1660 (s); ^{1}H NMR ($CDCl_3$) δ 7.93 (m, 2 H, arom), 7.43 (m, 3 H, arom), 7.10 (m, 5 H, arom), 3.35 (d, J = 13.5 Hz, 1 H, benzyl), 3.06 (d, J = 13.5 Hz, 1 H, benzyl), 3.03-2.70 (m, 2 H, H_2C5), 2.46-1.53 (m, 4 H, H_2C3, H_2C4); MS 174 (M^+ - 91, 80), 160 (100). Anal. Calcd for $C_{18}H_{19}NO$ (265.33): C, 81.47; H, 7.22; N, 5.28. Found: C, 81.33; H, 7.39; N, 5.08.

(±)-2-*tert*-Butyl-1-aza-3-oxabicyclo[3.2.0]heptan-4-one (41). According to the procedure described above for the preparation of compound **2**, 10 g (100 mmol) of L- or (*S*)-2-acetidinecarboxylic acid and 60 mL of pivalaldehyde were condensed during 6 days and 9 g (54%) of racemic **41** were obtained as a yellow oil: bp 90 °C (0.2 mm); ^{1}H NMR ($CDCl_3$) δ 4.53 (s, 1 H, H-C2), 4.16-3.36 (m, 3 H, H_2C7, H-C5), 3.03-2.03 (m, 2 H, H_2C6), 0.89 (s, 9 H, $(H_3C)_3C$-C2).

(2*R*,5*R*)-2-*tert*-Butyl-1-aza-3-oxa-7-thiabicyclo[3.3.0]octan-4-one (43). According to the procedure described for the preparation of compound **2**, 19.0 g (143 mmol) of **42**[34] and 100 mL of pivalaldehyde were condensed during 48 h. After crystallization from ether/pentane 22.4 g (78%) of **43** were obtained as pale yellow crystals. The product is very sensitive to moisture: mp 62 °C; $[\alpha]^{20}_D$ +86.0° (*c* 0.15; $CHCl_3$); IR (KBr) 2950 (m), 2870 (w), 1785 (s); ^{1}H NMR ($CDCl_3$) δ 4.47 (s, 1 H, H-C2), 4.30-3.93 (m, 3 H, H_2C8, H-C5), 3.57-3.03 (m, 2 H, H_2C6), 0.97 (s, 9 H, $(H_3C)_3C$-C2); MS 201 (M^+, 11), 146 (89), 100 (45), 96 (35), 54 (100). Anal. Calcd for $C_9H_{15}NO_2S$ (201.27); C, 53.70; H, 7.51; N, 6.96; S, 15.93. Found: C, 63.46; H, 7.57; N, 6.96; S, 15.80.

(*R*)-2-*tert*-Butyl-*N*-((methylthio)methyl)-4-methylidene-5-oxazolidinone (44). To a solution of 20.0 g (100 mmol) of **43** in 180 mL of THF stirred at -90° was added 120 mL of a 0.93 M LDA solution in THF/hexane 1:3. After the mixture was stirred for 30 min at -78 °C, 12 mL (188 mmol) of methyl iodide were added, and the temperature was allowed to rise to 0 °C overnight. The resulting mixture was partitioned between dichloromethane and water. The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. Recrystallization from ether gave 20.1 g (94%) of **44** as pale yellow crystals: mp 29 °C; bp 140 °C (0.1 mm); $[\alpha]^{25}_D$ -277° (*c* 1.6; $CHCl_3$); IR ($CHCl_3$) 2960 (m), 1775 (s); ^{1}H NMR ($CDCl_3$) δ 5.17 (s, 1 H, H-C2), 5.04 (d, J = 2 Hz, 1 H, olefin), 4.65 (d, J = 13 Hz, 1 H, H_2C-N), 4.43 (d, J = 2 Hz, 1 H, olefin), 4.21 (d, J = 13 Hz, 1 H, H_2C-N), 2.13 (s, 3 H, H_3C-S), 0.96 (s, 9 H, $(H_3C)_3C$-C2); MS 215 (M^+, 8), 168 (21), 158 (12), 82 (10), 61 (100). Anal. Calcd for $C_{10}H_{17}NO_2S$ (215.31): C, 55.78; H, 7.96; N, 6.51; S, 14.89. Found: C, 56.11; H, 8.17; N, 6.85; S, 14.71.

