Synthesis of Certain 1-β-D-Ribofuranosyl-1,2-dihydro-2-oxopyridines Structurally Related to Nicotinamide Ribonucleoside

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Several substituted 1-β-D-ribofuranosyl-1,2-dihydro-2-oxopyridines have been prepared as congeners of nicotinamide ribonucleoside. Direct glycosylation of the silylated 3-ethylcarboxylate **5** or 3-carbamoyl **6** derivative of 1,2-dihydro-2-oxopyridine with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**7**) in the presence of trimethylsilyl triflate gave the corresponding blocked nucleosides **8** and **9**, respectively in good yield. Ammonolysis of **8** and **9** with methanolic ammonia furnished 1-β-D-ribofuranosyl-1,2-dihydro-2-oxopyridine-3-carboxamide (**10**), the structure of which was established by single-crystal X-ray diffraction analysis. Thiation of **9** with Lawesson's reagent and subsequent deacetylation of the thiated product **11** with methanolic ammonia furnished 1-β-D-ribofuranosyl-1,2-dihydro-2-oxopyridine-3-thiocarboxamide (**12**). Modification of the carbonitrile function of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2-dihydro-2-oxopyridine-4-carbonitrile (**13**) gave a series of 4-substituted-1-β-D-ribofuranosyl-1,2-dihydro-2-oxopyridines, in which the 4-substituent is a thiocarboxamide **15**, carboxamide **16**, carboxamidoxime **17**, carboxamidine **18** and aminomethyl **19** group. None of these compounds exhibited any significant antitumor or antiviral effects *in vitro*.

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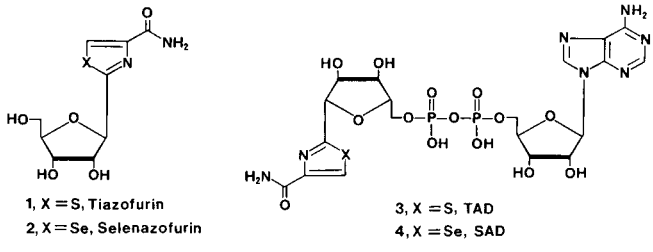
The synthetic oncolytic thiazole *C*-nucleoside, 2-β-D-ribofuranosylthiazole-4-carboxamide (tiazofurin, **1**) synthesized and reported from our laboratory [1], is a promising antitumor agent [2], currently undergoing phase II clinical trials [3,4]. In preclinical trials in experimental murine tumor systems, tiazofurin was found to be very efficacious against P388 and L1210 leukemias and Lewis lung carcinoma [5,6], the latter neoplasm being refractory to many chemotherapeutic agents. Tiazofurin was also active against four human lymphoid tumors in culture [7], *i.e.* CCRF-CEM, MOLT-4, HUT-8 (all T-cell leukemias) and NALM-1 (B-cell leukemia). The antitumor activity of tiazofurin is believed to be due to the intracellular enzymatic conversion of **1** to the corresponding nicotinamide adenine dinucleotide (NAD^+) analog **3** (TAD). The conversion of **1** to **3** has been observed in P388 animal tumors [8], as well as in transformed Chinese hamster ovary cells [9]. The dinucleotide **3** (TAD) has been shown to be an inhibitor of IMP dehydrogenase [5,8] and also an inhibitor of ADP-ribosylation. Since TAD is a carbon-linked nucleotide analog of NAD^+, there is no positive charge in the azole moiety. The charged nitrogen of the nicotinamide moiety of NAD^+ is a good leaving group, which is probably displaced by a nucleophile substituent in the enzymatic ADP-ribosylation reaction [10]. However, such a nucleophilic displacement is virtually impossible with TAD, and thus the resultant inhibition of ADP-ribosylation could be responsible for the observed antitumor activity. TAD is not incorporated into DNA or RNA [11].

The selenazole analog of **1** (2-β-D-ribofuranosylselenazole-4-carboxamide, **2**), also synthesized and reported from our laboratory [12], is highly active against a wide



spectrum of DNA and RNA viruses [13-18]. Against L1210 leukemia in mice, **2** is about ten times more potent than **1** with about the same therapeutic index [19]. Like tiazofurin, selenazofurin is also metabolized to a NAD analog **4** (SAD) in P388 leukemic cells [20-22]. SAD is a much more effective inhibitor of IMP dehydrogenase than the corresponding tiazofurin derivative TAD [20]. Thus, in an effort to prepare nucleosides with enhanced antitumor activity, we decided to synthesize 2-oxonicotinamide ribonucleosides which do not carry a positive charge at the pyridine nitrogen. These analogs are expected to be kinased intracellularly to the corresponding 5'-phosphate and then sequentially converted to the NAD analogs, which should possess the potential of inhibiting ADP-ribosylation due to the lack of a positive charge on the pyridine nitrogen.

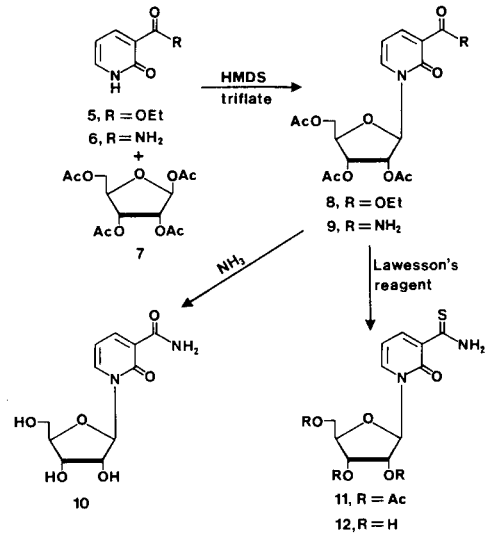
It is of particular interest that nicotinamide and certain related derivatives have exhibited a variety of interesting biological properties which include antiviral [23], antiinflammatory [24], antifibrillatory [25], coronary vasodilatory [25], hypertensive [25] and spasmolytic [25] activity. 6-Aminonicotinamide exhibited drastic inhibitory effects on the mitogen-stimulated increases in NAD and ATP levels, as well as on the metabolism of glucose [26]. It is conceivable that the nicotinamide derivatives in certain cases

may act by virtue of their conversion to the corresponding nucleoside or a NAD analog. For example, 2-hydroxynicotinic acid, an inhibitor of cholesterol and fatty acid synthesis in rats [27], has been shown to be converted to the corresponding 1-β-D-ribofuranosyl derivative in dogs and rats [28] when administered orally. The isolation of nicotinic acid ribonucleoside from the extracts of *Aspergillus niger* [29], and 1-β-D-ribofuranosyl-1,4-dihydro-4-oxopyridine-3-carboxamide from the urine of chronic myelogenous leukemia patients [30,31] has also been reported. Synthesis of the NAD(P) coenzyme metabolite 1-β-D-ribofuranosyl-1,6-dihydro-6-oxopyridine-3-carboxamide, isolated from human urine, has recently been documented [32].

