid ammonia resulted in overreduction, yielding adenine and 9-[5-deoxy-5-(methylthio)-β-D-arabinofuranosyl]purine (**70**) as by-products. If the reaction was stopped while a small amount of starting material remained (tlc), the production of these by-products could be minimized and a good yield of the desired 9-[5-deoxy-5-(methylthio)-β-D-arabinofuranosyl]adenine (**69**) obtained (Scheme IV).

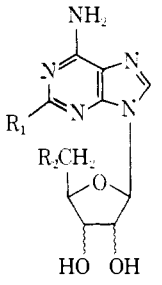
Biologic Evaluation. Only one of these 5′-deoxy-5′-(methylthio)adenosine analogs, 2-fluoro-5′-(ethylthio)adenosine (**51**), was highly toxic to H.Ep.-2 cells in culture.[22] H.Ep.-2 cells lacking adenine phosphoribosyltransferase (H.Ep.-2/FA/FAR)[23] were resistant to this analog, indicating that its cytotoxicity to the wild strain of H.Ep.-2 cells is due to cleavage to the 2-fluoroadenine. The 5′-alkylthio derivatives of other cytotoxic nucleosides were less toxic, with one exception (**54**), than the parent nucleosides (see Tables I and II) and, in the case of the ribonucleosides of toxic bases (Table III), less toxic than the bases, with the same single exception. Cytotoxic nucleosides such as 2-fluoroadenosine and 8-azaadenosine can be converted to their active form, the nucleotides, by direct phosphorylation or by cleavage to the bases, which can then be converted to the nucleotides by the adenine phosphoribosyltransferase. The 5′-(alkylthio)nucleosides cannot be phosphorylated directly, but could be enzymatically converted to the parent nucleosides, cleaved to the bases, or could cause cell death by a mechanism different from that of the parent nucleosides. The low order of cytotoxicity demonstrated by almost all of these nucleosides indicates that in most cases none of these things occur to a significant extent.

The low order of cytotoxicity of the compounds is reflected in their inability to affect the course of leukemia L1210 in mice and their lack of whole animal toxicity. Even **51** was tolerated at 100 mg/kg (days 1, 5, and 9).

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are not corrected. The pmr spectra were determined in the solvent indicated (Me_4Si) with a Varian SL-100-15 spectrometer, and the correct integrals were obtained for the assignments indicated; chemical shifts quoted for multiplets were measured from the approximate centers. The mass spectra were determined with a Hitachi Perkin-Elmer RMU-6D-3 spectrometer. Chromatographic analyses were carried out on tlc plates of silica gel H (Brinkmann or Analtech). The spots were detected by uv light after spraying with Ultraphor (WT, highly concentrated) and by

Table I. Cytotoxicity Data. Purine Nucleosides



Compd no.	R_1	R_2	Sugar	ED_{50}, μM[a]
	Cl	OH	β-Ribo	10
10a	Cl	MeS	β-Ribo	170[b]
11a	Cl	EtS	β-Ribo	90
12a	Cl	BuS	β-Ribo	90
13a	Cl	$H_2N(CH_2)_2$	β-Ribo	>50
9a	Cl	Cl	β-Ribo	25
	F	OH	β-Ribo	0.02
51	F	EtS	β-Ribo	0.16[b]
	NH_2	OH	β-Ribo	40
49	NH_2	MeS	β-Ribo	>60
50	NH_2	EtS	β-Ribo	60
	OH	OH	β-Ribo	>70
54	OH	EtS	β-Ribo	30[b]
20	BuS	BuS	β-Ribo	20
	H	OH	β-Arabino	>150
69	H	MeS	β-Arabino	>70
	H	OH	β-Xylo	50
β-41b	H	MeS	β-Xylo	160
β-40b	Cl	MeS	β-Xylo	45
α-41b	H	MeS	α-Xylo	>70
α-40b	Cl	MeS	α-Xylo	>120

[a] The concentration required to inhibit the growth of treated cells to 50% of controls.[22] [b] KB cells.

charring after spraying with aqueous ammonium sulfate. The 2-aminoethylthio compounds were also detected with ninhydrin spray.

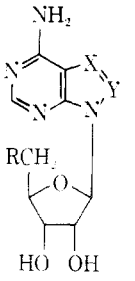
2-Chloro-2',3'-*O*-isopropylideneadenosine (2a). A solution of 2-chloroadenosine (1.21 g, 4 mmol) in 480 ml of acetone containing 1.42 ml of 2,2-dimethoxypropane and 1.88 ml of 70% perchloric acid was stirred for 0.5 hr before it was neutralized with 2.08 ml of dry pyridine and evaporated to dryness *in vacuo*. An aqueous solution of the residue was extracted three times with CH_2Cl_2. Evaporation of the combined, dried ($MgSO_4$) extracts gave a white solid, which was recrystallized from methanol: yield 1.05 g (77%); mp 290–291°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 211 (26.2), 264 (15.5). *Anal.* ($C_{12}H_{16}N_5O_4Cl$) C, H, N.

7-Amino-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (2b). In a similar manner as described for 2a, 8-azaadenosine (1.07 g, 4 mmol) was converted to **2b**: yield 1.045 g (85%); mp 184–185°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 279 (11.7). *Anal.* ($C_{12}H_{16}N_6O_4$) C, H, N.

2',3'-*O*-Anisylidene-2-chloroadenosine (3a). In the manner described for 3b, 2-chloroadenosine (3.70 g) was converted to its anisylidene derivative 3a: yield 2.60 g (51%). The tlc homogenous 3a was used without further purification.

7-Amino-3-(2,3-*O*-anisylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (3b). A solution of 8-azaadenosine (1.54 g) and anisaldehyde (1.5 ml) in a mixture of DMF (5 ml) and ethyl orthoformate (3 ml) containing 3.4 ml of 4 *N* HCl in dioxane was allowed to stand at room temperature for 4 days before it was poured into 2% Na_2CO_3 solution (100 ml). The resulting oil was extracted into $CHCl_3$ (700 ml). Evaporation of the dried ($MgSO_4$) $CHCl_3$ solution gave an oil, which was crystallized from 60 ml of EtOH: yield 947 mg (51%); mp 194–195°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 218 (20.9), 278 (12.6). *Anal.* ($C_{17}H_{18}N_6O_5$) C, H, N.

Table II. Cytotoxicity Data. Nucleosides of Purine Ring Analogs



Compd no.	X	Y	R	ED_{50}, μM[a]
	N	N	OH	20
9b	N	N	Cl	>70
10b	N	N	MeS	>130
23b	N	N	MeSO	>60
8b	N	N	$MeSO_2$	40
13b	N	N	$H_2N(CH_2)_2$	>90
	CH	N	OH	0.2
11c	CH	N	EtS	>60
	CH	CH	OH	0.04
12d	CH	CH	BuS	120

[a] The concentration required to inhibit the growth of treated cells to 50% of controls.[22]

Table III. Cytotoxicity Data. Purines and Ring Analogs

Compd	ED_{50}, μM[a]
2-Chloroadenine	10
2-Fluoroadenine	0.03
2-Aminoadenine	20
Isoguanine	600
8-Azaadenine	20
4-Aminopyrazolo[3,4-*d*]pyrimidine	3.0

[a] The concentration required to inhibit the growth of treated cells to 50% of controls.[22]

7-Amino-3-(2,3-*O*-methoxymethylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (4b). A suspension of 8-azaadenosine (2.68 g) in trimethyl orthoformate (10 ml) containing *p*-toluenesulfonic acid (2.28 g) was refluxed for 1 hr. The cooled mixture diluted with $CHCl_3$ was washed with $NaHCO_3$ solution, followed by water, and then dried over $MgSO_4$. Evaporation of the $CHCl_3$ gave a solid which was recrystallized from methanol: yield 886 mg (29%); mp 195–196°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 279 (11.5). *Anal.* ($C_{11}H_{14}N_6O_5$) C, H, N.

