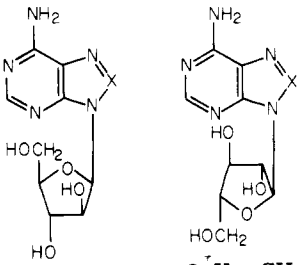
2-Substituted Derivatives of 9-α-D-Arabinofuranosyladenine and 9-α-D-Arabinofuranosyl-8-azaadenine

John A. Montgomery,* Anita T. Shortnacy, G. Arnett, and W. M. Shannon

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205. *Received August 25, 1976*

2-Substituted derivatives of 9-α-D-arabinofuranosyladenine were prepared via the fusion of tetra-*O*-acetyl-α-D-arabinofuranose with 2,6-dichloropurine followed by stepwise displacement of the chloro groups. A different approach, the reaction of 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl bromide with 2,6-bis(methylthio)-8-azapurine in refluxing toluene in the presence of molecular sieve followed by stepwise reaction of the blocked nucleoside with methanolic ammonia and then other nucleophiles, gave 2-substituted derivatives of 9-α-D-arabinofuranosyl-8-azaadenine. In contrast to the parent compounds, none of these 2-substituted derivatives showed significant antiviral activity.

The activity of 9-β-D-arabinofuranosyladenine (**1**) against DNA viruses is well known.[1,2] More recently the antiviral activity of the α-anomer (**3**) of **1** and 9-α-D-arabinofuranosyl-8-azaadenine (7-amino-9-α-D-arabinofuranosyl-1,2,3-triazolo[4,5-*d*]pyrimidine, **4**) has been demonstrated (**2**, the β-anomer of **4**, is cytotoxic but has no antiviral activity).[3] The activity of **4** has also been observed by Smith et al.[4] Since the α configuration is unnatural with the 5-hydroxymethyl group on the opposite side of the furanose ring from the purine base, whereas in the natural ribonucleosides, it is on the same side, the ability of these α-nucleosides to serve as substrates for adenosine kinase was then investigated, and they were found to be good substrates for this activating enzyme.[5] These results made the antiviral activity of the compounds appear more reasonable and, since little synthetic work on α-arabinonucleosides has been reported,[6] led us to undertake the synthesis of a few derivatives of **3** and **4** substituted at the 2 position for an investigation of their potential as antiviral agents.

