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The syntheses of 3-amino-4-methyl-1-(β -D-ribofuranosyl)-1,2,4-triazolin-5-one (**8a**) and its 2'-deoxy analog **8b** as well as 5-amino-2-methyl-1-(β -D-ribofuranosyl)-1,2,4-triazolin-3-one (**12**) have been accomplished. Compounds **8a** and **8b** were synthesized *via* glycosylation of 3-bromo-5-nitro-1,2,4-triazole which was followed by replacement in three steps of the 3-bromo function to yield 3-nitro-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazolin-5-one (**4a**) and its 2'-deoxy analog **4b**. Compounds **4a** and **4b** were methylated at N^2 , hydrogenated and deblocked to give 3-amino-4-methyl-1-(β -D-ribofuranosyl)-1,2,4-triazolin-5-one (**8a**) and the 2'-deoxy analog **8b**. Compound **12** was synthesized by glycosylation of 3-amino-1-methyl-1,2,4-triazolin-5(2*H*)-one (**10**). The structures of **8b** and **12** were confirmed by single crystal X-ray diffraction analysis.

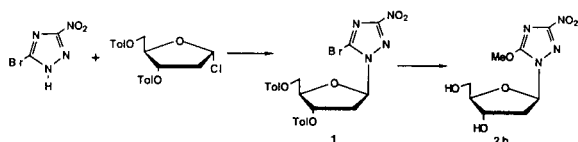
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1,2,4-Triazoles have been utilized for the synthesis of a wide variety of nucleoside derivatives which possess unusual biological activity [1-3]. Ribavirin, a broad spectrum antiviral drug, is now being used clinically worldwide. A number of multisubstituted 1,2,4-triazole analogs have been synthesized and have shown promising antidepressant activities [4]. The primary goal of the present work was the synthesis of a number of multisubstituted triazole nucleosides for evaluation as potential medicinal agents.

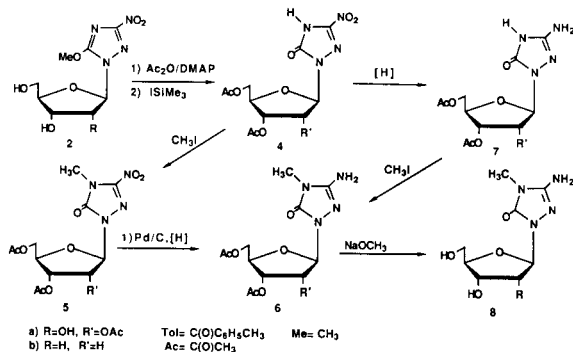
Results and Discussion.

We were especially interested in preparing new *N*-methyl derivatives of the cytosine analogue nucleosides. 3-Bromo-5-nitro-1,2,4-triazole was glycosylated and the bromo group was substituted with methoxide to produce 1-(2-deoxy- β -D-ribofuranosyl)-5-methoxy-3-nitro-1,2,4-triazole (**2b**) which is similar to the ribose analog **2a** previously reported by Witkowski and Robins [5] (Scheme I).

Scheme I



Scheme II



Compound **2a** was acetylated to **3a** which was used in a transalkylation reaction with iodotrimethylsilane [6] followed by hydrolysis of the trimethylsilyl group to give 3-nitro-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazolin-5-one (**4a**) (Scheme II).

Methylation of **4a** with methyl iodide [5] gave exclusively 4-methyl-3-nitro-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazolin-5-one (**5a**) which was catalytically reduced to 3-amino-4-methyl-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazolin-5-one (**6a**). Reduction of **4a** to 3-amino-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazolin-5-one (**7a**) followed by methylation provided another route. Nucleoside **6a** was then deblocked to 3-amino-4-methyl-1-(β -D-ribofuranosyl)-1,2,4-triazolin-5-one (**8a**). 3-Amino-1-(2-deoxy- β -D-ribofuranosyl)-4-methyl-1,2,4-triazolin-5-one (**8b**) was synthesized from 1-(2-deoxy- β -D-ribofuranosyl)-5-methoxy-3-nitro-1,2,4-triazole (**2b**) by a similar procedure. Nucleoside **8b** was recrystallized from methanol and the structure was established by single crystal X-ray diffraction analysis.

In another experiment, dimethyl cyanodithioimidocarbonate was condensed with methyl hydrazine according to the procedure of Heitke and McCarty [7]. Despite these authors' claim that the only isolated product was 5-amino-1-methyl-3-methylthio-1,2,4-triazole (**9a**), the only product