A number of *C*-glycosyl- [33-37] as well as *N*-glycosylpyridine derivatives [38-40] have been reported, including pyridine nucleoside analogs [41-47] of the naturally occurring pyrimidine nucleosides. Several methods of glycosylation have been employed in the synthesis of these pyridine nucleosides, most notably the silver salt and the mercury salt methods [39], rearrangement of the corresponding *O*-glycosides [48], and the Hilbert-Johnson method [42]. In view of the simplicity and often observed absence of side products, the Lewis acid (trimethylsilyl trifluoromethanesulfonate) catalyzed glycosylation method was employed in this study.

One of the starting materials ethyl 1,2-dihydro-2-oxopyridine-3-carboxylate (**5**), required for the glycosylation studies, was prepared as reported [49]. The synthesis of 1,2-dihydro-2-oxopyridine-3-carboxamide (2-hydroxynicotinamide, **6**) has also been reported [49] by sulfuric acid hydrolysis of 1,2-dihydro-2-oxopyridine-3-carbonitrile. However, in the present study, compound **6** was prepared by ammonolysis of **5** with methanolic ammonia at room temperature. The isolated yield of the desired crystalline 2-hydroxynicotinamide was more than 87%. For the glycosylation studies, the trimethylsilyl procedure, as described by Vorbrüggen and coworkers [50] was found to be very successful. Silylation of **5** with hexamethyldisilazane (HMDS) in the presence of ammonium sulfate gave the silylated product, which on reaction with one molar equivalent of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**7**) in the presence of 1.44 molar equivalent of trimethylsilyl trifluoromethanesulfonate (trimethylsilyl triflate) in anhydrous acetonitrile furnished a 75% yield of the protected nucleoside ethyl 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2-dihydro-2-oxopyridine-3-carboxylate (**8**). Compound **8** was the only nucleoside product which could be isolated from the reaction mixture, and no formation of either *O*-glycoside or the α-anomer was detected by chromatographic procedures (tlc or hplc). A similar glycosylation of **6** gave a 50% yield of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2-dihydro-2-oxopyridine-3-carboxamide (**9**). Ammonolysis of **8**

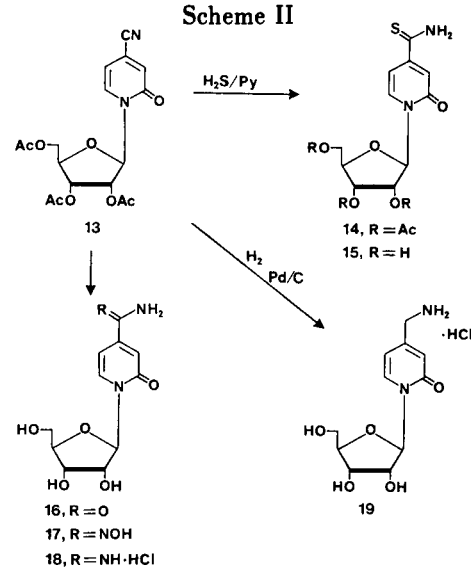
Scheme I



with methanolic ammonia (saturated at 0°) at room temperature gave the desired 1-β-D-ribofuranosyl-1,2-dihydro-2-oxopyridine-3-carboxamide (**10**) in 80% yield, as crystalline material. Deacetylation of **9** with methanolic ammonia at 4° also afforded a 74% yield of crystalline **10**. The structure of **10** was established by single-crystal X-ray diffraction analysis.

When the protected nucleoside **9** was reacted with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide [51] (Lawesson's reagent) in toluene at 100° for 3 hours, a mono-thiated nucleoside was formed, which was isolated and characterized as 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2-dihydro-2-oxopyridine-3-thiocarboxamide (**11**) on the basis of spectroscopic and elemental analysis (see Experimental). Deacetylation of **11** with methanolic ammonia furnished 1-β-D-ribofuranosyl-1,2-dihydro-2-oxopyridine-3-thiocarboxamide (**12**) in over 84% yield.

Scheme II



For the synthesis of 4-substituted-1-β-D-ribofuranosyl-1,2-dihydro-2-pyridinones, the recently described 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2-dihydro-2-oxopyridine-4-carbonitrile (**13**) [52] was found to be a versatile starting material. Compound **13** was prepared by stannic chloride catalyzed glycosylation of the trimethylsilyl derivative of 1,2-dihydro-2-oxopyridine-4-carbonitrile as reported [52], and treated with ammonium hydroxide and hydrogen peroxide in ethanol. After purification of the reaction product by flash chromatography over silica gel, 1-β-D-ribofuranosyl-1,2-dihydro-2-oxopyridine-4-carboxamide (**16**) was obtained as crystalline material in 44% yield. When **13** was allowed to react with hydroxylamine in ethanol at reflux temperature, 1-β-D-ribofuranosyl-1,2-dihydro-2-oxopyridine-4-carboxamidoxime (**17**) was formed. Catalytic hydrogenation of **17** in the presence of Raney nickel and ammonium chloride at 45 psi for 7 hours furnished a 56% yield of the corresponding 4-carboxamidine derivative **18**, which was isolated as the monohydrochloride salt. Our attempts to convert **13** directly to **18** with liquid ammonia and ammonium chloride at elevated temperature and pressure was not fruitful.

Transformation of **13** to the corresponding 4-thiocarboxamide derivative **14** was effected in 92% yield by the treatment of **13** with anhydrous hydrogen sulfide in dry pyridine and triethylamine. Deacetylation of **14** with sodium bicarbonate in methanol, followed by purification of the reaction mixture on a flash silica gel column gave 1-β-D-ribofuranosyl-1,2-dihydro-2-oxopyridine-4-thiocarboxamide (**15**) in a 50% yield. Treatment of **13** in a hydrogen atmosphere with Pd/C catalyst in 0.02 *N* methanolic hydrogen chloride at 45 psi for an hour, hydrogenated the carbonitrile function to an aminomethyl group with concomitant deacetylation to afford 4-aminomethyl-1-β-D-ribofuranosyl-1,2-dihydro-2-oxopyridine (**19**), isolated as the monohydrochloride salt. Nucleoside **19** was found to be rather hygroscopic. Since the structure of the starting nucleoside **13** has already been established [52], the glycosyl attachment and the β-anomeric configuration of the nucleosides **14-19** were confirmed.

Single-crystal X-ray Diffraction Analysis of Compound **10**.

