Synthesis of 4-β-D-Arabinofuranosyl-5,6-dihydro-2*H*-1,2,4-thiadiazin-3-one 1,1-Dioxide and X-Ray Diffraction Analysis of its 2',3-Anhydro Precursor

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Reaction of 2-amino-3',5'-bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran[1',2':4,5]-2-oxazoline with 2-chloroethylsulfonyl chloride in the presence of sodium bicarbonate followed by removal of the protecting groups gave 2',3-anhydro-4-β-D-arabinofuranosyl-5,6-dihydro-2*H*-1,2,4-thiadiazin-3-one 1,1-dioxide (**5**), which by treatment with ammonia was converted to 4-β-D-arabinofuranosyl-5,6-dihydro-2*H*-1,2,4-thiadiazin-3-one 1,1-dioxide (**6**). The structure of compound **5** was unequivocally established by means of an x-ray diffraction analysis. The compound crystallized in the space group $P2_12_12_1$ with unit cell dimensions a = 5.883(3), b = 9.352(2), c = 18.769(7) Å, Z = 4. Its structure was established by direct multisolution techniques and refined by the full matrix least squares method to a final R value of 0.058 for the 1515 reflections observed.

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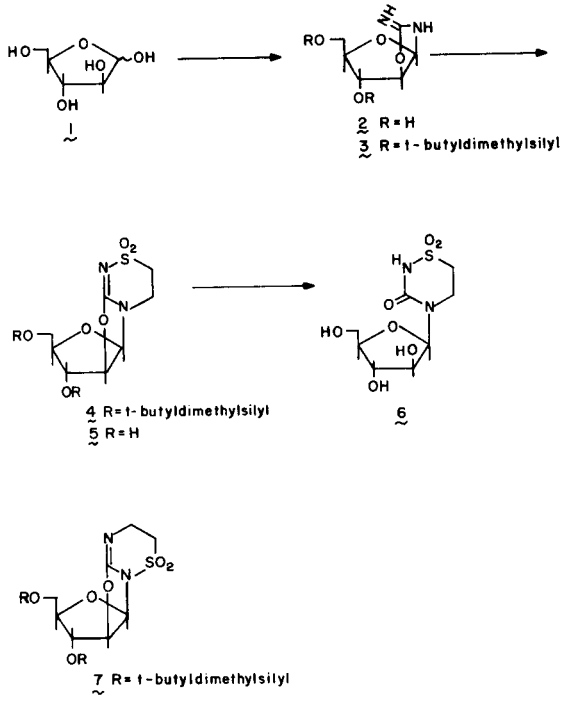
Introduction.

Various purine and pyrimidine analogs containing the sulfone moiety have been synthesized in the past (1-5) based on the rationale that this moiety can imitate the transition state that occurs during the enzymatic amination or deamination of their natural counterparts. Our interest in the preparation of potential inhibitors of cytidine deaminase led us to the synthesis of the title compound.

Scheme 1



Chemistry.

Since initial attempts at synthesizing the nucleoside analog by condensation of silylated 5,6-dihydro-2*H*-1,2,4-thiadiazin-3-one 1,1-dioxide with the appropriate 1-chloro or 1-*O*-acetyl sugar failed to provide the desired product in appreciable yield, the heterocyclic ring was constructed upon an appropriately substituted sugar (Scheme 1). The aminooxazoline derivative **2** was obtained by the procedure of Shannahoff and Sanchez (6) and blocking of the hydroxyl functions with *t*-butyldimethylsilyl groups according to Wierenga and Woltersom (7) afforded **3**. Treatment of this intermediate with 2-chloroethylsulfonyl chloride in ethyl acetate in the presence of solid sodium bicarbonate (8), gave a nucleoside product which, by nmr appeared to be a single isomer. Since 2-chloroethylsulfonyl chloride has the potential of initially reacting with either the endocyclic or exocyclic nitrogen atom of the aminooxazoline ring of **3**, two possible products, **4** and **7**, could be formulated. By deblocking the nucleoside product with tetra-*n*-butylammonium fluoride in tetrahydrofuran (7), a product was obtained which by x-ray crystallographic analysis was shown to be 2',3-anhydro-4-β-D-arabinofuranosyl-5,6-dihydro-2*H*-1,2,4-thiadiazin-3-one 1,1-dioxide (**5**), establishing in the process the structure of the nucleoside product as being **4** rather than **7**.

