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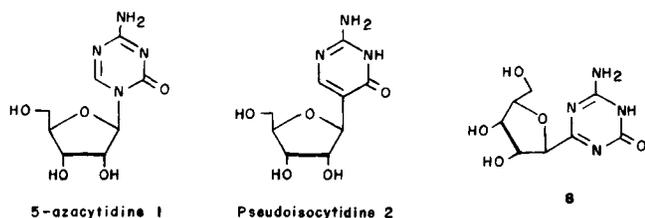
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The synthesis of the first [1,3,5]triazine carbon linked nucleosides are reported. 4-Amino-6-(β -D-ribofuranosyl)[1,3,5]triazin-2(1*H*)-one (**8**), an analog of 5-azacytidine and pseudoisocytidine was prepared. 2,5-Anhydro-D-allonamidine hydrochloride (**3**) was condensed with dimethyl cyanoiminodithiocarbonate (**4**) to give 4-methylthio-6-(β -D-ribofuranosyl)[1,3,5]triazin-2-amine (**5**). Compound **5** was reacted with *m*-chloroperbenzoic acid to give 4-methylsulfinyl-6-(β -D-ribofuranosyl)[1,3,5]triazin-2-amine (**6**). Displacement of the methyl sulfinyl with the appropriate nucleophile gave 6-(β -D-ribofuranosyl)[1,3,5]triazine-2,4-diamine (**7**), 4-amino-6-(β -D-ribofuranosyl)[1,3,5]triazin-2(1*H*)-one (**8**), and 4-amino-6-(β -D-ribofuranosyl)[1,3,5]triazine-2(1*H*)-thione (**9**). Dethiation of compound **5** with Raney nickel gave 4-(β -D-ribofuranosyl)[1,3,5]triazin-2-amine (**10**). The crystal structure of **7** was determined by single crystal X-ray.

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Introduction.

The present work describes the synthesis of the first carbon linked (*C*-nucleoside) derivative of the [1,3,5]triazine ring system. One of the most interesting and effective drugs used to treat leukemia is 5-azacytidine (**1**) [1]. This analog of cytidine, first synthesized by Piskala and Sorm [2] and later by Robins and Winkley [3], has been shown to be incorporated into the DNA of leukocytes where it inhibits DNA methyl transferase [4], and interferes with the post-replicative methylation of eukaryotic DNA. This methylation of progeny DNA after replication is important in maintaining the integrity of the genetic information in the DNA.



Another drug which acts in a similar manner to 5-azacytidine (**1**) is pseudoisocytidine (**2**) [5]. Pseudoisocytidine (**2**), first synthesized by Chu and coworkers [6], has advantages over 5-azacytidine (**1**) in that the glycosidic bond is not readily cleaved enzymatically and the pyrimidine base is not as susceptible to nucleophilic attack and degradation as is the triazine base of 5-azacytidine (**1**) [7]. Thus, the half life of pseudoisocytidine (**2**) in a living system is much longer than that of 5-azacytidine (**1**).

With these two nucleosides as models, it was decided to synthesize triazine analogs with certain characteristics of both pseudoisocytidine (**2**) and 5-azacytidine (**1**), which

would constitute a new class of *C*-nucleosides. It was desired that these analogs be *C*-nucleosides in order to avoid the enzymatic degradation of the glycosidic bond. It was also decided to employ the [1,3,5]triazine ring system which would provide the three nitrogen characteristics of 5-azacytidine (**1**).

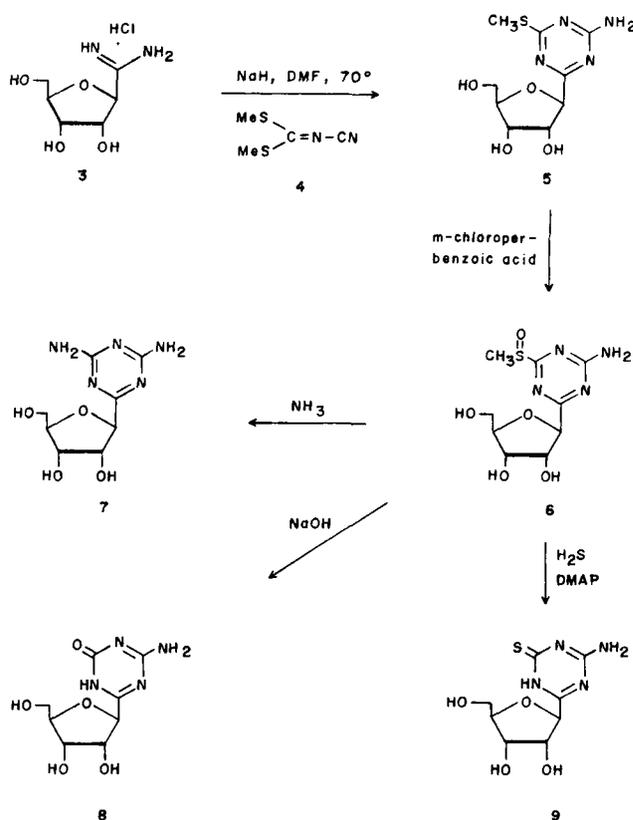


Table I

Positional ($\times 10^4$) and thermal ($\times 10^3$) parameters for the non-hydrogen atoms and hydrogen atoms of amine and hydroxy groups of **7**. Values in parenthesis are e.s.d. values.

