dose–response was sigmoidal, as is generally the case with LD's. Thus *S. cerevisiae* is more sensitive to DDI than any mammalian cell tested to date. Lowering the pH of the medium (which reduces lysosomotropism) conferred some protection, as did added ammonium ion (which raises lysosomal pH)[6-8] as the sulfate. These observations are all similar to those with mammalian cells.[7,8]

These results prompted us to put LD's through our antifungal screens. The results are given in Tables I–III.

It is clear that DDI and *N*-dodecylmorpholine (DDM; p$K$ = 7.6) are broad-spectrum antifungals since all organisms and strains are susceptible, even those resistant to other antifungals. DDI is more active than DDM as has been observed invariably with mammalian cells.[2-4] In activity, DDI surpasses ketoconazole and is somewhat less active than amphotericin B (AMB) except for AMB-resistant *Candida tropicalis* strain MY 1012. Since LD's kill cells not by chemical but rather by cooperative physical action, very low MIC's are not expected, and their potency is good considering their low toxicity. Furthermore, the slightly acidic pH of the medium in some experiments tends to reduce the apparent activity of LD's by inhibiting their entry into acidic intracellular compartments[7,8] (v.s.). At pH 7 their potency would be greater.

Whether LD's act on fungi by the same mechanism previously reported for mammalian cells is still uncertain. Supporting the idea is our observation that adding ammonium ion (76 mM) to the culture medium (v.s.) reduces the cytotoxicity of LD's to fungi (see Table I). In any event, LD's constitute a new class of broad-spectrum antifungal compounds whose mode of action differs from that of all previously known classes. They should prove to be useful tools in research, and possibly in therapy.

## Experimental Section

Lysosomotropic detergents were synthesized according to ref 2. Limits of error: disk diffusion assay, Table I, ±1 mm.; agar dilution assay, Table III, ±1 stage of dilution (each stage is twice the previous one).

**Registry No.** DDI, 4303-67-7; DDM, 1541-81-7; ketoconazole, 65277-42-1.

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# Preparation and Antileukemic Screening of Some New 6′-Deoxyhexopyranosyladenine Nucleosides

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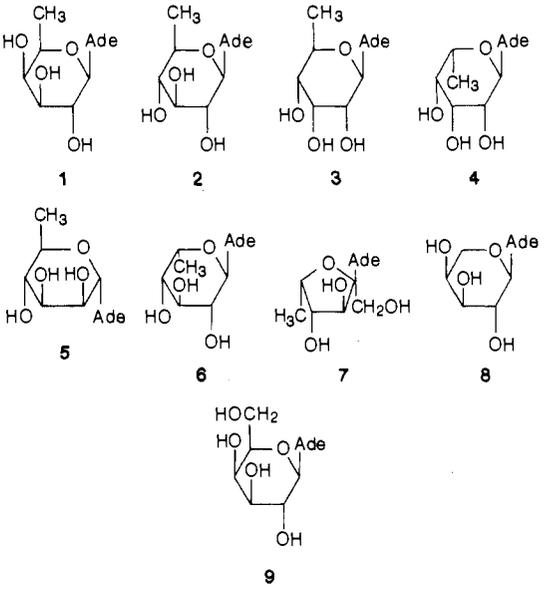
9-β-D-Fucopyranosyladenine (1) has weak antileukemic activity against L1210 cells grown in culture. Several new 6′-deoxyhexopyranosyladenine nucleosides were synthesized by standard procedures and assayed for activity. The new nucleosides were 9-(6-deoxy-β-D-glucopyranosyl)adenine (2), 9-(6-deoxy-β-D-allopyranosyl)adenine (3), 9-(6-deoxy-α-L-talopyranosyl)adenine (4), 9-α-D-rhamnopyranosyladenine (5), and 9-(6-deoxy-α-L-idopyranosyl)adenine (6). In addition, 9-(6-deoxy-α-L-sorbofuranosyl)adenine (7) was isolated from the same preparation as 6. None of the new nucleosides 2–7 had activity against L1210 cells in culture. A number of other known nucleosides related in structure to 1 were also tested for activity. One of these, 9-α-L-arabinopyranosyladenine, had activity, but was significantly weaker than 1.