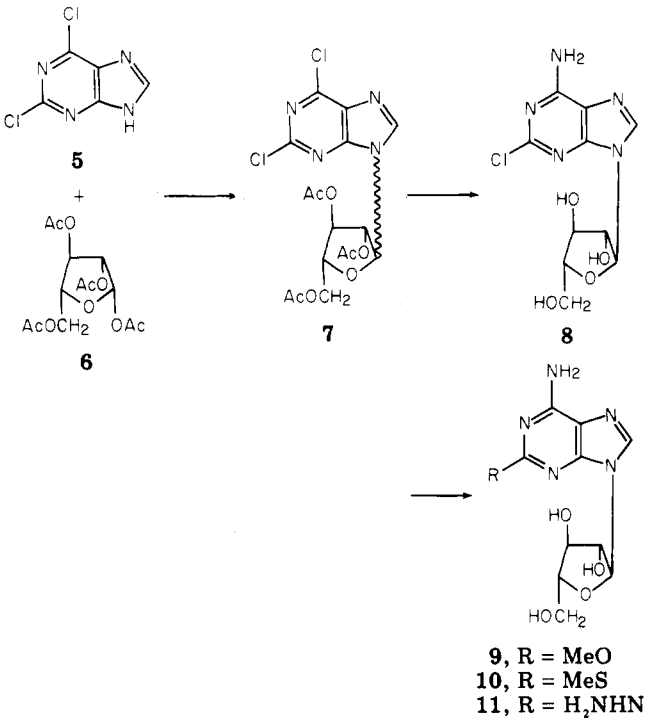


1, X = CH
2, X = N

3, X = CH
4, X = N

Chemistry. Fusion of tetra-*O*-acetyl-α-D-arabinofuranose with 2,6-dichloropurine has been reported to give the trans nucleoside, 9-(2,3,5-tri-*O*-acetyl-α-D-arabinofuranosyl)-2,6-dichloropurine (α-**7**), containing a small amount of the cis anomer (β-**7**),[7] in contrast to the fusion of tetra-*O*-acetyl-β-D-ribofuranose with this purine, which gave no detectable amount of the cis (α) anomer.[8] A reinvestigation of the fusion reaction with the arabino sugar by means of ^{1}H NMR spectrometry and high-pressure liquid chromatography revealed that the ratio of trans (α) to cis (β) nucleoside is actually about 4–5 to 1. If the fusion with the ribo sugar is carried out under the same conditions, more drastic than those previously employed,[8] even more of the cis nucleoside is formed; the ratio of trans (β) to cis (α) was 2–3 to 1. In any case, the fusion reaction is quite satisfactory for the preparation of α-arabinonucleosides since, after treatment of **7** with methanolic ammonia to give **8**, most of the β-anomer could be removed from the α by virtue of the greater solubility of the α-anomer in methanol.

Treatment of **8** with sodium methoxide, sodium methyl mercaptide, and hydrazine resulted in a smooth displacement of the chlorine at C-2 to give the desired 2-substituted derivatives (**9**–**11**) of 9-α-D-arabinofuranosyladenine.



9, R = MeO
10, R = MeS
11, R = H_2NHN

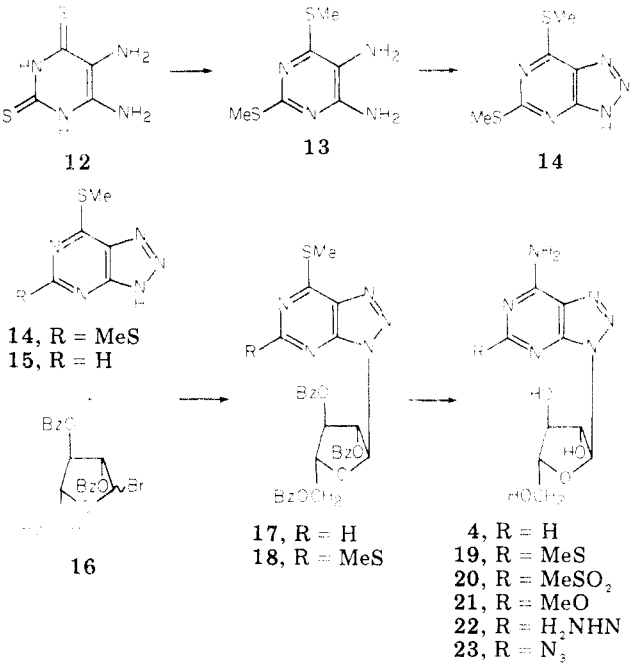
Originally, 9-α-D-arabinofuranosyl-8-azaadenine (**4**) was prepared by the debenzylation of 9-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-8-azaadenine, which in turn was obtained along with the β-anomer (2β:1α) from the reaction of the corresponding bromo sugar with *N*-nonanoyl-8-azaadenine.[9] This nucleoside is more conveniently prepared by a procedure previously described for the preparation of 8-azaadenosine.[10] 7-(Methylthio)-*v*-triazolo[4,5-*d*]pyrimidine (**15**) was allowed to react with 2,3,5-tri-*O*-benzoylarabinofuranosyl bromide (**16**) in refluxing toluene in the presence of molecular sieve. Treatment of the blocked nucleoside **17** with methanolic ammonia gave a 52% yield of pure 9-α-D-arabinofuranosyl-8-azaadenine (**4**). A very small amount of the 8-isomer (ca. 2%) was also obtained but was not isolated free of the 9-isomer. This procedure thus appears preferable to fusion reaction with **15**, which gives lower yields of the desired isomer (**17**) mixed with significant quantities of other position isomers and unreacted sugar and which requires, therefore, purification of **17** by chromatography before conversion to **4**.[4,11]