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Registry No. 1, 147-85-3; **2**, 81286-82-0; **3**, 86046-10-8; **4**, 71890-95-4; **5**, 86046-11-9; **6**, 42856-71-3; **7** (isomer 1), 86046-12-0; **7** (isomer 2), 86116-72-5; **8**, 81286-83-1; **8'**, 86116-73-6; **9**, 86046-13-1; **10**, 86046-14-2; **11**, 86046-15-3; **12**, 86064-60-0; **13**, 86046-16-4; **14**, 86046-17-5; **15** (isomer 1), 86046-18-6; **15** (isomer 2), 86116-74-7; **16** (isomer 1), 86046-19-7; **16** (isomer 2), 86116-75-8; **17**, 86046-20-0; **18** (isomer 1), 86046-21-1; **18** (isomer 2), 86116-76-9; **19** (isomer 1), 86046-22-2; **19** (isomer 2), 86116-77-0; **20** (isomer 1), 86046-23-3; **20** (isomer 2), 86116-78-1; **21** (isomer 1), 86046-24-4; **21** (isomer 2), 86116-79-2; **22** (isomer 1), 86064-61-1; **22** (isomer 2), 86117-44-4; **23** (isomer 1), 86046-25-5; **23** (isomer 2), 86116-80-5; **24** (isomer 1), 86046-26-6; **24** (isomer 2), 86116-81-6; **26** (isomer 1), 86046-27-7; **26** (isomer 2), 86116-82-7; **27** (isomer 1), 86046-28-8; **27** (isomer 2), 86116-83-8; **28**, 86046-29-9; **29**, 86046-30-2; **30**, 86046-31-3; **31**, 86116-84-9; **33**, 86046-32-4; **34**, 86046-33-5; **35**, 86046-34-6; **36**, 86046-35-7; **37** (R = Me), 86046-36-8; **38**, 86046-37-9; **39**, 86046-38-0; **40**, 2133-34-8; **41**, 86046-39-1; **42**, 34592-47-7; **43**, 86046-40-4; **44**, 86046-41-5; pivalaldehyde, 630-19-3; methyl iodide, 74-88-4; benzaldehyde, 100-52-7; allyl bromide, 106-95-6; benzyl bromide, 100-39-0; *N*,*N*-dimethylmethylenimmonium chloride, 30354-18-8; methyl α-bromoacetate, 96-32-2; *N*,*N*-dimethyl chloroacetamide, 2675-89-0; (benzene)(tricarbonyl)chromium, 12082-08-5; diphenyl disulfide, 882-33-7; acetaldehyde, 75-07-0; acetone, 67-64-1; methyl acetoacetate, 105-45-3; ω-nitroacetoveratrone, 46729-91-3; α-tetralone, 529-34-0; 6-methoxy-2-tetralone, 2472-22-2; 6,7-dimethoxy-2-pivaloyl-1,2,3,4-tetrahydroisoquinolin-4-one, 86046-42-6; 2-cyclohexen-1-one, 930-68-7; 3,4-dimethoxy-ω-nitrostyrene, 4230-93-7; acetic anhydride, 108-24-7; methyl 3,4-dimethoxybenzoate, 2150-38-1; methyl chloroformate, 79-22-1; *N*-benzylpyridine, 1753-62-4.

Supplementary Material Available: X-ray crystal structure determination and tables of *x*, *y*, *z*, and *U* values and bond lengths and angles for **7**, and a stereoview of the unit cell (6 pages). Ordering information is given on any current masthead page.

Structure and Conformation of 5-Methylarabinosylcytosine, a Potential Antiviral Nucleoside[1]

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Abstract: The three-dimensional structure of 1-β-D-5-methylarabinosylcytosine hydrate, a potential antiviral nucleoside, was determined by X-ray crystallography. The crystals belong to the orthorhombic space group $P2_12_12_1$ and the cell dimensions are a = 7.472 (1), b = 11.950 (1), and c = 13.723 (1) Å. Intensity data were measured on a diffractometer and the structure was determined by direct methods. Least-squares refinement, which included all hydrogen atoms, converged at R = 0.028 for 1457 observed reflections. The pyrimidine ring is significantly nonplanar and the methyl substitution at C(5) causes that atom to be pulled away from the center of the ring. The conformation about the glycosyl bond is anti with χ_{CN} = 22.6°. The arabinose ring is in an envelope conformation with a C(2') endo (^2E) pucker. The bond lengths and bond angles in the ring are discussed in relation to the ring's conformation and configuration.