A number of years ago, 9-β-D-fucopyranosyladenine [9-(6-deoxy-β-D-galactopyranosyl)adenine] (1, Chart I) was synthesized[1] as one of a series of starting materials for the preparation of acyclic nucleosides as inhibitors of adenosine deaminase.[2] No effort was made at the time to investigate the potential for biological activity because relatively few simple aldopyranosyl nucleosides derived from the common bases exhibited activity. Recently, during routine screening of nucleoside analogues, it was discovered that 1 inhibited the growth of leukemia L1210 cells in culture. At $10^{-4}$ M, this inhibition was about 75% at 48 h. The concentration that caused a 50% inhibition of growth after 48 h was $6 \times 10^{-5}$ M. Because the sample of 1 was more than 15 years old, its physical properties were carefully checked to make certain that it had remained unchanged over this period of time. To make absolutely certain, the nucleoside was synthesized again starting from D-fucose, and the biological results were confirmed. Although the biological activity of 1 is low compared to other inhibitors of L1210 cells, it is unusual that a nucleoside with this structure would have activity, particularly when the poor record of activity of other hexopyranose nucleosides is considered.[3] Therefore, we set out to prepare a

**Chart I**

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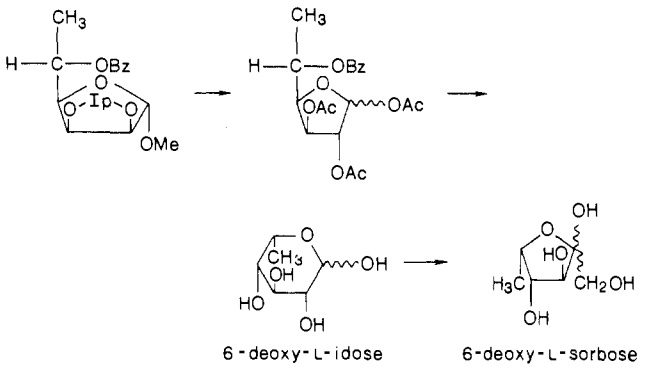
**Scheme I**




number of analogues of 1 from which we hoped to glean some information about the structural requirements of the carbohydrate moiety for activity, with the goal to design and synthesize a more powerful inhibitor based upon this structure.

**Chemistry.** The structures of the nucleosides are shown in Chart I. They were obtained by standard coupling procedures[4-6] and purified[7,8] as described in the Experimental Section.

The route to 9-(6-deoxy-α-L-idopyranosyl)adenine (**6**) also afforded 9-(6-deoxy-α-L-sorbofuranosyl)adenine (**7**). The reason has to do with the synthesis and handling of 6-deoxy-L-idose, which was prepared by acetolysis of methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranoside. Epimerization at C-2 afforded 1,2,3-tri-*O*-acetyl-5-*O*-benzoyl-L-idofuranose (Scheme I),[9] and deesterification gave the free sugar. However, 6-deoxy-L-idose is unstable and will slowly rearrange to 6-deoxy-L-sorbose.[10] This rearrangement may occur under acid or base catalysis,[10,11] and may have occurred during the base-catalyzed methanolysis of the ester groups, or upon standing as an impure syrup. The related hexose, L-idose, is known to undergo a similar transformation to L-sorbose,[11] possibly catalyzed by the glass surface of the vessel.[11,12] Periodate oxidation was used to distinguish **6** from **7**. Nucleoside **6** consumed 2 mol of periodate in less than 24 h, whereas **7** consumed only 1 mol of periodate over a 5-day period. This behavior of **7** is typical for furanose nucleosides and glycosides having vicinal ring hydroxyl groups oriented in a trans configuration.

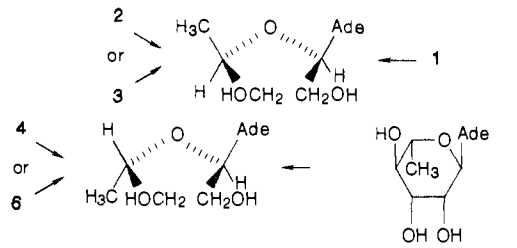
The structures of nucleosides **2–7** were supported by elemental analyses and UV spectra, which had the expected maxima near 260 nm, and indicated that the sugars were bonded to N-9 of adenine. Because **2** and **5** were enantiomers of known nucleosides,[7,13] it was only necessary to compare physical data to establish their identities. However, the anomeric configurations of **3**, **4**, and **6** had to be established. The major product of the condensation of a glycosyl halide having an acyl group adjacent to the anomeric carbon atom with a heavy metal salt of a purine is the nucleoside with the purine in a configuration trans to the hydroxyl group at C-2.[14] The configurations were confirmed by oxidation with $NaIO_4$, reduction to the dialcohols with $NaBH_4$, and measurement of the optical rotations. The results are shown in Table I and clearly establish the configurational relationships between nucleosides **1**, **2**, and **3** and between **4**, **5**, **6**, and 9-α-L-rhamnopyranosyladenine. These relationships are also illustrated in Scheme II. The optical rotation of the dialcohol derived from **5** has the same absolute value but opposite sign, as expected for the enantiomer of the dialcohol derived from **4**, **6**, or 9-α-L-rhamnopyranosyladenine.

**Table I.** Optical Rotations of Dialcohols Derived from Nucleosides

| nucleoside | $[\alpha]_D$ of dialcohol, deg[a] | nucleoside | $[\alpha]_D$ of dialcohol, deg[a] |
|---|---|---|---|
| **1** | +55[b] | **5** | −81 |
| **2** | +53 | **6** | +82 |
| **3** | +54 | 9-α-L-rhamnopyranosyladenine | +81[b] |
| **4** | +81 | | |

[a] Based upon the calculated dry weight of the dialcohol product. [b] From ref 2.