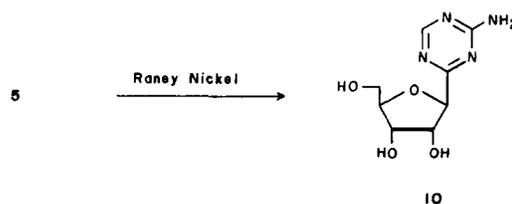
| atom | x | y | z | Ueq |
|-------|-----------|----------|-----------|-------------|
| N1A | -1399(8) | 4045(2) | 7606(2) | 31(2) |
| C2A | -234(9) | 4314(2) | 8162(2) | 27(2) |
| N2A | -1068(8) | 4918(2) | 8395(2) | 42(2) |
| H1N2A | -2247(91) | 5169(23) | 8142(2) | 82(18) [a] |
| H2N2A | -202(60) | 5133(15) | 8697(15) | 8(10) [a] |
| N3A | 1610(8) | 4013(2) | 8470(2) | 30(1) |
| C4A | 2368(9) | 3418(2) | 8192(2) | 29(2) |
| N4A | 4124(8) | 3086(2) | 8487(2) | 42(2) |
| H1N4A | 4834(73) | 2700(20) | 8359(19) | 38(13) [a] |
| H2N4A | 4673(68) | 3272(18) | 8785(16) | 16(11) [a] |
| N5A | 1450(7) | 3125(2) | 7617(2) | 26(1) |
| C6A | -390(9) | 3478(3) | 7362(2) | 29(2) |
| C1'A | -1396(9) | 3258(2) | 6675(2) | 28(2) |
| C2'A | -360(9) | 3718(2) | 6130(2) | 27(2) |
| O2'A | -1940(7) | 3752(2) | 5548(2) | 36(1) |
| HO2'A | -2142(86) | 4163(23) | 5456(20) | 68(16) [a] |
| C3'A | 1912(10) | 3322(2) | 5959(2) | 30(2) |
| O3'A | 3041(8) | 3493(2) | 5339(2) | 43(1) |
| HO3'A | 4800(96) | 3480(25) | 5369(24) | 85(19) [a] |
| C4'A | 1078(9) | 2571(2) | 5982(2) | 32(2) |
| C5'A | 2968(11) | 2038(2) | 6158(2) | 47(2) |
| O5'A | 3867(6) | 2116(2) | 6830(2) | 43(1) |
| HO5'A | 2891(122) | 2355(31) | 7119(30) | 173(28) [a] |
| O1'A | -729(6) | 2558(2) | 6500(2) | 33(1) |
| N1B | 10196(7) | 3799(2) | 10388(2) | 29(1) |
| C2B | 8826(9) | 3513(2) | 9899(2) | 30(2) |
| N2B | 9408(8) | 2852(2) | 9717(2) | 39(2) |
| H1N2B | 8811(82) | 2620(21) | 9349(19) | 62(16) [a] |
| H2N2B | 10636(72) | 2729(19) | 9829(18) | 34(13) [a] |
| N3B | 6900(7) | 3792(2) | 9617(2) | 32(1) |
| C4B | 6519(9) | 4458(3) | 9809(2) | 31(2) |
| N4B | 4590(8) | 4759(2) | 9543(2) | 40(2) |
| H1N4B | 4401(74) | 5198(20) | 9563(18) | 32(12) [a] |
| H2N4B | 3676(70) | 4564(18) | 9242(16) | 21(11) [a] |
| N5B | 7864(7) | 4822(2) | 10235(2) | 27(1) |
| C6B | 9634(9) | 4452(2) | 10517(2) | 27(2) |
| C1'B | 11086(8) | 4831(2) | 11048(2) | 26(2) |
| C2'B | 9688(9) | 4898(2) | 11712(2) | 26(2) |
| O2'B | 10619(6) | 5479(2) | 12081(2) | 33(1) |
| HO2'B | 9374(81) | 5697(20) | 12290(18) | 50(14) [a] |
| C3'B | 10376(9) | 4216(2) | 12055(2) | 26(2) |
| O3'B | 9873(7) | 4198(2) | 12761(1) | 41(1) |
| HO3'B | 9718(145) | 3799(35) | 12984(31) | 197(30) [a] |
| C4'B | 13007(9) | 4152(2) | 11876(2) | 25(2) |
| C5'B | 13962(9) | 3427(2) | 11837(2) | 37(2) |
| O5'B | 12627(6) | 3017(2) | 11375(2) | 33(1) |
| HO5'B | 12108(76) | 3297(19) | 11016(18) | 11(13) [a] |
| O1'B | 13222(6) | 4476(2) | 11220(1) | 29(1) |
| OW | -2070(9) | 994(2) | 5972(2) | 85(2) |

Ueq is defined as one-third of the trace of the orthogonalized Uij tensor.
[a] Value in the normal isotropic thermal parameter.