2-Chloro-2',3'-*O*-isopropylidene-5'-tosyladenosine (5a). A solution of 2a (1.04 g, 3.04 mmol) and tosyl chloride (1.17 g, 608 mmol) in 100 ml of dry pyridine (molecular sieve) was allowed to stand at −20° for 3 days before more tosyl chloride (585 mg) was added. After 3 more days, another portion of tosyl chloride (588 mg) was added and the solution allowed to stand another day before $CHCl_3$ and cold $NaHCO_3$ solution (500 ml) were added. The $CHCl_3$ and water layers were separated and the water was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with 1 *N* H_2SO_4 until the water layer remained acidic. Evaporation of the dried ($MgSO_4$) $CHCl_3$ solution gave a white glass that was recrystallized from EtOH: yield 1.27 g (84%); mp 290–291°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 211 (26.2), 264 (15.5). *Anal.* ($C_{13}H_{16}N_5O_4Cl$) C, H, N.

7-Amino-3-(2,3-*O*-isopropylidene-5-*O*-tosyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (5b). To a solution of 2b in 50 ml of pyridine at 0° was added tosyl chloride (614 mg) in 5 ml of $CHCl_3$. After standing overnight at room temperature, more tosyl chloride (614 mg) was added cold and the solution allowed to stand for 2 more days. Cold $NaHCO_3$ solution (200 ml) was added

and the $CHCl_3$ layer separated. The aqueous layer was extracted with $CHCl_3$ (2 × 100 ml) and the combined $CHCl_3$ extracts were washed with water and dried over $MgSO_4$ before they were evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH: yield 710 mg (53%); mp 171–173°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 281 (10.0). *Anal.* ($C_{10}H_{22}N_6O_6S$) C, H, N.

7-Amino-3-(2,3-*O*-anisylidene-5-*O*-tosyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (6b). Tosyl chloride (2.51 g, 13.14 mmol) was added to a solution of **3b** (2.54 g, 6.57 mmol) in dry pyridine (60 ml) cooled in a Dry Ice–acetone bath. After the solution was allowed to stand for 4 days at 20°, it was poured in 55 ml of ice and saturated $NaHCO_3$. The gummy solid that formed was triturated twice with H_2O before it was dissolved in $CHCl_3$ (40 ml). The washed (H_2O) and dried ($MgSO_4$) $CHCl_3$ solution was evaporated to dryness, and the residue was triturated with MeOH giving a crystalline solid: yield 2.15 g (65%). This intermediate was used without further purification.

7-Amino-3-[5-deoxy-5-(methylsulfonyl)-β-D-ribofuranosyl]-*v*-triazolo[4,5-*d*]pyrimidine (8b). A solution of **17b** (416 mg, 1.00 mmol) in a mixture of 10 ml of glacial acetic acid and 10 ml of 30% H_2O_2 was allowed to stand overnight at room temperature before it was evaporated to dryness *in vacuo* without heat. The residue was purified by chromatography on a thick silica gel plate developed with 3:1 $CHCl_3$–MeOH. The product was eluted with and recrystallized from MeOH: yield 124 mg (38%); mp 123–124° dec; λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl) 263 (12.4): λ_{max} (pH 7) 279 (11.3). *Anal.* ($C_{10}H_{14}N_6O_5S$) C, H, N.

2,5′-Dichloro-5′-deoxyadenosine (9a). A solution of 2-chloroadenosine (1a, 1.0 g) and $SOCl_2$ (1.5 ml) in hexamethylphosphoramide (10 ml) was allowed to stand for 16 hr at room temperature before it was poured into 90 ml of ice water. The yellow solid that precipitated was washed with water until the filtrate was neutral and then recrystallized twice from water: yield 640 mg (62%); mp 207–209°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 264 (14.6). *Anal.* ($C_{10}H_{11}N_5O_3Cl_2$) C, H, N.

7-Amino-3-(5-chloro-5-deoxy-β-D-ribofuranosyl)-*v*-triazolo-[4,5-*d*]pyrimidine (9b). To a solution of thionyl chloride (1.5 g) in hexamethylphosphoramide (10 ml) was added 8-azaadenosine (1.00 g, 3.72 mmol). After being stirred overnight, the solution was poured in 90 ml of H_2O and this solution poured onto a column of Dowex 50-X4 (H^+ form, 300 ml). The column was washed with water and then eluted with 1 *N* NH_4OH. After eluting with 1 l., the product came off in the next 1.5 l. Lyophilization gave a white solid that was recrystallized from water: yield 618 mg (58%); mp 180–182°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7 and 13) 278 (11.4). *Anal.* ($C_9H_{11}N_6O_3Cl$) C, H, N.

4-Amino-1-(5-chloro-5-deoxy-β-D-ribofuranosyl)pyrazolo-[3,4-*d*]pyrimidine (9c). 4-Amino-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (1c, 1 g) was added with stirring to a mixture of thionyl chloride (1.5 ml) and hexamethylphosphoramide (10 ml). After stirring overnight at room temperature, the mixture was poured into 90 ml of water, and the solution was poured onto a Dowex 50 X-4 (H^+ form, 300 ml). Elution of the column with 3 l. of 1 *N* NH_4OH gave a solution of the product which was lyophilized to give a white solid. Recrystallization from methanol gave **9c**: yield 855 mg (81%); mp 187–188°; λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl) 257 (10.7); λ_{max} (pH 7, 0.1 *N* NaOH) 260 (9.1), 274 (11.2). *Anal.* ($C_{10}H_{12}N_5O_3Cl$) C, H, N.

2-Chloro-5′-deoxy-5′-(methylthio)adenosine (10a). A. A solution of 14a (65 mg) in 26 ml of EtOH and 13 ml of 1 *N* H_2SO_4 was allowed to stand at room temperature for 4 days before it was neutralized with $Ba(OH)_2$ and filtered. Evaporation of the filtrate gave a white glass that gelled from hot water: yield 35 mg (62.5%); melting point indefinite; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 209 (28.9), 264 (15.4). *Anal.* ($C_{11}H_{14}N_5O_3ClS$) C, H, N.

B. A solution of **37a** (336 mg) in methanolic ammonia (100 ml, saturated at 0°) was allowed to stand at room temperature for 24 hr before it was evaporated to dryness *in vacuo*. The crude product was purified by chromatography on a thick silica gel plate using 15:1 $CHCl_3$–MeOH as the developer: yield 145 mg (57%). This material was identical with that prepared as described in A above.

7-Amino-3-[5-deoxy-5-(methylthio)-β-D-ribofuranosyl]-*v*-triazolo[4,5-*d*]pyrimidine (10b). A solution of **14b** (128 mg, 0.38 mmol) in a mixture of 25 ml of 1 *N* H_2SO_4 and 50 ml of ethanol was allowed to stand at room temperature for 5 days before it was neutralized with saturated $Ba(OH)_2$ solution. The $BaSO_4$ was removed by filtration, and the filtrate was evaporated to dryness. The residue was purified by chromatography on a thick silica gel plate developed with 4:1 $CHCl_3$–MeOH. The product was eluted with MeOH: yield 58 mg (51%); λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl) 262 (11.9); λ_{max} (pH 7) 279 (11.0). *Anal.* ($C_{10}H_{14}N_6O_3S \cdot 0.25MeOH$) C, H, N.

4-Amino-1-[5-deoxy-5-(ethylthio)-β-D-ribofuranosyl]pyrazolo[3,4-*d*]pyrimidine (11c). A solution of **9c** (246 mg, 1 mmol) and ethyl mercaptan (1 ml, 13 mmol) in 0.17 *N* NaOH was refluxed for 3 hr. After the addition of 1 ml of ethyl mercaptan and 2 ml of 1 *N* NaOH, the solution was refluxed another hour. The precipitate that formed was removed by filtration and recrystallized from water: yield 108 mg (34%); mp 160–162°; λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl) 217 (26.7), 257 (10.2); λ_{max} (pH 7, 0.1 *N* NaOH) 260 (9.5), 275 (11.0). *Anal.* ($C_{12}H_{17}N_5O_3S \cdot 0.5H_2O$) C, H, N.