**Scheme II**




The structure of 9-(6-deoxy-α-L-sorbofuranosyl)adenine (**7**) was deduced from the fact that 6-deoxy-L-sorbose cannot form a pyranose ring. The very slow consumption of 1 mol of periodate confirmed the ring structure and the trans relationship of the ring hydroxyl groups. The anomeric configuration is tentatively assigned as α-L on the basis of a favorable comparison of the molecular rotation with the molecular rotations of a number of other ketohexofuranosyl nucleosides and glycosides.

**Antileukemic Screening.** The nucleosides **1–9** were assayed for inhibitory activity against L1210 cells grown in culture. The inhibitory effect of **1** was reproduced, but with the exception of **8**, none of the other nucleosides had activity at $10^{-4}$ M. The activity of **8** was extremely weak, however, giving only 20% inhibition after 48 h at a concentration of $5 \times 10^{-4}$ M. It is of interest to note that the structure of **8** is almost identical with **1**, with the only difference being the methyl group at C-5′ of **1**. 9-β-D-Galactopyranosyladenine (**9**), which has an hydroxymethyl group at C-5′, was inactive.

In addition to the nucleosides whose chemistry is described in this paper, a number of other nucleosides whose structures are closely related to **1** have also been screened for activity. These nucleosides had been prepared as part of other projects, but it was thought that some additional information could be gleaned by comparison of their activities, if any, with **1**. The nucleosides studied, all of which

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were inactive at $10^{-4}$ M, were 9-α-D-fucopyranosyladenine,[1] 9-β-L-fucopyranosyladenine,[2] 9-β-D-fucofuranosyladenine,[9] 9-(6-deoxy-α-L-idofuranosyl)adenine,[9] 9-α-L-rhamnopyranosyladenine,[13] 9-(6-deoxy-β-L-glucopyranosyl)adenine,[13] and the crystalline dialcohols[2] obtained from 9-β-D-fucopyranosyladenine (1) and 9-β-L-fucopyranosyladenine. 9-(2,3,4-Tri-*O*-acetyl-β-D-fucopyranosyl)adenine[1] was also studied and found to inhibit growth by 35% at $10^{-4}$ M. We suspect that this compound is being slowly deacetylated to 1, which is the active compound. Finally, D-fucose and adenine were assayed to be certain that the breakdown products of nucleoside cleavage were not causing the inhibition, but these were also inactive.

## Experimental Section

**General Methods.** Melting points were determined with a Kofler hot stage and are corrected values. UV spectra were determined on a Beckman Model 25 spectrophotometer, and IR spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer. Optical rotations were obtained with a Perkin-Elmer Model 141 polarimeter. Elemental analyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, MI. Moist organic solutions were dried over anhydrous $MgSO_4$. Evaporations were conducted under reduced pressure with a rotary evaporator and a bath temperature of 40–45 °C unless otherwise stated. Paper chromatography was performed by a descending technique on 55-cm strips of Whatman No. 1 paper. The solvent systems used were (A) 5% aqueous $Na_2HPO_4$ and (B) 1-butanol–HOAc–$H_2O$ (5:2:3, v/v/v). Spots were located with a Mineralight lamp that produced UV radiation at 254 nm. The term $R_{Ade}$ is the ratio of the distance the nucleoside migrated to the distance that adenine migrated.

**6-Deoxyhexoses.** 6-Deoxy-D-glucose and D-rhamnose were available in this laboratory from previous work.[15] 6-Deoxy-D-allose[16] and 6-deoxy-L-talose[17] were prepared by acid hydrolysis of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside[16,18] and methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside,[19] two derivatives also available in this laboratory from previous work.[20,21]

**9-(6-Deoxy-β-D-glucopyranosyl)adenine (2).** 6-Deoxy-D-glucose[15] (1.11 g) was added to an ice-cold mixture of dry pyridine (11 mL) and acetic anhydride (7 mL), and the mixture was stirred for 1 h at 0 °C and at room temperature for 24 h. This mixture was poured on ice (40 g) and stirred for 2 h. The product was extracted with $CHCl_3$ (25 mL) by stirring for 10 min and then transferred to a separatory funnel. The $CHCl_3$ layer was removed and the aqueous layer was extracted further with $CHCl_3$ (3 × 15 mL). The $CHCl_3$ extracts were combined and washed with saturated $NaHCO_3$ solution (2 × 50 mL) and $H_2O$ (50 mL) and dried. The solvent was evaporated and the syrup coevaporated with toluene (3 × 25 mL) to get rid of traces of pyridine. The product crystallized at this stage to give an anomeric mixture of actates, 2.16 g (99% yield).