Non-hydrogen atomic parameters are listed in Table 1. The bond lengths and angles, given in Table 2, and the molecular conformations of the two independent molecules (labeled A and B), illustrated in Figure 1, indicate that the molecules are nearly identical except for the disposition of the C5′-O5′ side chain. The structural determination confirms that compound **10** is an *N*-nucleoside with the β-anomeric configuration. Table 3 lists selected torsion angles. The side chains are *guache-gauche* in molecule A and *gauche-trans* in molecule B. The ribose bond lengths are identical within experimental error; bond angles show a few inconsistencies between molecules, all of which involve C1′ and C4′. The conformation is C3′ *endo* for both conformers (^3E for A and $^3T_2$ for B) with pseudorotation angles (P) of 18.2° and 15.0° and amplitudes of pucker (τ_m) of 42.3° and 38.4° for A and B, respectively (after the convention of Altona and Sundaralingam [53]). The atoms C1′, C2′, C4′ and O4′ are planar [rms deviation: (A) 0.001(2) and (B) 0.012(2) Å] with C3′ deviating by 0.649(2) Å in A and 0.595(2) Å in B. This conformation is frequently observed in contrast to the C4′ *exo*-C3′ *endo* conformation of the naturally occurring congener, 1-β-D-ribofuranosyl-1,4-dihydro-4-oxopyridine-3-carboxamide [31].

The glycosidic bonds are longer than observed in the 4-oxo isomer [31]. Although the 4-oxo compound [31] and the molecules of **10** are considered to have the *anti* confor-

Table 1

Positional and Equivalent Isotropic Thermal Parameters for Non-hydrogen Atoms in Compound **10**

Atom	x/a	y/b	z/c	U_{eq} [a]
		Molecule A		
N1A	.5753(2)	.5	.9299(2)	.0346(5)
C2A	.6378(3)	.49903(12)	.7788(2)	.0348(5)
C3A	.6536(3)	.42572(12)	.7092(2)	.0333(5)
C4A	.6091(3)	.36405(13)	.7917(3)	.0378(6)
C5A	.5482(3)	.36872(13)	.9428(3)	.0411(6)
C6A	.5330(3)	.43740(13)	1.0099(3)	.0382(6)
O7A	.6746(3)	.55949(9)	.7164(2)	.0484(5)
C8A	.7221(3)	.41579(13)	.5492(3)	.0368(6)
O9A	.7452(3)	.35107(10)	.4985(2)	.0481(5)
N10A	.7591(3)	.47561(13)	.4676(2)	.0458(6)
C1′A	.5534(3)	.57580 (13)	1.0014(3)	.0396(6)
C2′A	.3757(3)	.60921(12)	.9471(2)	.0380(6)
C3′A	.2584(3)	.58299(11)	1.0769(2)	.0339(5)
C4′A	.3800(3)	.59372(13)	1.2189(2)	.0398(6)
C5′A	.3308(4)	.5523(2)	1.3652(3)	.0472(7)
O2′A	.3801(3)	.68832(9)	.9561(2)	.0513(6)
O3′A	.0918(2)	.61700(10)	1.0821(2)	.0443(5)
O4′A	.5488(2)	.56796(11)	1.1644(2)	.0454(5)
O5′A	.2888(3)	.47593(12)	1.3386(2)	.0566(6)
		Molecule B		
N1B	.1567(2)	.31689(10)	.7548(2)	.0352(5)
C2B	.0773(3)	.31631(13)	.8993(2)	.0345(5)
C3B	.0307(3)	.38853(12)	.9590(2)	.0338(6)
C4B	.0502(3)	.45103(13)	.8709(2)	.0371(6)
C5B	.1249(3)	.44744(13)	.7231(3)	.0403(6)
C6B	.1791(3)	.38031(14)	.6703(2)	.0396(6)
O7B	.0556(3)	.25566(9)	.9649(2)	.0461(5)
C8B	−.0422(3)	.39667(13)	1.1177(3)	.0354(6)
O9B	−.0541(3)	.45958(10)	1.1765(2)	.0513(6)
N10B	−.0903(3)	.33583(12)	1.1916(2)	.0432(6)
C1′B	.2195(3)	.24281(12)	.7005(2)	.0359(6)
C2′B	.0707(3)	.19687(12)	.6223(2)	.0362(6)
C3′B	.0936(3)	.21664(13)	.4516(3)	.0379(6)
C4′B	.2933(3)	.22145(13)	.4421(2)	.0385(6)
C5′B	.3568(4)	.2694(2)	.3111(3)	.0519(8)
O2′B	.1038(3)	.12014(10)	.6404(2)	.0481(5)
O3′B	.0140(3)	.16749(13)	.3425(2)	.0579(6)
O4′B	.3497(2)	.25385(10)	.5889(2)	.0431(5)
O5′B	.5421(3)	.26498(15)	.2973(3)	.0695(8)

[a] $U_{eq} = 1/3\ \Sigma_i\Sigma_j\ U_{ij}^*\ a_i^*\ a_j^*\ A_{ij}$, where A_{ij} is the dot product of the i^{th} and j^{th} direct-space unit-cell vectors

Table 2

Bond Lengths (Å) and Bond Angles (°) in Compound **10**

			Molecule A		Molecule B	
1	2	3	1-2	1-2-3	1-2	1-2-3
C2	N1	C6	1.397(3)	123.43(14)	1.397(3)	122.9(2)
C6	N1	C1'	1.362(3)	120.8(2)	1.366(3)	122.2(2)
C1'	N1	C2	1.506(2)	115.81(14)	1.494(3)	114.9(2)
C3	C2	O7	1.454(3)	126.2(2)	1.444(3)	126.3(2)
C3	C2	N1		115.4(2)		115.2(2)
O7	C2	N1	1.248(3)	118.4(2)	1.241(3)	118.5(2)
C4	C3	C8	1.364(3)	118.6(2)	1.366(3)	118.4(2)
C4	C3	C2		119.9(2)		120.8(2)
C8	C3	C2	1.496(3)	121.5(2)	1.495(3)	120.9(2)
C5	C4	C3	1.394(3)	122.0(2)	1.408(3)	121.1(2)
C6	C5	C4	1.369(3)	118.8(2)	1.358(3)	118.5(2)
N1	C6	C5		120.6(2)		121.4(2)
O9	C8	N10	1.257(3)	122.4(2)	1.243(3)	122.2(2)
O9	C8	C3		119.0(2)		119.6(2)
N10	C8	C3	1.319(3)	118.5(2)	1.322(3)	118.2(2)
C2'	C1'	O4'	1.535(3)	107.1(2)	1.537(3)	107.3(2)
C2'	C1'	N1		109.7(2)		112.3(2)
O4'	C1'	N1	1.411(3)	108.7(2)	1.411(3)	108.8(2)
C3'	C2'	O2'	1.522(3)	106.4(2)	1.526(3)	108.0(2)
C3'	C2'	C1'		100.5(2)		101.1(2)
O2'	C2'	C1'	1.425(3)	110.8(2)	1.410(3)	110.6(2)
C4'	C3'	O3'	1.521(3)	116.3(2)	1.521(3)	114.0(2)
C4'	C3'	C2'		101.3(2)		101.9(2)
O3'	C3'	C2'	1.405(3)	115.7(2)	1.412(3)	115.8(2)
C5'	C4'	O4'	1.518(3)	110.6(2)	1.509(4)	109.3(2)
C5'	C4'	C3'		116.5(2)		114.4(2)
O4'	C4'	C3'	1.452(3)	102.6(2)	1.444(3)	104.2(2)
O5'	C5'	C4'	1.426(4)	113.5(2)	1.416(4)	111.7(2)
C1'	O4'	C4'		109.7(2)		110.1(2)