5′-(Butylthio)-2-chloro-5′-deoxyadenosine (12a). A mixture of **9a** (320 mg, 1.00 mmol), butyl mercaptan (90.2 mg, 1.00 mmol), and K_2CO_3 (1.38 mg, 1.00 mmol) in DMF (10 ml) was heated at 125° for 30 min and then another 90 mg of butyl mercaptan was added and heating continued for another 30 min. Evaporation *in vacuo* of the filtered reaction mixture gave an orange syrup that was dissolved in EtOH. The addition of 1 mmol of picric acid gave a solid that was recrystallized from EtOH: mp 116–119°. *Anal.* ($C_{20}H_{23}N_8O_{10}ClS$) C, H, N (ΔN, 0.50).

Treatment of a solution of the picrate with Dowex 1-X8 (CO_3^{2-}) gave a white glass which was precipitated from water: yield 181 mg (48%); λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 265 (14.7). *Anal.* ($C_{14}H_{20}N_5O_3ClS$) C, H, N (ΔC, 0.43).

4-Amino-7-[5-(butylthio)-5-deoxy-β-D-ribofuranosyl]pyrrolo-[2,3-*d*]pyrimidine (12d). After being stirred for 16 hr at room temperature, a solution of 4-amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine (**1d**, 266 mg, 1 mmol) and thionyl chloride (0.41 ml) in hexamethylphosphoramide (2.7 ml) was evaporated to an oil (**9d**) *in vacuo* without heat, and the oil was poured into a mixture of 1 ml of butyl mercaptan and 20 ml of 2 *N* NaOH. After being heated at 90° for 1 hr, the solution was chilled overnight. The solid that precipitated was dissolved in $CHCl_3$ and the solution washed with water, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was recrystallized from water: yield 150 mg (41%); mp 130–132°; λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl) 227 (23.0), 271 (11.0); λ_{max} (pH 7, 0.1 *N* NaOH) 270 (11.9). *Anal.* ($C_{15}H_{22}N_4O_3S$) C, H, N.

5′-(2-Aminoethylthio)-2-chloro-5′-deoxyadenosine (13a). A solution of **15a** (205 mg) in a mixture of 1.5 ml of EtOH and 1.5 ml of 1 *N* H_2SO_4 was allowed to stand at room temperature for 6 days and then stored for 2 weeks at −15°. Upon the addition of 6 ml of EtOH, the gum that had formed solidified, and the solid (146 mg) was removed by filtration. It was dissolved in water (12 ml) and precipitated with EtOH (48 ml): yield 48 mg (22%); melting point indefinite; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 264 (13.1); pmr (DMSO-d_6) δ 2.75 (m, $2H_{5'}$), 2.92 (m, $-CH_2CH_2-$), 4.1 (m, $H_{3'}$ and $H_{4'}$), 4.65 (m, $H_{2'}$), 5.85 (d, $J_{1'2'}$ = 5 Hz, $H_{1'}$), 7.8 (br, NH_2), 8.4 (s, H_8). *Anal.* ($C_{12}H_{17}N_6O_3ClS \cdot 0.5H_2SO_4 \cdot 0.5H_2O \cdot 0.1$-EtOH) C, H, N.

7-Amino-3-[5-(2-aminoethylthio)-5-deoxy-β-D-ribofuranosyl]-*v*-triazolo[4,5-*d*]pyrimidine (13b). A solution of **16b** (190 mg) in 17 ml of 0.1 *N* H_2SO_4 was allowed to stand at room temperature overnight before it was carefully concentrated to 5 ml *in vacuo* without heat. EtOH (15 ml) was added and the solution chilled for 2 hr. The white precipitate was removed by filtration, washed with EtOH, and dried: yield 106 mg (60%); λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl) 263 (12.2); λ_{max} (pH 7) 279 (11.3); pmr (DMSO-d_6) δ 2.75 (m, $2H_{5'}$), 2.95 (m, $-CH_2CH_2-$), 4.2 (m, $H_{4'}$), 4.4 (t, $H_{3'}$), 4.9 (t, $H_{2'}$), 6.2 (d, $J_{1'2'}$ = 4 Hz, $H_{1'}$), 7.7 (br, NH_2), 8.35 (s, H_2). *Anal.* ($C_{11}H_{17}N_7O_3S \cdot H_2SO_4 \cdot 0.75H_2O$) C, H, N.

2-Chloro-5′-deoxy-2′,3′-*O*-isopropylidene-5′-(methylthio)adenosine (14a). To a 0.1 *N* sodium methoxide in methanol solution saturated with methyl mercaptan at 0° was added 5.84 g of **5a**. The solution was allowed to stand at room temperature overnight before it was neutralized with HOAc and evaporated to dryness *in vacuo*. A solution of the residue in $CHCl_3$ was washed with water, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was crystallized from EtOH: yield 3.7 g (95%); mp 195–197°. *Anal.* ($C_{14}H_{18}N_5O_3ClS \cdot 0.25EtOH$) C, H, N.

7-Amino-3-[5-deoxy-2,3-*O*-isopropylidene-5-(methylthio)-β-D-ribofuranosyl]-*v*-triazolo[4,5-*d*]pyrimidine (14b). A mixture of **5b** (535 mg, 1.16 mmol) in 58 ml of 0.1 *N* sodium methoxide in methanol saturated with methyl mercaptan (at 0°) was refluxed for 2 hr before it was evaporated to dryness. The solution of the residue in $CHCl_3$ was washed with water and dried over $MgSO_4$. Evaporation of the $CHCl_3$ gave a yellow glass that crystallized from ethanol: yield 156 mg (40%); mp 121–122°; λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl) 262 (12.2); λ_{max} (pH 7, 0.1 *N* NaOH) 280 (11.8). *Anal.* ($C_{13}H_{18}N_6O_3S$) C, H, N.

5′-(2-Aminoethylthio)-2-chloro-5′-deoxy-2′,3′-*O*-isopropylideneadenosine (15a). A mixture of **5a** (991 mg, 2 mmol), 2-aminoethanethiol hydrochloride (228 mg, 2 mmol), K_2CO_3 (552 mg, 4 mmol), and DMA (25 ml) was heated with stirring at 125° for 25 min and then more 2-aminoethanethiol hydrochloride (228 mg) and K_2CO_3 (552 mg) were added, and the mixture was heated for another 25 min. Evaporation *in vacuo* of the filtered reaction mixture gave a gum that partially dissolved in $CHCl_3$. Evaporation of the filtered $CHCl_3$ solution gave a yellow syrup that was purified by chromatography on thick silica gel plates using 3:1 $CHCl_3$-MeOH as developer. Elution of the bands from the plates gave **5a** (126 mg, 13% recovery) and the product **14a** (205 mg, 26% based on unrecovered **5a**). This tlc homogeneous material was used in the next step without further purification.

7-Amino-3-[5-(2-aminoethylthio)-2,3-*O*-anisylidene-5-deoxy-β-D-ribofuranosyl]-*v*-triazolo[4,5-*d*]pyrimidine (16b). Small pieces of sodium were added to a solution of 2-aminoethanethiol hydrochloride (208 mg, 1.83 mmol) in liquid ammonia (*ca.* 40 ml) until the blue color persisted for 10 min. Compound **6b** (465 mg, 0.915 mmol) was then added slowly with stirring and ammonia solution allowed to evaporate slowly. The residue was dried *in vacuo* before it was shaken with equal volumes (20 ml) of $CHCl_3$ and ice-cold 1 *N* H_2SO_4. The $CHCl_3$ layer was extracted twice with cold 1 *N* H_2SO_4 (10 ml). The total acid solution was chilled and neutralized with 50% NaOH. The resulting precipitate was extracted in $CHCl_3$, which was washed with water and dried over $MgSO_4$. Evaporation of the $CHCl_3$ gave an orange syrup which was purified by chromatography on thick silica gel plates developed with MeOH. The product was eluted with MeOH which was evaporated to give a residue that was dissolved in $CHCl_3$. After filtration through Celite, the $CHCl_3$ solution was evaporated to dryness to give a white glass. An attempt to crystallize this glass from EtOH failed: yield 76 mg (19%); λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl) 265 (15.8); λ_{max} (pH 7) 278 (12.7). *Anal.* ($C_{19}H_{23}N_7O_4S \cdot 0.6C_2H_5OH$) C, H, N.

