# Synthesis and Antitumor Activity of 7- and 9-(6′-Deoxy-α-L-talofuranosyl)hypoxanthine and 9-(6′-Deoxy-α-L-talofuranosyl)-6-thiopurine

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Reaction of 6-deoxy-2,3,5-tris-*O*-(*p*-nitrobenzoyl)-L-talofuranosyl bromide (1) with the trimethylsilyl derivative of hypoxanthine, followed by removal of blocking groups, afforded 9- (6) and 7-(6′-deoxy-α-L-talofuranosyl)hypoxanthine (7). A study of the published optical rotations and circular dichroic (CD) spectra of pentofuranosylpurines and of (6′-deoxy-β-D-allo- and -α-L-talofuranosyl)purines prepared here suggests that the sign of rotation and the sign of the longer wavelength Cotton effect is determined solely by the configuration of C-1′ and its position of attachment to the purine ring. For C-1′ *R* nucleosides, the sign is negative for N-9-linked purine nucleosides and positive for the N-7-linked isomers, and vice versa for C-1′ *S* purine nucleosides. Reaction of 1 with the trimethylsilyl derivative of 6-chloropurine afforded 4, which upon treatment with thiourea and deblocking yielded 9-(6′-deoxy-α-L-talofuranosyl)-6-thiopurine (8). Unlike the previously prepared 7-(6′-deoxy-β-D-allofuranosyl)hypoxanthine which strongly inhibited purine nucleoside phosphorylase, compounds 6–8 did not inhibit this enzyme. Compound 8 significantly inhibited the growth of L1210 tumor cells in vitro and in vivo.

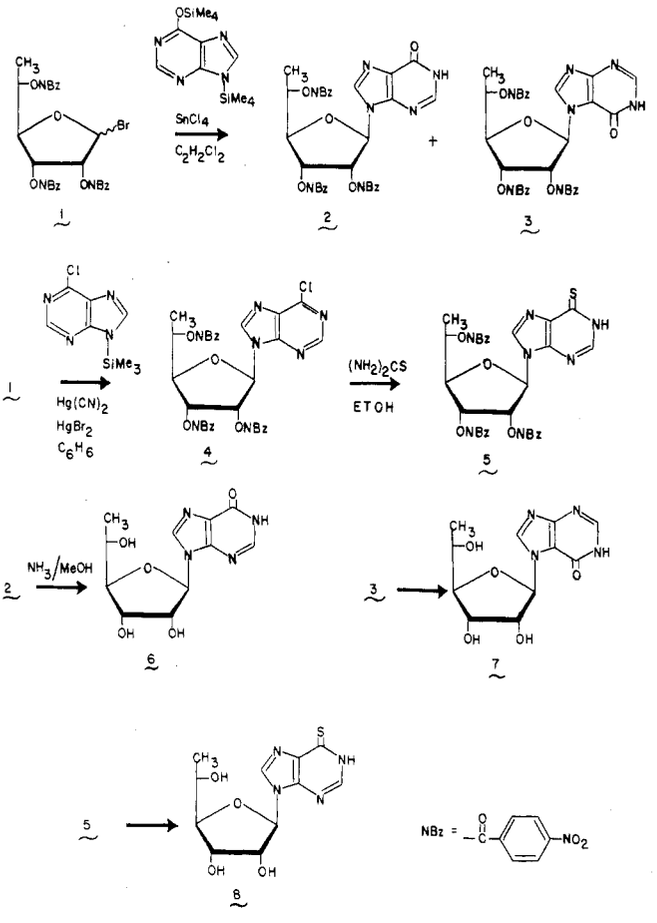
There has been considerable interest in hypoxanthine and guanine nucleosides modified in the sugar moiety, which inhibit the enzyme purine nucleoside phosphorylase (PNPase), as potential antitumor agents.[1-3] A possible modification of inosine and guanosine that has received little attention is the introduction of a methyl group at C-5 of the ribose moiety. This creates a new chiral center and changes the primary hydroxyl group to a secondary one, which should lower its rate of esterification.