The success of the bromo sugar procedure for the synthesis of **4** suggested its use for the preparation of

Table I. ^{1}H NMR Data[a]

	2-Me	$H_{5'}$	$H_{4'}$	$H_{3'}$	$H_{2'}$	$H_{1'}$ ($J_{1'2'}$, Hz)
Major product	2.53	3.60	4.12		5.09	6.06 (6)
Minor product	2.45	3.56	4.05		4.79	5.96 (5)
2		3.60	4.06	4.30	4.90	6.21 (5)
24		3.63	4.10	4.35	4.64	6.12 (3.5)

[a] δ in parts per million.



2-substituted derivatives of 9-α-D-arabinofuranosyl-8-azaadenine via 2,6-bis(methylthio)-8-azapurine [5,7-bis-(methylthio)-1,2,3-triazolo[4,5-*d*]pyrimidine (**14**)], because of both the difficulty in preparing 2,6-dichloro-8-azapurine (5,7-dichloro-1,2,3-triazolo[4,5-*d*]pyrimidine) and the unusual reactivity of the chlorine at C-6 of this compound, making its isolation and utilization a problem.[12] In spite of the fact that the methylthio group of 2-(methylthio)-adenosine is difficult to displace,[13] the use of the methylthio group seemed indicated since the additional nitrogen of the triazole ring in the 8-azapurine series should enhance the reactivity of this group. Consequently, 2,6-bis(methylthio)-8-azapurine (**14**) was prepared by the nitrosation of 4,5-diamino-2,6-bis(methylthio)pyrimidine (**13**),[14] which in turn was prepared by the methylation of 4,5-diamino-1,6,2,3-tetrahydropyrimidine-2,6(1,3*H*)-dithione (**12**). Reaction of **14** with **16** was carried out in toluene in the presence of molecular sieve, as described above. Treatment of the crude nucleoside, which was identified by its chromatographic behavior (see above), with methanolic ammonia at room temperature resulted in O-debenzoylation and displacement of the 7-methylthio group, the latter reaction being evidence of the enhanced reactivity of the methylthio group of this ring system. From this reaction, two nucleosides were obtained, a major and a very minor product. The identification of the major product is based on the results described above in the reaction of **16** with **15** and, since the pure 8-isomer could not be isolated in this case because of its low yield, on previous work—the reaction of 7-(methylthio)-1,2,3-triazolo[4,5-*d*]pyrimidine with 1,2,3-tri-*O*-acetyl-D-ribofuranosyl chloride under the same condition (followed by conversion by ammonia to the corresponding amino compounds)[10]—and on a comparison of the ^{1}H NMR spectra of the major product and its isomer with those of 8-azaadenosine (**2**) and its 8-isomer (**24**)[10] (see Table I). In both cases the doublet from anomeric protons of major products occurs downfield from that of the minor product (**24** is the minor product[10]) and has a larger coupling constant. On this basis, structure **19** is proposed for the major product and the minor product is presumed to be the 8-isomer of **19**. HPLC analysis of **19** showed it contained 3% of the minor product and of the minor product showed it contained about 6% of **19**.

Attempted displacement of the methylthio group of **19** by the methoxide ion to prepare **21** resulted in cleavage of the sugar from the 8-azapurine, whereas displacement by hydrazine to give **22** occurred. Identity of the product as **22** is based on spectral data and elemental analyses, which, although all the elements (C, H, N) were slightly low for **22** indicating an impurity, have the proper ratio. Treatment of **22** with nitrous acid gave a mixture from which a nucleoside was isolated by HPLC that was homogeneous and showed a strong azide band at 2150 cm^{-1} in its infrared spectrum, and a field desorption mass spectrum gave the molecular ion (M + 1) for the structure **23**. The small amount of material obtained pure did not allow further characterization.

Since displacement of the methylthio group of **19** by methoxide could not be accomplished, it was oxidized to the methylsulfonyl group, a better leaving group. Treatment of the resulting nucleoside (**20**) with sodium methoxide in methanol resulted in smooth displacement with the production of the desired 9-α-D-arabinofuranosyl-2-methoxy-8-azaadenine (**21**).