The most common synthesis of the [1,3,5]triazine ring system has been *via* cyclotrimerization of nitriles or isocyanates. Dimethyl cyanoiminodithiocarbonate (**4**) has been used for numerous condensations with amines as well as the synthesis of substituted imidazoles [8], and thiazoles [9]. There are two precedents in the literature where an isothiourea has been condensed with **4** to give methylthio[1,3,5]triazinamines. Wittenbrook [10] has reported the condensation of *S*-methylisothiourea with dimethyl cyanoiminodithiocarbonate (**4**) to give 4,6-dimethylthio[1,3,5]triazin-2-amine. Evers and Fischer [11] reported the condensation of thio-bisformamidines with **4** to give 2-amino-4-isothioureido-6-methylthio[1,3,5]triazines.

Dimethyl cyanoiminodithiocarbonate (**4**) was prepared according to the procedure of Wittenbrook [12]. 2,5-Anhydro-D-allonamide hydrochloride (**3**) [13] was dissolved in dimethylformamide, neutralized with sodium hydride, and condensed with **4** to give 4-methylthio-6-(β -D-ribofuranosyl)[1,3,5]triazin-2-amine (**5**) in 56% yield. This is the first reported ring closure of dimethyl cyanoiminodithiocarbonate (**4**) with an amidine to give a [1,3,5]triazine.

The low yields obtained from attempts to displace the methylthio group with various nucleophiles (hydroxide, ammonia, hydrosulfide), which required heat, appeared to be due to degradation of the ring under strong alkaline conditions. It was decided to form the corresponding sulfoxide since the sulfinyl group is usually more readily displaced by nucleophiles than is the methylthio group. The synthesis of 4-methylsulfinyl-6-(β -D-ribofuranosyl)[1,3,5]triazin-2-amine (**6**) was accomplished in 70% yield *via* oxidation with *m*-chloroperbenzoic acid in ethanol solution. Hence, the displacement of the sulfinyl group with ammonia was studied with aqueous ammonia, methanolic ammonia, and liquid ammonia. All three reactions gave a mixture of 6-(β -D-ribofuranosyl)[1,3,5]triazine-2,4-diamine (**7**) and 4-amino-6-(β -D-ribofuranosyl)[1,3,5]triazin-2(1*H*)-one (**8**). The triazinone, **8**, was also prepared in 71% yield by treating the sulfoxide, **6**, in dilute sodium hydroxide solution. A solution of the sulfoxide, **6**, in liquid hydrogen sulfide using 4-dimethylamino pyridine as a catalyst gave 4-amino-6-(β -D-ribofuranosyl)[1,3,5]triazine-2(1*H*)-thione (**9**) in 35% yield.



The final compound in this series, 4-(β -D-ribofuranosyl)[1,3,5]triazin-2-amine (**10**) was synthesized *via* Raney nickel dethiation of **5**. Care was taken during this reaction to prevent reductive degradation of the ring itself by care-

Table II
Hydrogen Bond Data Amine and Hydroxy Hydrogens of 7

| D | H | A | H...A(Å) | D...A(Å) | D-H...A(deg) | Translation of A |
|------|-------|------|----------|----------|--------------|---|
| N2A | H1N2A | O3'B | 2.07(5) | 3.005(8) | 169(4) | $\frac{1}{2} - x, 1 - y, z - \frac{1}{2}$ |
| N2A | H2N2A | OW | 2.19(3) | 2.997(8) | 152(3) | $-x, \frac{1}{2} + y, 1\frac{1}{2} - z$ |
| N4A | H1N4A | O5'B | 2.15(4) | 2.908(8) | 143(3) | $x - \frac{1}{2}, \frac{1}{2} - y, 2 - z$ |
| N4A | H2N4A | N3B | 2.29(4) | 3.045(8) | 171(4) | x, y, z |
| O2'A | HO2'A | N5B | 2.04(4) | 2.865(7) | 177(2) | $\frac{1}{2} - x, 1 - y, z - \frac{1}{2}$ |
| O3'A | HO3'A | O2'A | 1.90(6) | 2.887(8) | 162(4) | $1 + x, y, z$ |
| O5'A | HO5'A | N5A | 1.96(6) | 2.837(8) | 160(6) | x, y, z |
| N2B | H1N2B | O5'B | 2.00(4) | 2.912(8) | 171(4) | $x - \frac{1}{2}, \frac{1}{2} - y, 2 - z$ |
| N4B | H1N4B | OW | 2.27(4) | 2.950(8) | 136(3) | $-x, \frac{1}{2} + y, 1\frac{1}{2} - z$ |
| N4B | H2N4B | N3A | 2.19(4) | 3.060(8) | 176(3) | x, y, z |
| O2'B | HO2'B | N1A | 1.85(4) | 2.741(8) | 165(4) | $\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$ |
| O3'B | HO3'B | O5'A | 1.86(7) | 2.720(7) | 160(6) | $\frac{1}{2} + x, \frac{1}{2} - y, 2 - z$ |
| O5'B | HO3'B | N1B | 1.90(3) | 2.817(7) | 163(3) | x, y, z |

fully monitoring the reaction by tlc. Raney nickel, which had been thoroughly washed until neutral, was added to an ethanolic solution of **5** and the resultant suspension refluxed until no starting material could be detected which

gave 4-(β -D-ribofuranosyl)[1,3,5]triazin-2-amine (**10**) in 43% yield.