We have recently reported the synthesis of hypoxanthine, guanine, and 6-thiopurine nucleosides of 6-deoxy-D-allofuranose.[4] When tested as PNPase inhibitors, both the N-7 and N-9 isomers of the guanosine analogue were inactive, as were the 6-thiopurine nucleoside and the N-9 inosine analogue. The N-7 inosine analogue, however, was a significant inhibitor of PNPase ($K = 8.8 \times 10^{-5}$). When the above-mentioned nucleosides were tested against L1210 tumor cells in vivo, only the 6-thiopurine nucleoside was significantly active (T/C = 148).

6-Deoxy-D-allofuranose and its 5-epimer, 6-deoxy-L-talofuranose, may be thought of as derived from D-ribofuranose by replacement of one of the hydrogen atoms attached to C-5 by a methyl group. In order to further explore the effect of the newly introduced chiral center at the 5-position on PNPase inhibition and antitumor activity, we have synthesized hypoxanthine and 6-thiopurine nucleosides of 6-deoxy-L-talofuranose. The guanine compounds were not investigated, since the corresponding 6-deoxy-D-allofuranosyl nucleosides were inactive.

**Chemistry.** The starting point of the synthesis was 6-deoxy-L-talofuranosyl bromide (1),[5] which was coupled with bis(trimethylsilyl)hypoxanthine in the presence of tin tetrachloride to yield a mixture of blocked hypoxanthine nucleosides, **2** and **3**, bearing links to positions 9 and 7 of the base, respectively (Scheme I). Compound **1** was also coupled to (trimethylsilyl)-6-chloropurine in the presence of mercuric bromide and mercuric cyanide to yield a blocked chloropurine nucleoside **4**. 6-Chloropurine couples

Scheme I




with glycosyl halides only at the N-9 position, so only one isomer was isolated. Compound **4** was treated with thiourea in refluxing ethanol to yield blocked thiopurine nucleoside **5**. The blocked nucleosides were each deblocked with methanolic ammonia to yield the N-9- and N-7-linked (6′-deoxy-L-talofuranosyl)hypoxanthines **6** and **7** and (6′-deoxy-L-talofuranosyl)-6-thiopurine **8**.

The position of the linkage of the sugar moiety to the purine ring and the α-L configuration[6] of the compounds prepared were determined by using the same methods used

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(6) In the L-talofuranose series the configuration is α if the purine lies on the same side of the furanose ring as C-5 and C-6.

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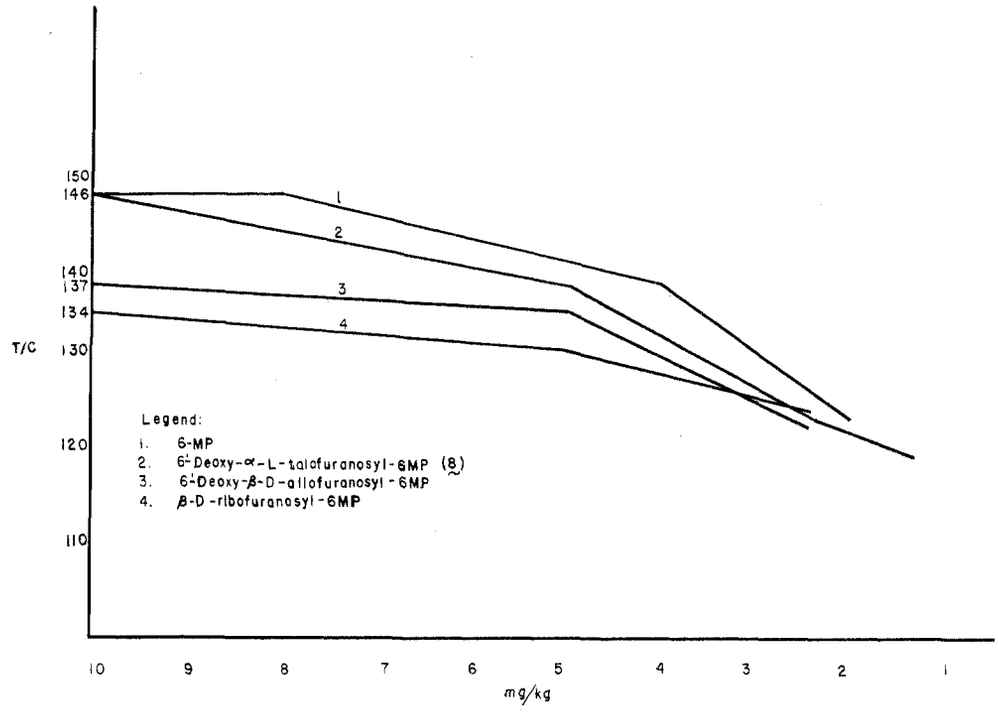