Several arabinonucleosides are known to possess antiviral and/or anticancer properties. Arabinofuranosylcytosine (ara-C) is the mainstay of the treatment of acute myeloblastic leukemia in adults.[3] Arabinofuranosyladenine (ara-A, vidarabine) and arabinofuranosylthymine (ara-T) show activity against herpes and vaccinia viruses.[4,5] 2'-Fluoro-5-iodoarabinofuranosylcytosine (FIAC) was found to be especially capable of suppressing the replication of various strains of herpes simplex virus types 1 and 2, as well as of herpes zoster and cytomegalovirus.[6] When an

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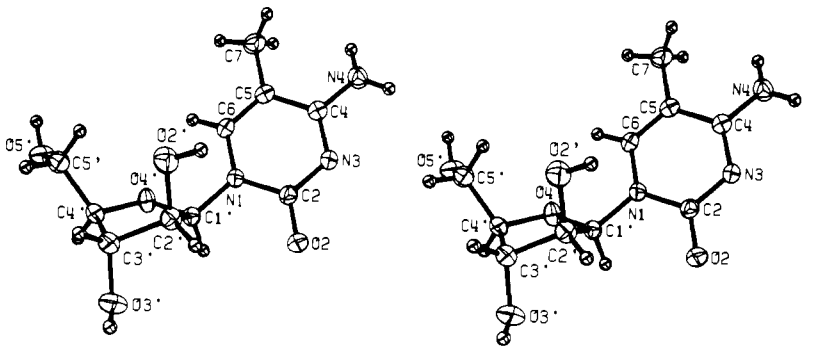

Figure 1. Stereoscopic view of m^5 ara-C. The ellipsoids correspond to 50% probability.

amino group is present in the pyrimidine or purine ring, the nucleoside may be deaminated by a deaminase to a less active compound. Thus, ara-A is deaminated to the less potent arabinosylhypoxanthine[7] while ara-C is deaminated to give the inactive arabinosyluracil (ara-U).[8] On the basis of a kinetic study, it was recently suggested that the enzymatic deamination of nucleosides depends on the conformation of the sugar ring.[9] Consequently, it appeared to be of interest to carry out an X-ray analysis of 5-methylarabinosylcytosine (m^5ara-C) because this compound, unlike ara-A, requires deamination to ara-T in order to function as an antiviral substance.[10a] In cells able to deaminate it, it behaves very much like ara-T, whether in cell culture systems or in animals.[10b] This investigation is considered to be valuable not only because it extends our structural studies of chemotherapeutic nucleosides[11] but also because X-ray data on arabinonucleosides are relatively scarce.[12] Additional crystallographic data will facilitate comparisons with theoretical calculations[13] and NMR studies.[14]

Experimental Section

1-β-D-5-Methylarabinosylcytosine hydrate, $C_{10}H_{15}N_3O_5 \cdot H_2O$, was crystallized from 25% aqueous ethanol. Precession photographs indicated the orthorhombic space group $P2_12_12_1$. A colorless crystal, measuring 0.5 × 0.5 × 0.5 mm, was mounted on a CAD-4 diffractometer. The unit cell dimensions were determined from angular settings of 22 reflections with θ in the range 47–59°. The following data were obtained: a = 7.472 (1), b = 11.950 (1), and c = 13.723 (1) Å, V = 1225.33 Å^3, D_x = 1.49 g cm^{-3}, Z = 4 (21 °C; Cu Kα_1, λ = 1.54056 Å), $F(000)$ = 576, μ(Cu Kα) = 10.1 cm^{-1}.

Table I. Final Atomic Parameters and Their Standard Deviations[a]