Table III

Crystal and Experimental Data for 7

| | |
|----------------------------------|---|
| Formula | $C_8H_{13}N_5O_4 \cdot \frac{1}{2} H_2O$ |
| Formula Weight | 252.2 |
| F(000) | 1064 |
| crystal size (mm.) | .40 \times .15 \times .10 |
| radiation | $M\alpha$ (0.71073 Å) |
| μ (cm^{-1}) | 1.21 |
| Space group | P2 ₁ 2 ₁ 2 ₁ |
| a (Å) | 5.605(1) |
| b(Å) | 19.283(5) |
| c(Å) | 19.780(6) |
| α (°) | 90 |
| β (°) | 90 |
| γ (°) | 90 |
| V(Å ³) | 2137.9(3) |
| Z | 8 |
| d_x ($g\text{cm}^{-3}$) | 1.57 |
| unique observed data | 1530 |
| unobserved data | 665 |
| $\sin \theta/\lambda$ limit | 0.59 |
| R | 0.059 |
| R_w | 0.034 |
| ρ max. ($e\text{Å}^{-3}$) | 0.36 |
| ρ min. ($e\text{Å}^{-3}$) | -0.34 |

The conformations of the two molecules of compound **7** found in a unit cell of the single crystal X-ray as well as the atom labels are shown in Figure 1. The figure clearly shows that both nucleoside molecules of the asymmetric unit are in the β -anomeric configuration. The atomic positional and thermal parameters are listed in Table 1. One of the interesting features of the crystal structure is the base pairing between an amino group of one molecule of the asymmetric unit and a base ring nitrogen atom of the other. This in part causes the two base groups to be related by a pseudo-center of symmetry located at $-0.0552(175), 0.3936(30), 0.8996(51)$. These coordinates were obtained by calculating the midpoint between corresponding atoms of bases (N1A and N1B, C2A and C2B etc.) and averaging the six values. The dihedral angle between the least-squares planes of the bases is 15° . The hydrogen bond data for the base pairing interactions as well as for all the hydrogen bonds are listed in Table 2.

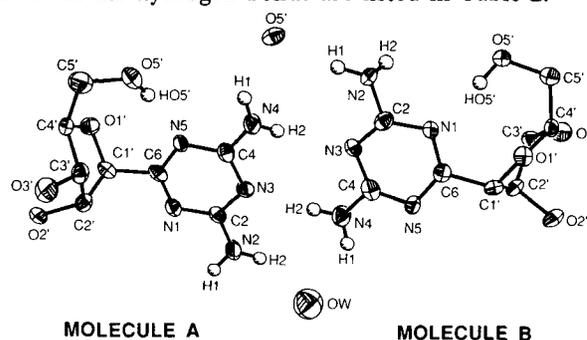


Figure 1. Computer drawing of the two nucleoside molecules of the asymmetric unit. The water and symmetry related O5' are translated from that given in Table 2. The labels of the atoms have been shortened for brevity.