Biologic Evaluation. The α-arabinonucleosides described in this report were quantitatively evaluated for in vitro antiviral activity against several DNA-containing and several RNA-containing viruses by means of preliminary screening tests designed to determine the ability of each compound to inhibit specific virus-induced cytopathogenic effects (cpe) in cell culture. These tests were performed using MicroTest II plates (Falcon Plastics, Division of BioQuest, Cockeysville, Md.) and replicate culture tubes containing susceptible cells grown in monolayer culture under either Eagle's basal medium (BME) with twice the usual concentration of vitamins and amino acids plus 5% fetal bovine serum or Eagle's minimum essential medium (MEM) plus 2% fetal bovine serum. Compounds were tested against herpes simplex virus type 1 (strain HF), varicella-zoster virus (strain Ellen), cytomegalovirus (strain AD 169), human adenovirus type 2 (strain Adenoid-6), respiratory syncytial virus (strain Long), and human rhinovirus type 1A (strain 2060). The herpes simplex virus (HSV) and respiratory syncytial (RS) virus were propagated and assayed in continuous-passage human epidermoid carcinoma of the larynx (H.Ep.-2) cells, while the adenovirus (Ad) and rhinovirus (RV) were propagated and assayed in continuous-passage human carcinoma of the nasopharynx (KB) cells using BME as the cell culture medium. For antiviral assays, the cells were pregrown in the MicroTest II plates and, after decanting the growth medium, 0.1 ml of fresh medium containing a given concentration of test compound and 0.1 ml of stock virus preparation were added to each plate well to yield a final virus concentration of 32 $CCID_{50}$ (cell culture infectious dose, 50%) units per well. Seven drug concentrations were tested in triplicate in each experiment and these were selected to range, in half-log dilutions, from cytotoxic to noncytotoxic levels. Uninfected cultures receiving medium alone served as normal cell controls. Virus-infected control cultures receiving medium and virus (but no drug) and drug cytotoxicity control cultures receiving medium and

drug (but no virus) were also run simultaneously with the virus-infected, drug-treated cultures in each experiment. The plates were sealed and incubated at 33 °C for the anti-RV tests and at 37 °C for the other antiviral assays. At 4 days after virus inoculation, the cell monolayers were examined microscopically for virus-induced cpe and the amount of reduction in cpe caused by the compound was determined.

The varicella-zoster (V-Z) virus and the cytomegalovirus (CMV) were propagated and assayed in diploid human embryonic lung (WI-38) fibroblasts using MEM as the culture medium. For antiviral assays, the growth medium was decanted from 7-day-old cell monolayers grown in culture tubes and fresh medium containing the appropriate amount of test compound was added to the tubes (in triplicate). To each cell culture, 0.25 ml of virus suspension was then added to yield approximately 32 $CCID_{50}$ units of challenge virus per culture. Cytotoxicity controls, virus controls, and cell controls were included in each experiment. All tubes were incubated at 37 °C for 48 h, after which the medium was removed and replaced with fresh growth medium containing drug. The medium was changed again after an additional 48-h period of incubation at 37 °C and the cell monolayers were examined for virus-induced cpe at 7 days postvirus inoculation.

The virus rating (VR), a defined measurement of antiviral activity that takes into account the degree of cpe inhibition and the degree of drug cytotoxicity, was calculated for each test compound and virus combination by a modification of the method of Ehrlich et al.,[15] as described by Sidwell and Huffman.[16]

6-Amino-9-α-D-arabinofuranosyl-9*H*-purine (**3**) and 7-amino-3-α-D-arabinofuranosyl-3*H*-*v*-triazolo[4,5-*d*]pyrimidine (**4**) demonstrated highly significant activity against HSV with VR's of 0.6 and 1.0, respectively, and these compounds served as positive controls. None of the 2-substituted derivatives of **3** and **4** which were examined were found to possess definite antiviral activity. Miyai et al.[17] prepared a number of 2-substituted derivatives of 9-β-D-arabinofuranosyladenine (2-methoxy-, 2-methylthio-, 2-benzyloxy-, and 2-chloro-β-ara-A). Of these compounds, only the 2-chloro-β-ara-A demonstrated significant antiviral activity in vitro and in vivo. The parent compound (**1**) was shown to be a much more effective antiviral agent than the 2-chloro derivative, however, in all of the quantitative comparisons of relative activity which were performed in those particular studies.