The arabinonucleoside **6** was prepared from **5** by treatment with dilute aqueous ammonia. This conversion is accompanied by an upfield shift of the sugar protons in the nmr spectrum of **6**, analogous to the shift seen upon the transformation of other 2,2'-anhydro nucleosides to their arabinosyl derivatives (9).

Biological Activity.

Compound **6** inhibited the growth of *E. coli* K-12 by

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50% at a concentration of $4 \times 10^{-5}M$, whereas in the same test system compound **5** was inactive at $10^{-3}M$. Both compounds (**5** and **6**) failed to inhibit cytidine deaminase obtained from human liver, and were inactive against L1210 cells *in vitro* and against *Herpes simplex* virus Type I (KOS) grown in CV-1 monkey kidney cells. These results were determined according to procedures previously described (10-13).

X-Ray Crystallography.

Crystals of 2',3-anhydro-4-β-D-arabinofuranosyl-5,6-dihydro-2*H*-1,2,4-thiadiazin-3-one 1,1-dioxide (**5**) were obtained by slow evaporation from a hot ethanol/water mixture. The crystals are orthorhombic, space group $P2_12_12_1$. The unit cell dimensions (at 22 ± 3°) are a = 5.883(3), b = 9.352(2), c = 18.769(7) Å, Z = 4, V = 1032 Å^3, μ = 29.6 cm^{-1}, D_m = 1.68 g. cm^{-3} (flotation in a mixture of bromoform and benzene), D_c = 1.681 g. cm^{-3}, F(000) = 540.

Complete three-dimensional intensity data were collected on a CAD-4 diffractometer, by the $\omega/2\theta$ technique. The intensities of 2329 reflections comprising all the reflections with Bragg angle values of $2\theta \leq 150°$ were measured using CuKα radiation (λ = 1.5418 Å). The scan widths were calculated using the relation (A + B tan θ)° with values of 0.5 and 0.15° for A and B, respectively. Aperture widths were determined using the equation (3.0 + 1.2 tan θ) mm. The maximum time spent on any reflection measurement was 100 seconds and the background count time was half the scan time. A faster scan was used for strong reflections. The intensities were monitored by measuring three reflections after every hour of x-ray exposure, and the variation of intensities was less than 3% during the complete data collection. The orientation matrix was checked every 100 reflections. Out of the 2329 reflections measured, 1515 reflections were considered significant, based on the fact that the net count = peak − 2 (left background + right background) was greater than 3σ (I). Lorentz and polarization corrections were applied to all reflections. The intensities of three reflections at $\chi \cong 90°$ were measured for all values of ϕ from 0 to 360° and the resultant curve of transmission as a function of ϕ was used to calculate the absorption for all the reflections. The average transmission factor was 0.84.

The structure was established by application of the multisolution technique (14), which yielded all the non-hydrogen atoms in the molecule. It was refined by the full matrix least squares method, the function minimized being $\Sigma w(|kF_o| - |F_c|)^2$ (15). A difference Fourier map was used to locate the atomic positions of all hydrogen atoms in the molecule. The structure was further refined using isotropic temperature factors for the hydrogen atoms and anisotropic thermal parameters for the non-