Table IV
Bond Lengths and Bond and Torsion Angles of 7

| 1 | 2 | 3 | 4 | Molecule A | | | Molecule B | | |
|-----|-----|-----|-----|------------|------------|--------------|------------|------------|--------------|
| | | | | 1-2 Å | 1-2-3(deg) | 1-2-3-4(deg) | 1-2 Å | 1-2-3(deg) | 1-2-3-4(deg) |
| C6 | N1 | C2 | N2 | 1.322(7) | 113.5(4) | 174.3(4) | 1.323(6) | 113.0(4) | 176.5(4) |
| C6 | N1 | C2 | N3 | a | a | -5.4(7) | a | a | -8.5(7) |
| N1 | C2 | N3 | C4 | 1.380(7) | 124.7(4) | 1.8(7) | 1.352(7) | 126.6(4) | 7.4(7) |
| N1 | C2 | N2 | | a | 115.9(4) | — | a | 115.7(4) | — |
| N2 | C2 | N3 | C4 | 1.337(6) | 119.5(4) | -178.3(4) | 1.364(7) | 117.5(4) | -177.6(4) |
| C2 | N3 | C4 | N5 | 1.333(7) | 115.4(4) | 2.5(7) | 1.329(7) | 113.2(4) | -0.3(7) |
| C2 | N3 | C4 | N4 | a | a | -177.6(4) | a | a | -179.4(4) |
| N3 | C4 | N5 | C6 | 1.343(7) | 125.0(4) | -2.6(7) | 1.356(7) | 126.0(5) | -4.6(7) |
| N3 | C4 | N4 | | a | 118.1(4) | — | a | 115.4(4) | — |
| N4 | C4 | N5 | C6 | 1.311(7) | 116.9(4) | 177.4(4) | 1.334(7) | 118.7(4) | 174.5(4) |
| C4 | N5 | C6 | N1 | 1.369(6) | 113.3(4) | -1.7(7) | 1.331(7) | 113.6(4) | 3.4(7) |
| N5 | C6 | N1 | C2 | 1.335(7) | 127.9(4) | 5.3(7) | 1.344(7) | 127.0 | 2.5(7) |
| C4 | N5 | C6 | C1' | a | a | 172.9(4) | a | a | -175.3(4) |
| N5 | C6 | C1' | C2' | a | 118.6(4) | -98.0(5) | a | 115.3(4) | 74.8(5) |
| N5 | C6 | C1' | O1' | a | a | 19.4(6) | a | a | -167.1(4) |
| N1 | C6 | C1' | C2' | a | 113.4(4) | 77.3(5) | a | 117.7(4) | -104.0(5) |
| N1 | C6 | C1' | O1' | a | a | -165.3(4) | a | a | 14.1(6) |
| C6 | C1' | C2' | C3' | 1.531(7) | 109.1(4) | 88.1(4) | 1.516(7) | 111.1(4) | 87.8(4) |
| C6 | C1' | C2' | O2' | a | a | -154.6(4) | a | a | -156.2(4) |
| C1' | C2' | C3' | C4' | 1.512(7) | 100.6(4) | 39.8(4) | 1.535(7) | 100.3(4) | 39.9(4) |
| C1' | C2' | C3' | O3' | a | a | 163.2(4) | a | a | 164.2(4) |
| C1' | C2' | O2' | | a | 110.9(4) | — | a | 108.4(4) | — |
| O2' | C2' | C3' | C4' | 1.454(6) | 110.8(4) | -77.6(4) | 1.435(6) | 110.7(4) | -74.4(4) |
| O2' | C2' | C3' | O3' | a | a | 45.8(6) | a | a | 49.8(5) |
| C2' | C3' | C4' | O1' | 1.524(8) | 102.3(4) | -33.1(4) | 1.530(7) | 102.2(4) | -31.9(4) |
| C2' | C3' | C4' | C5' | a | a | -152.6(4) | a | a | -152.0(4) |
| C2' | C3' | O3' | | a | 116.6(4) | — | a | 113.9(4) | — |
| O3' | C3' | C4' | O1' | 1.419(7) | 112.7(4) | -159.1(4) | 1.424(6) | 114.7(4) | -155.7(4) |
| O3' | C3' | C4' | C5' | a | a | 81.4(5) | a | a | 84.3(5) |
| C3' | C4' | O1' | C1' | 1.521(7) | 104.8(4) | 12.7(5) | 1.521(8) | 104.7(4) | 10.3(5) |
| C3' | C4' | C5' | O5' | a | 115.9(5) | 65.1(6) | a | 115.7(4) | 55.6(5) |
| C4' | O1' | C1' | C2' | 1.441(7) | 109.6(3) | 13.2(5) | 1.447(6) | 110.7(4) | 15.7(4) |
| C4' | O1' | C1' | C6 | a | a | -106.0(4) | a | a | -105.6(4) |
| C4' | C5' | O5' | | 1.516(8) | 112.9(4) | — | 1.500(7) | 111.3(4) | — |
| O5' | C5' | C4' | O1' | 1.429(6) | a | -52.3(5) | 1.421(6) | a | -62.1(5) |
| C5' | C4' | O1' | C1' | a | 108.4(4) | 137.0(4) | a | 109.1(4) | 134.7(4) |
| O1' | C1' | C2' | C3' | 1.443(6) | 106.2(4) | -33.1(5) | 1.420(6) | 105.4(4) | -34.7(4) |
| O1' | C1' | C2' | O2' | a | a | 84.2(5) | a | a | 81.4(4) |
| O1' | C1' | C6 | N5 | a | 112.2(4) | 19.4(6) | a | 112.7(4) | -167.1(4) |
| C1' | C6 | N1 | C2 | a | a | -169.4(4) | a | a | -178.8(4) |

The base portion of the molecules are joined by interactions in addition to the hydrogen bonds discussed above. The water of hydration (translated by $-x, \frac{1}{2} + y, 1\frac{1}{2} - z$) forms a hydrogen bond with N2A of molecule A and with N4B of molecule B. A similar situation exists with O5'B (translated by $\frac{1}{2} - x, 1 - y, z - \frac{1}{2}$). It participates in a hydrogen bond with N4A of molecule A and to N2B of molecule B (see Figure 1 and Table 2). The asymmetric unit then consists of two nucleosides linked directly by base pairing hydrogen bonds and also linked indirectly by two sets of hydrogen bonds each involving a common acceptor atom.