atom	x	y	z	B_{eqv} or B
N(1)	24497 (18)	51912 (10)	13571 (9)	1.7
C(2)	18734 (22)	57864 (12)	5474 (11)	1.8
O(2)	25293 (19)	55711 (10)	−2643 (8)	2.5
N(3)	5975 (19)	65793 (11)	6613 (9)	1.9
C(4)	−654 (20)	68057 (13)	15440 (11)	1.8
N(4)	−12044 (20)	76560 (13)	16225 (11)	2.3
C(5)	4595 (21)	61811 (13)	23951 (10)	1.9
C(6)	17492 (21)	54043 (13)	22603 (11)	1.8
C(7)	−3767 (26)	63931 (17)	33716 (12)	2.8
C(1')	39158 (21)	43892 (12)	12053 (11)	1.8
C(2')	57692 (22)	49444 (13)	12037 (11)	2.0
O(2')	59148 (18)	57378 (9)	19534 (10)	2.6
C(3')	69392 (21)	39427 (13)	14638 (11)	2.0
O(3')	71586 (19)	32410 (11)	6350 (9)	2.7
C(4')	57915 (21)	33137 (12)	22039 (11)	1.8
O(4')	39484 (15)	36222 (9)	19923 (9)	2.1
C(5')	62083 (23)	35315 (13)	32647 (12)	2.2
O(5')	54015 (19)	26723 (10)	38251 (8)	2.5
O(W)	51209 (24)	13340 (14)	3878 (14)	4.2
H1(N4)	−152 (4)	799 (2)	111 (2)	3.0 (0.5)
H2(N4)	−179 (4)	775 (2)	217 (2)	3.4 (0.5)
H(6)	220 (3)	501 (2)	276 (2)	2.0 (0.4)
H(71)	11 (4)	589 (2)	383 (2)	3.0 (0.5)
H(72)	−14 (5)	715 (3)	355 (2)	5.0 (0.7)
H(73)	−166 (4)	632 (2)	333 (2)	3.9 (0.6)
H(1')	368 (3)	400 (2)	61 (1)	1.3 (0.3)
H(2')	609 (4)	525 (2)	57 (2)	3.0 (0.5)
H(O2')	559 (4)	638 (3)	172 (2)	4.2 (0.6)
H(3')	804 (3)	417 (2)	175 (2)	2.7 (0.4)
H(O3')	810 (4)	350 (2)	29 (2)	4.1 (0.6)
H(4')	592 (3)	256 (2)	208 (2)	2.3 (0.4)
H(5')	576 (3)	422 (2)	345 (2)	2.8 (0.4)
H(5'')	746 (3)	352 (2)	336 (2)	2.8 (0.4)
H(O5')	515 (4)	293 (2)	440 (2)	2.8 (0.4)
H(W1)	577 (5)	195 (3)	42 (2)	4.5 (0.6)
H(W2)	581 (5)	83 (3)	50 (3)	5.3 (0.7)

[a] The non-hydrogen coordinates were multiplied by 10^5 and the hydrogen coordinates by 10^3.

Table II. Pyrimidine Least-Squares Plane and Deviations of Atoms from It[a]

atom	Δ, Å	atom	Δ, Å
N(1)	−0.002 (1)	C(1')	−0.095 (2)
C(2)	0.001 (2)	O(2)	0.009 (1)
N(3)	0.008 (1)	H(O5')[b]	0.28 (3)
C(4)	−0.020 (2)	N(4)	−0.125 (2)
C(5)	0.017 (2)	C(7)	0.070 (2)
C(6)	−0.006 (2)	H(6)	−0.04 (2)

[a] Atoms in the left-hand column were used to calculate the plane $0.7128X + 0.6820Y + 0.1638Z = 5.8380$. [b] Proton donated by another molecule to N(3).

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Table III. Torsion Angles (in Degrees)[a]

C(6)-N(1)-C(1')-O(4')	22.6	H(1')-C(1')-C(2')-H(2')	38	O(3')-C(3')-C(4')-H(4')	25
C(6)-N(1)-C(1')-C(2')	-94.2	C(1')-C(2')-C(3')-O(3')	76.9	H(3')-C(3')-C(4')-O(4')	145
C(6)-N(1)-C(1')-H(1')	141	C(1')-C(2')-C(3')-H(3')	-156	H(3')-C(3')-C(4')-H(4')	-100
C(2)-N(1)-C(1')-H(1')	-43	O(2')-C(2')-C(3')-C(4')	78.8	H(3')-C(3')-C(4')-C(5')	22
C(2)-N(1)-C(1')-C(2')	81.7	O(2')-C(2')-C(3')-H(3')	-40	H(4')-C(4')-O(4')-C(1')	-116
C(2)-N(1)-C(1')-O(4')	-161.5	O(2')-C(2')-C(3')-O(3')	-166.7	C(5')-C(4')-O(4')-C(1')	125.3
N(1)-C(1')-C(2')-C(3')	157.4	H(2')-C(2')-C(3')-H(3')	84	C(3')-C(4')-C(5')-H(5')	76
N(1)-C(1')-C(2')-H(2')	-84	H(2')-C(2')-C(3')-O(3')	-43	C(3')-C(4')-C(5')-O(5')	-163.8
N(1)-C(1')-C(2')-O(2')	43.1	H(2')-C(2')-C(3')-C(4')	-157	H(4')-C(4')-C(5')-H(5')	-163
O(4')-C(1')-C(2')-H(2')	157	C(2')-C(3')-C(4')-C(5')	-97.3	H(4')-C(4')-C(5')-O(5')	-42
O(4')-C(1')-C(2')-O(2')	-75.9	C(2')-C(3')-C(4')-H(4')	141	O(4')-C(4')-C(5')-H(5')	-44
H(1')-C(1')-C(2')-C(3')	-81	O(3')-C(3')-C(4')-O(4')	-90.9	O(4')-C(4')-C(5')-O(5')	75.9
H(1')-C(1')-C(2')-O(2')	165	O(3')-C(3')-C(4')-C(5')	146.5	N(1)-C(1')-O(4')-C(4')	-145.4

[a] The esd's are 0.1-0.2° for angles not involving hydrogen atoms and 1-2° for those which do.