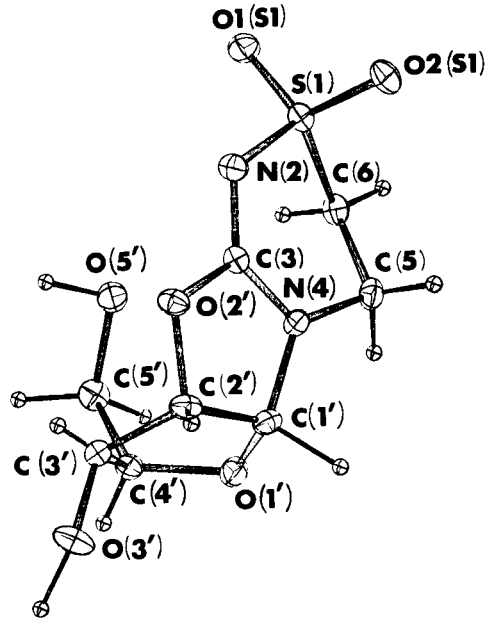

Figure 1: An ORTEP drawing of the 2',3-anhydro-4-β-D-arabinofuranosyl-5,6-dihydro-2*H*-1,2,4-thiadiazin-3-one 1,1-dioxide molecule showing the conformational details and the numbering scheme used.

hydrogen atoms, and the final reliability factor R defined as

$$\frac{\Sigma \| kF_o | - | F_c \|}{\Sigma | kF_o |}$$

was 0.058 for the 1515 reflections when the atomic coordinates of Table 1 were used. The mirror image of the structure had a higher R factor (0.065), indicating that the coordinates given in Table 1 correspond to the absolute configuration of the molecule. The atomic scattering factors and the anomalous dispersion corrections for carbon, nitrogen, oxygen, hydrogen and sulfur were taken from the "International Tables of X-ray Crystallography" (16).

The structure of the title compound is shown in Figure 1 (17), its final fractional atomic coordinates are given in Table 1, and the bond distances and angles together with their standard deviations are provided in Table 2. The bond length involving the two sp^3 carbon atoms C(5) and C(6) is 1.510(6) Å, slightly shorter than the usual C(sp^3) − C(sp^3) bond distance. Similarly, the C(1') − C(2') distance of 1.491 (6) Å is shorter than that found in other cyclonucleosides (18,19).

The thiadiazine ring is puckered; the atoms S(1) and C(6) deviate from the plane of the other four atoms of the ring by −0.17 and −0.82 Å, respectively. In dihydrouracil (20), dihydrouridine (21,22) and dihydrouridine-3'-monophosphate (23), the saturation of the C(5) - C(6) bond

causes C(5) and C(6) to deviate markedly out of plane. The presence of a sulfur atom further changes the pucker of the base giving rise to a torsional angle around S(1) - C(6) of −48.4°, around N(2) − S(1) of 16.8° and around C(5) − C(6) of 55.5°. Because of the pucker of the heterocycle, the deviation of C(1′) is −0.15 Å from the best four-atom plane through N(2), C(3), N(4) and C(5), whereas O(2′) almost lies in that plane (deviation of 0.02 Å).

Table 1

Final Fractional Positional Parameters with Estimated Standard Deviations Given in Parentheses