7-Amino-3-[2,3-*O*-anisylidene-5-deoxy-5-(methylthio)-β-D-ribofuranosyl]-*v*-triazolo[4,5-*d*]pyrimidine (17b). A mixture of **6b** (2.03 g, 4.0 mmol) in 40 ml of 1 *N* methanolic sodium methoxide saturated with methyl mercaptan was refluxed with stirring for 40 min before it was evaporated to dryness *in vacuo*. A solution of the residue in $CHCl_3$ was washed with 0.1 *N* acetic acid several times and then with water before it was dried over $MgSO_4$. Evaporation of the $CHCl_3$ gave a solid that crystallized from MeOH: yield 985 mg (59%); melting point indefinite; λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl) 264 (16.1); λ_{max} (pH 7) 278 (12.6). *Anal.* ($C_{18}H_{20}N_6O_4S$) C, H, N.

2,5′-Di(butylthio)-5′-deoxyadenosine (20). A solution of **9a** (320 mg, 1.00 mmol) and butyl mercaptan (2 ml) in 30 ml of 2 *N* NaOH was heated at 80° for 2 hr. The solid that precipitated from the cold solution was dissolved in $CHCl_3$, and the solution was washed with water and dried over $MgSO_4$. Evaporation of the $CHCl_3$ gave a white solid that was recrystallized from benzene: yield 273 mg (64%); mp 150–152°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 236 (19.5), 275 (13.1). *Anal.* ($C_{18}H_{29}N_5O_3S_2$) C, H, N.

7-Amino-3-[5-deoxy-5-(methylsulfinyl)-β-D-ribofuranosyl]-*v*-triazolo[4,5-*d*]pyrimidine (23b). A solution of **10b** (475 mg, 1.6 mmol) in 15 ml of 50% acetic acid containing 0.16 ml of 30% H_2O_2 was allowed to stand 4 hr at room temperature before it was evaporated to dryness *in vacuo* without heat. The residue was twice dissolved in water and the solution evaporated to dryness. The resultant white glass was crystallized from MeOH. Recrystallization from MeOH gave 345 mg of **22b** (69%): mp 227–229°; λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl) 262 (12.7); λ_{max} (pH 7) 279 (11.5). *Anal.* ($C_{10}H_{14}N_6O_4S$) C, H, N.

1,2,3-Tri-*O*-acetyl-5-deoxy-5-(ethylthio)-D-ribofuranose (30). A solution of **24** (19.3 g, 53.8 mmol) and ethyl mercaptan (40 ml, 538 mmol) in 270 ml of 1 *N* sodium methoxide in EtOH was refluxed for 2 hr. The chilled solution was neutralized with HOAc before evaporation to dryness *in vacuo*. A $CHCl_3$ solution of the residue was washed with $NaHCO_3$ solution, followed by water, and then dried over $MgSO_4$. Evaporation of the $CHCl_3$ gave about 14 g of **26**, which was dissolved in a mixture of 74 ml of dioxane and 184 ml of 0.1 *N* H_2SO_4. After the solution was refluxed for 2 hr, it was neutralized with $Ba(OH)_2$. The filtered solution was evaporated *in vacuo* and the residue dissolved in dry pyridine which was evaporated to dryness. The process was repeated giving about 11 g of **28**, which was dissolved in 97 ml of dry pyridine. Acetic anhydride (24.4 ml) was added dropwise with stirring to the chilled solution. After 1 hr the solution was allowed to warm to room temperature and stand overnight before it was poured into a mixture of 715 ml of ice and 860 ml of $CHCl_3$. The $CHCl_3$ solution was washed with four portions (340 ml) of ice-cold 1 *N* H_2SO_4, followed by water and $NaHCO_3$ solution. Evaporation of the dried $CHCl_3$ solution gave 16.8 g of **30** as an oil characterized by tlc and mass spectrum. It was used in the fusion reaction without further purification.

5-Deoxy-1,2-*O*-isopropylidine-5-(methylthio)-α-D-xylofuranose (32). A solution of 1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose[16] (**31**, 3.44 g, 10 mmol) in 50 ml of 1 *N* sodium methoxide saturated with methyl mercaptan was refluxed for 4 hr before it was evaporated to dryness. The $CHCl_3$ solution of the residue was washed twice with H_2O and then dried over $MgSO_4$ before it was evaporated to dryness. The residue was recrystallized from ether: yield 1.10 g (50%); mp 88–91°. *Anal.* ($C_9H_{16}O_4S$) C, H, N.

1,2,3-Tri-*O*-acetyl-5-deoxy-5-(methylthio)-D-xylofuranose (34). A solution of **32** (3.25 g, 14.8 mmol) in a mixture of 21 ml of dioxane and 51 ml of 0.1 *N* H_2SO_4 was heated at 100° for 2 hr before neutralization with barium hydroxide. The $BaSO_4$ was removed by filtration, and the filtrate was evaporated to dryness to give **33** as an orange oil which was dissolved in dry pyridine (25 ml). Acetic anhydride (6.8 g, 67 mmol) was added slowly to the chilled solution. The solution was allowed to stand overnight at room temperature before it was poured on ice (450 ml) and $CHCl_3$ added. The water was extracted twice with $CHCl_3$ and the combined $CHCl_3$ solution was washed with cold 1 *N* H_2SO_4 until the aqueous layer remained acidic, then with H_2O, then with saturated $NaHCO_3$ solution, and finally with water. Evaporation of the dried ($MgSO_4$) $CHCl_3$ solution gave **34** as a light orange syrup that was used in the fusion reaction without further purification: yield 4 g (89%).

9-[2,3-Di-*O*-acetyl-5-deoxy-5-(methylthio)-β-D-ribofuranosyl]-2,6-dichloropurine (37a). A mixture of 2,6-dichloropurine (**35**) and 1,2,3-tri-*O*-acetyl-5-deoxy-5-(methylthio)ribofuranose (**29**)[11] was fused at 130° with vigorous stirring for 45 min under a 25-mm vacuum. The brown melt was purified by chromatography on a silica gel column using 99:1 $CHCl_3$-MeOH as the eluent: yield of colorless glass, 2.03 g (80%); pmr ($CDCl_3$) δ 2.08, 2.18, 2.20 (3 s, Me), 3.0 (d, CH_2), 4.47 (q, $H_{4'}$), 5.55 (q, $H_{3'}$), 5.86 (t, $H_{2'}$), 6.21 (d, $J_{1'2'}$ = 5 Hz, $H_{1'}$), 8.4 (H_8). This material was used in subsequent reactions without further purification.

2,6-Dichloro-9-[2,3-di-*O*-acetyl-5-deoxy-5-(ethylthio)-β-D-ribofuranosyl]purine (39a). In the manner described for **37a**, **35** (9.9 g) and **30** (16.8 g) gave 16.7 g (71%) of **39a**.