Scheme III

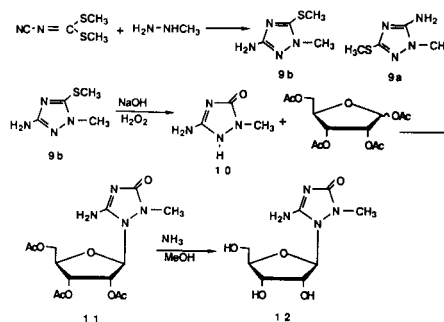


Table 1
Positional and Isotropic Thermal Parameters for Atoms in 8b and 12

Atom	x/a	y/b	z/c	U_{eq} [a]	Atom	x/a	y/b	z/c	U_{eq} [a]
8b-A									
N1A	.4437(3)	.39273(10)	.25655(9)	.0416(5)	N2A	.3827(3)	.31486(11)	.23164(9)	.0419(5)
C3A	.3784(3)	.26950(13)	.29153(11)	.0420(6)	N4A	.4340(3)	.31360(11)	.35280(9)	.0445(5)
C5A	.4726(3)	.39357(13)	.33087(11)	.0433(6)	N6A	.3288(4)	.18891(13)	.29467(13)	.0604(7)
C7A	.4437(5)	.2847(2)	.42936(12)	.0605(9)	O8A	.5236(3)	.45160(10)	.37037(9)	.0570(6)
C1'A	.4892(3)	.45878(12)	.20664(10)	.0391(6)	C2'A	.5604(3)	.42880(12)	.13228(11)	.0389(6)
C3'A	.5134(3)	.50130(11)	.08157(10)	.0333(5)	C4'A	.3384(3)	.53485(12)	.11484(10)	.0335(5)
C5'A	.1644(3)	.50814(14)	.07637(12)	.0432(6)	O3'A	.6452(2)	.56630(9)	.08440(8)	.0399(4)
O4'A	.3311(2)	.50723(10)	.19033(7)	.0484(5)	O5'A	.0086(2)	.54348(10)	.11157(9)	.0445(5)
H6A1	.339(4)	.162(2)	.3359(14)	.053(7)	H6A2	.263(4)	.165(2)	.2549(14)	.064(8)
H7A1	.339(2)	.2468(12)	.4381(7)	.13(2)	H7A2	.436(3)	.3341(5)	.4621(5)	.067(8)
H7A3	.562(2)	.2552(13)	.4358(7)	.096(12)	H1'A	.582(3)	.4927(14)	.2421(12)	.041(6)
H2'A1	.487(3)	.3790(13)	.1163(11)	.032(5)	H2'A2	.690(4)	.418(2)	.1297(15)	.063(8)
H3'A	.508(3)	.4836(13)	.0320(11)	.033(5)	H4'A	.346(3)	.5985(12)	.1161(10)	.024(5)
H5'A1	.185(4)	.526(2)	.0217(13)	.047(6)	H5'A2	.135(3)	.448(2)	.0835(13)	.048(6)
HO3'A	.753(4)	.552(2)	.081(2)	.063(9)	HO5'A	.037(5)	.592(2)	.107(2)	.072(10)
8b-B									
N1B	.6209(3)	.74348(9)	.76132(8)	.0384(5)	N2B	.5983(3)	.66688(9)	.72474(8)	.0384(5)
C3B	.5652(3)	.61528(11)	.77802(10)	.0338(5)	N4B	.5635(3)	.65387(9)	.84604(8)	.0373(5)
C5B	.5958(3)	.73677(11)	.83518(10)	.0386(6)	N6B	.5451(3)	.53210(10)	.77087(9)	.0429(5)
C7B	.5488(4)	.61549(13)	.91868(10)	.0519(8)	O8B	.6002(3)	.79115(9)	.88361(8)	.0521(5)
C1'B	.6366(3)	.81929(11)	.71966(10)	.0380(6)	C2'B	.7773(4)	.81616(14)	.65807(13)	.0476(7)
C3'B	.6870(3)	.86429(12)	.59605(10)	.0428(6)	C4'B	.4844(3)	.84351(13)	.60636(11)	.0432(6)
C5'B	.4286(5)	.7632(2)	.56981(13)	.0609(9)	O3'B	.7022(3)	.95191(9)	.60674(9)	.0483(5)
O4'B	.4638(2)	.83751(8)	.68571(7)	.0403(4)	O5'B	.2425(3)	.7443(2)	.58443(10)	.0808(8)
H6B1	.480(4)	.509(2)	.8107(15)	.056(7)	H6B2	.478(4)	.515(2)	.725(2)	.065(8)
H7B1	.4187(10)	.6010(14)	.9286(8)	.110(14)	H7B2	.593(3)	.6557(8)	.9568(5)	.14(2)
H7B3	.625(3)	.5643(9)	.9200(7)	.088(11)	H1'B	.657(3)	.8644(14)	.7534(10)	.033(5)
H2'B1	.804(4)	.765(2)	.645(2)	.075(9)	H2'B2	.900(4)	.844(2)	.6668(13)	.054(7)
H3'B	.726(4)	.848(2)	.5495(13)	.051(7)	H4'B	.404(3)	.8917(14)	.5903(12)	.040(6)
H5'B1	.438(5)	.768(2)	.5146(4)	.086(10)	H5'B2	.496(4)	.715(2)	.5902(15)	.049(7)
HO3'B	.811(5)	.964(2)	.608(2)	.084(12)	HO5'B	.231(5)	.729(2)	.6380(6)	.088(11)
OW	.3936(13)	.0896(5)	.0312(5)	.125(4)					
12									
N1	.6978(3)	.3617(2)	.36740(10)	.0281(4)	N2	.9017(2)	.4005(2)	.34720(11)	.0291(4)
C3	1.0207(3)	.2922(2)	.35256(11)	.0287(5)	N4	.9076(3)	.1944(2)	.38453(11)	.0315(5)
C5	.7170(3)	.2383(2)	.39388(12)	.0277(5)	C6	.9303(4)	.4913(2)	.2773(2)	.0388(6)
O7	1.2028(2)	.2869(2)	.32908(10)	.0385(4)	N8	.5616(3)	.1701(2)	.4257(2)	.0412(6)
C1'	.5525(3)	.4499(2)	.40495(12)	.0271(5)	C2'	.6365(3)	.5404(2)	.47368(11)	.0278(5)
C3'	.4576(3)	.6351(2)	.47671(12)	.0298(5)	C4'	.3934(3)	.6432(2)	.38205(13)	.0325(6)
C5'	.4627(4)	.7604(2)	.3347(2)	.0444(7)	O2'	.6878(2)	.48292(15)	.55162(8)	.0337(4)
O3'	.2915(3)	.5825(2)	.52491(10)	.0394(5)	O4'	.4778(2)	.53238(13)	.34037(8)	.0335(4)
O5'	.6810(3)	.7774(2)	.33896(11)	.0462(5)	H6A	.875(5)	.574(3)	.296(2)	.060(9)
H6B	.876(6)	.457(3)	.224(2)	.075(11)	H6C	1.081(6)	.504(3)	.268(2)	.051(8)
H8A	.442(5)	.191(3)	.413(2)	.042(7)	H8B	.592(6)	.090(3)	.439(2)	.068(10)
H1'	.440(4)	.392(2)	.431(2)	.035(6)	H2'	.753(4)	.579(2)	.450(2)	.030(6)
H3'	.504(4)	.719(3)	.498(2)	.041(7)	H4'	.252(4)	.637(2)	.3791(15)	.029(6)
H5'A	.423(6)	.746(3)	.275(2)	.074(11)	H5'B	.390(5)	.835(3)	.363(2)	.043(7)
HO2'	.576(6)	.438(3)	.569(2)	.068(10)	HO3'	.282(6)	.630(4)	.571(2)	.067(10)
HO5'	.716(6)	.789(3)	.284(2)	.068(10)					

[a] For non-hydrogen atoms (except OW in 8b), U is $U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* A_{ij}$, 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 **8b**

			8b-A		8b-B	
1	2	3	1-2	1-2-3	1-2	1-2-3
N2	N1	C5	1.406(2)	112.0(2)	1.410(2)	112.19(14)
C5	N1	C1'	1.361(3)	125.3(2)	1.353(2)	126.5(2)
C1'	N1	N2	1.435(3)	122.27(15)	1.440(2)	120.41(14)
C3	N2	N1	1.307(3)	103.9(2)	1.296(2)	103.55(14)
N4	C3	N6	1.378(3)	122.8(2)	1.378(2)	122.1(2)
N4	C3	N2		111.8(2)		112.1(2)
N6	C3	N2	1.349(3)	125.4(2)	1.354(2)	125.7(2)
C5	N4	C7	1.377(3)	124.1(2)	1.370(2)	123.8(2)
C5	N4	C3		108.2(2)		108.07(14)
C7	N4	C3	1.463(3)	127.7(2)	1.456(2)	127.9(2)
O8	C5	N1	1.234(3)	128.8(2)	1.239(2)	129.6(2)
O8	C5	N4		127.2(2)		126.3(2)
N1	C5	N4		104.1(2)		104.05(15)
C2'	C1'	O4'	1.521(3)	105.6(2)	1.518(3)	106.9(2)
C2'	C1'	N1		113.6(2)		114.2(2)
O4'	C1'	N1	1.427(3)	110.3(2)	1.437(3)	109.1(2)
C3'	C2'	C1'	1.525(3)	102.2(2)	1.515(3)	103.3(2)
C4'	C3'	O3'	1.515(3)	107.26(14)	1.533(4)	105.9(2)
C4'	C3'	C2'		103.0(2)		102.7(2)
O3'	C3'	C2'	1.425(2)	112.8(2)	1.429(2)	111.8(2)
C5'	C4'	O4'	1.514(3)	108.5(2)	1.509(3)	110.4(2)
C5'	C4'	C3'		115.3(2)		113.3(2)
O4'	C4'	C3'	1.437(2)	107.4(2)	1.446(2)	103.7(2)
O5'	C5'	C4'	1.426(3)	110.8(2)	1.421(4)	111.2(2)
C1'	O4'	C4'		109.61(15)		110.2(2)