Atom	X	Y	Z
S(1)	−0.1706(2)	−0.5632(1)	−0.3189(6)
O1(S1)	−0.2122(7)	−0.4300(4)	−0.3556(2)
O2(S1)	−0.1103(7)	−0.6822(4)	−0.3644(2)
O(2′)	0.1466(6)	−0.5522(4)	−0.1475(1)
O(1′)	−0.3270(7)	−0.6256(4)	−0.0582(2)
O(5′)	−0.2675(7)	−0.3601(4)	−0.1505(2)
O(3′)	0.0727(7)	−0.5207(5)	0.0410(2)
N(4)	−0.1655(8)	−0.6729(4)	−0.1724(2)
N(2)	0.0272(7)	−0.5370(5)	−0.2612(2)
C(5)	−0.3525(10)	−0.7239(5)	−0.2162(3)
C(6)	−0.4141 (9)	−0.6096(6)	−0.2697(3)
C(3)	−0.0035 (8)	−0.5866(5)	−0.1971(2)
C(1′)	−0.1467(10)	−0.6898(5)	−0.0949(2)
C(2′)	0.0672 (9)	−0.6103(6)	−0.0793(3)
C(3′)	−0.0035(10)	−0.4893(5)	−0.0285(3)
C(5′)	−0.3562(10)	−0.3668(6)	−0.0805(3)
C(4′)	−0.2612 (9)	−0.4930(5)	−0.0347(3)
H1(C6)	−0.492 (9)	−0.728 (6)	−0.181(3)
H1(C5)	−0.531 (8)	−0.640 (6)	−0.300(2)
H1(C5′)	−0.343 (9)	−0.260 (5)	−0.059(2)
H(C1′)	−0.171(10)	−0.818 (6)	−0.081(2)
H2(C5′)	−0.501(10)	−0.419 (8)	−0.082(3)
H(C4′)	−0.316 (9)	−0.464 (5)	0.009(2)
H(C3′)	0.055 (7)	−0.428 (5)	−0.037(2)
H(05′)	−0.146(11)	−0.281 (6)	−0.141(3)
H(C2′)	0.197 (7)	−0.659 (4)	−0.065(2)
H2(C5)	−0.442 (8)	−0.527 (6)	−0.255(2)
H2(C6)	−0.310 (9)	−0.822 (6)	−0.236(3)
H(03′)	−0.009(16)	−0.492(11)	0.095(6)

The disposition of the base to the arabinose ring is constrained to be low-anti (high-syn) due to the 2,3′-cyclization, with a glycosidic torsion angle (C(5) − N(4) − C(1′) − O(1′)) of −59.8°. The arabinose ring has the envelope conformation C(4′) endo (^{4}E) with C(4′) deviating from the mean plane of the other four atoms by 0.38 Å, in the same direction as C(5′). The conformation around C(4′) − C(5′) is g$^+$ with the torsion angles O(1′) − C(4′) − C(5′) − O(5′) and C(3′) − C(4′) − C(5′) − O(5′) being −68.1° and 53.1° respectively. Packing and hydrogen bonding in the crystal structure are depicted in Figure 2. Both oxygens of the SO_2 group take part in hydrogen bonding, forming a

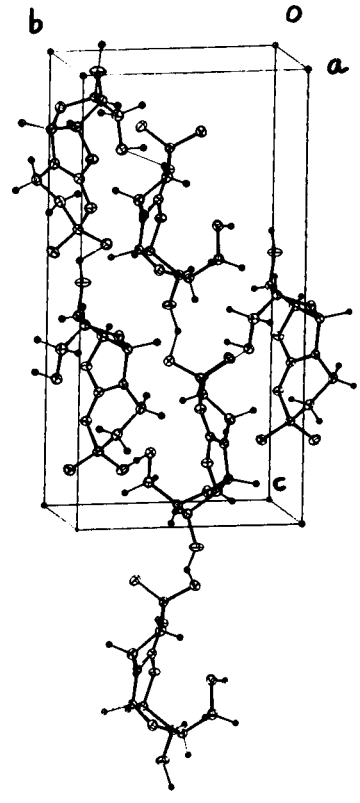

Figure 2: Representation of the packing of the molecules in the unit cell. Both the oxygens of the SO_2 group take part in hydrogen bonding (H (05′) ..02(S1), 1.8 Å; O(5′) -H(05′)..02 (S1), 164.9°; H(03′)..01(S1), 2.06 Å; O(3′) -H(03′)..01(S1), 131.3°).