Table 3

Selected Torsion Angles (°) in Compound **10**

	1	2	3	4	1-2-3-4 A	1-2-3-4 B
θ_0	C1'	C2'	C3'	C4'	40.2(2)	37.1(2)
θ_1	C2'	C3'	C4'	O4'	–41.1(2)	–36.8(2)
θ_2	C3'	C4'	O4'	C1'	25.7(2)	21.7(2)
θ_3	C2'	C1'	O4'	C4'	.2(3)	2.6(2)
θ_4	O4'	C1'	C2'	C3'	–25.9(2)	–25.4(2)
ϕ_{oo}	O4'	C4'	C5'	O5'	–69.2(3)	70.3(3)
ϕ_{co}	C3'	C4'	C5'	O5'	47.4(3)	–173.3(2)
χ_{CN}	C6	N1	C1'	O4'	20.6(3)	20.2(3)
χ^1_{CN}	O4'	C1'	N1	C2	–160.4(2)	–158.5(2)

mation, the glycosidic torsion angle (χ_{CN}) of the former (66.9°) is about 46° larger than observed in the latter [20.6(3)° and 20.2(3)° in A and B, respectively]. This difference can be attributed to steric hindrance between O7 and H1' [d(07··H1') = 2.33(3) and 2.31(3) Å for A and B]. Rotation about the glycosyl linkage toward χ_{CN} = 66° would further reduce the O7··H1' distance, which is already 0.3 Å shorter than the van der Waals contacts. The pyridine ring is strictly planar in A [rmsd: 0.002(2) Å] and slightly non-planar in B [rmsd: 0.019(2) Å]. The carboxamide groups, which are intramolecularly hydrogen bonded to the 2-oxo moieties, are twisted with respect to the pyridine rings; in A, the dihedral angle is only 3.92(9)° whereas in B it is 12.62(9)°. Although the twist is greater in B, the N10B··O7B distance is shorter than the corresponding distance in A due to the fact that N10B and O7B are on the same side of the pyridine plane whereas N10A and O7A are on opposite sides of the plane in A.

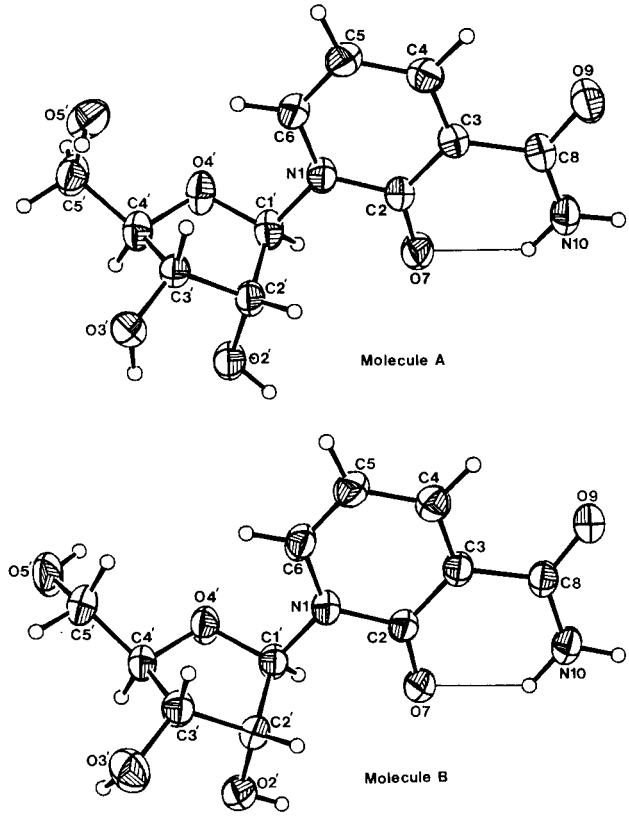


Figure 1. Perspective illustration of the two independent molecules in the asymmetric unit of the crystal structure of 10 showing the congruency of the two forms except for the C5'-O5' side chain. In (a), molecule A is gauche-gauche with a possible C6-H6···O5' interaction. In (b), molecule B is gauche-trans. Thermal ellipsoids are drawn at the 50% probability level.

The base moieties form layers parallel to the crystallographic 201 plane. The hydrogen bonding interactions (Table 4) are similar between the two molecules except for the interaction of O2'; O2'A hydrogen bonds to O5'B, while O2'B bonds to O3'A. This is a consequence of the different side chain orientations. In A, O5' very possibly is interacting with H6A [d(O5'A··H6A = 2.58(3) Å, ∠C6A-H6A··O5'A = 157(3)°]. Molecules A and B form two dimeric units in which the two molecules are bound by two hydrogen bonds. A head-to-head dimer is formed by the N10

Table 4

Hydrogen Bonding in Compound **10**

D	—	H	···	A	Symmetry of A relative to D	d(H··· A) (Å)	d(D··· A) (Å)	∠(D-H·· A) (°)
N10A		H10A1		O9B	1.0+x, y, z-1.0	2.927(3)	2.00(3)	172.(3)
N10A		H10A2		O7A	x, y, z	2.711(3)	1.97(4)	138.(4)
O2'A		HO2'A		O5'B	1.0-x, 0.5+y, 1.0-z	2.661(3)	1.77(5)	168.(5)
O3'A		HO3'A		O7B	-x, 0.5+y, 2.0-z	2.758(3)	2.05(4)	143.(4)
O5'A		HO5'A		O9B	x, y, z	2.929(3)	2.05(6)	170.(5)
N10B		H10B1		O9A	x-1.0, y, 1.0+z	2.965(3)	2.04(4)	177.(3)
N10B		H10B2		O7B	x, y, z	2.690(3)	1.93(3)	133.(3)
O2'B		HO2'B		O3'A	-x, y-0.5, 2.0-z	2.848(3)	2.10(4)	148.(4)
O3'B		HO3'B		O7A	1.0-x, y-0.5, 1.0-z	3.110(3)	2.06(6)	164.(5)
O5'B		HO5'B		O9A	x, y, z	2.758(3)	1.96(5)	158.(5)

atom of one molecule donating to O9 of the other. A head-to-tail dimer is formed by O5' of one molecule donating to O9 of the other with concommitant partial base stacking, C6 to C6 and C4 to C4 with C3 of one molecule over the cavity of the pyridine ring of the other.