**Figure 1.** CD spectra of N-7- and N-9-linked (6′-deoxy-β-D-allofuranosyl)- and (6′-deoxy-α-L-talofuranosyl)hypoxanthines.

for the corresponding 6′-deoxy-β-D-allofuranoside,[4] namely, UV maxima, optical rotation, and CD. Thus, the fact that the linkage was actually through N-9 in compound **6** and through N-7 in compound **7** was verified by measuring their ultraviolet absorption maxima [$\lambda_{max}$ 249 and 257 nm ($H_2O$, pH 7), respectively] and matching the observed maxima with those of the corresponding 6′-deoxy-D-allofuranose derivatives[4] and the maxima for published ribofuranosyl derivatives.

It has been observed that NMR spectra provide a convenient way to distinguish the N-9-linked from the N-7-linked isomers of (6′-deoxy-D-allofuranosyl)purines. Thus, in 9-(6′-deoxy-D-allofuranosyl)hypoxanthine[4] the signal due to the proton attached to C-5′ appeared as a quartet at 3.48 ppm, whereas in the N-7-linked isomer this proton is hidden under an OH absorption at about 3.8 ppm. In the 6-deoxy-L-talofuranose nucleosides discussed here the situation is reversed. The H-5′ signal of the N-7 isomer **7** appears as a quartet at 3.55 ppm, while in the N-9 isomer **6** this signal is obscured by other absorbances at about 3.8 ppm.

The rules governing the sign of rotation and the sign of the Cotton effect of N-9-substituted purine nucleosides stipulate that these are governed by the anomeric configuration; β-D isomers exhibit a negative rotation and a negative Cotton effect, whereas the α-D forms exhibit a positive rotation and a positive Cotton effect.[7] Since the D and L configuration of the parent sugars determines whether a certain anomeric configuration of a nucleoside is assigned an α or β notation, one could better state this rule in a general form as follows: The sign of rotation and the sign of the longer wavelength Cotton effect of N-9-linked purine nucleosides are negative for C-1′ *R* isomers and positive for C-1′ *S* isomers. The situation seems to be reversed for nucleosides having the sugar moiety joined to the purine ring at N-7. Thus, it is known that 7-β-D-ribofuranosylhypoxanthine exhibits a positive specific rotation [$[\alpha]^{24}_D$ +30.0° ($H_2O$)], while the α-D anomer has a negative rotation [$[\alpha]^{24}_D$ −78.1° ($H_2O$)], which is the opposite of the case for the N-9 isomers.[7] Since in nucleosides the sign of rotation (sodium line) is the same as the sign of the longer wavelength Cotton effect, one would expect N-7-substituted compounds to have Cotton effects of the opposite sign than those of the N-9 nucleosides of the same configuration, i.e., the C-1′ *R* isomers will have positive Cotton effects and the C-1′ *S* isomers negative ones. Figure 1 shows that all the 7- and 9-substituted hexofuranosylhypoxanthine and guanine nucleosides we prepared here and in our previous paper,[4] and which all have *R* configurations at C-1′, follow the above general rule, i.e., the N-9-substituted derivatives exhibit negative Cotton effects, whereas the N-7 ones exhibit positive Cotton effects.