linear hydrogen bond with O(5′) and a bent hydrogen bond with O(3′). Selection of the hydrogen bonds was based on the distance between the hydrogen atom and the acceptor being at least 0.5 Å less than the sum of their van der Waals radii, and that the angle at the hydrogen atom was about 165° for the linear bond and 131° for the bent bond.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian XL-100 spectrometer using tetramethylsilane as an internal standard for **4** and as an external standard for **5** and **6**. Infrared spectra were obtained on a Perkin Elmer 457 spectrophotometer and mass spectra were determined on a Dupont/CEC 21-491 mass spectrometer using the direct inlet probe. Preparative thin-layer chromatography was carried out on Merck Silica Gel 60 F-254 2mm thick plates (20 × 20 cm) and elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

2′,3-Anhydro-4-[3,5-bis(*O*-*t*-butyldimethylsilyl)-β-D-arabinofuranosyl]-5,6-dihydro-2*H*-1,2,4-thiadiazin-3-one 1,1-Dioxide (**4**).

A solution of 500 mg. (1.24 mmoles) of **3** in 20 ml. of warm anhydrous

Table 2

Bond Distances (Å) and Bond Angles (°) Between the Non-Hydrogen Atoms with Estimated Standard Deviations Given in Parentheses

Bond Distances		Bond Angles	
S(1) – N(2)	1.608(3)	S(1) – N(2) – C(3)	117.9(3)
N(2) – C(3)	1.302(5)	N(2) – C(3) – N(4)	129.6(4)
C(3) – N(4)	1.333(5)	C(3) – N(4) – C(5)	122.9(3)
N(4) – C(5)	1.454(5)	N(4) – C(5) – C(6)	109.0(3)
C(5) – C(6)	1.510(6)	C(5) – C(6) – S(1)	109.2(3)
C(6) – S(1)	1.760(4)	C(6) – S(1) – N(2)	105.8(2)
S(1) – 01(S1)	1.444(3)	01(S1) – S(1) – N(2)	108.2(2)
S(1) – 02(S1)	1.446(3)	02(S1) – S(1) – C(6)	108.7(2)
N(4) – C(1')	1.467(4)	01(S1) – S(1) – 02(S1)	115.1(2)
C(1') – C(2')	1.491(6)	C(3) – N(4) – C(1')	110.9(3)
C(2') – C(3')	1.537(6)	C(5) – N(4) – C(1')	125.6(3)
C(3') – C(4')	1.522(6)	N(4) – C(1') · C(2')	101.9(3)
C(4') – 0(1')	1.457(5)	C(1') – C(2') – C(3')	105.1(3)
O(1') – C(1')	1.400(5)	C(2') – C(3') – C(4')	104.5(4)
C(2') – 0(2')	1.467(4)	C(3') – C(4') – 0(1')	104.7(3)
0(2') – C(3)	1.324(4)	C(4') – 0(1') – C(1')	109.9(3)
C(3') – 0(3')	1.410(5)	N(4) – C(1') – 0(1')	112.6(3)
C(4') – C(5')	1.493(6)	N(4) – C(3) – 0(2')	112.3(3)
C(5') – 0(5')	1.415(5)	C(3) – 0(2') – C(2')	108.2(3)
		N(2) – C(3) – 0(2')	118.2(3)
		C(2') – C(3') – 0(3')	109.5(3)
		C(3') – C(4') – C(5')	116.4(4)
		0(1') – C(4') – C(5')	113.1(3)
		C(4') – C(5') – 0(5')	115.4(3)
		0(3') – C(3') – C(4')	113.3(4)
		C(1') – C(2') – 0(2')	106.3(3)

ethyl acetate was added dropwise to a stirred mixture of 184 mg. of 2-chloroethanesulfonyl chloride (1.13 mmoles), 1.12 g. of sodium bicarbonate and 10 ml. of anhydrous ethyl acetate. Stirring was continued at 40-45° for 5 hours and then at room temperature overnight. The mixture was filtered and concentrated to give 600 mg. of an off-white foam of crude **4**. This product was used in the next step without additional purification.