Experimental Section

All evaporations were carried out in vacuo with a rotary evaporator. Analytical samples were normally dried in vacuo over P_2O_5 at room temperature for 16 h. Analtech precoated (250 μm) silica gel G(F) plates were used for TLC analyses; the spots were detected by irradiation with a Mineralight and by charring after spraying with saturated $(NH_4)_2SO_4$. Compounds containing amino groups were also detected with ninhydrin spray. All analytical samples were essentially TLC homogeneous. Melting points were determined with a Mel-Temp apparatus and are not corrected. The UV absorption spectra were determined in 0.1 N HCl, pH 7 buffer, and 0.1 N NaOH with a Cary 17 spectrophotometer; the maxima are reported in nm ($\epsilon \times 10^{-3}$). The ^1H NMR spectra were determined with a Varian XL-100-15 spectrometer in Me_2SO-d_6 with tetramethylsilane as an internal reference; chemical shifts (δ in ppm) quoted in the case of multiplets are measured from the approximate center. The high-pressure liquid chromatographic analysis was carried out with a Waters Associates ALC-242 chromatograph with an M-6000 pump and equipped with a μBondapak C_{18} column (0.25 in. × 30 cm) using 9:1 H_2O–CH_3CN as the solvent. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

9-α-D-Arabinofuranosyl-8-azaadenine (4). A mixture of 6-(methylthio)-8-azapurine (7.16 g, 43 mmol), 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl bromide (22.5 g, 43 mmol), and Linde AW-500 molecular sieve (86 g) in 1700 ml of dry toluene was refluxed for 1 h before an addition of molecular sieve (46 g). After refluxing for 16 h, the mixture was treated with charcoal, cooled, and filtered. The toluene was removed in vacuo and the residual syrup (21.8 g) dissolved in methanolic ammonia (500 ml, saturated at 0 °C). The solution was allowed to stand in a bomb at room temperature for 4 days before it was evaporated to dryness. The residue, after two triturations with $CHCl_3$ (250 ml), was recrystallized from ca. 650 ml of H_2O: yield 6 g (52%). This material was identical in all respects with the material previously prepared by the literature procedure.[8]

9-(2,3,5-Tri-*O*-acetyl-D-arabinofuranosyl)-2,6-dichloropurine (7). A mixture of 1,2,3,5-tetra-*O*-acetylarabinofuranose (18 g, 56.5 mmol) and 2,6-dichloropurine (10 g, 53 mmol) was stirred magnetically in a preheated 150 °C oil bath at 10 mm until a melt occurred and vigorous bubbling ceased. The vacuum was broken, and *p*-toluenesulfonic acid (300 mg) was added. The mixture was heated at 140 °C with stirring at 10 mm until bubbling nearly ceased, ~45 min. The melt was allowed to stand at room temperature overnight before it was dissolved in $CHCl_3$ and filtered to remove any unreacted purine. The dark $CHCl_3$ solution (250 ml) was washed with 2 × 50 ml of saturated $NaHCO_3$ and then with 2 × 100 ml of H_2O before it was dried over $MgSO_4$ overnight. The $MgSO_4$ was removed by filtration and the filtrate evaporated to dryness: yield 20 g (84%); ^1H NMR 1.9 (CH_3 of cis Ac), 2.1–2.2 (3 s, CH_3 of Ac), 4.4 (m, $H_{5'}$), 4.7 (m, $H_{4'}$), 5.4 (m, $H_{3'}$), 5.8 (m, $H_{2'}$), 6.25 (d, $J_{1'2'}$ = 2.8 Hz, $H_{1'}$ α), 6.6 (d, $J_{1'2'}$ = 4 Hz, $H_{1'}$ β), 8.3 (s, H_8 α), 8.35 (s, H_8 β). From the ^1H NMR data the ratio of α- to β-anomer was calculated to be about 4.5:1. This material was used in the next step without further purification.