The acetate was suspended in 14 mL of 32% HBr in glacial HOAc. The mixture was swirled intermittently until the sugar acetate dissolved, whereupon crystals began to form after 15 min. After 50 min, ethanol-free $CHCl_3$ (20 mL) was added to dissolve the solid material, and the solution was allowed to stand for another 30 min. It was then diluted with more $CHCl_3$ (80 mL), transferred to a separatory funnel, washed with ice-cold $H_2O$ (3 × 150 mL), and dried. Evaporation (25 °C) gave the white, crystalline bromide, 2.27 g (99% yield), which was used immediately.

6-Benzamido-9-(chloromercuri)purine (3.2 g, 6.75 mmol), Celite-545 (3.2 g), and sodium-dried xylene (200 mL) were placed in a reaction flask equipped with a condenser, a drying tube (Drierite), and a take-off adapter. A portion (50 mL) of the xylene was distilled to remove traces of moisture. The bromide (2.27 g, 6.4 mmol) was dissolved in hot xylene (50 mL) and added to the reaction mixture. An additional 35 mL of xylene was used to wash in residual sugar, 55 mL of xylene was distilled, and the mixture was boiled under reflux and vigorous stirring for 3 h.[4] The hot mixture was filtered through a pad of Celite-545 (suction) and the filter cake was washed with hot $CHCl_3$ (75 mL). The solvents were evaporated, and the residue was dissolved in $CHCl_3$ (100 mL), washed with 30% aqueous KI (2 × 100 mL) and $H_2O$ (100 mL), and dried. Evaporation of the solvent gave a foam weighing 3.8 g, which was dissolved in MeOH (100 mL) and treated with 1 N methanolic NaOMe (10 mL) for 1 h under reflux. The solution was cooled to room temperature, neutralized with glacial HOAc, and evaporated. The residue was dissolved in $H_2O$ (100 mL) and washed with $CHCl_3$ (3 × 25 mL). The $H_2O$ layer was evaporated to dryness and the residue dissolved in MeOH (25 mL), whereupon crystals formed. After the crystals were chilled on ice for 1 h, they were filtered off to afford 229 mg.

The filtrate was treated with 10% methanolic picric acid (45 mL), which crystallized immediately and was chilled on ice for 1 h. The picrate was obtained by filtration, washed with ice-cold MeOH, and dried in vacuo for several days to give 1.78 g. The picrate was dissolved in stirring hot $H_2O$ (300 mL) and treated with small portions of Bio-Rad AG1-X8 ($CO_3^{2-}$) resin until the color was discharged.[7] The resin was removed by filtration and washed well with hot $H_2O$. Evaporation gave a crystalline material, which was recrystallized from EtOH–$H_2O$. The product (890 mg) was obtained in four crops, which were identical with the previous 229-mg fraction obtained prior to the formation of the picrate, for a total yield of 1.119 g (62% from the bromide). Recrystallization of the entire amount from EtOH–$H_2O$ afforded 895 mg as rosettes on the walls of the flask, also in four crops. The first crop of crystals (298 mg) were glittering white, but the other crops were very slightly buff-colored. The latter were purified further by passage through a column (17 × 1.8 cm) of Bio-Rad AG1-X2 ($OH^-$, 200–400 mesh) resin with 30% aqueous MeOH as the solvent. Crystallization in two crops afforded 535 mg of **2** as glittering, white rosettes. Under the microscope the crystals appeared as tiny prisms; mp 290–293 °C dec; $[\alpha]^{24}_D$ −20.9° (*c* 1.17, $H_2O$); UV max (pH 1) 257 nm (ε 14 470), ($H_2O$) 260 (14 520), (pH 13) 261 (14 820); UV min (pH 1) 227 nm (ε 2370), ($H_2O$) 226 (1630), (pH 13) 231 (3260); $R_{Ade}$ 1.82 (A), 0.92 (B). The IR spectrum was identical with that of the L nucleoside prepared many years ago in this laboratory[13] and which had mp 290–294 °C dec and $[\alpha]^{23}_D$ +21° (*c* 1.26, $H_2O$). Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

**9-(6-Deoxy-β-D-allopyranosyl)adenine (3).** Acetylation of 6-deoxy-D-allose (1.6 g) was performed in the same manner as described above. Upon pouring of the reaction mixture on ice, white crystals formed, which were filtered off when the ice had completely melted and air-dried for several days, affording 2.15 g (66% yield) of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-D-allopyranose; mp 114–115° (lit.[22] mp 109–110 °C).