Table 3
Bond Lengths (Å) and Bond Angles (°) in **12**

1	2	3	1-2	1-2-3
N2	N1	C5	1.419(2)	104.9(2)
C5	N1	C1'	1.372(3)	123.1(2)
C1'	N1	N2	1.447(2)	120.7(2)
C3	N2	C6	1.381(3)	121.0(2)
C3	N2	N1		105.52(15)
C6	N2	N1	1.464(3)	118.2(2)
N4	C3	O7	1.361(3)	126.0(2)
N4	C3	N2		110.5(2)
O7	C3	N2	1.237(2)	123.5(2)
C5	N4	C3	1.327(3)	106.0(2)
N8	C5	N1	1.333(3)	123.8(2)
N8	C5	N4		123.7(2)
N1	C5	N4		112.5(2)
C2'	C1'	O4'	1.537(3)	103.70(14)
C2'	C1'	N1		116.9(2)
O4'	C1'	N1	1.418(2)	109.14(15)
C3'	C2'	O2'	1.531(3)	115.8(2)
C3'	C2'	C1'		99.15(15)
O2'	C2'	C1'	1.400(2)	115.0(2)
C4'	C3'	O3'	1.539(3)	109.0(2)
C4'	C3'	C2'		102.2(2)
O3'	C3'	C2'	1.427(3)	109.5(2)
C5'	C4'	O4'	1.510(3)	109.2(2)
C5'	C4'	C3'		115.9(2)
O4'	C4'	C3'	1.446(3)	106.6(2)
O5'	C5'	C4'	1.427(4)	112.0(2)
C1'	O4'	C4'		107.76(14)

isolated from this reaction was 3-amino-1-methyl-5-methylthio-1,2,4-triazole (**9b**) as determined by single-crystal X-ray diffraction analysis of both **9b** and the final product

12 (Scheme III). This reaction was carried out in various solvents, both polar and nonpolar, and under various conditions, producing the identical product in every case. Compound **9b** was then treated with sodium hydroxide and hydrogen peroxide [8] to give 3-amino-1-methyl-1,2,4-triazolin-5-one (**10**). Glycosylation of **10** with 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose gave 5-amino-2-methyl-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazolin-3-one (**11**), which was deblocked with methanolic ammonia to give 5-amino-2-methyl-1-(β -D-ribofuranosyl)-1,2,4-triazolin-3-one (**12**). None of the nucleosides described here exhibited any significant *in vitro* antiviral or antitumor activity.

Single-crystal X-ray Diffraction Analysis of 3-Amino-1-(2-deoxy- β -D-ribofuranosyl)-4-methyl-1,2,4-triazolin-5-one (**8b**) and 5-Amino-2-methyl-1-(β -D-ribofuranosyl)-1,2,4-triazolin-3-one (**12**).

Crystallographic coordinates for nucleosides **8b** and **12** are listed in Table 1. Tables 2 and 3 contain bond lengths and bond angles for **8b** and **12**, respectively.

Nucleoside **8b**.

Compound **8b** exists in the crystal structure in two crystallographically independent conformations (referred to as A and B) which are illustrated in Figure 1. The compound was confirmed to have the β configuration. The bond lengths and most bond angles in the heterocycles of the two conformers of **8b** are identical within experimental error. The triazole rings are planar within 0.02 Å and the oxo groups are within 0.04 Å of their respective planes; however, in A the amino and methyl groups are in the plane of the triazole, whereas, in B they are -0.073 Å and -0.145 Å out of the plane, respectively. Furthermore, the sugar C1' atom is 0.178 and 0.165 Å out of the triazole plane in A and B, respectively. The torsion angle about the glycosidic bond, defined as $\chi_{CN} = O4'-C1'-N1-C5$, is -99.4(2)° for both conformers. The glycosidic bond lengths are 1.435(3) and 1.440(2) Å for A and B, respectively. The C5'-O5' side chains are likewise similarly oriented [*gauche-trans*; $\phi_{oo} = 60.0(2)^\circ$ and $60.8(3)^\circ$; $\phi_{eo} = -179.6(2)^\circ$ and $176.7(2)^\circ$] with respect to the furanose ring. Despite all the similarities in the two conformations, the sugar puckering is different; hence, conformer A has the C₂'-endo conformation with pseudorotation angle P = 161.3° and amplitude of pucker $\tau_m = 34.4^\circ$ whereas conformer B has the C₃'-exo conformation, P = 200.9° and $\tau_m = 36.1^\circ$ [9]. The bond lengths and bond angles of the sugar moieties are normal.

Figure 2 illustrates how four hydrogen bonds involving three protons bind the two independent molecules into a dimeric unit. All hydroxyl and amino hydrogens are involved in hydrogen bonding. Table 4 gives details of the hydrogen bonding geometries. Figure 3 illustrates the crystal packing. The dimers are hydrogen bonded in a net-

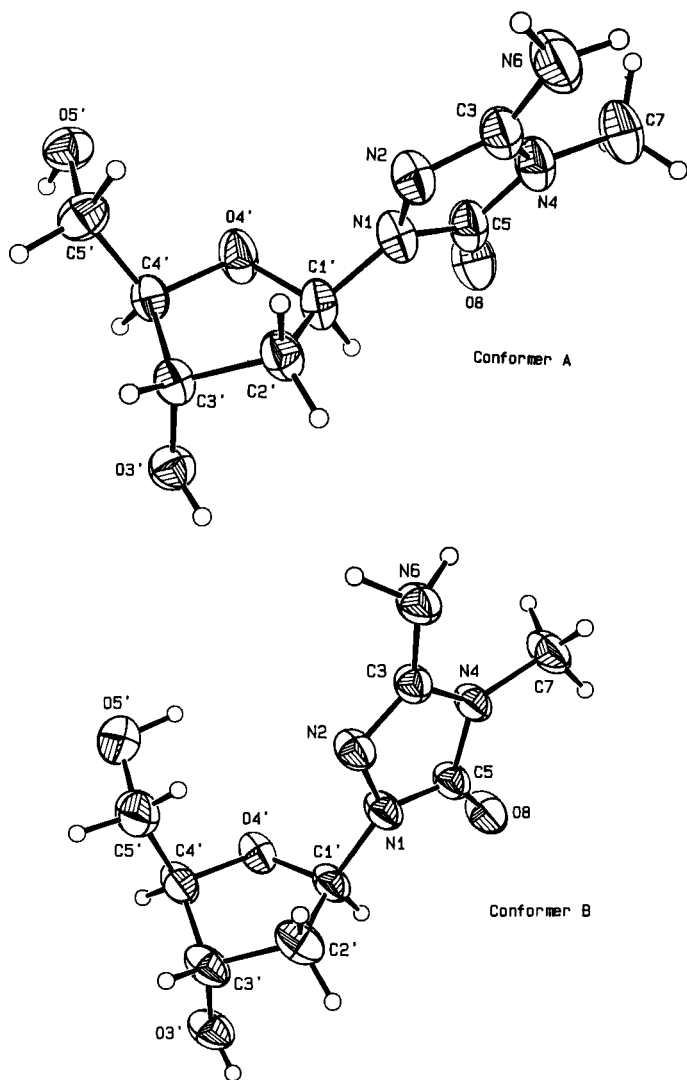


Figure 1. Perspective drawings of the two conformers of **8b** illustrating conformational differences and atom labeling. Thermal ellipsoids are drawn at the 50% probability level.