9-α-D-Arabinofuranosyl-2-chloroadenine (8). A solution of 9-(2,3,5-tri-*O*-acetyl-α-D-arabinofuranosyl)-2,6-dichloropurine (20 g, 44.6 mmol) in 500 ml of dry MeOH saturated with NH_3 at 0 °C was allowed to stand at room temperature in a stainless steel bomb for 1 week before it was evaporated to dryness. The addition of 95 ml of H_2O to the dark gummy residue caused it to solidify. The ^1H NMR spectrum of this material indicated that the α- to β-anomer ratio was about 5:1, and this approximate ratio was confirmed by HPLC, which showed a ratio of 4.5:1. The total solids (6.4 g) recovered from the water treatment were recrystallized from EtOH with charcoal treatment. The first crop of crystals was primarily 9-β-D-arabinofuranosyl-2-chloroadenine: yield 1.1 g (8%); mp 240 °C dec. The subsequent crops were essentially pure α-anomer **8**: total yield 4.7 g (35%); mp 230 °C dec; UV (pH 1) 211, 264 (23.0, 14.1); UV (pH 7) 209, 264 (25.4, 15.3); UV (pH 13) 264.5 (15.4); ^1H NMR 3.6 (m, $2H_{5'}$), 4.1 (m, $H_{3'}$ and $H_{4'}$), 4.6 (t, $H_{2'}$), 5.8 (d, $J_{1'2'}$ = 4 Hz, $H_{1'}$), 7.8 (s, NH_2), 8.4 (s, H_8). Anal. ($C_{10}H_{12}ClN_5O_4$) C, H, N.

9-α-D-Arabinofuranosyl-2-methoxyadenine (9). To 2-chloro-9-α-D-arabinofuranosyladenine (623 mg, 2.06 mmol) in 50 ml of dry MeOH was added solid sodium methoxide (223 mg, 4.12 mmol) in one portion. The mixture was heated under reflux for 4 days before it was chilled in an ice bath, neutralized with glacial acetic acid, and evaporated to dryness. The white solid residue was recrystallized three times from 10 ml of hot water: yield 368 mg (60%); mp 242–245 °C; UV (pH 1) 247, 274 (8.0, 11.8); UV (pH 7, 13) 250 sh, 266.5 (12.0); ^1H NMR 3.57 (m, 2 $H_{5'}$), 3.95 (s, CH_3O), 4.0 (m, $H_{4'}$), 4.16 (m, $H_{3'}$), 4.7 (m, $H_{2'}$), 4.85 (t, $O_{5'}H$), 5.62 and 5.75 (2 d, $O_{2'}H$ and $O_{3'}H$), 5.78 (d, $J_{1'2'}$ = 4.5 Hz, $H_{1'}$), 7.27 (s, NH_2), 8.15 (s, H_8); $[\alpha]^{25}D$ 88.2 ± 0.6° (*c* 1, Me_2SO). Anal. ($C_{11}H_{15}N_5O_5$) C, H, N.

9-α-D-Arabinofuranosyl-2-(methylthio)adenine (10). To a saturated solution of methyl mercaptan in 12 ml of 2 N methanolic sodium methoxide was added a solution of 9-α-D-arabinofuranosyl-2-chloroadenine (400 mg, 1.33 mmol) in 2-methoxyethanol (15 ml). This solution was heated at 100 °C for 3 h and then allowed to stand at room temperature for 41 h before it was chilled and the precipitated solid removed by filtration. Recrystallization from H_2O (60 ml) gave 176 mg (42%): mp 275–276.5 °C dec; UV (pH 1) 208, 269 (20.0, 16.0), 290 sh; UV (pH 7, 13) 234, 274 (21.1, 14.3); ^1H NMR 2.7 (s, CH_3S), 3.6 (m, $2H_{5'}$), 3.9 (m, $H_{3'}$), 4.1 (m, $H_{4'}$), 4.0–4.4 ($O_{5'}H$), 4.7 (t, $H_{2'}$), 5.6 and 5.7 (2 d, $O_{2'}H$ and $O_{3'}H$), 5.8 (d, $J_{1'2'}$ = 5 Hz, $H_{1'}$), 7.6 (br s, NH_2),