**Synthesis of 3. Method A.** 6-Deoxy-D-allopyranose tetraacetate (2.1 g, 6.3 mmol) was dissolved in 32% HBr in HOAc (12 mL) and kept at room temperature for 1.75 h, with occasional swirling. Toluene (5 mL) was added and the solution was evaporated to a syrup. Addition and evaporation of toluene (5-mL portions) was continued several more times until no odor of HBr or HOAc was noticeable. During this time the syrup darkened considerably in color. It was immediately dissolved in xylene (50 mL) and added to a mixture of 6-benzamido-9-(chloromercuri)-purine (3.1 g, 6.5 mmol), Celite-545 (3.1 g), $CdCO_3$ (1.6 g), and xylene (150 mL) and heated under reflux for 4 h. The same work-up procedure as described above gave a dark-orange syrup, 3.3 g. The blocking groups were removed with NaOMe and the solution neutralized with HOAc. The product, a brown gum, was converted to the picrate, 1.12 g. Regeneration of the free nucleoside with a $CO_3^{2-}$ form resin yielded a foam, which was dissolved in 15 mL of MeOH. Clusters of fine needles formed, which were collected by filtration, 279 mg. An additional 50 mg were

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obtained from the mother liquor for a total of 329 mg (16% yield from the acetate) of **3**. The behavior of these crystals upon heating is rather complex. They soften at ~159 °C, whereupon the clear needles fog up and slowly lose their crystalline lattice structure as observed by a loss of the polarizing spectrum. However, the crystals retain their shape and a condensate begins to form on the cover slip at ~190 °C. The crystals melt at 193–195 °C to a free-flowing liquid; $[\alpha]^{23}_D$ −21.1° (*c* 1.04, $H_2O$); UV max (pH 1) 258 nm (ε 15 190), ($H_2O$) 261 (15 310), (pH 13) 261 (15 650); UV min (pH 1) 229 nm (ε 3060), ($H_2O$) 228 (2150), (pH 13) 232 (3970); $R_{Ade}$ 1.63 (A), 0.95 (B). Nucleoside **3** crystallized from MeOH as the monomethanolate. Anal. ($C_{11}H_{15}N_5O_4 \cdot CH_3OH$) C, H, N.

**Method B.** 6-Deoxy-D-allopyranose tetraacetate (1.97 g, 5.93 mmol), 6-benzamido-9-(chloromercuri)purine (3.53 g, 7.44 mmol), Celite-545 (3.5 g), and dry 1,2-dichloroethane (250 mL) were stirred in a flask outfitted with a reflux condenser, drying tube, and a take-off adapter. Some of the solvent (50 mL) was distilled to remove any traces of moisture, and $TiCl_4$ (1.0 mL) was added dissolved in 50 mL of fresh, dry 1,2-dichloroethane. The mixture was stirred under reflux for 22 h, cooled to room temperature, and then treated with saturated $NaHCO_3$ solution (120 mL). After being stirred for 1 h, the mixture was filtered through a Celite pad, and the filter cake was washed with 125 mL of hot 1,2-dichloroethane. The organic layer was separated and evaporated to dryness. The residue was dissolved in $CHCl_3$ (80 mL), washed with 30% aqueous KI (2 × 100 mL) and $H_2O$ (100 mL), and dried. Evaporation left a brown foam, 2.37 g. The blocking groups were removed with NaOMe, and the picrate (1.479 g) was prepared as previously described. The free nucleoside was regenerated with the $CO_3^{2-}$ resin, and evaporation of the $H_2O$ gave a slightly buff-colored solid residue. This was recrystallized from MeOH (20 mL) to give 559 mg (30% yield from the acetate) of **3** in two crops. The product was recrystallized one more time to afford 534 mg, which was identical with the product reported in method A.

**9-(6-Deoxy-α-L-talopyranosyl)adenine (4).** 6-Deoxy-L-talose (1.1 g) was acetylated as described previously and converted to the syrupy bromide (2.3 g). This was immediately added to a mixture containing 6-benzamido-9-(chloromercuri)purine (3.2 g, 6.75 mmol), Celite-545 (3.2 g), $CdCO_3$ (2.2 g), and xylene (200 mL) and heated under reflux for 3 h.[5,6] After the usual workup, a thick, orange syrup (3.4 g) remained. The blocking groups were removed with methanolic NaOMe; however, in this case the solution was neutralized with Amberlite CG-120($H^+$) ion-exchange resin. The resin was filtered off and washed thoroughly with MeOH, and the solvent was evaporated. The residue was dissolved in $H_2O$ (100 mL) and washed with $CHCl_3$ (3 × 25 mL). The aqueous layer was evaporated to ~25 mL and the solution was placed on top of a column (30 cm × 2.2 cm) of Bio-Rad AG1-X2 ($OH^-$, 200–400 mesh) that had been packed with $H_2O$.[8] Fractions (12 mL) were collected, and at tube 61 the solvent was changed to 30% aqueous MeOH. The product appeared in tubes 77–117. These were pooled and evaporated to a clear, colorless gum, which began to crystallize when it was heated with several milliliters of EtOH. Filtration and drying gave 806 mg of **4**. The nucleoside was recrystallized from EtOH containing enough $H_2O$ at the boiling point to cause dissolution, and the volume was reduced to ~15 mL by boiling. Upon seeding, white crystals formed, which were filtered off, washed with absolute EtOH, and dried in vacuo. These crystals weighed 679 mg, and an additional 68 mg was obtained from the mother liquor for a total yield of 747 mg (41% from the bromide); mp 243–245 °C dec; $[\alpha]^{24}_D$ −71.9° (*c*, 1.04, $H_2O$); UV max (pH 1) 259 nm (ε 15 120), ($H_2O$) 262 (15 250), (pH 13) 262 (15 500); UV min (pH 1) 229 nm (ε 2480), ($H_2O$) 228 (1840), (pH 13) 232 (3210); $R_{Ade}$ 1.42 (A), 0.90 (B). Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