work parallel to the *ab* plane; no hydrogen bonding between network layers is observed (Figure 3a). The triazoline bases are approximately parallel to the *bc* plane and exhibit considerable overlap; the interplanar spacing within the dimeric units is ~ 4.0 Å, but between dimeric units translated along the *a* direction the interplanar spacing is ~ 3.2 Å (Figure 3b). In the crystal lattice of **8b** there is water of hydration, the occupancy of which refined to 40%. Interatomic distances and the lack of available protons in **8b** indicate that the nucleoside molecules do not donate protons to the water; however, it appears that the water molecule acts as a donor to O5'B and O8A. The O5'B \cdots OW \cdots O8A angle is 123.4° .

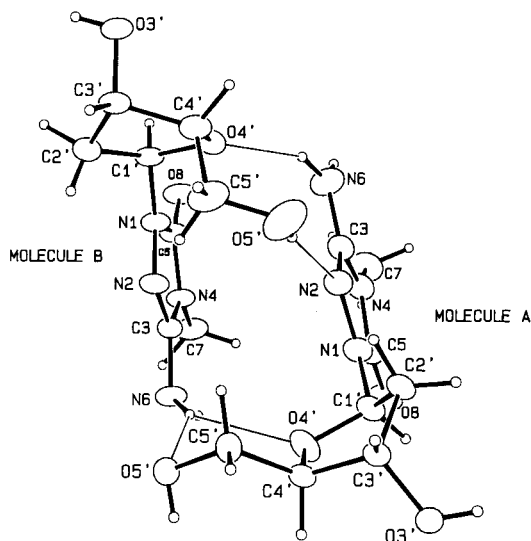


Figure 2. Perspective drawing of the dimeric interactions in **8b**. Conformer A hydrogen bonds to B via N6A-H6A2 \cdots O4'B. Conformer B hydrogen bonds to A through O5'B-HO5'B \cdots N2 and the bifurcated bond N6B-H6B2 \cdots O4'A and N6B-H6B2 \cdots O5'A. Participation of the furanose ring oxygen O4' is unusual, but is observed twice in this structure.

Nucleoside 12.

The conformation of compound **12** is depicted in Figure 4 which confirms the β -anomeric configuration at C1' and the structure of the triazole **9b**. The triazole ring is less planar than observed for **8b**; N2 deviates from the plane by 0.043 Å. The substituents deviate significantly from the plane as well; thus, N8 is 0.089 , O7 is -0.155 , C6 is -0.686 and C1' is 0.576 Å out of the plane. Nitrogens N1 and N2, therefore, appear to have considerable sp^3 character. Also, the fact that C6 and C1' are on opposite sides of the triazole plane suggests that some steric hindrance is present. The glycosidic linkage is characterized by $\chi_{CN} = -145.1(2)^\circ$ and a bond length of $1.447(2)$ Å. The glycon moiety has normal bond lengths and angles. The C5'-O5' side chain is *gauche-gauche* [$\phi_{\infty} = -64.6(2)^\circ$ and $\phi_{co} = 55.8(3)^\circ$]. The conformation is C_2 -endo/ C_1 -exo with $P = 147.8^\circ$ and $\tau_m = 44.2^\circ$ [9].

Crystal packing for **12** is illustrated in Figure 5. Geometries of hydrogen bonds are given in Table 4. As in **8b**, all hydroxyl and amino protons are involved in hydrogen bonding. H1' also is within van der Waals contact of O7 [$2.48(3)$ Å] of an adjacent molecule translated along the *a* direction. The O5'-HO5' hydrogen bond approaches O7 nearly perpendicular to the C3-O7 double bond. Molecules are bound in sheets parallel to the *bc*-plane. The N8 \cdots O7 hydrogen bonds between molecules translated along *a* binds the sheets together. There is no base stacking in the lattice.

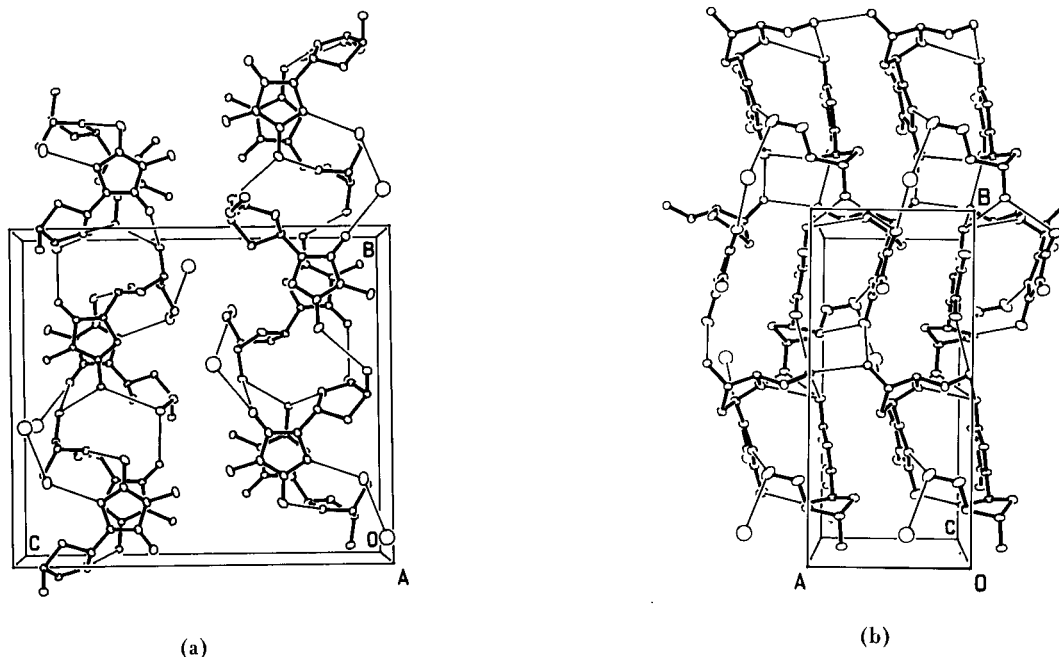


Figure 3. Crystal packing diagram of **8b**. (a) View along the *a*-axis showing the nearly complete overlap of triazole rings. Some molecular pairs that are shown are dimeric units as shown in Figure 2 while others are not. The degree of base overlapping is not much different in the two pairings. It can be seen that layers of molecules parallel to the *ab* plane do not interact through hydrogen bonding. (b) View along the *c*-axis showing one hydrogen-bonded layer parallel to the *ab* plane.