A portion of crude **4** (103 mg.) was purified by preparative thin-layer chromatography using 5:1 ethyl acetate-hexane to give a white foam (76 mg.); nmr (deuteriochloroform): δ 0.08, 0.14 and 0.16 (s, 12H, CH_3), 0.91 and 0.92 (s, 18H, *t*-butyl), 3.00 – 4.18 (m, 7H, CH_2CH_2, $C_4'H$ and $C_5'H$), 4.52 (dd, 1H, J = 2.6 and 0.90 Hz, $C_3'H$), 5.03 (dd, 1H, J = 5.8 and 0.90 Hz, $C_2'H$), 5.84 (d, 1H, J = 5.8 Hz, $C_1'H$); ir (mineral oil): 1633 cm^{-1} (C=N), absence of NH; ms: m/e (relative abundance) M^+ 493 (0.6), 478 (6), 436 (100).

2',3-Anhydro-4-β-D-arabinofuranosyl-5,6-dihydro-2*H*-1,2,4-thiadiazin-3-one 1,1-Dioxide (**5**).

To a solution of 368 mg. of crude **4** in 9 ml. of anhydrous tetrahydrofuran was added dropwise with stirring 1.9 ml. of a 1*M* solution of tetra-*n*-butylammonium fluoride in anhydrous tetrahydrofuran. The resulting mixture was stirred under nitrogen at room temperature for 2¼ hours, then concentrated under reduced pressure to a syrup, which was partitioned between water and chloroform. The organic layer was washed once with water. The combined aqueous layers were concentrated and applied in water to a small column of 5 ml. of Bio-Rad AG 50W-X8 50-100 mesh (H^+ form) ion exchange resin. The product was eluted with water and the eluate passed through 5 ml. of Mallinckrodt Amberlite IR-45 (OH^- form) ion exchange resin in a column. The column was then washed with water, and the eluate concentrated to yield 169 mg. (0.64 mmoles) of a clear glass, which, upon addition of 1-2 ml. of absolute ethanol, yielded 72 mg. of white crystals of **5**, m.p. 192.5-193.5°; nmr (deuterium oxide): δ 3.96 (m, 4H, CH_2CH_2), 4.47 (m, 2H, $C_5'H$), 4.76 (m, 1H, $C_4'H$), 4.98 (m, 1H, $C_3'H$), 5.71 (m, 1H, $C_2'H$), 6.49 (d, 1H, J = 5.8 Hz, $C_1'H$); ms: m/e (relative abundance) M + 1 265 (8), 233 (18), 215 (18), 205 (50), 175 (100).

Anal. Calcd. for $C_8H_{12}N_2O_6S$: C, 36.36; H, 4.58; N, 10.60; S, 12.14. Found: C, 36.41; H, 4.79; N, 10.44; S, 12.02.

4-β-D-Arabinofuranosyl-5,6-dihydro-2*H*-1,2,4-thiadiazin-3-one 1,1-Dioxide (**6**).

To a solution of **5** (24 mg., 0.091 mmoles) in 1 ml. of water was added 0.5 ml. of 5% ammonium hydroxide. The mixture was kept at room temperature for two days and was then concentrated to 27 mg. (0.096 mmoles, 100%) of a stiff foam which resisted crystallization. It was evaporated from ethanol to give a stiff syrup of **6**; nmr (deuterium oxide): δ 4.04 (m, 4H, CH_2CH_2), 4.31 (m, 2H, $C_5'H$), 4.67 (m, 1H, $C_4'H$), 4.88 (m, 1H, $C_3'H$), 5.45 (m, 1H, $C_2'H$), 6.40 (d, 1H, J = 5.8 Hz, $C_1'H$); ms: m/e (relative abundance) M + 1 283 (2), 251 (7), 233 (8), 193 (79), 176 (100).

Anal. Calcd. for $C_8H_{14}N_2O_7S \cdot \frac{1}{3} C_2H_5OH$: C, 34.97; H, 5.42; N, 9.41. Found: C, 34.67; H, 5.60; N, 9.09.

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