While it was expected that the planar base portions of molecule A and B would have similar torsion angles, the similar torsion angles of the sugar moieties of the two molecules was surprising. Both sugars have a 3T configuration with the torsion angles involving chemically similar atoms differing by only a few degrees. The only structurally similar torsion angles that differ by large amounts are those involving atoms of the glycosidic bond. For example C4-N5-C6-C1' in A is $172.9(4)^\circ$ and in B is $-175.3(4)^\circ$; N5-C6-C1'-C2' in A is $-98.0(5)^\circ$ and B is $74.8(5)^\circ$; N5-C6-C1'-O1' in A is $19.4(6)^\circ$ and in B is $-167.1(4)^\circ$. All torsion angles as well as bond lengths are listed in Table 4. The result of the similarities and differences in certain corresponding torsion angles cause the sugar rings to be related by a pseudo two-fold axis (see Figure 1). Each sugar of the asymmetric unit contains an intramolecular hydrogen bond linking O5' to a base ring nitrogen atom. Because of the near 2-fold symmetry of the sugars, the base nitrogens in this hydrogen bonding are not those related by the pseudo inversion center mentioned earlier. The other alcoholic hydrogens of the sugars are involved in intermolecular hydrogen bonds (see Table 2).

EXPERIMENTAL

General Procedures.

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^1H nmr) spectra were determined at 89.6 MHz with a JEOL FX 90Q spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard for ^1H nmr. The presence of solvent as indicated by elemental analysis was verified by ^1H nmr. Infrared spectra (ir) were obtained on a Mattson Sirius 100 FT-IR and ultraviolet spectra (uv, sh = shoulder) were recorded on Cary Model 15 or Cary Model 118 spectrophotometers. Elemental analyses were performed by Robertson Labs, Florham Park, NJ. Thin layer chromatography (tlc) was run on silica gel 60 F-254 plates (EM Reagents). Preparative scale chromatography was conducted by using flash chromatography techniques. J. T. Baker silica gel (40 μm) or Kiesel gel 60 EM Reagents (40-63 μm) was used for flash chromatography. Solvent E is the saturated upper phase of a 4/1/2 mixture of ethyl acetate/1-propanol/water. Solvent E₂ is a 2/1/1 mixture of ethyl acetate/ethanol/water. Detection of components on TLC was by uv light and with 10% sulfuric acid in methanol spray followed by heating. Evaporations were carried out under reduced pressure with the bath temperature below 35° .

4-Methylthio-6-(β -D-ribofuranosyl)[1,3,5]triazin-2-amine (5).

To a solution of the amidine **3** [13] (10.0 g, 47.1 mmoles) in dimethylformamide at 70° was added sodium hydride (2.5 g, 60% oil dispersion) portionwise. After five minutes stirring, dimethyl cyanoiminodithiocarbonate (**4**) (8.3 g, 56.4 mmoles) was added. The suspension was allowed to stir for 18 hours at 65° . The reaction mixture was cooled and the dimethylformamide removed *in vacuo*. The residue was dissolved in ethanol and silica gel (20 g, 60-200 mesh) added. The ethanol was removed and the resultant powder placed on top of a flash column (silica gel, 200-400 mesh, 45×5 cm) and eluted with 9/1 chloroform/methanol to yield 7.2 g (56%) of a fluffy white product. Recrystallization of **5** from 9:1 chloroform/methanol gave an analytical sample: mp $176-178^\circ$, tlc (20% methanol in chloroform) Rf 0.54; uv: λ max (pH 1) 228 nm (ϵ 14608) 238 nm (sh, 12915); (pH 7) 223 nm (17220) 267 (ϵ 3444); (pH 11) 250 nm (ϵ 4428); ^1H nmr (DMSO- d_6): δ 2.43 (s, 3, S-CH₃), 4.38 (d, 1, J = 3.39 Hz, C₁-H), 7.60 (br s, 2, NH₂) and other sugar protons.

Anal. Calcd. for C₉H₁₄N₄O₅S: C, 39.41; H, 5.14; N, 20.43; S, 11.69. Found: C, 39.19; H, 4.99; N, 20.16; S, 11.39.

4-Methylsulfinyl-6-(β -D-ribofuranosyl)[1,3,5]triazin-2-amine (6).

To a solution of **5** (6.2 g, 22.6 mmoles) in absolute ethanol (250 ml) was added a solution of *m*-chloroperbenzoic acid (80%, 14.63 g, 67.8 mmoles) in ethanol (50 ml). Within three minutes a precipitate had formed. The reaction was allowed to continue for 45 minutes after which the mixture was cooled in an ice bath and the precipitate filtered. The white solid was washed thoroughly with ethanol and dried to yield 4.6 g (70%) of a fine white powder, mp $200-202^\circ$; tlc (solvent E₂), Rf 0.59; ir (potassium bromide): ν 1051 (S=O) cm^{-1} ; uv: λ max (pH 1) 228 nm (ϵ 2766) 265 (sh, 922); (pH 7) 228 nm (ϵ 2184) 260 (sh, 1262); (pH 11) 218 nm (2378) 258 (1067); ^1H nmr (DMSO- d_6): δ 2.82 (s, 3, CH₃), 4.48 (d, 1, J = 3.39 Hz, C₁-H), 8.22 (d, 2, J = 8.8 Hz, NH₂), and other sugar protons.