Table 4
Hydrogen Bonding and Close Intermolecular Contacts in **8b** and **12**

D	H	A	Symmetry of A relative to D	d(D···A) (Å)	d(H···A) (Å)	∠(D-H···A) (°)
8b						
N6A	H6A1	O3'A	1.0-x,y-0.5,0.5-z	2.954(3)	2.11(3)	164.(2)
N6A	H6A2	O4'B	0.5-x,1.0-y,z-0.5	2.943(3)	2.08(3)	151.(3)
O3'A	HO3'A	O5'A	1.0+x,y,z	2.732(2)	1.96(3)	156.(3)
O5'A	HO5'A	O8B	x-0.5,1.5-y,1.0-z	2.749(2)	1.94(3)	169.(3)
N6B	H6B1	O3'B	1.0-x,y-0.5,1.5-z	3.139(2)	2.20(3)	173.(2)
N6B	H6B2	O4'A	0.5-x,1.0-y,0.5+z	3.181(3)	2.38(3)	136.(2)
N6B	H6B2	O5'A	0.5-x,1.0-y,0.5+z	3.153(2)	2.25(3)	148.(2)
O3'B	HO3'B	O8A	0.5+x,1.5-y,1.0-z	2.852(3)	2.11(4)	151.(4)
O5'B	HO5'B	N2A	0.5-x,1.0-y,0.5+z	2.974(2)	2.019(13)	158.(2)
OW		O5'B	0.5-x,1.0-y,z-0.5	3.015(9)		
OW		O8A	1.0-x,y-0.5,0.5-z	2.912(9)		
O5'B	OW	O8A				123.4(3)
12						
N8	H8A	O7	x-1,y,z	3.034(3)	2.27(3)	154.(3)
N8	H8A	O2'	x-0.5,0.5-y,1-z	2.933(3)	2.53(3)	111.(2)
N8	H8B	O3'	0.5+x,0.5-y,1-z	3.149(3)	2.31(4)	158.(3)
C1'	H1'	O7	x-1,y,z	3.082(2)	2.48(3)	117.(2)
O2'	HO2'	N4	x-0.5,0.5-y,1-z	2.791(2)	1.92(4)	162.(3)
O2'	HO2'	O3'	x,y,z	2.806(2)	2.49(4)	101.(3)
O3'	HO3'	O5'	x-0.5,1.5-y,1-z	2.688(2)	1.84(4)	163.(4)
O5'	HO5'	O7	2-x,0.5+y,0.5-z	2.734(2)	1.84(4)	171.(3)

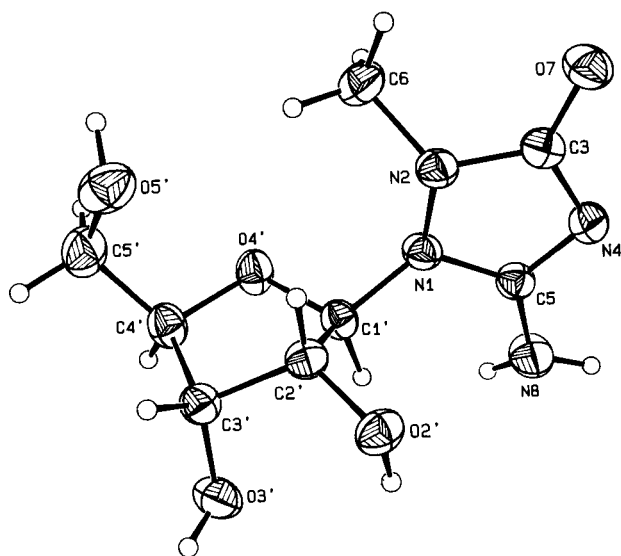


Figure 4. Perspective drawing of **12** illustrating molecular conformation and atom labeling. Thermal ellipsoids are drawn at the 50% probability level.

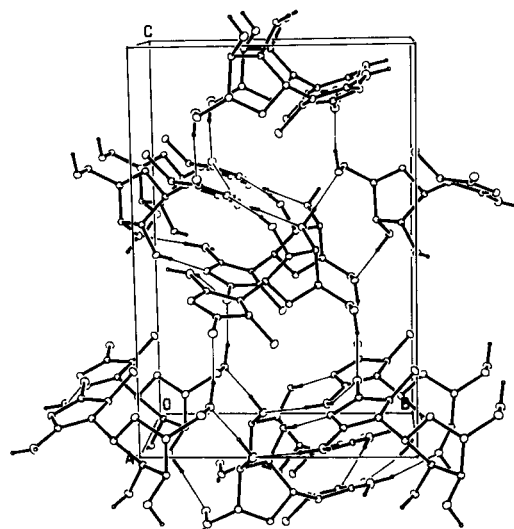


Figure 5. Unit-cell packing diagram of **12** viewed approximately along the *a*-axis.

Table 5
Crystal and Experimental Data [a] for Compounds **8b** and **12**

	8b	12
Empirical formula	C ₈ H ₁₄ N ₄ O ₄ ·0.2H ₂ O	C ₈ H ₁₄ N ₄ O ₅
Formula weight	233.83	246.22
Crystal system	orthorhombic	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁	P2 ₁ 2 ₁ 2 ₁
<i>a</i> (Å)	7.3241(9)	6.479(2)
<i>b</i> (Å)	16.110(3)	10.550(3)
<i>c</i> (Å)	18.088(4)	15.626(4)
<i>V</i> (Å ³)	2134.2(6)	1068.1(5)
<i>Z</i>	8	4
ρ_{calcd} (g cm ⁻³)	1.455	1.531
<i>F</i> (000) (electrons)	1024	520
Radiation, λ (Å)	CuK α , 1.54178	CuK α , 1.54178
Crystal dimensions (mm)	0.36 x 0.19 x 0.145	0.42 x 0.155 x 0.105
Crystal volume (mm ³)	0.00797	0.00600
μ (cm ⁻¹)	9.443	10.532
Max 2 θ (°)	152	152
Total refls, measd, unique	4951, 4407	4803, 2217
<i>R</i> _{int}	0.0213	0.0215
Decay correction range	1.000-1.004	1.000-1.005
Transmission factor range	0.754-0.892	0.734-0.904
Observed refls ($F \geq 4\sigma_F$)	3764	2060
No. of variables	409	211
<i>S</i> (goodness of fit)	1.580	1.995
<i>R</i> , <i>wR</i> [b]	0.0361, 0.0507	0.0313, 0.0536
Extinction parameter	5.5(6) x 10 ⁻⁷	2.8(3) x 10 ⁻⁶
Max Δ/σ	0.005	0.0015
Max, min in $\Delta\rho$ map (e/Å ³)	0.31, -0.25	0.32, -0.29

[a] Unit-cell parameters were obtained by least-squares refinement of the setting angles of 25 reflections in the ranges: 56.6<2 θ <59.9° for **8b**; 51.1<2 θ <58.0° for **12**. [b] Function minimized was $\Sigma w(|F_o| - |F_c|)^2$, where $w = (\sigma_F^2 + 0.0004F^2)^{-1}$ for both structures. *R* and *wR* have conventional definitions. $\sigma_F = F\sigma_I/2I$ and $\sigma_I = (N_{pk} + N_{bg1} + N_{bg2})^{1/2}$

EXPERIMENTAL

General Information.