Intensities were measured with Ni-filtered Cu Kα radiation up to $2\theta = 150°$, using the $\omega/2\theta$ scan technique with $\Delta\omega = 1.2 + 0.2 \tan\theta$ and a maximum scan time of 150 s per reflection. Three reflections, monitored every 100 min, showed intensity variations <1%. Of the 1472 unique reflections, only 13 had $I < 3\sigma(I)$ and were considered unobserved. The intensities were corrected for Lorentz and polarization factors; absorption corrections were unnecessary.

The structure was determined by direct methods with the aid of the computer program MULTAN78.[15] Of the ten starting sets subjected to tangent refinement, the solution with the highest combined figure of merit yielded an E map on which all 19 nonhydrogen atoms were located. The atomic parameters were refined by the block-diagonal least-squares method with anisotropic temperature parameters. All hydrogen atoms were located on difference Fourier maps and refined with isotropic temperature parameters. The scattering factors were taken from the "International Tables for X-Ray Crystallography"[16] and the oxygen curve was corrected for anomalous dispersion. Throughout the refinement the function $\sum w(|F_o| - |F_c|)^2$ was minimized and a factor of 0.8 was applied to all shifts. The following weighting scheme was used during the final stages: $w = w_1 w_2$, where $w_1 = 1$ for $|F_o| \leq 13$, $w_1 = 13/|F_o|$ for $|F_o| > 13$, $w_2 = \sin^2\theta/0.6$ for $\sin^2\theta < 0.6$, and $w_2 = 1$ for $\sin^2\theta \geq 0.6$. This scheme made the average values of $w(\Delta F^2)$ independent of $|F_o|$ and $\sin^2\theta$. After the final cycle the average parameter shift equalled 0.1σ and the largest 0.5σ. Two strong reflections (120 and 012) suffered from extinction effects and were given zero weights. The final conventional residual index R is 0.028 and the weighted index R_w is 0.033 for 1457 observed reflections. The coordinates are listed in Table I; lists of anisotropic temperature parameters and of observed and calculated structure factors are available (see paragraph at the end of the paper). The overall conformation and the atomic numbering scheme are shown in Figure 1.

Results and Discussion

Aglycon Moiety. The pyrimidine ring is not completely planar (Table II). The largest deviations from the mean plane are those of C(4), -0.020 (2) Å, and C(5), 0.017 (2) Å, while the endocyclic torsion angles range from 0.4 (2) to 4.3 (2)°. These highly significant deviations are relevant to a recently published conclusion that the average geometry of a base residue in a nucleoside is precisely planar.[17] According to these authors, the conclusion is consistent with either of the following hypotheses: (a) the equilibrium geometry of the isolated base residue is precisely planar; (b) the equilibrium geometry is not precisely planar, but deviations from planarity occur with equal facility on either side of the base mean plane. It should be pointed out that N(3) is displaced to the same side as H(O5') which it accepts from another molecule while C(4) is displaced to the same side as N(4) which participates in two hydrogen bonds. Furthermore, C(5) is on the same side of the mean plane as the methyl group attached to it. It appears, therefore, that displacements of ring substituents, due to electrostatic or steric effects, can easily pull ring atoms from their mean plane. This implies that hypothesis (b), quoted above, is the correct one.

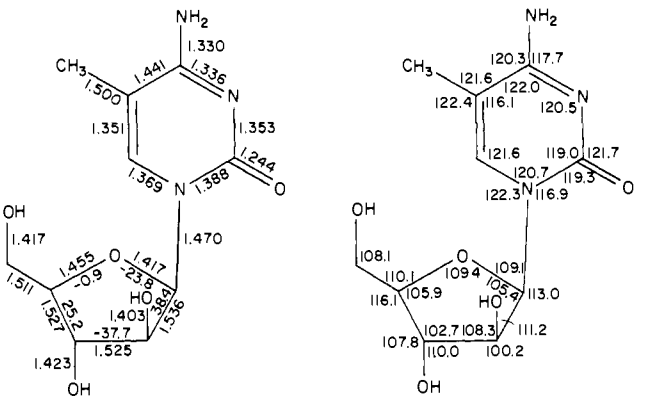

Figure 2. (Left) Bond distances (Å) and endocyclic torsion angles (deg). Their estimated standard deviations (esd's) are 0.002 Å and 0.15°, respectively. (Right) Bond angles (deg); their esd's are 0.11-0.14°.