## Biological Results

Compounds **6**–**8** were found to be inactive as inhibitors of PNPase. This contrasts with the 6-deoxy-D-allofuranose nucleosides where the N-7 hypoxanthine derivative was significantly active.[4] It seems, therefore, that the configuration at C-5′ does play a role in the affinity of such nucleosides toward this enzyme. Like its D-allofuranosyl counterpart,[4] compound **7** was inactive against L1210 tumor cells in vivo. The thiopurine nucleoside **8**, on the other hand, was active against L1210 tumor cells in vivo, showing a maximum T/C of 146 at a dose of 10000 μg/kg (see Figure 2), and in vitro (50% inhibition of growth at 1 μg/mL). Since this activity is similar to that of the isomeric 9-(6′-deoxy-D-allofuranosyl)-6-thiopurine (T/C = 137 and 148 in vivo and 50% inhibition at 0.5 μg/mL in vitro),[4] further work is needed to rule out the possibility that the antitumor activity of the 6-thiopurine nucleosides is due to their hydrolysis to the free base.

## Experimental Section

Ultraviolet spectra were measured on a Perkin-Elmer Lambda 3 spectrometer. Infrared spectra were taken on a Perkin-Elmer 735B spectrophotometer. Nuclear magnetic resonance spectra

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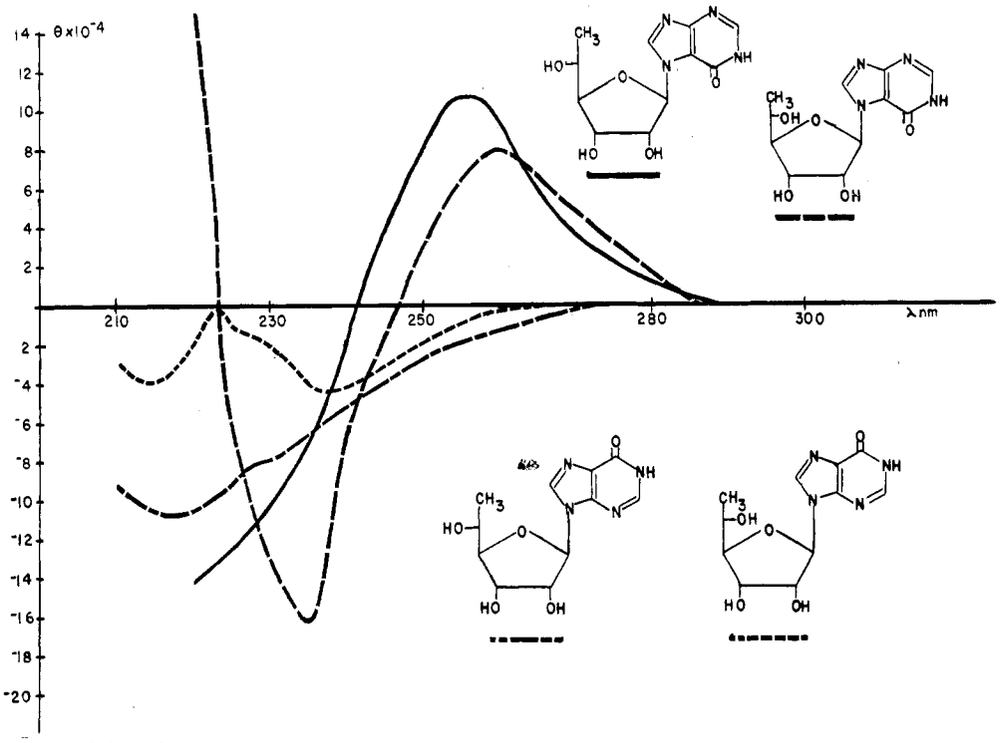


**Figure 2.** Antitumor activity of 6-mercaptopurine and its nucleosides, measured in the same experiment.

were recorded on a Varian EM-360A spectrometer with tetramethylsilane as an internal standard. Optical rotations were measured with a Bendix Series 1100 automatic polarimeter. Circular dichroism measurements were performed at the Michigan Molecular Institute, Midland, MI. In vitro tests were performed at the National Cancer Institute, Silver Springs, MD. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. The nucleoside analogues were tested for inhibitory activity of calf spleen purine nucleoside phosphorylase (EC. 2.4.2.1) from Sigma Chemical Co., by using a coupled assay following the method of Hoffee et al.[9] In vitro screening was performed by Dr. David Kessel, Department of Oncology, Wayne State University, Detroit, MI.