Biological Evaulations.

Compounds **6**, **10**, **12** and **15-19** were evaluated *in vitro* for their ability to inhibit the growth of L1210 murine lymphocytic leukemia, WI-L2 human B-lymphoblastic leukemia, and CCRF-CEM human T-lymphoblastic leukemia cell lines using the methodology as reported from our laboratory [54]. The highest concentration of compounds tested was 100 μM. These compounds were also evaluated *in vitro* for their antiviral effects against several unrelated DNA and RNA viruses, which include herpes simplex virus type 2 (MS), adenovirus type 2 (Adenoid 6), parainfluenza virus type 3 (C243), rhinovirus type 1-A (2060), influenza A virus (Chile), Semliki forest virus (original) and visna virus (1513). Evaluation of virus-induced cytopathic effect and calculation of virus rating were performed by the method described by Sidwell [55]. None of the compounds tested exhibited any significant antitumor or antiviral effects in these cell lines.

EXPERIMENTAL

Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting-point apparatus. Elemental analyses were performed by Robertson Laboratory, Madison, NJ. The presence of water as indicated by elemental analysis was verified by ^{1}H nmr spectroscopy. Thin layer chromatography (tlc) was performed on plates of silica gel 60F-254 (EM Reagents). Silica gel (E. Merck; 230-400 mesh) was used for flash column chromatography. All solvents used were reagent grade. Detection of nucleoside components in tlc was by uv light, and with 10% sulfuric acid in methanol spray followed by heating. Evaporations were conducted under diminished pressure with the bath temperature below 30°. Infrared (ir) spectra were recorded in potassium bromide with a Perkin-Elmer 1420 spectrophotometer and ultraviolet spectra (uv) were recorded on a Beckman DU-50 spectrophotometer. Nuclear magnetic resonance (^{1}H nmr) spectra were recorded at 300 MHz with an IBM NR/300 spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as the internal standard (key: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad).

1,2-Dihydro-2-oxopyridine-3-carboxamide (**6**).

A suspension of ethyl 1,2-dihydro-2-oxopyridine-3-carboxylate (**5**, 1.67 g, 10 mmoles) [49] in methanolic ammonia (50 ml, saturated at 0°) was placed in a pressure bottle and stirred at room temperature for 15 hours. The clear solution was filtered and the filtrate concentrated to about 20 ml. The precipitated crystalline material was collected by filtration, washed with cold methanol (2 × 25 ml) and dried to yield 1.2 g (87%) of **6**, mp 272-273° (lit [49] 266-267°); ir: ν max 1645 (C=O), 1670 (C=O of amide), 2800-3400 (NH, NH_2) cm^{-1}; uv (*p*H 1): λ max 320 nm (ϵ 7,100); (*p*H 7): 320 nm (ϵ 7,000); (*p*H 11): 323 nm (ϵ 6,900); ^{1}H nmr (DMSO-d_6): δ 6.44 (t, 1 H, C_5H), 7.57 and 9.09 (2 s, 2 H, $CONH_2$), 7.69 (q, 1 H, C_4H), 8.31 (q, 1 H, C_6H) and 11.80 (br s, 1 H, N*H*).

Ethyl 1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-1,2-dihydro-2-oxopyridine-3-carboxylate (**8**).

A mixture of **5** (1.67 g, 10 mmoles), hexamethyldisilazane (HMDS, 30 ml) and ammonium sulfate (0.10 g) was heated under reflux (135°, oil bath temperature) for 1 hour. The excess of HMDS was removed by distillation under reduced pressure at 50°. The residual syrup was co-evaporated with toluene (2 × 30 ml) and held at high vacuum for 2 hours at 50°. To a stirred solution of the above dry silylated pyridinone in anhydrous acetonitrile (50 ml) was added successively 1,2,3,5-tetra-*O*-acetyl-β-D-ri-

bofuranose (**7**, 3.18 g, 10 mmoles) and trimethylsilyl triflate (2.78 ml, 14.4 mmoles) at room temperature. After stirring for 15 hours at ambient temperature, the reaction mixture was evaporated. The residue was dissolved in ethyl acetate (200 ml) and washed with cold 5% aqueous solution of sodium bicarbonate (2 × 100 ml), followed by water (2 × 100 ml). After drying over anhydrous sodium suflate, the solvent was evaporated and the residue was purified on a flash silica gel column (2 × 30 cm). The column was eluted successively with 200 ml portions of dichloromethane:-methanol (98:2, 96:4 and 94:6, v/v). The homogeneous fractions were pooled and evaporated to yield 3.2 g (75%) of **8** as white foam; ir (neat): ν max 1650 (C=O), 1740 (C=O of ester) cm^{-1}; uv (*p*H 1): λ max 327 nm (ϵ 9,400); (*p*H 7): 326 nm (ϵ 11,600); (*p*H 11): 328 nm (ϵ 11,100); ^1H nmr (DMSO-d_6): δ 1.25 (t, 3 H, $COOCH_2CH_3$), 2.05, 2.06, 2.07 (3 s, 9 H, 3 $COCH_3$), 4.20 (q, 2 H, $COOCH_2CH_3$), 4.26-4.40 (2 m, 3 H, $C_{4'}H$ and $C_{5'}CH_2$), 5.37 (t, 1 H, $C_{3'}H$), 5.46 (m, 1 H, $C_{2'}H$), 6.08 (d, 1 H, J = 3.4 Hz, $C_{1'}H$), 6.44 (t, 1 H, C_5H), 8.01 (m, 1 H, C_4H) and 8.08 (m, 1 H, C_6H).

Anal. Calcd. for $C_{19}H_{23}NO_{10}$ (425.38): C, 53.64; H, 5.41; N, 3.29. Found: C, 53.34; H, 5.56; N, 3.19.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-1,2-dihydro-2-oxopyridine-3-carboxamide (**9**).

In a similar manner as for **8**, silylation of **6** (1.38 g, 10 mmoles) with HMDS (30 ml) and ammonium sulfate (0.10 g) gave the silylated pyridine derivative, which on reaction with **7** (3.18 g, 10 mmoles) in the presence of trimethylsilyl triflate (2.78 ml, 14.4 mmoles) gave 2.0 g (50%) of **9** as white foam; ir: ν max 1670 (C=O), 1740 (C=O of acetate), 3300-3600 (NH_2) cm^{-1}; uv (*p*H 1): λ max 327 nm (ϵ 8,400); (*p*H 7): 326 nm (ϵ 10,900); (*p*H 11): 323 nm (ϵ 10,100); ^1H nmr (DMSO-d_6): δ 2.05, 2.06, 2.08 (3 s, 9 H, 3 $COCH_3$), 4.27-4.41 (2 m, 3 H, $C_{4'}H$ and $C_{5'}CH_2$), 5.36 (t, 1 H, $C_{3'}H$), 5.49 (m, 1 H, $C_{2'}H$), 6.20 (d, 1 H, J = 3.5 Hz, $C_{1'}H$), 6.62 (t, 1 H, C_5H), 7.69 and 8.75 (2 s, 2 H, $CONH_2$), 8.06 (m, 1 H, C_4H), and 8.35 (m, 1 H, C_6H).