Table IV. Conformational Parameters of β-D-Arabinonucleosides in Anti Conformation

structure	P, deg	χ_{CN}, deg	ref
arabinosyladenine·HCl	9.3	29.7	12a
arabinosylcytosine-5'-phosphate	12.6	30.7	12b
arabinosyl-4-thiouracil	13.0	36.6	12c
arabinosyladenine	24.8	57.8	12d
arabinosyl-5-propynyluracil	28.3	33.7	12e
arabinosyl-8-*n*-butylaminoadenine	38.4	52.7	12f
arabinosylthymine	105.5	24.1	12g
arabinosyl-5-bromouracil	107.5	30.4	12h
arabinosyluracil	156.3	34.0	12i
arabinosylcytosine	162.3	28.8	12j
arabinosyl-5-methylcytosine	162.7	22.6	
(3-*O*-methylarabinosyl)cytosine	167.8	28.7	12k
arabinosylcytosine·HCl	169.0	26.7	12l

It is of interest to compare the bond lengths and bond angles in our structure (Figure 2) with recently compiled average values.[17] Such a comparison reveals a significant change of the ring geometry due to the methyl substitution at C(5). The main differences are the 1.5° decrease of the angle C(4)-C(5)-C(6) from the average value of 117.6 (2)° and the 0.014-0.015 Å increases of the bond lengths C(4)-C(5) and C(5)-C(6) from their average values 1.426 (4) and 1.337 (2) Å, respectively. These changes, presumably resulting from a slightly altered hybridization state of C(5), are equivalent to C(5) being pulled away from the center of the ring and the extent can be assessed by a comparison of the C(2)···C(5) distance (2.787 Å) with the N(1)···C(4) distance (2.705 Å). Methyl substitution at C(5) and C(6) also affects the geometry of uracil rings[18] and it should therefore be pointed out that the recently calculated "standard geometry" of a uracil residue[19] was derived from both substituted (primarily at C(5))

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Table V. Distances and Angles for Hydrogen Bonds

			distances, Å			angles, deg
D	*A*	*A* at	*D*···*A*	H···*A*	H···A_{corr}	*D*-H···*A*
N(4)-H1(N4)···O(2)		$^1/_2 + x, {}^3/_2 - y, \bar{z}$	2.976	2.19	2.01	155
N(4)-H2(N4)···O(4')		$\bar{x}, {}^1/_2 + y, {}^1/_2 - z$	3.025	2.24	2.10	149
O(2')-H(O2')···O(5')		$1 - x, {}^1/_2 + y, {}^1/_2 - z$	2.730	1.86	1.77	172
O(5')-H(O5')···N(3)		$^1/_2 - x, 1 - y, {}^1/_2 + z$	2.776	1.91	1.81	175
O(3')-H(O3')···O(W)		$^1/_2 + x, {}^1/_2 - y, \bar{z}$	2.670	1.79	1.72	166
O(W)-H(W1)···O(3')		x, y, z	2.762	1.88	1.80	174
O(W)-H(W2)···O(2)		$^1/_2 + x, {}^1/_2 - y, \bar{z}$	2.907	2.13	1.98	160