2-Chloro-9-[5-deoxy-5-(methylthio)-D-xylofuranosyl]adenine (40b). A mixture of **35** (1.24 g, 6.54 mmol) and **34** (2.00 g, 6.54 mmol) was heated in a 135° oil bath at 25 mm of pressure for 15 min before it was cooled and *p*-toluenesulfonic acid (33 mg) added. The mixture was again heated in the 135° oil bath at 25 mm of pressure for 40 min. A $CHCl_3$ solution of the dark glass was washed with saturated $NaHCO_3$ solution and then with H_2O before it was dried ($MgSO_4$) and evaporated to dryness: pmr ($CDCl_3$) δ 1.90 (s, CH_3 of Ac of α anomer), 2.2 (several s, SCH_3), 2.85 (m, $2H_{5'}$), 4.6, 4.9, 5.2, 5.5 (m's, $H_{2'}$, $H_{3'}$, $H_{4'}$), 6.18 (d, $J_{1'2'}$ = 2 Hz, $H_{1'}$ of β anomer), 6.65 (d, $J_{1'2'}$ = 5 Hz, $H_{1'}$ of α anomer), 8.2 (s, H_8 of α anomer), 8.35 (s, H_8 of β anomer). The dark syrup **37b** (2.31 g) was dissolved in ethanolic ammonia (saturated at 0°) and the solution allowed to stand at room temperature overnight before it was evaporated to dryness. The residue was chromatographed on a silica gel column. The column was eluted with $CHCl_3$ (600 ml), 99:1 $CHCl_3$-MeOH (600 ml), and then 17:1 $CHCl_3$-MeOH. After 1425 ml of the 19:1 mixture, the β anomer was eluted in the next 510 ml. After an additional 450 ml, the α anomer was eluted in the next 600 ml. Evaporation of the fractions containing the β anomer gave 402 mg (18%) of this compound (**β-40b**) as a glass: λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1 and 7) 264 (14.9); pmr (DMSO-d_6) δ 2.12 (s, CH_3), 2.85 (m, $2H_{5'}$), 4.1 and 4.35 (2 m, $H_{2'}$, $H_{3'}$, $H_{4'}$), 5.57 and 5.59 (2 d, OH), 5.82 (d, $J_{1'2'}$ = <2 Hz, $H_{1'}$), 7.75 (s, NH_2), 8.22 (H_8). *Anal.* ($C_{11}H_{14}ClN_5O_3S$) C, H, N.

Evaporation of the column fractions containing **α-40b** gave a solid that was recrystallized from H_2O: yield 120 mg (6%); mp 190–192°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1 and 7) 264 (17.6); pmr δ 2.14 (s, CH_3), 2.75 (m, $2H_{5'}$), 4.15 (m, $H_{2'}$, $H_{3'}$), 4.5 (m, $H_{4'}$), 5.5–5.9 (OH), 6.26 (d, $J_{1'2'}$ = 4 Hz, $H_{1'}$), 7.7 (br s, NH_2), 8.12 (H_8). *Anal.* ($C_{11}H_{14}ClN_5O_3S \cdot 0.4H_2O$) C, H, N.

9-[5-Deoxy-5-(methylthio)-D-xylofuranosyl]adenine (41b). A mixture of **34** (1.72 g, 5.62 mmol) and 6-chloropurine (**36**, 868 mg, 5.62 mmol) was heated in a 135° oil bath at 25 mm for 15 min. To the cooled melt was added 30 mg of *p*-toluenesulfonic acid, and the mixture was heated at 135° again for about 1 hr. A $CHCl_3$ so-

lution of the cooled reaction mixture was washed with saturated $NaHCO_3$ solution, then H_2O, and dried over $MgSO_4$. Evaporation of the $CHCl_3$ gave a dark solid (1.53 g) that was dissolved in 200 ml of ethanolic ammonia (saturated at 0°). This solution was heated at 80° for 16 hr before it was evaporated to dryness *in vacuo*. The dark residue (1.2 g) was purified by chromatography on thick silica gel plates developed twice in 9:1 $CHCl_3$–MeOH. The two major bands were eluted with methanol giving two nucleosides (586 mg of the faster moving compound and 236 mg of the slower moving). These nucleosides were converted to their picrates in H_2O. The larger sample gave 450 mg (22%) of a picrate: mp 199–201°. Recrystallization from H_2O did not change the melting point. *Anal.* ($C_{11}H_{15}N_5O_3S \cdot C_6H_3N_3O_7$) C, H, N.

Treatment of a solution of the picrate in 9:1 MeOH–H_2O with Dowex 1-X8 (CO_3^{2-} form) gave a colorless solution which was combined with water washes of the resin and evaporated to dryness to give β-41b as a white glass: yield 188 mg (90% from picrate); λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7 and 13) 259 (14.2); pmr (DMSO-d_6) δ 2.14 (s, CH_3), 2.8 (m, $2H_{5'}$), 4.04 (m, $H_{3'}$), 4.3 (m, $H_{2'}$, $H_{4'}$), 5.9 and 6.05 (2 d, OH), 5.9 (d, $J_{1'2'}$ = <2 Hz, $H_{1'}$), 7.3 (br s, NH_2), 8.16 and 8.25 (H_2, H_8).

The picrate of the smaller sample was converted to the free nucleoside in the same manner: yield of essentially pure material, 77 mg (6.8%). This material crystallized from water: mp 172–173°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7 and 13) 259 (14.9); pmr (DMSO-d_6) δ 2.15 (s, CH_3), 2.7 (m, $2H_{5'}$), 3.3–3.8 (OH), 4.18 (m, $H_{2'}$, $H_{3'}$), 4.55 (m, $H_{4'}$), 6.35 (d, $J_{1'2'}$ = 4 Hz, $H_{1'}$), 7.18 (br s, NH_2), 8.14 (s, H_2, H_8). *Anal.* ($C_{11}H_{15}N_5O_3S \cdot 0.5H_2O$) C, H, N.

2-Chloro-5'-deoxy-5'-(ethylthio)adenosine (42a). A solution of **39a** (3.3 g) in 250 ml of ethanolic ammonia (saturated at 0°) was allowed to stand at room temperature for 2 days before it was evaporated to dryness *in vacuo*. The residue was dissolved in water and treated with 1 equiv of picric acid in water. Treatment of the picrate with Dowex 1-X8 (CO_3^{2-}) gave a cream-colored glass that was chromatographed on a silica gel column using 9:1 $CHCl_3$–MeOH as the eluent. The product obtained from this column finally crystallized from water on long standing: yield 561 mg. An additional amount of pure material (292 mg) was obtained from the filtrate by chromatography on a thick plate using 9:1 $CHCl_3$–MeOH as developer: total yield 853 mg (36%); melting point indefinite; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 264 (15.3); pmr (DMSO-d_6) δ 1.15 (t, CH_3), 2.5 (m, CH_2 + DMSO-d_5), 2.9 (m, $2H_{5'}$), 4.1 (m, $H_{3'}$, $H_{4'}$), 4.7 (t, $H_{2'}$), 5.85 (d, $J_{1'2'}$ = 5 Hz, $H_{1'}$), 7.7 (br, NH_2), 8.38 (s, H_8). *Anal.* ($C_{12}H_{16}N_5O_3ClS$) C, H, N.

Elution of a second band on the thick plate gave 56 mg of another nucleoside identified by its uv, mass, and pmr spectra as 2-chloro-5'-deoxy-5'-(ethylsulfinyl)adenosine: λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 264 (12.5); mass spectrum (70 eV) *m/e* 332 (M^+ – Et), 316 (M^+ – OEt), 284 (M^+ – EtSO); 198 (B^+ + CH_2O), 169 (B^+ + H); pmr (DMSO-d_6) δ 1.2 (sextet, CH_3), 2.8 (m, CH_2 of Et), 3.3 (m, $2H_{5'}$), 4.3 (m, $H_{3'}$, $H_{4'}$), 4.75 (m, $H_{2'}$), 5.9 (3, $J_{1'2'}$ = 6 Hz, $H_{1'}$), 7.8 (br, NH_2), 8.38 (s, H_8).

9-[2,3-Di-*O*-acetyl-5-deoxy-5-(methylthio)-β-D-ribofuranosyl]-2,6-diazidopurine (43). A solution of **37a** (921 mg, 2.12 mmol) and sodium azide (277 mg, 4.24 mmol) in a mixture of 15 ml of EtOH and 1 ml of H_2O was refluxed for 1 hr, filtered, and evaporated to dryness *in vacuo*. A $CHCl_3$ solution of the residue was washed with H_2O, dried over $MgSO_4$, and then evaporated to dryness *in vacuo*: yield 981 mg.