Anal. Calcd. for $C_{17}H_{20}N_2O_9$ (396.35): C, 51.51; H, 5.09; N, 7.07. Found: C, 51.40; H, 5.04; N, 6.83.

1-β-D-Ribofuranosyl-1,2-dihydro-2-oxopyridine-3-carboxamide (**10**).

Method A.

A solution of **9** (0.40 g, 1 mmole) in methanolic ammonia (30 ml, saturated at 0°) was stored at 4° overnight, and then evaporated to dryness. The residue was triturated with ethanol, the solid that separated was collected by filtration and crystallized from ethanol to yield 0.2 g (74%) of **10**, mp 175-177°; ir: ν max 1650 (C=O), 1670 (C=O of amide), 3100-3600 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 323 nm (ϵ 9,000); (*p*H 7): 325 nm (ϵ 9,100); (*p*H 11): 324 nm (ϵ 9,200); ^1H nmr (DMSO-d_6): δ 3.64 (m, 2 H, $C_{5'}CH_2$), 3.79-3.97 (m, 3 H, $C_{2',3',4'}H$), 5.10 (d, 1 H, $C_{3'}OH$), 5.23 (t, 1 H, $C_{5'}OH$), 5.55 (d, 1 H, $C_{2'}OH$), 6.08 (d, 1 H, J = 1.17 Hz, $C_{1'}H$), 6.55 (t, 1 H, C_5H), 7.63 and 8.96 (2 br s, 2 H, $CONH_2$), 8.32 (m, 1 H, C_4H) and 8.42 (m, 1 H, C_6H).

Anal. Calcd. for $C_{11}H_{14}N_2O_6$ (270.24): C, 48.89; H, 5.22; N, 10.37. Found: C, 48.79; H, 5.15; N, 10.37.

Method B.

A solution of **8** (1.27 g, 3 mmoles) in methanolic ammonia (50 ml) was stirred at room temperature overnight, and then evaporated to dryness. The residue was crystallized from ethanol to yield 0.65 g (80%) of **10**, mp 174-176°. This product was found to be identical with **10** prepared by Method A.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-1,2-dihydro-2-oxopyridine-3-thiocarboxamide (**11**).

A mixture of **9** (0.5 g, 1.2 mmoles), 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide [51] (Lawesson's reagent, 0.25 g, 0.6 mmole) and anhydrous toluene (10 ml) was heated at 100° for 3 hours with the exclusion of moisture. The reaction mixture was allowed to cool to ambient temperature and poured into water (50 ml). The aqueous solution was extracted with ethyl acetate (2 × 75 ml). The organic phase was washed with water (50 ml). After drying over anhydrous sodium sulfate, the solvent was evaporated and the residue was purified on a flash silica gel column (2 × 20 cm). The column was eluted successively with 200 ml portions of dichloromethane:methanol (98:2, 96:4, v/v). The homogeneous fractions were pooled and evaporated to yield 0.25 g (51%) of **11** as yellow foam; ir: ν max 1240 (C=S), 1645 (C=O), 1750 (C=O of ester), 3300-3550 (NH_2) cm^{-1}; uv (*p*H 1): λ max 357 nm (ϵ 6,900); (*p*H 7): 357 nm (ϵ 6,500); (*p*H 11): 357 nm (ϵ 7,100); ^1H nmr (DMSO-d_6): δ 2.03, 2.05, 2.08 (3 s, 9 H, 3 $COCH_3$), 4.22-4.41 (2 m, 3 H, $C_{4'}H$ and $C_{5'}CH_2$), 5.37 (t, 1 H, $C_{3'}H$), 5.51 (m, 1 H, $C_{2'}H$), 6.20 (d, 1 H, J = 3.1 Hz, $C_{1'}H$), 6.70 (t, 1 H, C_5H), 8.13 (d, 1 H, C_4H), 8.95 (d, 1 H, C_6H), 10.15 and 10.81 (2 s, 2 H, $CONH_2$).

Anal. Calcd. for $C_{17}H_{20}N_2O_8S$ (412.41): C, 49.51; H, 4.89; N, 6.79; S, 7.77. Found: C, 49.68; H, 5.01; N, 6.68; S, 7.92.

1-β-D-Ribofuranosyl-1,2-dihydro-2-oxopyridine-3-thiocarboxamide (**12**).

In a similar manner as described for **10** (Method A), deacetylation of **11** (0.2 g, 0.5 mmole) with methanolic ammonia (30 ml) gave the title compound. The product was purified by flash chromatography over silica gel using dichloromethane:methanol (8:2, v/v) as the eluent and crystallized from methanol to yield 0.12 g (84%) of **12**, mp 175-177° (dec); ir: ν max 1250 (C=S), 1645 (C=O), 3300-3600 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 352 nm (ϵ 9,500); (*p*H 7): 352 nm (ϵ 9,600); (*p*H 11): 353 nm (ϵ 9,500); ^1H nmr (DMSO-d_6): δ 3.70 (m, 2 H, $C_{5'}CH_2$), 3.97 (m, 3 H, $C_{2',3',4'}H$), 5.10 (d, 1 H, $C_{3'}OH$), 5.26 (t, 1 H, $C_{5'}OH$), 5.57 (d, 1 H, $C_{2'}OH$), 6.07 (s, 1 H, $C_{1'}H$), 6.62 (t, 1 H, C_5H), 8.52 (d, 1 H, C_4H), 8.93 (d, 1 H, C_6H), 10.16 and 11.09 (2 s, 2 H, $CONH_2$).

Anal. Calcd. for $C_{11}H_{14}N_2O_5S$ (286.30): C, 46.14; H, 4.93; N, 9.78; S, 11.20. Found: C, 46.36; H, 5.00; N, 9.90; S, 10.92.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-1,2-dihydro-2-oxopyridine-4-thiocarboxamide (**14**).