Anal. Calcd. for C₉H₁₄N₄O₅S: C, 37.23; H, 4.86; N, 19.30; S, 11.04. Found: C, 37.22; H, 5.06; N, 18.99; S, 11.01.

6-(β -D-Ribofuranosyl)[1,3,5]triazine-2,4-diamine (7).

A solution of the sulfoxide **6** (1.3 g, 4.5 mmoles) in liquid ammonia (20 ml) sealed in an autoclave was allowed to warm to room temperature and to stir for 16 hours after which time the ammonia was allowed to evaporate. The residue was dissolved in water and silica gel (10 g, 60-200 mesh) was added and the water removed *in vacuo*. The resultant dry powder was placed on top of a flash column (silica gel, 200-400 mesh, 26×5 cm) and eluted with 7/1/1 ethyl acetate/acetone/methanol/water to yield 320 mg (29%). Recrystallization of **7** from absolute ethanol gave an analytical sample, mp $180-182^\circ$, tlc (solvent E₂) Rf 0.65; uv: λ max (pH 1), 248 nm (ϵ , sh, 3640); (pH 7) 256 nm (ϵ 3970); (pH 11), 256 nm (ϵ 3640); ^1H nmr (DMSO- d_6): δ 4.28 (d, 1, J = 2.71 Hz, C₁-H), 6.73 (br s, 4, NH₂).

Anal. Calcd. for C₉H₁₃N₅O₄ 1/4 H₂O: C, 38.78; H, 5.49; N, 28.27. Found: C, 38.84; H, 5.97; N, 27.89.

4-Amino-6-(β -D-ribofuranosyl)[1,3,5]triazin-2(1H)-one (8).

To a solution of the sulfoxide, **6** (500 mg, 1.72 mmoles) in water (50 ml) was added 1 *N* sodium hydroxide (0.4 ml). The solution was allowed to stir 18 hours after which it was neutralized with strong cation exchange resin (Dowex 50W-X8, H⁺ form). The water was removed *in vacuo* yielding 300 mg (71%) of **8**. Recrystallization of **8** from ethanol/water gave an analytical sample, mp $185-187^\circ$. Compound **8** was obtained in 23% yield from the reaction of the sulfoxide **6** with liquid ammonia, tlc (solvent E₂) Rf 0.53; ir (potassium bromide): ν 1693 (C=O) cm^{-1} ; uv: λ max (pH 1), 248 nm (7888); (pH 7) 242 nm (4259); (pH 11) 251 nm (3691); ^1H nmr (DMSO- d_6): δ 4.37 (d, 1, J = 2.71, C₁-H), 7.39 (br s, 2, NH₂), 11.24 (br s, NH).

Anal. Calcd. for C₉H₁₂N₄O₅ 1/2 H₂O: C, 37.95; H, 5.17; N, 22.13. Found: C, 38.08; H, 5.01; N, 22.09.

4-Amino-6-(β -D-ribofuranosyl)[1,3,5]triazine-2(1H)-thione (9).

A solution of the sulfoxide, **6**, (1.0 g, 3.4 mmoles) and 4-dimethylamino pyridine (30 mg) in liquid hydrogen sulfide (40 ml) sealed in an autoclave

was allowed to stir at room temperature for 24 hours. After this time the hydrogen sulfide was allowed to evaporate and the gray residue dissolved in methanol. To this solution was added silica gel (10 g, 60-200 mesh) and the suspension evaporated to dryness. The resultant powder was placed on top of a flash column (silica gel, 200-400 mesh, 25 × 5 cm) and eluted with 4/1 chloroform/methanol yielding 310 mg (35%). Recrystallization of **9** from absolute ethanol gave an analytical sample, mp 218-220°; tlc (20% methanol in chloroform) Rf 0.24; ir (potassium bromide): ν 1649 (C=S) cm^{-1} ; uv: λ max (pH 1) 267 nm (ϵ 15820); (pH 7) 279 nm (ϵ 14799); (pH 11) 275 nm (ϵ 12418); ^1H nmr (DMSO- d_6): δ 4.43 (d, 1, J = 2.38 Hz, C₁H), 7.92 (br s, 2, NH₂), and other sugar protons.

Anal. Calcd. for C₈H₁₂N₄O₈S: C, 36.92; H, 4.65; N, 21.53; S, 12.32. Found: C, 36.80; H, 4.66; N, 21.29; S, 12.23.

4-(β -D-Ribofuranosyl)[1,3,5]triazin-2-amine (**10**).