Ultraviolet spectra were recorded on a Beckman DU-50 spectrophotometer. The nmr spectra were recorded on an IBM NR/300 nmr spectrometer. The chemical shift values are expressed in δ values (parts per million) and referenced with tetramethylsilane (for ^1H nmr) or dioxane (for ^{13}C nmr). Data for non-anomeric protons of the glycons have been omitted. Melting points were taken on a Haake Buchler melting point apparatus and are uncorrected. EM silica gel (230-400 mesh) was used for flash column chromatography. Tlc were run on silica gel 60 F-254 plates (EM Reagents). The components were detected by uv light, and with 10% sulfuric acid in methanol spray followed by heating. The tlc systems were methylene chloride/acetone (3:2) or methanol/chloroform (1:9). Hplc was run on a Rainin Rabbit-HP analytical instrument equipped with a reverse phase (C-18) column and a Waters Diode Array model 990 detector. Ir spectra were recorded on a Perkin-Elmer model 1420 ratio recording instrument.

X-ray Diffraction Analysis.

Pale yellow, transparent crystalline plates of **8b** were obtained from methanol solution. Crystals of **12** were obtained from methanol/ethyl acetate solution as long needles. An Enraf-Nonius CAD4 diffractometer equipped with a graphite monochromator and $\text{CuK}\alpha$ radiation was employed for all measurements. Using the SDP-Plus program package [11], reflection intensities were corrected for Lorentz and polarization factors, absorption and decay, and subsequently reduced to structure factors. Both compounds crystallized in the orthorhombic space group $\text{P}2_12_12_1$. Crystal and experimental data are given in Table 5. There are two crystallographically independent molecules ($Z = 8$) and partial occupancy (40%) of a water of hydration in **8b**; there is one molecule per asymmetric unit in **12** ($Z = 4$). The program SHELXS86 [12] afforded positional parameters for all non-hydrogen atoms in each structure except the water molecule. All non-hydrogen atoms in both structures were treated anisotropically except OW in **8b**. All hydrogen atoms of the nucleosides were located in difference maps; however, in **8b** the methyl hydrogens were idealized and $\text{HO}5'\text{B}$ and $\text{H}5'\text{B1}$ were constrained to have bond lengths of 1.00 Å. The hydrogens of the water molecule were never located. All other hydrogens in both structures were fully refined. Refinement of all parameters, subject to the constraints above, was accomplished for each structure with SHELX76 [13]. Atomic scattering factors and anomalous-dispersion corrections for non-hydrogen atoms were taken from "International Tables for X-ray Crystallography" [14]. Scattering factors for hydrogen atoms were taken from Stewart, Davidson and Simpson [15]. All figures were produced with ORTEPII [16]. Tables were produced with FUER [17]. Least-squares planes were calculated with the program PLANES [18].

Methods.

5-Bromo-3-nitro-1-(2-deoxy-3,5-di-*O*-toluoyl- β -D-ribofuranosyl)-1,2,4-triazole (**1**).

3-Bromo-5-nitro-1,2,4-triazole [5] (8 g, 41.4 mmoles) was dissolved in dry acetonitrile (600 ml). Sodium hydride (60% in oil, 2 g, 50 mmoles) was added and the mixture was stirred for 30 minutes at room temperature before 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl- α -D-erythropentofuranose [11] (16.2 g, 41.7 mmoles) was added in one lot. The mixture was stirred overnight. The reaction

mixture was evaporated to dryness, adsorbed onto silica gel and placed on top of a flash silica gel column. The column was eluted with methylene chloride. The appropriate fractions were evaporated to provide 13.8 g (63%) of **1**, mp 68-70°; ^1H nmr (deuteriochloroform): δ 2.44 and 2.46 (2s, 6, toluoyl methyls), 6.4 (t, 1, H-1'), 7.26-7.99 (m, 8, toluoyl aromatic protons); uv (methanol): λ max 240 nm (ϵ 39,600).

Anal. Calcd. for $\text{C}_{23}\text{H}_{21}\text{BrN}_4\text{O}_7$: C, 50.66; H, 3.88; N, 10.27. Found: C, 50.92; H, 3.71; N, 9.99.

1-(2-Deoxy- β -D-ribofuranosyl)-5-methoxy-3-nitro-1,2,4-triazole (**2b**).

Compound **1** (13.7 g, 25 mmoles) was added to a solution of sodium (8 g, 34.7 mmoles) dissolved in methanol (75 ml) and the resulting solution was stirred at room temperature for 3 hours. After neutralization with Dowex-50 (H^+), the solution was filtered, and the filtrate was evaporated to dryness, adsorbed onto silica gel and placed on the top of a flash silica gel column. The column was eluted first with methylene chloride, then with methylene chloride/methanol (9:1, v/v). Appropriate fractions were combined and evaporated to give 4.3 g of **2b** (69%), mp 112-114°; ^1H nmr (deuteriochloroform): δ 4.27 (s, 3, OCH_3), 6.2 (t, 1, H-1').

Anal. Calcd. for $\text{C}_8\text{H}_{12}\text{N}_4\text{O}_6$: C, 36.93; H, 4.65; N, 21.53. Found: C, 36.92; H, 4.68; N, 21.53.

5-Methoxy-3-nitro-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole (**3a**).

A mixture of **2a** [5] (4 g, 14.5 mmoles), acetic anhydride (140 ml), and dimethylaminopyridine (0.3 g) was stirred for 15 hours at room temperature. Acetic anhydride was evaporated and the residue was dissolved in ethyl acetate (300 ml). The organic layer was washed with 5% aqueous sodium bicarbonate (2 x 50 ml), followed by water (2 x 50 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent, and purification of the residue on a silica gel column using methylene chloride/methanol (97:3, v/v) as eluent gave 4.9 g (83%) of **3a** as white crystals, mp 113-114°; ^1H nmr (deuteriochloroform): δ 2.06 (s, 9, $\text{C}(\text{O})\text{CH}_3$), 4.17 (s, 3, OCH_3), 5.80 (d, 1, J = 3.9 Hz, H-1'); uv λ max (pH 1): 280 nm (ϵ 6,400), 217 (9,300); (pH 7): 278 nm (6,700), 218 (9,400); (pH 11): 280 nm (ϵ 7,000) and 234 (4,700).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_{10}$: C, 41.80; H, 4.51; N, 13.93. Found: C, 41.98; H, 4.51; N, 13.87.

1-(2-Deoxy-3,5-di-*O*-acetyl- β -D-ribofuranosyl)-5-methoxy-3-nitro-1,2,4-triazole (**3b**).

Compound **2b** (4.3 g, 16.5 mmoles) was acetylated according to the procedure described for **3a**. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (2:1) as the eluent gave, after evaporation of appropriate fractions, 5.2 g of **3b** (93%) as colorless syrup; ^1H nmr (deuteriochloroform): δ 2.05 (m, 6, $\text{C}(\text{O})\text{CH}_3$), 4.17 (s, 3, OCH_3).

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_8$: C, 41.86; H, 4.68; N, 16.27. Found: C, 41.92; H, 4.77; N, 16.22.

3-Nitro-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazolin-5-one (**4a**).