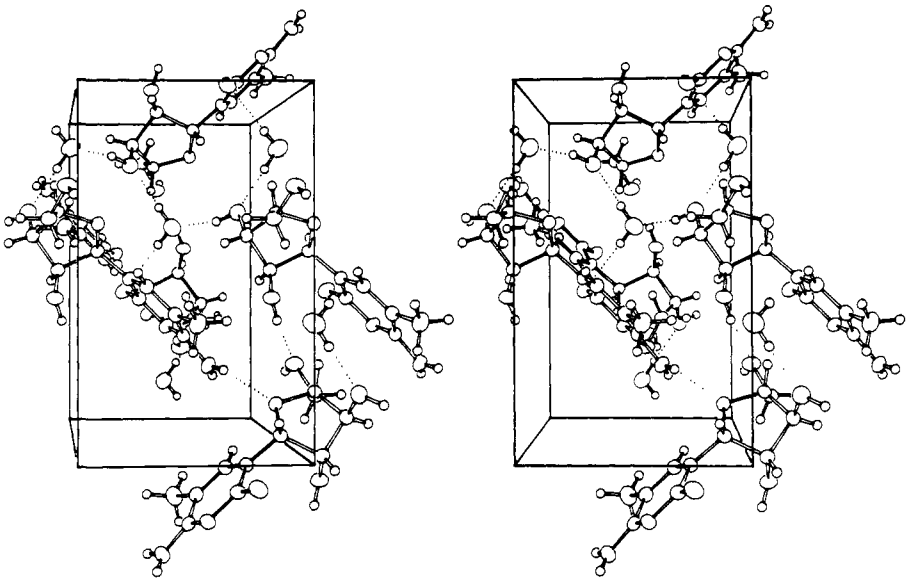

Figure 3. Stereoscopic view of the molecular packing in the crystal. Some hydrogen bonds are indicated by dotted lines.

and unsubstituted rings. Thus, it is not surprising that the largest range of observed values (5.1°) and the largest standard deviation (1.3°) are related to the angle C(4)–C(5)–C(6). On the other hand, if only 13 unsubstituted uracil residues are taken into account, the average angle increases from 119.2 (2) to 119.7(2)°, the range of observed values decreases to 2.5°, and the standard deviation of the distribution decreases to 0.7°.

Conformation about the Glycosyl Bond. The conformation about the glycosyl bond is anti and the torsion angle χ_{CN} [C(6)–N(1)–C(1')–O(4')] is 22.6° (Table III). In previously determined structures of arabinonucleosides in anti formation (Table IV) this angle has been found, with two exceptions, in the relatively narrow range 24.1–36.6°. This is in very good agreement with the favored range of 20–45° which was calculated with semiempirical potential functions.[13b] In contrast to ribonucleosides, there is no discernible correlation between the glycosyl torsion angle and the pucker of the furanose ring in arabinosides.

Arabinose Moiety. The furanose ring is in an envelope conformation, corresponding to a C(2') endo (^2E) pucker. The phase angle of pseudorotation (P) is 162.7° and the maximum amplitude of puckering (τ_m) is 39.5°.[20] In this conformation there are two favorable gauche C–O/C–O interactions [C(2')–O(2')/C(1')–O(4') and C(3')–O(3')/C(4')–O(4')] and one unfavorable trans interaction [C(2')–O(2')/C(3')–O(3')]. In the C(3') endo conformation the situation is reversed: there are two trans interactions [C(1')–O(4')/C(2')–O(2') and C(3')–O(3')/C(4')–O(4')] and one gauche interaction [C(2')–O(2')/C(3')–O(3')]. If the gauche effect[21] is the major determinant of ring puckering apart from nonbonded interactions,[22] one would expect the majority of arabinonucleosides to crystallize in the C(2') endo conformation. The limited data available thus far do not seem to support this hypothesis. This is not entirely surprising when one considers that the gauche effect is rather weak for C–O/C–O interactions (0.6 kcal mol^{-1})[23] and could be easily overcome in the solid state by hydrogen bonds and/or other forces.

It is of interest to note that the same C(2') endo conformation was found in the crystal structures of ara-C[12j] and its hydrochloride.[12l] On the other hand, ara-T, the product of the enzymatic deamination of m^5 ara-C, adopts the rather unusual O(4') endo–C(1') exo (^0_1T) pucker.[12g]

In view of the exact C(2') endo conformation and the average extent of ring puckering (τ_m = 39.5°), the bond lengths and angles of this arabinose ring could be taken as standard values, particularly because this appears to be the most precisely determined structure of an arabinonucleoside. Several years ago, it was suggested that the endocyclic bond lengths in the furanose ring in nucleosides depend on the conformation of the ring and the configuration of the –OH substituents.[24] A more recent and more detailed survey[25] led to the conclusion that these bond lengths are virtually independent of the pseudorotation parameters. However, this conclusion may simply reflect the fact that very few structures are known in which an exocyclic C–O bond eclipses another exocyclic C–O or C–N bond. When this does occur, a lengthening of the endocyclic bond is observed.[26] In contrast to this conformational dependence, a configurational dependence appears to be unlikely. An examination of bond lengths in arabino-,[12] xylo-,[26b,27] and lyxonucleosides,[28] admittedly very limited data,

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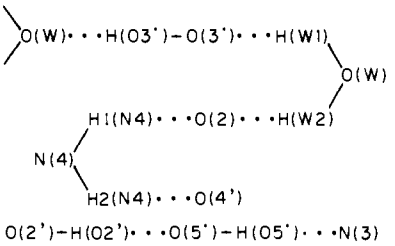
does not reveal any systematic and statistically significant differences from the values found in ribonucleosides.[25]