2-Azido-5'-deoxy-5'-(methylthio)adenosine (46). A solution of **43** (890 mg) in 50 ml of absolute EtOH containing 5% Pd/C (184 mg) was hydrogenated at room temperature and atmospheric pressure. The hydrogen atmosphere was changed at 0.5, 1, and 2 hr. Evaporation of the filtered solution *in vacuo* gave a cream-colored glass (**45**) that was dissolved in methanolic ammonia (saturated at 0°). After standing overnight at room temperature, the solution was evaporated *in vacuo* giving an orange syrup (655 mg), which was converted to its picrate in water. The picrate was converted back to **46** by treatment with Dowex 1-X8 (CO_3^{2-}). After much difficulty, a crystalline solid was finally obtained: yield 89 mg (17%); melting point indefinite; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 231 (5.18), 272 (14.1), 310 (sh), 323 (sh); ir strong band at 2230 cm^{-1} (azide); pmr (DMSO-d_6) δ 2.1 (s, CH_3), 2.85 (m, $2H_{5'}$), 4.1 (m, $H_{3'}$, $H_{4'}$), 4.7 (t, $H_{2'}$), 5.25 and 5.45 (2 d, OH), 5.82 (d, $J_{1'2'}$ = 6 Hz, $H_{1'}$), 7.55 (br s, NH_2), 8.28 (H_8). *Anal.* ($C_{11}H_{14}N_8O_3S$) C, H, N.

2-Amino-5'-deoxy-5'-(methylthio)adenosine (49) Picrate. A solution of **43** (981 mg) in 50 ml of absolute EtOH containing 200 mg of 5% Pd/C was hydrogenated at room temperature and atmospheric pressure. The hydrogen atmosphere was changed at 0.5, 1, and 2 hr. The procedure had to be repeated with fresh catalyst to obtain complete reduction of **43**. After filtration, the solution was evaporated to a cream-colored glass (**47**): yield 516 mg (61%).

A solution of **47** in 28 ml of 0.28 *N* sodium methoxide in methanol was refluxed for 45 min and then neutralized with acetic acid. The residue from evaporation of the solution was dissolved in water and treated with 1 equiv of picric acid. The resulting solid was recrystallized from water: yield 227 mg (32%); mp 198° dec. *Anal.* ($C_{11}H_{16}N_6O_3S \cdot C_6H_3N_3O_7 \cdot 0.2H_2O$) C, H, N.

Treatment of the picrate (175 mg) with Dowex 1-X8 (CO_3^{2-}) gave 76 mg of **49** as a white glass: λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 253 (11.3), 293 (9.82); λ_{max} (pH 7) 256 (9.15), 280 (9.75).

2-Amino-5'-deoxy-5'-(ethylthio)adenosine (50). Reaction of **39** (12.6 g) with sodium azide as described for **37** gave **44**: yield 12.09 g (93%). Reduction of **44** (12.0 g) as described for **43** gave **48**: yield 9.9 g (92%). Treatment of **48** (1.25 g) with sodium methoxide as described for **47** gave **50**: yield 531 mg (53%); mp 183–185°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7) 257 (9.75), 280 (10.4). *Anal.* ($C_{12}H_{18}N_6O_3S$) C, H, N.

5'-Deoxy-5'-(ethylthio)-2-fluoroadenosine (51). A solution of **52** (220 mg) in ethanolic ammonia (25 ml, saturated at 0°) was allowed to stand at 5° overnight before it was evaporated to dryness. The residue was recrystallized from ethanol: yield 100 mg (57%); mp 189–190°; λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl, 0.1 *N* NaOH) 262 (14.6), 267 (sh). *Anal.* ($C_{12}H_{16}N_5O_3FS$) C, H, N.

5'-Deoxy-5'-(ethylthio)-2-fluoroadenosine 2',3'-Diacetate (52) and 5'-Deoxy-5'-(ethylthio)isoguanosine 2',3'-Diacetate (53). To a suspension of **48** (1.11 g, 2.7 mmol) in fluoboric acid (14.5 ml) was added $NaNO_2$ (338 mg, 4.9 mmol) in H_2O (0.7 ml) with vigorous stirring at −20°. After 40 min, 50 ml of $CHCl_3$ was added and the mixture neutralized at −20° with *ca.* 5 ml of 5% NaOH. Evaporation of the dried $CHCl_3$ layer gave a cream-colored glass: yield 910 mg. A solution of this material in benzene was poured onto a silica gel column (300 g, Davidson, 140–200 mesh). It was eluted with a linear gradient of 2 l. of ethyl acetate into 2 l. of benzene at a flow rate of 10 ml/min. From the column was obtained 405 mg of **52** (37%) and 170 mg of **53** (15%). Identification was based on their uv spectra.

5'-Deoxy-5'-(ethylthio)isoguanosine (54). Compound **53** (170 mg) was deacetylated as described above for **52**: yield 40 mg (30%); mp 205° dec; λ_{max} nm ($\epsilon \times 10^{-3}$) (0.1 *N* HCl) 236 (5.66), 282 (8.82); λ_{max} (0.1 *N* NaOH) 254 (6.57), 284 (7.55). *Anal.* ($C_{12}H_{17}N_5O_4S \cdot 1.25H_2O$) C, H, N.

Methyl 2,3-Di-*O*-benzyl-5-*O*-tosyl-α-D-arabinofuranoside (56). A solution of methyl 2,3-di-*O*-benzyl-α-D-arabinofuranoside[19] (**55**, 4.5 g, 13.1 mmol) and tosyl chloride (3.7 g, 19 mmol) was allowed to stand at −20° for 4 days before 1.35 ml of H_2O was added, and the solution was stirred at room temperature for 45 min. It was then poured into 200 ml of saturated $NaHCO_3$ solution containing ice, which was then extracted with three 50-ml portions of $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, 0.1 *N* H_2SO_4, and then water and dried over $MgSO_4$ before evaporation to dryness: yield of syrup 6.3 g; mass spectrum (70 eV) *m/e* 498 (M^+), 467 (M^+ – OMe), 439 (M^+ – MeO_2CH), 407 (M^+ – $C_6H_5CH_2$), 375 (M^+ – $C_6H_6CH_2$ – CH_3OH); pmr (DMSO-d_6) δ 2.4 (s, CH_3 on phenyl), 3.24 (s, OCH_3), 3.9 and 4.15 (m's, $H_{2'}$, $H_{3'}$, $H_{4'}$, $2H_{5'}$), 4.5 (m, $2CH_2$ of benzyl), 4.9 (s, $H_{1'}$), 7.3 and 7.8 (m's, phenyl).

Methyl 2,3-Di-*O*-benzyl-5-deoxy-5-(methylthio)-α-D-arabinofuranoside (57). A solution of **56** (6.3 g, 12.5 mmol) in 62 ml of 1 *N* NaOMe in MeOH (saturated with MeSH at 0°) was refluxed for 5 hr before it was evaporated to dryness. A $CHCl_3$ (200 ml) suspension of the residue was washed with saturated $NaHCO_3$ solution and then with water before it was dried over $MgSO_4$. Evaporation of the $CHCl_3$ gave a yellow oil: yield 4.0 g; mass spectrum (70 eV) *m/e* 343 (M^+ – OCH_3), 283 (M^+ – $C_6H_5CH_2$); pmr (DMSO-d_6) δ 2.1 (s, SCH_3), 2.75 (d, $J_{4'5'}$ = 6 Hz, $2H_{5'}$), 3.3 (s, OCH_3), 3.85 (q, $H_{3'}$), 3.95 (m, $H_{2'}$), 4.1 (q, $H_{4'}$), 4.58 (m, $2CH_2$ of benzyl), 4.97 (s, $H_{1'}$), 7.4 (m, phenyl).

2,3-Di-*O*-benzyl-5-deoxy-5-(methylthio)-D-arabinose (58). A solution of **57** in 9:1 trifluoroacetic acid–water (40 ml) was allowed to stand at room temperature for 2 hr before it was poured onto 400 ml of ice. The aqueous solution was extracted with methylene chloride which was washed twice with saturated $NaHCO_3$ and then twice with H_2O before it was dried over $MgSO_4$ and evaporated to dryness. The dark residue was purified by chromatography on a silica gel column: yield 1.24 g (51%).