8.2 (H_8). Anal. ($C_{11}H_{15}N_5O_4S$) C, H, N.

9-α-D-Arabinofuranosyl-2-hydrazinoadenine (11). A solution of 9-α-D-arabinofuranosyl-2-chloroadenine (600 mg, 2.0 mmol) in hydrazine (95%, 30 ml) was stirred at room temperature for 18 h before it was evaporated to dryness with two additions of 2-propanol. The residue was recrystallized three times from a mixture of water and ethanol: yield 332 mg (56%); mp 209–211 °C; UV (pH 1) 214, 255, 277 (19.5, 8.66, 9.56); UV (pH 7, 13) 217, 257, 279.5 (23.1, 10.5, 8.9); ^{1}H NMR 3.5 (m, $2H_{5'}$, OH or NH), 3.9 (m, $H_{3'}$), 4.15 (m, $H_{4'}$), 4.65 (t, $H_{2'}$), 4.8 and 5.6 (br, OH), 5.75 (d, $J_{1'2'}$ = 4 Hz, $H_{1'}$), 6.86 (s, NH_2), 7.43 (s, NH), 7.96 (s, H_8); $[\alpha]^{25}D$ 50.0 ± 0.9° (*c* 0.69, H_2O). Anal. ($C_{10}H_{15}N_7O_4$) C, H, N.

4,5-Diamino-2,6-bis(methylthio)pyrimidine (13). To a stirred suspension of 4,5-diamino-2,6-dimercaptopyrimidine (**12**, 20 g, 115 mmol) in 264 ml of 1 N KOH and 20 ml of H_2O was added with stirring methyl iodide (16.4 ml, 258 mmol). After the mixture was stirred an additional 1.5 h, it was chilled and the solid that had precipitated was removed by filtration. This material was recrystallized from EtOH (800 ml): yield 18.9 g (82%); mp 195–197 °C (lit.[11] mp 192–193 °C); ^{1}H NMR 2.4 and 2.5 (2 s, CH_3S), 4.1 and 6.4 (2 br s, 2 NH_2).

2,6-Bis(methylthio)-8-azapurine (14). A solution of $NaNO_2$ (6.45 g, 94 mmol) in H_2O (67 ml) was added with stirring to a solution of 4,5-diamino-2,6-bis(methylthio)pyrimidine (16.7 g, 83.7 mmol) in 990 ml of 1:1 HOAc–H_2O at 5 °C. After 30 min, the solid that had precipitated was collected by filtration, washed with water, and dried. It was recrystallized from 500 ml of 1:1 HOAc–H_2O: yield 15.6 g (88%); mp 228–232 °C; UV (pH 1) 233, 262, 289, 317 sh (14.1, 11.6, 14.3); UV (pH 7, 13) 215, 242, 270, 318 (10.3, 17.3, 12.1, 9.45); ^{1}H NMR 2.6 and 2.73 (2 s, CH_3S). Anal. ($C_6H_7N_5S_2$) C, H, N.

9-(2,3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl)-2,6-bis(methylthio)-8-azapurine (18). A solution of 2,6-bis(methylthio)-8-azapurine (**14**, 19 g, 89.5 mmol) and 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl bromide (**16**, 47 g, 89.5 mmol) in 2 l. of dry toluene containing 178 g of AW-500 molecular sieve was heated under reflux with stirring for 1 h. Another 178 g of sieve was added and heating continued for an additional 18 h. The reaction mixture was treated with charcoal and then filtered before it was evaporated to dryness. The clear glass (16 g) was used in the next step without further purification.