**7-[6′-Deoxy-2′,3′,5′-tris-*O*-(*p*-nitrobenzoyl)-α-L-talofuranosyl]hypoxanthine (3).** 6-Deoxy-2,3,5-tris-*O*-(*p*-nitrobenzoyl)-α-L-talofuranosyl bromide (1) (2.3 g, 3.7 mmol) was stirred in dichloroethane (50 mL) with bis(trimethylsilyl)hypoxanthine (1.3 g, 4.6 mmol) and tin tetrachloride (0.6 mL) at room temperature overnight. Ethanol (8 mL) and triethylamine (2 mL) were added, and the mixture was evaporated to a glassy foam. This material was dissolved in chloroform, washed with aqueous sodium bicarbonate, and filtered through Celite. The solvent was removed by evaporation, and the crude material was chromatographed on silica gel. Elution with ethyl acetate yielded a nonpolar material, which was discarded, followed by the mixture of blocked nucleoside isomers. Recrystallization from ethyl acetate yielded the title compound as white crystals: yield 1.2 g (20%); mp 208–210 °C. Anal. ($C_{32}H_{23}N_7O_{14}$) C, H, N.

**9-[6′-Deoxy-2′,3′,5′-tris-*O*-(*p*-nitrobenzoyl)-α-L-talofuranosyl]hypoxanthine (2).** The blocked nucleoside mixture from a second synthesis was chromatographed on a large silica gel column. Elution with ethyl acetate–ether (1:1) initially yielded part of the product mixture without separation, followed by the title compound in 10% yield: mp 150–160 °C. Anal. ($C_{32}H_{23}N_7O_{14}$) C, H, N.

**7-(6′-Deoxy-α-L-talofuranosyl)hypoxanthine (7).** Compound 3 was treated with methanolic ammonia (100 mL) for 2 days. The mixture was evaporated to dryness, dissolved in distilled water, and washed five times with chloroform. The aqueous phase was filtered and evaporated to dryness. The residue was dissolved in ethanol, and ether was added to precipitate a flocculent solid. Filtration yielded the product as an amorphous powder in 63% yield: $[\alpha]^{24}_D$ +26.0° ($H_2O$); UV $\lambda_{max}$ ($H_2O$) 253 nm (pH <1), 256.5 (~5–7), 264.2 (>12); NMR ($Me_2SO$-$d_6$/$CDCl_3$) σ 1.18 (d, 3 H, $J_{5',6'}$ = 6Hz, H-6′), 3.55 (q, 1 H, H-5′), 3.90 (m, 1 H, H-4′), 4.23 (m, 1 H, H-3′), 4.47 (m, 1 H, H-2′), 5.0–7.6 (m, 3 H, OH), 6.38 (d, 1 H, $J_{1',2'}$ = 6 Hz, H-1′), 8.15 (s, 1 H, H-8), 8.82 (s, 1 H, H-2); IR (KBr) $\nu_{max}$ 3600–2400 (OH, NH), 1690 (C=O), 1595, 1405, 1345, 1220, 1050, 795, 620 $cm^{-1}$. Anal. ($C_{11}H_{11}N_4O_5$) C, H, N.