**9-α-D-Rhamnopyranosyladenine (5).** 1,2,3,4-Tetra-*O*-acetyl-D-rhamnose was prepared by acetylation of D-rhamnose (2 g) as described before. The acetate (4.05 g, 100% yield from the sugar) was converted to the bromide (4.19 g, 99%) with 32% HBr in HOAc and worked up as already described for this process. The glycosyl bromide (4.19 g, 11.9 mmol) was condensed with 6-benzamido-9-(chloromercuri)purine (5.8 g, 12.2 mmol) in a mixture also containing Celite-545 (5.8), $CdCO_3$ (4 g), and xylene (300 mL). This mixture was heated under reflux for 4 h and worked up as described above to give 7.36 g of a thick syrup. After removal of the blocking groups with NaOMe, the picrate (3.9 g) was prepared. Treatement of this with the $CO_3^{2-}$ resin in hot $H_2O$ gave the free nucleoside as a clear syrup (1.6 g), which crystallized after standing for 2 days. The crystals were triturated with EtOH and removed by filtration. Recrystallization was effected from EtOH–$H_2O$ to yield 1.322 g (51% from the bromide) in three crops. An analytical sample was prepared by recrystallization of 300 mg, which required drying under high vacuum at 100 °C over $P_2O_5$ to get rid of traces of solvent; mp 213–215 °C; $[\alpha]^{23}_D$ +67.3° (*c* 0.468, $H_2O$). The IR spectrum was identical with that of the L nucleoside,[2,13] for which Baker and Hewson[7] had reported mp 210–211 °C and $[\alpha]$ −54°. However, the samples of the L form available in this laboratory from previous work[2,13] had mp 214–216 °C and $[\alpha]^{23}_D$ −67.7° (*c* 0.49, $H_2O$). UV max (pH 1) 259 nm (ε 13 960), ($H_2O$) 261 (14 540), (pH 13) 261 (14 850); UV min (pH 1) 229 nm (ε 2280), ($H_2O$) 227 (1530), (pH 13) 231 (3180); $R_{Ade}$ 1.46 (A), 0.87 (B). Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

**6-Deoxy-L-idose and 6-Deoxy-L-sorbose.** Methyl 5-*O*-benzoyl-2,3-*O*-isopropylidene-6-deoxy-β-L-gulofuranoside was subjected to acetolysis as described earlier[9] to effect epimerization at C-2. The product, 1,2,3-tri-*O*-acetyl-5-*O*-benzoyl-6-deoxy-L-idofuranose, was deacetylated with methanolic NaOMe, neutralized with Amberlite CG-120($H^+$) resin, and decolorized with activated charcoal. Evaporation, followed by three coevaporations with $H_2O$ that removed methyl benzoate as an azeotrope, left a clear, colorless syrup. When this product resisted attempts at crystallization over several days, it was used directly in the preparation described below.

**9-(6-Deoxy-α-L-idopyranosyl)adenine (6) and 9-(6-Deoxy-α-L-sorbofuranosyl)adenine (7).** The syrup (1.5 g) described above was dissolved in dry pyridine (14 mL), chilled in an ice bath, and treated with acetic anhydride (8 mL). The solution was stirred at 0 °C for 1 h and at room temperature for 22 h, then poured on ice (100 g), and stirred for 2 h. $CHCl_3$ (25 mL) was added and the mixture was transferred to a separatory funnel and the $CHCl_3$ layer separated. After further extractions with $CHCl_3$ (2 × 15 mL), the $CHCl_3$ extracts were combined, and the solution was washed with $H_2O$ (2 × 75 mL), saturated $NaHCO_3$ solution (50 mL), and $H_2O$ (75 mL) and dried. Evaporation and coevaporation with toluene (4 × 20 mL) yielded a clear syrup, 2.76 g (91%).

The syrup was dissolved in dry 1,2-dichloroethane (350 mL) and placed in a reaction flask containing 6-benzamido-9-(chloromercuri)purine (5 g) and Celite-545 (5 g), and some of the solvent (90 mL) was distilled to ensure a moisture-free environement. $TiCl_4$ (1.5 mL) was added dissolved in 50 mL of fresh 1,2-dichloroethane and the stirring mixture was refluxed for 20 h, cooled to room temperature, and treated with saturated $NaHCO_3$ (165 mL). After being stirred for 1 h, the mixture was filtered through a Celite pad and the filter cake washed with hot 1,2-dichloroethane (200 mL). The organic layer was separated and evaporated to dryness. The residue was dissolved in $CHCl_3$ (80 mL), washed with 30% aqueous KI (2 × 100 mL) and $H_2O$ (100 mL), and dried. Evaporation of the solvent gave a dark foam (3.43 g).