In order to cleave the methoxy bond of **3a**, to a solution of the blocked nucleoside (4.5 g, 11 mmoles) and sodium iodide (4.5 g, 30 mmoles) in dry acetonitrile (50 ml) was added chlorotrimethylsilane (4.5 ml) slowly with continuous stirring. The reaction mixture was stirred at room temperature until the reaction was complete as monitored by tlc on silica gel with methanol/methylene

chloride (2:8) as eluent. The reaction was quenched with water and partitioned into methylene chloride. The organic layer was washed with sodium thiosulfate (to remove iodine) and brine, and dried over sodium sulfate. Evaporation of the methylene chloride layer gave pure enolic product: yield 4.2 g (92%), mp 160-162°; ¹H nmr (deuteriochloroform): δ 2.11 (m, 9, C(O)CH₃); uv (pH 1): λ max 309 nm (ε 3,400), 203 (3,900); (pH 7): 344 nm (2,100), 206 (8,200); (pH 11): 342 nm (2,300) and 202 (17,000).

Anal. Calcd. for C₁₃H₁₆N₄O₁₀·H₂O: C, 38.43; H, 4.47; N, 13.79. Found: C, 38.07; H, 4.29; N, 13.49.

1-(2-Deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)-3-nitro-1,2,4-triazolin-5-one (**4b**).

Compound **3b** (5.6 g, 16.2 mmoles) was converted to **4b** by a procedure similar to the one described above for **4a**. Evaporation of the solvent, and purification of the residue on a silica gel column using the same eluent gave 4.1 g (76%) of **4b** as yellow crystals, mp 183°; uv (pH 1): λ max 310 nm (ε 5,100), 205 (5,600); (pH 7): 342 nm (3,000), 203 (11,400); (pH 11): 341 nm (3,100) and 207 (10,500).

Anal. Calcd. for C₁₁H₁₄N₄O₈·1.5 H₂O: C, 36.98; H, 4.80; N, 15.68. Found: C, 36.82; H, 4.79; N, 15.96.

4-Methyl-3-nitro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazolin-5-one (**5a**).

Methyl iodide (1.64 g, 10 mmoles) and potassium carbonate (1.5 g, 11 mmoles) were added to a solution of **4a** (4 g, 9.8 mmoles) in dimethylformamide (100 ml). The mixture was stirred at room temperature for 10 hours. The solvent was evaporated and the residue was dissolved in methylene chloride, washed with water and dried over sodium sulfate. The crude product was purified on a silica gel column using methylene chloride/methanol (95:5, v/v) as eluent to give 3.8 g (95%) of **5a** as yellow crystals after filtering appropriate fractions, mp 74-76°; ¹H nmr (deuteriochloroform): δ 2.03, 2.05, 2.08 (3s, 9, C(O)CH₃), 3.56 (s, 3, NCH₃), 5.9 (d, 1, J = 4.68 Hz, H-1'); uv (pH 1): λ max 278 nm (ε 3,900), 219 (5,700); (pH 7): 277 nm (4,300), 219 (6,300); (pH 11): 278 nm (4,400) and 240 (2,600).

Anal. Calcd. for C₁₄H₁₈N₄O₁₀: C, 41.80; H, 4.50; N, 13.92. Found: C, 42.13; H, 4.49; N, 13.74.

1-(2-Deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)-4-methyl-3-nitro-1,2,4-triazolin-5-one (**5b**).

Compound **4b** (4 g, 12 mmoles) was methylated according to the procedure described for **5a** above. The crude product was purified on a silica gel column using methylene chloride/methanol (95:5, v/v) as eluent to give 3.4 g (83%) of **5b** as a syrup following evaporation of selected fractions; ¹H nmr (deuteriochloroform): δ 2.0 (s, 6, C(O)CH₃), 3.55 (s, 3, NCH₃), 6.18 (t, 1, H-1').

Anal. Calcd. for C₁₂H₁₆N₄O₈·0.4 H₂O: C, 41.01; H, 4.82; N, 15.94. Found: C, 41.28; H, 4.42; N, 15.52.

3-Amino-4-methyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazolin-5-one (**6a**).

A solution of **5a** (3.5 g, 8.7 mmoles) in ethanol and 10% palladium-on-carbon catalyst (0.8 g) was shaken on a Parr hydrogenation apparatus at 45 psi for 10 hours at room temperature. The catalyst was removed by filtration through celite, and the filtrate was evaporated to dryness to give pure **6a**, yield 2.78 g (85%), mp 63-65°; ¹H nmr (deuteriochloroform): δ 2.04, 2.05, 2.06 (3s, 9, C(O)CH₃), 3.12 (s, 3, NCH₃), 5.87 (d, 1, J = 3.39, H-1'); ir (potassium bromide): ν 1650, 1750 (C=O), 3320 br (NH₂) cm⁻¹.

Anal. Calcd. for C₁₄H₂₀N₄O₈: C, 45.16; H, 5.41; N, 15.05. Found: C, 44.89; H, 5.30; N, 14.79.

Methylation of **7a** by the above procedure gave **6a** in 76% yield. The products obtained from **5a** and **7a** were identical with respect to chromatographic and spectral properties.

3-Amino-1-(2-deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)-4-methyl-1,2,4-triazolin-5-one (**6b**).

A solution of **5b** (2.7 g, 7.8 mmoles) in ethanol was catalytically hydrogenated according to the procedure described for **6a** above. The catalyst was removed by filtration through celite, and the filtrate was evaporated to dryness. The product was purified on a silica gel column using methylene chloride/methanol (9:1, v/v) as eluent to give 1.7 g (68%) of **6b** as an oil following evaporation of selected fractions; ¹H nmr (deuteriochloroform): δ 2.0 (s, 6, C(O)CH₃), 3.12 (s, 3, NCH₃), 6.12 (t, 1, H-1'); uv (pH 1): λ max 260 nm (ε 200), 208 (3,600); (pH 7): 262 nm (280), 207 (9,600); (pH 11): 262 nm (310) and 210 (9,100); ir (neat): ν 1650, 1740 (C=O), 3330 (NH₂) cm⁻¹.

Anal. Calcd. for C₁₂H₁₆N₄O₈: C, 45.86; H, 5.77; N, 17.83. Found: C, 45.59; H, 5.75; N, 17.59.

3-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazolin-5-one (**7a**).

A solution of **4a** (0.5 g, 1.2 mmoles) in ethanol and 10% palladium-on-carbon catalyst (0.1 g) was shaken on a Parr hydrogenation apparatus at 45 psi for 3 hours at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to dryness and the residue was purified on a silica gel column using methylene chloride/methanol (8:2) to give 0.32 g (70%) of **7a** (foam); ¹H nmr (deuteriochloroform): δ 2.06, 2.08 (m, 9, C(O)CH₃), 5.75 (d, 1, J = 3.33, H-1'), 6.7 (br, 2, NH₂).

Anal. Calcd. for C₁₃H₁₈N₄O₈·0.75 H₂O: C, 41.99; H, 5.29; N, 15.07. Found: C, 42.33; H, 5.25; N, 14.70.

3-Amino-4-methyl-1-(β-D-ribofuranosyl)-1,2,4-triazolin-5-one (**8a**).