A solution of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2-dihydro-2-oxopyridine-4-carbonitrile [52] (**13**, 1.0 g, 2.6 mmoles) in anhydrous pyridine (50 ml) containing triethylamine (10 ml) was saturated with dry hydrogen sulfide gas at room temperature. After stirring the reaction mixture in a sealed reaction vessel at room temperature overnight, the excess of hydrogen sulfide was removed by purging with nitrogen. The mixture was evaporated to dryness and co-evaporated several times with toluene. The residue was purified by flash chromatography over silica gel using hexane:ethyl acetate (3:7, v/v) as the eluent. The homogeneous fractions were pooled, evaporated to dryness and the gummy residue was triturated with anhydrous ether. The solid that separated was collected by filtration and dried under vacuum to yield 1.0 g

(92%) of **14**, mp 80°; ir: ν max 1230 (C=S), 1665 (C=O), 1750 (C=O of acetate), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 314 nm (ε 8,400); (*p*H 7): 312 nm (ε 8,200); (*p*H 11): 310 nm (ε 7,600); ^1H nmr (deuteriochloroform): δ 2.13, 2.16, 2.18 (3 s, 9 H, 3 $COCH_3$), 4.38-4.47 (m, 3 H, $C_{4'}H$ and $C_{5'}CH_2$), 5.36 (t, 1 H, $C_{3'}H$), 5.47 (m, 1 H, $C_{2'}H$), 6.17 (d, 1 H, J = 3.54 Hz, $C_{1'}H$), 6.76 (d, 1 H, J = 1.9 Hz, C_3H), 6.86 (dd, 1 H, J = 7.4 Hz, C_5H), 7.63 (d, 1 H, J = 7.4 Hz, C_6H), 7.80 and 7.93 [2 br s, 2 H, C(S)NH_2].

Anal. Calcd. for $C_{17}H_{20}N_2O_8S$ (412.4): C, 49.55; H, 4.88; N, 6.79; S, 7.76. Found: C, 49.33; H, 5.10; N, 6.52; S, 7.70.

1-β-D-Ribofuranosyl-1,2-dihydro-2-oxopyridine-4-thiocarboxamide (**15**).

A mixture of **14** (0.50 g, 1.2 mmoles), sodium bicarbonate (0.70 g) and methanol (150 ml) was stirred at room temperature for 18 hours. The reaction mixture was filtered and the filtrate was neutralized with Amberlite IRC-50 resin, before it was evaporated to dryness. The residue was purified by flash chromatography over silica gel using dichloromethane:methanol (8:2, v/v) as the eluent. The homogeneous fractions were pooled and evaporated to dryness. The residue was crystallized from a mixture of dichloromethane/methanol to give 0.17 g (50%) of **15**, mp 204-205°; ir: ν max 1275 (C=S), 1650 (C=O), 3100-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 309 nm (ε 10,700); (*p*H 7): 311 nm (ε 10,200); (*p*H 11): 310 nm (ε 9,500); ^1H nmr (DMSO-d_6): δ 3.65 (m, 2 H, $C_{5'}CH_2$), 3.75-3.98 (m, 3 H, $C_{2',3',4'}H$), 5.07 (d, 1 H, $C_{3'}OH$), 5.16 (t, 1 H, $C_{5'}OH$), 5.46 (d, 1 H, $C_{2'}OH$), 5.99 (d, 1 H, J = 3.0 Hz, $C_{1'}H$), 6.56 (d, 1 H, J = 7.0 Hz, C_5H), 6.57 (d, 1 H, J = 2.0 Hz, C_3H), 8.00 (d, 1 H, J = 7.0 Hz, C_6H), 9.69 and 10.15 [2 s, 2 H, C(S)NH_2].

Anal. Calcd. for $C_{11}H_{14}N_2O_5S$ (286.24): C, 46.14; H, 4.93; N, 9.78; S, 11.20. Found: C, 45.96; H, 4.72; N, 9.69; S, 11.39.

1-β-D-Ribofuranosyl-1,2-dihydro-2-oxopyridine-4-carboxamide (**16**).

A solution of **13** (0.41 g, 1.08 mmoles) in ethanol (10 ml) was adjusted to *p*H 9 with ammonium hydroxide and treated with hydrogen peroxide (30%, 5 ml). The reaction mixture was stirred at room temperature in a pressure bottle for 15 hours. The pressure bottle was cooled, opened carefully and the contents evaporated to dryness. The residue was dissolved in methanol (10 ml), adsorbed onto silica gel (5 g) and purified by flash chromatography over silica gel using dichloromethane:methanol (8:2, v/v) as the eluent. The homogeneous fractions were pooled and the solvent evaporated to dryness. The pure product was crystallized from a mixture of dichloromethane/methanol to give 0.13 g (44%) of **16**, mp 189-190°; ir: ν max 1650 (C=O), 1670 (C=O of amide), 3200-3400 (NH_2, OH) cm^{-1}; uv: (*p*H 1): λ max 321 nm (ε 4,800); (*p*H 7): 320 nm (ε 5,100); (*p*H 11): 321 nm (ε 5,100); ^1H nmr (DMSO-d_6): δ 3.65 (m, 2 H, $C_{5'}CH_2$), 3.91-4.00 (m, 3 H, $C_{2',3',4'}H$), 5.07 (d, 1 H, $C_{3'}OH$), 5.16 (t, 1 H, $C_{5'}OH$), 5.47 (d, 1 H, $C_{2'}OH$), 6.00 (d, 1 H, J = 3.0 Hz, $C_{1'}H$), 6.54 (dd, 1 H, J = 7.1 Hz, C_5H), 6.80 (d, 1 H, J = 1.65 Hz, C_3H), 8.09 (d, 1 H, J = 7.1 Hz, C_6H), 7.67 and 8.09 (2 s, 2 H, $CONH_2$).

Anal. Calcd. for $C_{11}H_{14}N_2O_6$ (270.24): C, 48.89; H, 5.22; N, 10.36. Found: C, 48.60; H, 5.16; N, 10.21.

1-β-D-Ribofuranosyl-1,2-dihydro-2-oxopyridine-4-carboxamidoxime (**17**).

A solution of **13** (0.23 g, 0.6 mmole) and hydroxylamine (0.50 g) in absolute ethanol (50 ml) was heated at reflux for 15 hours. Ethanol was evaporated to dryness and the residue was purified by flash chromatography over silica gel using dichloromethane:methanol (8:2, v/v) as the eluent. The pure product was crystallized from absolute ethanol to give 0.12 g (67%) of **17**, mp 179-180°; ir: ν max 1690 (C=O), 3300-3420 (NH_2, OH) cm^{-1}; uv: (*p*H 1): λ max 323 nm (ε 5,000); (*p*H 7): 301 nm (ε 7,000); (*p*H 11): 310 nm (ε 7,700); ^1H nmr (DMSO-d_6): δ 3.64 (m, 2 H, $C_{5'}CH_2$), 3.90-3.97 (m, 3 H, $C_{2',3',4'}H$), 5.14 (m, 2 H, $C_{3',5'}OH$), 5.43 (d, 1 H, $C_{2'}OH$), 5.92 [s, 2 H, C(NOH)NH_2], 6.02 (d, 1 H, J = 2.8 Hz, $C_{1'}H$), 6.54 (dd, 2 H, J = 7.5 Hz, C_5H), 6.72 (d, 1 H, J = 1.8 Hz, C_3H), 7.91 (d, 1 H, J = 7.5 Hz, C_6H), and 10.22 [s, 1 H, C(NOH)NH_2].