The foam was dissolved in MeOH (100 mL), 1 N methanolic NaOMe (10 mL) was added, and the solution was heated at reflux for 1 h. The cooled solution was neutralized with glacial HOAc and evaporated to dryness. The residue was dissolved in $H_2O$ (100 mL), washed with $CHCl_3$ (3 × 25 mL), and evaporated again to dryness. The residue was dissolved in MeOH (25 mL), 10% methanolic picric acid (60 mL) was added, and the flask was chilled in ice for 2 h. The picrate was filtered off, washed with ice-cold MeOH, and dried; 2.205 g. The nucleosides were regenerated with Bio-Rad AG1-X8($CO_3^{2-}$) resin as already described above. Evaporation of the $H_2O$ afforded a glasslike foam, 860 mg. This was dissolved in a minimum amount of $H_2O$ and placed on a column (30 cm × 2.2 cm) of Bio-Rad AG1-X2 ($OH^-$, 200–400 mesh) resin that had been packed with $H_2O$, and 12-mL fractions were collected. At tube 90, the solvent system was changed to 30% aqueous MeOH, and at tube 202 it was changed again to 60% aqueous MeOH. The main UV-absorbing peaks appeared in tubes 106–134 (peak 1) and in tube 211–242 (peak 2). The contents of the tubes in each peak were pooled and evaporated to dryness.

Crystallization of the residue from peak 1 from MeOH (15 mL) gave 203 mg in two crops, which was recrystallized to afford 178 mg of pure **6** as prismatic crystals; mp 242–243 °C dec; $[\alpha]^{23}_D$

−63.8° (*c* 1.05, $H_2O$); UV max (pH 1) 259 nm (ε 15660), ($H_2O$) 260 (15680), (pH 13) 261 (16000); UV min (pH 1) 229 nm (ε 3240), ($H_2O$) 227 (2280), (pH 13) 231 (4050); $R_{Ade}$ 1.40 (A), 0.75 (B). The nucleoside consumed 1.95 molar equiv of periodate in nearly 24 h. Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

The nucleoside from peak 2 was crystallized from EtOH to afford 268 mg of white crystals in two crops. Recrystallization gave the analytical sample (154 mg) of **7** and a second crop (88 mg) for a total of 242 mg; mp 211–213 °C; $[\alpha]^{27}_D$ −37.4° (*c* 1.05, $H_2O$); UV max (pH 1) 259 nm (ε 14800), ($H_2O$) 261 (15090), (pH 13) 261 (15230); UV min (pH 1) 233 nm (ε 4160), ($H_2O$) 229 (2450), (pH 13) 233 (4450); $R_{Ade}$ 1.34 (A), 1.00 (B). The nucleoside consumed 0.94 molar equiv of periodate in 5 days. Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

**9-α-L-Arabinopyranosyladenine (8).** The synthetic route was similar to that described for the D nucleoside.[2] 6-Benzamido-9-(chloromercuri)purine (5.6 g, 11.8 mmol) was condensed with 2,3,4-tri-*O*-benzoyl-L-arabinopyranosyl bromide (6.7 g, 12.7 mmol) by the procedure of Davoll and Lowy.[4] Unlike the case with the D form, the L nucleoside would not crystallize after removal of the blocking groups. Therefore, the crude nucleoside was dissolved in hot MeOH (40 mL) and treated with 10% methanolic picric acid (50 mL). After the mixture was chilled in an ice bath for 3 h, the picrate was filtered off and dried, affording 4.07 g. The free nucleoside was regenerated with the $CO_3^{2-}$ resin in the usual way, and evaporation of the $H_2O$ gave a residue, which began to crystallize upon standing. Warm $H_2O$ was added and crystallization allowed to proceed in the refrigerator. This yielded 1.702 g, followed by an additional 0.213 g from the mother liquor (total yield 1.915 g, 53% from the bromide). This material was recrystallized from $H_2O$ to give 1.643 g (45% from the bromide) of **8** as clear prismatic crystals; mp 164–166 °C with softening beginning at ~162 °C. The crystals melt to a very viscous liquid, which upon further heating crystallizes again in the form of spokelike threads at ~220 °C and melts at 258–261 °C; $[\alpha]^{25}_D$ +35.9° (*c* 1.02, $H_2O$); $R_{Ade}$ 1.01 (A), 0.55 (B). The IR spectrum was identical with that of the D nucleoside. Anal. ($C_{10}H_{13}N_5O_4 \cdot H_2O$) C, H, N.