The correlation between endocyclic bond angles in furanose rings and their conformation is well established.[29] On the basis of an analysis of ribose rings by Westhof and Sundaralingam,[29c] we recently derived a general equation which correlates these angles with the conformational parameters P and τ_m.[29d] This equation gives the following calculated values for the angles at O(4'), C(1'), ..., C(4'): 109.5, 105.6, 100.6, 102.4, 106.1°. As can be seen, the agreement with the observed angles is very good (within two standard deviations) for all angles except that at C(2'), for which the calculated value is 0.4° (3.3σ) higher than the observed one. While it may be tempting to ascribe this to the different configuration at C(2'), we do not believe that this is justified. We compared the observed and calculated angles at C(2') for a number of arabinosides and did not detect any systematic trend in the deviations. It appears therefore that, contrary to earlier indications,[24] the bond angles in furanose rings do not depend on the configuration of the substituents and that the equation which we derived[29d] can be applied to all such rings. On the other hand, exocyclic bond angles involving C–OH bonds vary greatly from structure to structure. These bonds can be easily distorted so as to optimize the geometry of the hydrogen bonds in which the –OH groups participate.

The conformation of the $-CH_2OH$ side is trans, the angle ψ [C(3')–C(4')–C(5')–O(5')] being –163.8°. While not as common as the gauche$^+$ rotamer, the trans rotamer is also favored by the gauche interaction C(4')–O(4')/C(5')–O(5'). Given the C(2') endo conformation of the arabinose ring in this structure, a gauche$^+$ conformation would lead to a short contact between O(2') and O(5'). In ara-C[12j] and ara-U[12i] this contact is favored by an *intra*molecular hydrogen bond O(2')–H···O(5'). In the present structure, however, a strong *inter*molecular O(2')–H···O(5') hydrogen bond shifts the equilibrium in favor of the trans conformation.

Hydrogen Bonding and Packing. Five protons in the nucleoside molecule and two in the water molecule are capable of participating in hydrogen bonding and all of them are involved in intermolecular hydrogen bonds. The network can be represented schematically as follows:



The geometrical details of these hydrogen bonds are given in Table V. As commonly observed in X-ray analyses, the O–H and N–H bonds appear shorter than their real values of 0.97 and 1.04 Å, respectively. By extending the covalent bond lengths to their nominal values, one obtains corrected H···A distances which reflect more accurately the strengths of these hydrogen bonds. It can be seen that those hydrogen bonds in which –OH groups participate as both donors and acceptors are the strongest. The weakest one is that involving the ring oxygen atom O(4'). Apart from these hydrogen bonds, all intermolecular distances are longer than the sums of van der Waals radii. The packing of the molecules in the crystal can be seen in Figure 3.

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Registry No. 5-Methylarabinosylcytosine, 6829-31-8.

Supplementary Material Available: Tables of anisotropic temperature parameters of the non-hydrogen atoms and a list of observed and calculated structure amplitudes (7 pages). Ordering information is given on any current masthead page.

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Desulfurization of the Epidithiopiperazinedione Sirodesmin PL with Triphenylphosphine: Retention of Configuration at the Bridgehead Carbon Atoms

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Abstract: Sirodesmin PL (**3**), an epidithiopiperazinedione toxin produced by the fungus *Phoma lingam* Tode, easily reacts with triphenylphosphine to give the corresponding monosulfide **4**. The stereochemical course of the reaction has been studied through chemical transformations of **4** and X-ray analysis of its diacetyl derivative **12**. The desulfurization of **3** is shown to proceed with retention of configuration at both bridgehead carbon atoms, the parent compound **3** and the afforded monosulfide **4** having the same *R,R* chirality at these centers. This result is in contrast with the inversion of configuration previously reported for the conversion of the analogue **5** of gliotoxin having *R,R* chirality into the corresponding *S,S* monosulfide **6**. Moreover the two enantiomeric episulfides **4** and **6** surprisingly exhibit CD curves with similar signs of the Cotton effects. A possible mechanism for the desulfurization of sirodesmin PL (**3**) is proposed, and these conflicting results are discussed.

The triphenylphosphine desulfurization of the bridged disulfur piperazinedione system **1**, common to a large family of natural, biologically active metabolites,[1-3] into the corresponding monosulfide **2** is a well-known reaction.[4-6] Sirodesmin PL (**3**), a toxic

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