9-α-D-Arabinofuranosyl-2-(methylthio)-8-azaadenine (19). A solution of 9-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-2,6-bis(methylthio)-8-azaadenine (**18**, 16 g, 24.3 mmol) in 1 l. of dry MeOH saturated with NH_3 at 5 °C was allowed to stand in a bomb at room temperature for 4 days before it was evaporated to dryness and the residue triturated with $CHCl_3$. The solid thus obtained was recrystallized twice from water: yield 3.72 g (49%) [a second run gave 17.2 g (61%)]; mp 218–220 °C; UV (pH 1) 240.5, 277 (14.0, 16.2); UV (pH 7, 13) 247, 288 (20.0, 13.0). Anal. ($C_{10}H_{14}N_6O_4S$) C, H, N.

A second nucleoside (110 mg, ca. 1.5%), presumably the 8-isomer of **19**, was recovered from the mother liquors from the purification of **19**. This material traveled slower than **19** on TLC (silica gel, 5:1 $CHCl_3$–MeOH); UV (pH 1) 231, 245 sh, 283.5, 303 (12.8, 13.5, 13.0); UV (pH 7) 223, 247, 278, 304 (16.0, 14.0, 10.2, 9.7); UV (pH 13) 222, 246.5, 276, 307.5 (14.5, 14.7, 10.1, 10.1).

9-α-D-Arabinofuranosyl-2-methylsulfonyl-8-azaadenine (20). A solution of 9-α-D-arabinofuranosyl-2-(methylthio)-8-azaadenine (**19**, 15 g, 47.7 mmol) in glacial acetic acid (240 ml) containing 30% H_2O_2 (35 ml) was allowed to stand 23 h at room temperature and an additional 18 h at 4 °C before it was evaporated to dryness with an addition of EtOH and four additions of H_2O. The white solid residue was suspended in cold water, removed by filtration, and washed with several portions of H_2O and then recrystallized from water. Additional material recovered from the mother liquors was also recrystallized from H_2O: total yield 7.9 g (48%); mp 197–199 °C dec; UV (pH 1 and 7) 258, 288 (5.82, 9.58); UV (pH 13) 225, 290 (20.1, 10.2); ^{1}H NMR 3.36 (s, CH_3SO_2), 3.6 (m, 2 $H_{5'}$), (m, $H_{3'}$ and $H_{4'}$), 4.83 (t, $O_{5'}H$), 5.0 (m, $H_{2'}$), 5.6 (d, $O_{3'}H$), 5.86 (d, $O_{2'}H$), 6.15 (d, $J_{1'2'}$ = 5 Hz, $H_{1'}$), 9.0 and 9.25 (2 br s, NH_2). Anal. ($C_{10}H_{11}N_6O_6S$) C, H, N.

9-α-D-Arabinofuranosyl-2-methoxy-8-azaadenine (21). A solution of 9-α-D-arabinofuranosyl-2-methylsulfonyl-8-azaadenine (**20**, 242 mg, 0.7 mmol) in 61.4 ml of dry MeOH containing sodium methoxide (1.4 mmol) was heated under reflux for 45 min before it was cooled, neutralized with HOAc, and evaporated to dryness. The residue was recrystallized from water: yield 176 mg (85%); mp 210–212 °C dec; UV (pH 1) 254 sh, 269 (10.6); UV (pH 7, 13) 216, 273 (23.6, 11.0); ^{1}H NMR 3.6 (m, 2 $H_{5'}$), 3.9 (s, CH_3O), 4.1 (m, $H_{3'}$ and $H_{4'}$), 4.8 (t, $O_{5'}H$), 5.04 (m, $H_{2'}$), 5.4 (d, $O_{3'}H$), 5.8 (d, $O_{4'}H$), 6.0 (d, $J_{1'2'}$ = 6 Hz, $H_{1'}$). Anal. ($C_{10}H_{14}N_6O_5$) C, H, N.

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