The D nucleoside was previously reported to have mp 167–169 °C, $[\alpha]^{24}_D$ −35.5° (*c* 2.79, $H_2O$).[2] Martinez et al.[23] reported mp 167–168 °C, $[\alpha]_D$ −34°. In fact, the double melting behavior of **8** was missed. A sample of the D nucleoside from the original work[2] had the same melting behavior as described above, with mp 167–169 °C and the second mp at 256–258 °C. Fuertes et al.[24] prepared **8** by another route, which was also a monohydrate. However, they obtained crystals from EtOH that melted at 269–270 °C, whereas crystals obtained from aqueous EtOH had mp 235–236 °C, $[\alpha]^{25}_D$ +35.3° (*c* 1, $H_2O$). When we recrystallized **8** from EtOH–$H_2O$, there was no change in the melting point behavior as described above.

**9-β-D-Galactopyranosyladenine (9). Method A.** 2,3,4,6-Tetra-*O*-benzoyl-D-galactopyranosyl bromide was condensed with 6-benzamido-9-(chloromercuri)purine by the same procedure used for the synthesis of **8**. The picrate of the deblocked nucleoside was obtained in 71% yield, mp 230–232 °C (lit.[25] mp 230–232 °C). Removal of the picrate ion with the $CO_3^{2-}$ resin and recrystallization from aqueous EtOH gave fluffy, ill-defined, threadlike crystals in 45% yield from the bromide. This material was identical with the one in method B by melting point, mixture melting point, optical rotation, and IR spectrum.

**Method B.** This procedure was the same as reported by Wolfrom et al.[25] except that 6-benzamido-9-(chloromercuri)purine was used in place of 6-acetamido-9-(chloromercuri)purine. The yield of **9** from the glycosyl bromide was 46%; mp 198–201 °C; (lit.[25] mp 198–200 °C); $[\alpha]^{23}_D$ +31.6° (*c* 0.6, $H_2O$); $R_{Ade}$ 1.85 (A), 0.59 (B). The specific rotation reported[25] was +95.5°, which is possibly a typographical error. Dr. Carl Bergmann, working in the laboratory of Professor Derek Horton at the Ohio State University, has kindly measured the rotation of an original sample in their collection and has found $[\alpha]_D$ +36°. He also reports that the crystals are not in the form of needles. The elemental analyses of various samples of **9** never gave really acceptable results, especially for carbon, even after several recrystallizations and chromatography. This was also true in the original paper.[25]

**Periodate Consumption.** The uptake of periodate by nucleosides **6** and **7** was determined by the spectrophotometric method of Rammler and Rabinowitz.[26]

**Polarimetric Studies.** Between 9 and 11 mg of each nucleoside was dissolved in hot $H_2O$ (0.75 mL) in a 2-mL volumetric flask and then cooled to room temperature. To the solution was added 0.25 M $NaIO_4$ (0.5 mL). The reaction mixture was stored in the dark at room temperature. At the end of the reaction time (24–70 h), $NaBH_4$ (60 mg) was added. After 1 h, the excess hydride was destroyed by slow addition of 20% aqueous HOAc (0.4 mL). When effervescence stopped (1–2 h), the volume was adjusted with $H_2O$ to 2 mL and the optical rotation was measured. The results are shown in Table I. Nucleoside **9** gave a value of +59°, in excellent agreement with previous work,[3] thereby proving its anomeric configuration, which had not previously been done.

**Antileukemic Assay.** All culture reagents were purchased from Gibco. Dulbecco's Modified Eagle Medium (cat. no. H-16) also contained $NaHCO_3$ (44 mM), D-glucose (4 mg/mL), L-asparagine (0.2 mg/mL), penicillin (50 units/mL), streptomycin (50 units/mL), and 10% horse serum (cat. no. 200-6050). L1210 lymphoma cells were carried as ascites tumors in B6D2F1 mice. The cells were washed three times in Ringer's solution and were inoculated into cultures with 75 $cm^2$ and 150 $cm^2$ flasks (Corning). The total volumes were 30 and 100 mL, respectively, and the initial cell density was $0.2 \times 10^6$/mL. Cultures were incubated at 38 °C under an atmosphere of air 5% $CO_2$. When the cell density reached (1–2) $\times 10^6$ cells/mL, the cultures were diluted back to $0.2 \times 10^6$ cells/mL.

Growth inhibitors were dissolved in distilled $H_2O$ at a concentration of $10^{-3}$ M and sterilized by filtration. Aliquots from these solutions were transferred to 25 $cm^2$ culture flasks containing $4 \times 10^5$ cells in 2 mL of medium, and the flasks were incubated for 48 h. Cell counts and viability were assessed by Trypan Blue exclusion in an hemocytometer at 24-h intervals. All assays were performed in duplicate. Several standard drugs, 5-fluorouracil, cytosine arabinoside, and methotrexate were used as controls to monitor normal inhibitory responses.

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