To a solution of **6a** (0.5 g) in methanol (10 ml) was added sodium methoxide until the pH of the solution was 9-10, and the mixture was stirred at room temperature for 10 hours with the exclusion of moisture. The solution was acidified with Dowex-50 (H⁺) resin to pH 2 and evaporated to dryness to give 0.2 g (56%) of **8a**, mp 157°; ¹H nmr (DMSO-d₆): δ 3.34 (s, 3, NCH₃), 5.3 (d, 1, J = 4.59 Hz, H-1'), 5.99 (s, 2, NH₂).

Anal. Calcd. for C₈H₁₄N₄O₅·0.6 H₂O: C, 37.38; H, 5.96; N, 21.80. Found: C, 37.58; H, 5.67; N, 21.53.

3-Amino-1-(2-deoxy-β-D-ribofuranosyl)-4-methyl-1,2,4-triazolin-5-one (**8b**).

To a solution of **6b** (0.5 g, 1.6 mmoles) in methanol (10 ml) was added sodium methoxide until the pH of the solution was 9-10, and the mixture was stirred at room temperature for 10 hours with the exclusion of moisture. The solution was neutralized with Dowex-50 (H⁺) and evaporated to dryness. The residue was purified on a silica gel column using methylene chloride/methanol (8:2, v/v). Evaporation of the solvent gave 0.3 g (79%) of **7b**, mp 127°; ¹H nmr (DMSO-d₆): δ 3.37 (s, 3, NCH₃), 5.84 (t, 1, H-1'), 5.99 (s, 2, NH₂).

Anal. Calcd. for C₈H₁₄N₄O₄·0.2 H₂O: C, 41.09; H, 6.21; N, 23.96. Found: C, 41.32; H, 6.02; N, 23.97.

3-Amino-1-methyl-5-methylthio-1,2,4-triazole (**9b**).

To a magnetically stirred solution of dimethyl cyanodithio-

imidocarbonate (14.6 g, 100 mmoles) in toluene (100 ml), surrounded by a cold bath at -5° was added methyl hydrazine (4.6 g, 100 mmoles). After the initial exothermic reaction, a precipitate formed. The reaction mixture was stirred overnight. The precipitate was collected by suction filtration and washed with cold toluene (20 ml) and dried. The precipitate was recrystallized from toluene to give 13.5 g (94%), mp 104-106 $^{\circ}$; ^1H nmr (deuteriochloroform): δ 2.55 (s, 3, SCH_3), 3.52 (s, 3, NCH_3) and 4.2 (s, 2, NH_2); uv (pH 1): λ max 255 nm (ϵ 6,500); (pH 7): 244 (4,900); (pH 11): 244 (4,900).

Anal. Calcd. for $\text{C}_4\text{H}_8\text{N}_4\text{S}$: C, 33.32; H, 5.59; N, 38.86. Found: C, 33.25; H, 5.57; N, 38.74.

This reaction was also done in benzene, methanol, and acetonitrile and under cold and refluxing conditions. In all cases the same product was obtained.

3-Amino-1-methyl-1,2,4-triazolin-5-one (10)

Compound **9** (6 g, 45 mmoles) was dissolved in 400 ml of 0.25 N sodium hydroxide solution and cooled to 0° . Hydrogen peroxide (30%, 80 ml) was added dropwise. The solution was allowed to stir at 0° for 1 hour, then allowed to warm to room temperature and heated at 100° for 2 hours. At this point the pH was adjusted to 1 with Dowex-50 (H^+). The resin was filtered and the filtrate evaporated and purified on a silica gel column using methanol/methylene chloride (2:8, v/v) which after crystallization from ethanol gave 2.78 g (58%) of **10**, mp 291-292 $^{\circ}$; ^1H nmr (DMSO- d_6): δ 3.04 (s, 3, NCH_3), 5.43 (s, 2, NH_2), 10.47 (s, 1, NH); uv (pH 1): λ max 208 nm (ϵ 6,500); (pH 7): 207 (7,800); (pH 11): 209 (6,100); ir (potassium bromide): ν 1700 cm^{-1} (C=O).

Anal. Calcd. for $\text{C}_5\text{H}_8\text{N}_4\text{O}\cdot\text{H}_2\text{O}$: C, 27.68; H, 6.15; N, 42.40. Found: C, 27.41; H, 6.46; N, 42.15.

5-Amino-2-methyl-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazolin-3-one (11)

A mixture of dry **10** (1.5 g, 11.3 mmoles), hexamethyldisilazane (25 ml) and ammonium sulfate (0.1 g) in 15 ml of dry pyridine was heated under reflux for 10 hours with the exclusion of moisture. Excess hexamethyldisilazane was removed by distillation to provide the trimethylsilyl derivative of **10** which was dissolved in anhydrous methylene chloride (150 ml). To this solution was added tetra-*O*-acetyl- β -D-ribofuranose (4.4 g, 13.8 mmoles). The resulting mixture was stirred for 10 minutes before trimethylsilyltrifluoromethane sulfonate (3.86 ml) was added. The reaction mixture was stirred for 24 hours at ambient temperature. The acetonitrile was evaporated and the residue dissolved in ethyl acetate (250 ml). The organic layer was washed successively with aqueous saturated sodium bicarbonate solution (3 x 50 ml), saturated brine solution (2 x 50 ml), water (3 x 50 ml) and dried over sodium sulfate. The solvent was evaporated and the residue was purified on a silica gel column using methylene chloride/methanol (9:1, v/v) as eluent to yield 1 g (20%) of the title compound, mp 128-130 $^{\circ}$; ^1H nmr (deuteriochloroform): δ 2.06, 2.10, 2.13 (3s,

9, C(O) CH_3), 3.16 (s, 3, NCH_3), 5.74 (d, 1, $J = 5.04$ Hz, H-1'), 8.18 (s, 2, NH_2); uv (pH 1): λ max 211 nm, 224; (pH 7): 209, 230; (pH 11): 208, 231, 265; ir (potassium bromide): ν 1750 cm^{-1} (C=O).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_8$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.57; H, 5.58; N, 14.93.

5-Amino-2-methyl-1-(β -D-ribofuranosyl)-1,2,4-triazolin-3-one (12)

Compound **11** (0.46 g, 1.23 mmoles) and methanolic ammonia (methanol saturated with ammonia at 0° , 25 ml) were placed in a steel reaction vessel and allowed to stand at room temperature for 15 hours, after which the ammonia was evaporated. The residue was crystallized from methanol/ethyl acetate to yield 280 mg (93%) of **12**, mp 192-194 $^{\circ}$; ^1H nmr (DMSO- d_6): δ 3.94 (s, 3, NCH_3), 5.29 (d, 1, $J = 5.28$ Hz, H-1'), 6.7, 7.31 (2s, 2, NH_2); uv (pH 1): λ max 222 nm (ϵ 7,200); (pH 7): 208 (15,400), 228 (7,300); (pH 11): 209 (14,400), 227 (7,000).

Anal. Calcd. for $\text{C}_8\text{H}_{14}\text{N}_4\text{O}_5$: C, 39.02; H, 5.73; N, 22.76. Found: C, 39.25; H, 5.55; N, 22.51.

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