Methyl 2,3-Di-*O*-benzyl-5-*O*-benzoyl-α-D-arabinofuranoside (59). A mixture of **55** (12.8 g, 37.2 mmol) and benzoyl chloride

(6.3 g, 45 mmol) in dry pyridine (165 ml) was allowed to stir overnight at room temperature before it was poured into 420 ml of ice water. The water was extracted with three 250-ml portions of $CHCl_3$, which were combined and washed with saturated $NaHCO_3$ solution (250 ml), three 300-ml portions of 3 *N* H_2SO_4, and four 250-ml portions of H_2O before being dried over $MgSO_4$ and evaporated to dryness: yield of syrup 16.1 g; pmr ($CDCl_3$) δ 3.4 (s, CH_3), 4 (m, $2H_5$), 4.5 (m, H_2, H_3, H_4, CH_2 of benzyl), 4.99 (s, H_1), 7.3 and 8.0 (2 m, phenyl). The material was converted, without further purification, to the chloro sugar **60**.

9-[2,3-Di-*O*-benzyl-5-deoxy-5-(methylthio)-D-arabinofuranosyl]adenine (63). A. A mixture of *N*-benzoyladenine (84 mg, 0.35 mmol), **64** [prepared from 100 mg (0.28 mmol) of **58**], and Linde 4A molecular seive (1 g) in ethylene chloride (20 ml) was stirred at 55° for 11 days before it was filtered and the solids were washed with hot benzene. The residue from evaporation of the benzene (filtrate and wash) was purified by chromatography on thick silica gel plates developed twice in 99:1 $CHCl_3$–MeOH. Elution gave 40 mg of *N*-benzoyladenine and 45 mg of nucleosides that were refluxed for 0.5 hr in 10 ml of 0.1 *N* sodium methoxide in methanol. The solution was neutralized with acetic acid and evaporated to dryness. The residue was purified by chromatography on a thick silica gel plate developed in 19:1 $CHCl_3$–MeOH. Elution with MeOH gave an orange semisolid (35 mg): pmr (DMSO-d_6) δ 2.10 (s, CH_3 of β), 2.16 (s, CH_3 of α), 2.85 (d, $J_{4',5'}$ = 6 Hz, $2H_{5'}$ of α), 2.55 (d, $J_{4',5'}$ = 6 Hz, $2H_{5'}$ of β), 4.2 and 4.4 (2 m, $H_{2'}$, $H_{3'}$, $H_{4'}$), 4.4 (s, CH_2 of 2'-*O*-benzyl of β), 4.65 (s, CH_2 of 2'- and 3'-*O*-benzyl of α), 2.7 (s, CH_2 of 3'-*O*-benzyl of β), 4.8 (t, $H_{2'}$ of α), 6.3 (d, $J_{1',2'}$ = 3 Hz, $H_{1'}$ of α), 6.47 (d, $J_{1',2'}$ = 4 Hz, $H_{1'}$ of β), 7 and 7.4 (m's, phenyl and NH_2), 8.19 and 8.20 (2 s, H_2 and H_8 of β), 8.22 and 8.27 (2 s, H_2 and H_8 of α). The ratio of β to α was about 3:2.

B. A mixture of *N*-benzoyladenine (480 mg, 2 mmol), **64** [prepared from 384 mg (1.07 mmol) of **58**], and Linde AW-500 molecular seive (1 g) in benzene (100 ml) was heated with stirring at 55° for 4 days before it was filtered and the solids were washed with benzene. The benzene (filtrate and wash) was evaporated to an orange syrup (300 mg) which was refluxed for 0.5 hr in 22 ml of 0.1 *N* NaOMe in methanol. This solution was neutralized with acetic acid before it was evaporated to an orange syrup that was purified by chromatography on thick silica gel plates developed in 19:1 $CHCl_3$–MeOH. Elution of the major band with MeOH gave the product as a syrup (50 mg). The pmr spectrum was very similar to that of the products obtained as described in A above, except that it showed the anomer ratio to be about 1β:2α.

2,3-Di-*O*-benzyl-5-deoxy-5-(methylthio)-α-D-arabinofuranosyl Chloride (64). A solution of **58** (36 mg) in 5 ml of ethereal HCl (saturated at 0°) was allowed to stand at 5° for 3 days before it was evaporated to dryness. The residue was twice dissolved in benzene and the solution evaporated to dryness, giving a syrup whose identity was established by its reaction with methanol to give methyl 2,3-di-*O*-benzyl-5-deoxy-5-(methylthio)-β-D-arabinofuranoside: pmr (DMSO-d_6) δ 2.1 (s, SCH_3), 2.7 (m, $2H_5$), 3.32 (s, OCH_3), 4.0 (m, H_2, H_3, H_4), 4.55 and 4.65 (2 m, $2CH_2$ of benzyl), 4.92 (d, J_{12} = 4 Hz, H_1), 7.34 (m, phenyl).

9-(5-*O*-Benzoyl-2,3-di-*O*-benzyl-β-D-arabinofuranosyl)-*N*-benzoyladenine (65). A solution of **59** (16.1 g, 36 mmol) in 225 ml of glacial acetic acid saturated with dry HCl at 10° was allowed to stand for 3 hr before evaporation to dryness *in vacuo*. Toluene was added and the solution again evaporated to dryness *in vacuo*. A solution of the residue in 500 ml of ether saturated with HCl at 0° was allowed to stand 3 days at 4° before it was evaporated to dryness *in vacuo*. Three times the residue was dissolved in toluene and the toluene removed *in vacuo*: pmr ($CDCl_3$) δ 4.03 and 4.5 (2 m, H_2, H_3, H_4, $2H_5$), 6.17 (s, H_1), 7.3 and 8.0 (2 m, phenyl). A solution of the residue **60** and *N*-benzoyladenine (8.6 g, 36 mmol) in dichloroethane (600 ml) containing Linde 4A molecular seive (72 g) was heated with stirring at 60° for 3 days. More seive (36 g) was added and the heating continued for 9 more days before the mixture was filtered and the filtrate taken to dryness *in vacuo*. A solution of the residue in ethanol was treated, charcoal filtered through a Celite pad, and evaporated to dryness: yield 19.5 g of beige foam that was used in the next step without further purification; pmr ($CDCl_3$) δ 4.2–4.8 (m's, $H_{2'}$, $H_{3'}$, $H_{4'}$, $2H_{5'}$), 6.58 (d, $J_{1',2'}$ = 4 Hz, $H_{1'}$), 6.9–7.6 and 8 (m's, phenyl), 8.32 and 8.75 (2 s, H_2, H_8), 9.2 (br s, NH).

***N*-Benzoyl-9-(2,3-di-*O*-benzyl-5-*O*-tosyl-β-D-arabinofuranosyl)adenine (67).** A two-phase mixture of **65** (10 g, 15.2 mmol), pyridine (154 ml), and 2 *N* NaOH (154 ml) was stirred at room temperature for 1.5 hr before it was neutralized with Ag 50W X4 resin to pH 7. The resin was removed by filtration and washed with $CHCl_3$, and the $CHCl_3$ was combined with the $CHCl_3$ used to extract the filtrate (three 300-ml portions). The $CHCl_3$ solution was washed with H_2O and dried over $MgSO_4$ before concentration to a small volume: pmr ($CDCl_3$) δ 3.9 (m, $2H_{5'}$), 4.15 (m, $H_{4'}$), 4.3 and 4.4 (2 m, H_2, H_3, CH_2 of 2'-*O*-benzyl), 4.7 (s, CH_2 of 3'-*O*-benzyl), 6.4 (d, $J_{1',2'}$ = 4 Hz, $H_{1'}$), 6.9, 7.2, and 7.4 (3 m, phenyl), 8.03, 8.27 (H_2, H_8). A solution of this material (66) and tosyl chloride (4.5 g, 23.6 mmol) in 200 ml of pyridine was allowed to stand at −20° for 6 days before H_2O (2 ml) was added and 45 min later the mixture poured into 350 ml of saturated $NaHCO_3$ solution containing ice. This solution was extracted with three 200-ml portions of $CHCl_3$, which were combined and washed with water (250 ml), four 250-ml portions of ice-cold 1 *N* H_2SO_4, and then three 250-ml portions of H_2O before drying over $MgSO_4$. Evaporation of the $CHCl_3$ gave a pale yellow foam (10.9 g) which was used in the next step without further purification: pmr ($CDCl_3$) δ 2.44 (s, CH_3), 4.2–4.7 (m's, $H_{2'}$, $H_{3'}$, $H_{4'}$, $2H_{5'}$), 6.4 (d, $J_{1',2'}$ = 4 Hz, $H_{1'}$), 6.8–8.1 (m's, phenyl), 8.13 and 8.62 (C_2, C_8), 9.1 (br s, NH).