**9-(6′-Deoxy-α-L-talofuranosyl)hypoxanthine (6).** Compound 2 was deblocked as described above to yield the product in 72% yield: $[\alpha]^{24}_D$ −23.4° ($H_2O$); UV $\lambda_{max}$ 249.2 nm ($H_2O$, pH 7); NMR ($Me_2SO$-$d_6$) σ 1.15 (d, 3 H, $J_{5',6'}$ = 6 Hz, H-6′), 3.43 (m, 1 H, OH), 3.83 (m, 2 H, H-2′, H-5′), 4.20 (m, 1 H, H-3′), 4.50 (d of d, 1 H, H-2′), 5.03 (m, 2 H, 20 H), 5.93 (d, 1 H, $J_{1',2'}$ = 6 Hz, H-1′), 8.20 (s, 1 H, H-8), 8.50 (s, 1 H, H-2); IR (KBr) $\nu_{max}$ 3600–2600 (NH, OH), 1695 (C=O), 1490, 1410, 1220, 1070, 855 $cm^{-1}$. Anal. ($C_{11}H_{13}N_4O_5 \cdot {}^1/_2H_2O$) C, H, N.

**9-[6′-Deoxy-2′,3′,5′-tris-*O*-(*p*-nitrobenzoyl)-α-L-talofuranosyl]-6-chloropurine (4).** Compound 1 (1.9 g, 2.8 mmol) was stirred in dichloroethane (30 mL) with (trimethylsilyl)-6-chloropurine (0.7 g, 3.0 mmol) and molecular sieves as mercuric bromide (1.12 g) and mercuric cyanide (0.07 g) were added. The mixture was stirred at room temperature overnight, then ethanol (30 mL) and triethylamine (10 mL) were added, and the mixture was evaporated to dryness. The residue was dissolved in chloroform, washed with aqueous sodium bicarbonate, and filtered, and the filtrate was evaporated to dryness. The glassy residue was chromatographed on silica gel. Elution with benzene–ethyl acetate (1:1) yielded the product as a gummy solid. This material was dissolved in ethyl acetate–ethanol, and an amorphous solid slowly precipitated: yield 1.9 g (91%). Anal. ($C_{32}H_{23}N_7O_{13}Cl$) C, H, N, Cl.

**9-[6′-Deoxy-2′,3′,5′-tris-*O*-(*p*-nitrobenzoyl)-α-L-talofuranosyl]-6-thiopurine (5).** Compound 4 (2 g, 2.7 mmol) was refluxed 6 h in ethanol (100 mL) with thiourea (2 g, excess). The mixture was cooled and filtered to give the product as a yellowish solid: yield 1.5 g (74%). The solid softens without melting at 227–244 °C dec. Anal. ($C_{32}H_{23}N_7O_{13}S$) C, H, N, S.

**9-(6′-Deoxy-α-L-talofuranosyl)-6-thiopurine (8).** Compound 5 was deblocked with methanolic ammonia in the above manner to yield the product in 85% yield: mp 218–222 °C dec; NMR ($Me_2SO$-$d_6$) σ 1.17 (d, 3 H, $J_{5',6'}$ = 6Hz, H-6′), 3.83 (m, 2 H, H-4′, H-5′), 4.20 (m, 1 H, H-3′), 4.48 (m, 1 H, H-2′), 3.0–5.6 (m, 4 H, 3 OH, NH), 5.98 (d, 1 H, $J_{1',2'}$ = 6 Hz, H-1′), 8.33 (s, 1 H, H-2), 8.68 (s, 1 H, H-8); IR (KBr) $\nu_{max}$ 3600–2400 (OH, NH), 1600, 1420,

(9) R. M. Hoffee and B. C. Robertson, *Methods Enzymol.*, **51**, 518 (1978).

1340, 1210, 1130, 1040 $cm^{-1}$. Anal. ($C_{11}H_{14}N_4O_4S \cdot {}^1/_2H_2O$) C, H, N, S.

**Biological Experiments.** In vitro testing was performed by incubation of L1210 cells with the compound for 24 h, followed by a 1:1 dilution with fresh medium and further incubation for 24 h. Total cell number was recorded as percent of control (untreated) growth.