Anal. Calcd. for $C_{11}H_{15}N_3O_6$ (285.25): C, 46.32; H, 5.30; N, 14.73. Found: C, 46.09; H, 5.29; N, 14.73.

1-β-D-Ribofuranosyl-1,2-dihydro-2-oxopyridine-4-carboxamidine Hydrochloride (**18**).

A solution of **17** (0.50 g, 1.75 mmoles), Raney nickel (1.0 g, wet weight) and ammonium chloride (0.16 g) in 50% aqueous ethanol (100 ml) was shaken on a Parr hydrogenator at 45 psi for 7 hours. The catalyst was removed by filtration over a Celite pad and the filtrate evaporated to dryness. The residue was purified by hplc using C_{18} reverse phase column using water as the eluent. The homogeneous fractions were pooled and evaporated to dryness to afford 0.3 g (56%) of **18** as hygroscopic amorphous solid; ir: ν max 1650 (C=O), 3200-3400 (NH_2, OH) cm^{-1}; uv: (*p*H 1): λ max 323 nm (ε 7,000); (*p*H 7): 322 nm (ε 3,500); (*p*H 11): 317 nm (ε 3,200); ^1H nmr (DMSO-d_6): δ 3.64 (m, 2 H, $C_{5'}CH_2$), 3.92-3.97 (m, 3 H, $C_{2',3',4'}H$), 5.15 (br s, 1 H, $C_{3'}OH$), 5.27 (t, 1 H, $C_{5'}OH$), 5.53 (m, 1 H, $C_{2'}OH$), 5.98 (d, 1 H, J = 2.9 Hz, $C_{1'}H$), 6.54 (dd, 1 H, J = 7.3 Hz, C_5H), 6.85 (d, 1 H, J = 1.8 Hz, C_3H), 8.31 (d, 1 H, J = 7.3 Hz, C_6H) and 9.28 [br s, 4 H, (NH)NH_2·HCl].

Anal. Calcd. for $C_{11}H_{15}N_3O_5$·HCl·½ H_2O (305.71): C, 41.98; H, 5.44; N, 13.35. Found: C, 41.75; H, 5.63; N, 13.07.

4-Aminomethyl-1-β-D-ribofuranosyl-1,2-dihydro-2-oxopyridine Hydrochloride (**19**).

A solution of **13** (0.38 g, 1 mmole) in 0.02 *N* methanolic hydrogen chloride (100 ml) was hydrogenated over Pd/C catalyst (10%, 0.30 g) in a Parr hydrogenator at 45 psi for 1 hour. The bottle was opened, 1 *N* ethanolic hydrogen chloride (0.5 ml) was added to the contents and filtered through a Celite pad under argon atmosphere. The filtrate was evaporated to dryness and the residue was stirred with 0.01 *N* ethanolic hydrogen chloride (50 ml) overnight. The solid that separated was collected by filtration, dried and crystallized from absolute ethanol to give 0.15 g (50%) of **19**, mp 204-205° dec; ir: ν max 1655 (C=O), 2930-3420 (NH_2, OH) cm^{-1}; uv: (*p*H 1): λ max 303 nm (ε 6,500); (*p*H 7): 301 nm (ε 6,200); (*p*H 11): 296 nm (ε 6,000); ^1H nmr (DMSO-d_6): δ 3.65 (m, 2 H, $C_{5'}CH_2$), 3.90 (s, 2 H, CH_2NH_2), 3.92-3.98 (m, 3 H, $C_{2',3',4'}H$), 5.11 (d, 1 H, $C_{3'}OH$), 5.19 (t, 1 H, $C_{5'}OH$), 5.44 (d, 1 H, $C_{2'}OH$), 5.98 (d, 1 H, J = 3.5 Hz, $C_{1'}H$), 6.37 (dd, 1 H, J = 7.3 Hz, C_5H), 6.45 (s, 1 H, C_3H), 8.04 (d, 1 H, J = 7.3 Hz, C_6H) and 8.47 (br s, 3 H, CH_2NH_2·HCl).

Anal. Calcd. for $C_{11}H_{16}N_2O_5$·HCl (292.7): C, 45.13; H, 5.85; N, 9.57; Cl, 12.10. Found: C, 44.93; H, 5.84; N, 9.38; Cl, 12.28.

X-Ray Crystallography.

Colorless, square-pyramidal crystals suitable for X-ray diffraction studies were obtained from an ethanol solution to which a few drops of water had been added. The specimen used for these studies measured 0.35 × 0.31 × 0.21 mm in size. They possess symmetry pertaining to the monoclinic space group $P2_1$ with cell

parameters a = 7.5810(10), b = 17.981(3), c = 8.6018(10) Å, β = 91.686(10)° and V = 1172.1(3) Å^3. There are two molecules per asymmetric unit (Z = 4) resulting in a calculated density φ_{calc} = 1.535 g-cm^{-3}. Data were collected at room temperature on an Enraf-Nonius CAD4 diffractometer by a variable speed ω-2θ scan procedure with scan range in ω of 0.80 + 0.15 tan θ. A total of 5246 reflections were measured. These data were corrected for Lorentz and polarization effects, decay based on three check reflections (exposure time: 45.8 hours, correction factor: 1.000-1.001) and absorption (CuKα radiation; λ = 1.54178 Å, μ = 10.351 cm^{-1}; transmission factor: 0.743-0.854) and reduced to F's with the programs of the *SDP Plus* [56] after which they were merged to give 4816 unique reflections (R_{int} = 0.015). All thirty-eight non-hydrogen positions were obtained with *SHELXS86* [57]. All hydrogen atoms were located in two ΔF maps (peaks: 0.24-0.92 e/Å^3) at R = 0.059. The structure was refined in two blocks, one molecule per block, by the full-matrix least-squares procedure (*SHELX76*) [58]. The function minimized was $\Sigma w(|F_o|-|F_c|)^2$ where $w = (\sigma_F^2 + 0.0004F^2)^{-1}$. An extinction parameter refined to a value of 1.68(14) × 10^{-6}. Residual electron density in the final difference map was in the range $-0.33 \leq \Delta\rho \leq 0.34$ e/Å^3. The final R was 0.0379 (wR = 0.0611) and S was 2.13 for 4503 reflections having $F \geq 4\sigma_F$. Atomic scattering factors and anomalous-dispersion corrections for non-hydrogen atoms were taken from the "International Tables for X-ray Crystallography" [59]. For hydrogen, these parameters were taken from Stewart, Davidson and Simpson [60]. Figures were drawn with *ORTEPII* [61]; least-squares planes program was obtained from Cordes [62].

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