9-[2,3-Di-*O*-benzyl-5-deoxy-5-(methylthio)-β-D-arabinofuranosyl]adenine (68). A solution of **67** (10.7 g, 15.2 mmol) in 25 ml of 1 *N* sodium methoxide in methanol (saturated at 0° with methyl mercaptan) was allowed to stand at room temperature overnight before it was neutralized with glacial acetic acid and then evaporated to dryness *in vacuo*. A suspension of the residue in H_2O was boiled to remove methyl benzoate by steam distillation. The cooled water suspension was then extracted with $CHCl_3$, which was dried over $MgSO_4$ before evaporation to dryness. The residue crystallized from MeOH (charcoal): yield 2.55 g (39%). Part of this material (718 mg) was recrystallized from MeOH: yield 641 mg; mp 126–127°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7 and 13) 260 (14.0); pmr (DMSO-d_6) δ 2.51 (s, CH_3), 2.91 (d, J = 6 Hz, $2H_{5'}$), 4.2 and 4.4 (2 m, $H_{2'}$, $H_{3'}$, $H_{4'}$, CH_2 of 2'-*O*-benzyl), 4.72 (s, CH_2 of 3'-*O*-benzyl), 6.46 (d, $J_{1',2'}$ = 4 Hz, $H_{1'}$), 7.0 and 7.35 (2 m, phenyl), 8.18 and 8.21 (2 s, C_2, C_8). The difference in the positions of the signals from the benzyl methylene groups results from the upfield shift of the benzyloxy group cis to and thus shielded by the purine ring.[24] *Anal.* ($C_{11}H_{15}N_5O_3S$) C, H, N.

9-[5-Deoxy-5-(methylthio)-β-D-arabinofuranosyl]adenine (69). To a suspension of **68** (635 mg, 1.33 mmol) in liquid ammonia (25 ml) was added slowly with stirring tiny pieces of sodium (213 mg). After the ammonia had evaporated, the residue was purified by chromatography on thick silica gel plates developed in 3:1 $CHCl_3$–MeOH. Elution of the principal band with hot MeOH gave a white solid that was recrystallized from water: yield 256 mg (65%); mp 202–204°; λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7 and 13) 259 (15.3); pmr (DMSO-d_6) δ 2.1 (s, Me), 2.88 (d, $J_{4',5'}$ = 6 Hz, $2H_{5'}$), 3.9 (m, $H_{4'}$), 4.14 (m, $H_{2'}$ and $H_{3'}$), 5.6 and 5.7 (2 d, OH), 6.3 (d, $J_{1',2'}$ = 4 Hz, $H_{1'}$), 7.2 (s, NH_2), 8.13 and 8.15 (2 s, H_2 and H_8). *Anal.* ($C_{11}H_{15}N_5O_3S$) C, H, N.

Material from the minor band was rechromatographed giving an additional 10 mg of **69** and 26 mg of another nucleoside (**70**): λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 7 and 13) 259 (15.4); pmr (DMSO-d_6) δ 3.95 (d, $J_{4',5'}$ = 6 Hz, $2H_{5'}$), 4.0 (m, $H_{4'}$), 4.25 (m, $H_{2'}$, $H_{3'}$), 6.5 (d, $J_{1',2'}$ = 4 Hz, $H_{1'}$), 8.6 (H_8), 8.95 (H_2), 9.18 (H_6).

9-[2-*O*-Benzyl-5-deoxy-5-(methylthio)-β-D-arabinofuranosyl]adenine (71). To a suspension of palladium (from the reduction of 40 mg of $PdCl_2$) in MeOH (15 ml) was added **68** (27 mg). Reduction was carried out at 50 psi at room temperature in a Parr shaker. Two 20-mg portions of $PdCl_2$ were added during the course of 2 hr. After removal of the catalyst, the solution was evaporated to dryness, and the residue was purified by chromatography on a thick plate developed in 9:1 $CHCl_3$–MeOH. **68** (10 mg) was recovered, and 6 mg of **71** was obtained by elution: pmr (DMSO-d_6) δ 2.1 (s, CH_3), 2.9 (d, $J_{4',5'}$ = 6 Hz, $2H_{5'}$), 3.95 and 4.3 (m's, H_2, H_3, H_4, CH_2 of benzyl), 6.48 (d, $J_{1',2'}$ = 4.5 Hz, $H_{1'}$), 6.8 and 7.3 (2 m, phenyl), 8.18 and 8.21 (2 s, H_2, H_8). The lower field signal from the CH_2 group, the 3-*O*-benzyl group of **68**, is missing from this spectrum, and the higher field signal from the CH_2 of the benzyl group appears as an AB pair, indicating nonequivalence of the two protons. These facts are only compatible with the *O*-benzyl group at C-2 cis to the purine ring.

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Nucleoside Peptides. 6. Synthesis of Certain *N*-[5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]amino Acids Related to Naturally Occurring Intermediates in the Purine Biosynthetic Pathway

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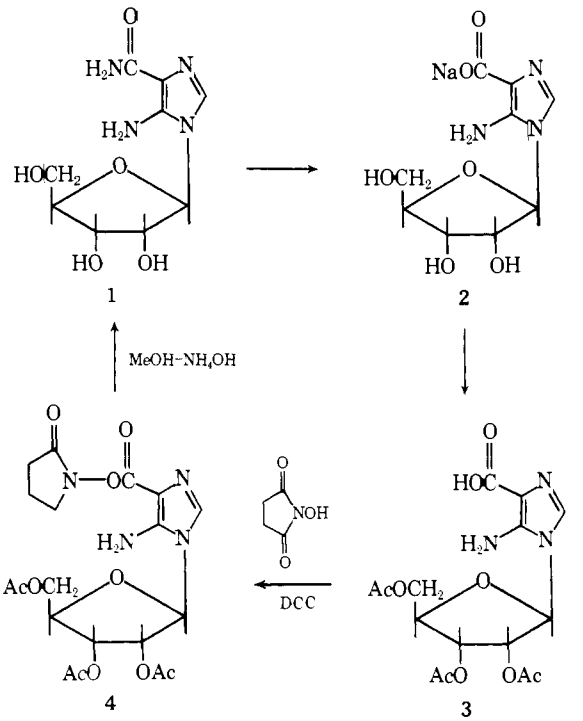
Alkaline hydrolysis of AICA ribonucleoside has provided a new synthesis of sodium 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate in good yield. Selective acetylation of this product afforded 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid. Various appropriately blocked amino acids have been coupled to the 4-carboxy group of this compound *via* the *N*-hydroxysuccinimidyl ester. Subsequent deblocking procedures have provided good yields of the title compounds.

AICAR [5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide 5′-phosphate],[1] an intermediate in the *de novo* purine biosynthetic pathway, has been synthesized enzymatically from 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylic acid 5′-phosphate *via* the amino acid nucleotide *N*-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]-L-aspartic acid 5′-phosphate.[2] These nucleotides, as well as the corresponding nucleosides, have been synthesized chemically, but in such small yields that the physical characteristics of these compounds for the most part have not yet been studied.† It was of interest to investigate the laboratory scale synthesis of the nucleoside analogs of these interesting imidazole intermediates, as well as a number of their amino acid and peptide derivatives. It seemed reasonable that these nucleoside peptides might well possess special biological properties which would provide useful medicinal agents as discussed in the first paper of this series.[4,5] The recent commercial availability of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide‡ (1, AICA ribonucleoside) provided the necessary source of starting material to initiate this study (Scheme I).

It is well known that conversion of carboxamides to carboxylic acids can be effected either by alkaline or acid conditions.[6] The use of acidic media was precluded because the glycosyl linkage of 1 (Scheme I) is acid labile.

Scheme I



†For a recent review of the subject of imidazole nucleosides and nucleotides, see ref 3.

‡Purchased from ICN Nutritional Biochemicals Corp., Cleveland, Ohio 44128.