To solution of **5** (1.4 g, 5.1 mmoles) in absolute ethanol was added portionwise Raney nickel (20 g, Aldrich, 50 μ , 80-100 m²/g) that had been washed with water until neutral. The suspension was brought to reflux for 30 minutes during which time the reaction was monitored every five minutes by tlc. When all starting material had disappeared, the mixture was quickly filtered through a Celite pad and the resultant filtrate reduced to dryness yielding 500 mg (41%) of **10**. Recrystallization of **10** from ethanol/ethyl acetate gave an analytical sample, mp 165-167°; tlc (20% methanol in chloroform) Rf 0.31; uv λ max (pH 1) 248 nm (ϵ , sh, 3640); (pH 7) 256 nm (ϵ 3970); (pH 11) 256 nm (ϵ 3640); ^1H nmr (DMSO- d_6): δ 4.42 (d, 1, J = 2.71 Hz, C₁H), 7.64 (br s, 2, NH₂), 8.45 (d, 1, J = 0.9 Hz, C₂H), and other sugar protons.

Anal. Calcd. for C₈H₁₂N₄O₄·H₂O: C, 39.03; H, 5.73; N, 22.74. Found: C, 39.14; H, 5.48; N, 22.44.

Single Crystal X-Ray.

Crystallization of **7** from methanol without drying gave a suitable crystal of the compound which was mounted on a Nicolet R3 diffractometer which utilized graphite monochromated Mo radiation ($\lambda = 0.71073 \text{ \AA}$). Lattice parameters and the orientation matrix were obtained using a least-square procedure involving 19 centered reflections, $12.69^\circ < 2\theta < 23.54^\circ$. Crystal data and other experimental conditions are listed in Table III. The space group P2₁2₁2₁, which contains 4 equivalent positions, coupled with the density measurement indicated that the asymmetric unit contained 2 molecules. Single crystal data were collected using a variable θ - 2θ scan and the intensities were reduced to F values using programs of the Nicolet system. Reflections with $F < 3\sigma(F)$ were considered unobserved. The trial model was obtained using the direct methods program RANT of the SHELXTL [14] program package. The initial difference map revealed the two crystallographically independent molecules of the asymmetric unit and contained an additional peak which was not bonded to either of the nucleoside molecules. It was established that this was a water of hydration. All non-hydrogen atoms were

refined anisotropically. Initially unit weights based on counting statistics were employed. It was possible to locate positions for most of the hydrogen atoms in difference maps but positions for all hydrogens bonded to carbon atoms were calculated based on geometrical considerations. These atoms were allowed to ride on their neighboring carbon atoms and the temperature parameters were set equal to 1.2 times the initial Ueq of those carbon atoms and held fixed at that value. Hydrogen atoms bonded to oxygen and nitrogen atoms were located in difference maps and refined isotropically. It was not possible to obtain positions for the hydrogen atoms of the water molecule. The final R values were R = 0.059 and R_w = 0.034. All computer programs used in the solution, refinement and display of the structure are contained in SHELXTL. An empirical extinction correction was used in the refinement. Atomic scattering factors were obtained from Volume IV of the International Tables for X-ray Crystallography [15].

REFERENCES AND NOTES

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- [1] D. D. Von Hoff and M. Slavik, *Adv. Pharm. Chem.*, **14**, 285 (1977).
- [2] A. Piskala and F. Sorm, *Collect. Czech. Chem. Commun.*, **29**, 2060 (1964).
- [3] M. W. Winkley and R. K. Robins, *J. Org. Chem.*, **35**, 491 (1970).
- [4] P. A. Jones and S. M. Taylor, *Cell*, **20**, 85 (1980).
- [5] M. S. Zedeck, *Biochem. Pharm.*, **28**, 1440 (1979).
- [6] C. K. Chu, K. A. Watanabe and J. J. Fox, *J. Heterocyclic Chem.*, **12**, 817 (1975).
- [7] D. D. Von Hoff and M. Slavik, *Adv. Pharm. Chem.*, **14**, 303 (1977).
- [8] R. Gompper, M. Gaeng and F. Saygin, *Tetrahedron Letters*, 1885 (1966).
- [9] K. Dewald, P. Blauschmidt and R. Mayer, *J. Prakt. Chem.*, **35**, 97 (1967).
- [10] L. S. Wittenbrook, *J. Heterocyclic Chem.*, **12**, 37 (1975).
- [11] R. Evers and E. Fischer, *Z. Chem.*, **19**, 290 (1979).
- [12] R. J. Timmons and L. S. Wittenbrook, *J. Org. Chem.*, **32**, 1566 (1967).
- [13] T. A. Riley, W. J. Hennen, N. K. Dalley, B. E. Wilson and R. K. Robins, *J. Org. Chem.*, **51**, in Press (1986).
- [14] G. M. Sheldrick, "SHELXTL. An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data", 4th revision, University of Gohingen: Federal Republic of Germany, 1983.
- [15] "International Tables for X-Ray Crystallography", Vol 4, J. A. Ibers and W. C. Hamilton, eds, Kynock Press, Birmingham, England, 1974, p 99.