In vivo tests were done on L1210 by the NCI according to the protocol described in Instruction 14, Screening Data Summary Interpretation and Outline of Current Screen, Drug Evaluation Branch, Drug Research and Development Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD. Tumor inoculum: $10^5$ ascites cells implanted into $BDF_1$ mice. Each mouse was inoculated once and observed for 30 days. Evaluation: MST = median survival time in days. % T/C = MST of treated/MST of control × 100. Criteria: % T/C = 125 considered moderate; % T/C = 150 considered significant antitumor effect.

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**Registry No.** 1, 80851-32-7; 2, 86527-18-6; 3, 86527-17-5; 4, 86527-21-1; 5, 86527-22-2; 6, 86527-20-0; 7, 86527-19-7; 8, 86527-23-3; PNPase, 9030-21-1; bis(trimethylsilyl)hypoxanthine, 86527-16-4; (trimethylsilyl)-6-chloropurine, 32865-86-4.

# An Evaluation of Certain Chain-Extended Analogues of 9-β-D-Arabinofuranosyladenine for Antiviral and Cardiovascular Activity[1]

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Several nucleosides modified and chain extended at the 5′-position have been synthesized as follows: $N^6$-benzamido-9-(2,3-di-*O*-benzoyl-β-D-*arabino*-pentodialdo-1,4-furanosyl)adenine, O=CHR, $\xrightarrow{a}$ (*E*)-EtOCOCH=CHR (**2**) $\xrightarrow{b}$ $EtOCOCH_2CH_2R$ (**3**) $\xrightarrow{c}$ $H_2NCOCH_2CH_2R$ (**6**) $\xrightarrow{d}$ 1-(adenin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronamide (**8**); **3** $\xrightarrow{e}$ ethyl 1-(adenin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronate (**5**) $\xrightarrow{f}$ 1-(adenin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronic acid (**4**); **5** $\xrightarrow{g}$ 9-(5,6-dideoxy-β-D-*arabino*-hepto-1,4-furanosyl)adenine (**7**) [where a = EtOCOCH=$PPh_3$; b = $H_2$, Pd/C; c = $Me_2AlNH_2$; d = $NH_3$/MeOH; e = NaOEt/EtOH; f = NaOH/MeOH; g = $LiAlH_4$]. Both **7** and **8** show activity against herpes simplex virus type 1. The mechanism for such activity is unknown. Compounds **5** and **8** exhibited weak coronary vasodilation effects in dogs.

Over the past 2 decades a number of 5′-modified, chain-extended nucleosides have been described in the literature.[2-10] The rationale behind the synthesis of such compounds has generally been that these derivatives would be isosteric with the nucleoside 5′-phosphates or their homologues and, thus, might function as chemotherapeutic agents by selective enzyme inhibition. Early examples include a "6′-deoxyhomoadenosine" phosphonate proposed by Montgomery and Hewson[2] and reported some years later by Jones and Moffatt[3,4] and a "homoadenosine-6′-phosphonic acid" described by Hampton and co-workers.[5] These compounds were found, in general, to be substrates or inhibitors for adenosine monophosphate (AMP) utilizing enzymes. A further extension of these compound types has been the carboxy analogues of the phosphonates that include both two-carbon[6,7,10] and one-carbon[8,9] chains at the 5′-position of both purines[6-9] and pyrimidines.[8-10] The adenosine analogues were also substrates for several AMP-metabolizing enzymes.[11,12] α-Diazo ketone derivatives of the pyrimidine analogues have been utilized as active-site-directed inhibitors for pyrimidine-metabolizing enzymes.[10]

Inasmuch as all the examples cited in the foregoing were derivatives of D-ribonucleosides, it was deemed worthwhile to investigate similar compounds derived from the antiviral purine nucleoside 9-β-D-arabinofuranosyladenine (**1a**, *ara*-A, VIRA-A). The carboxy analogues **4** and **8** (Scheme I), which in the D-ribonucleoside series had seemed the most interesting biologically,[12] were targeted for synthesis. Potential areas of biological interest included the antiviral, anticancer and cardiovascular[13,14] fields.

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[⊥] Southern Research Institute.
[§] University of Michigan.

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