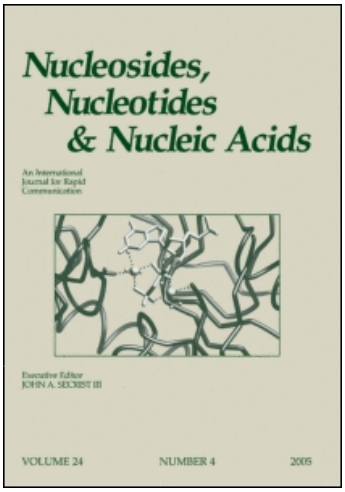

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SYNTHESIS AND X-RAY CRYSTAL STRUCTURE OF 3-AMINO-1-β-D-RIBOFURANOSYL-s-TRIAZOLO[5,1-c]-s-TRIAZOLE[1]

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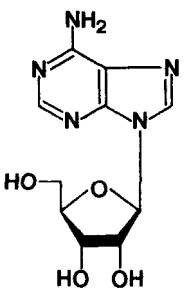
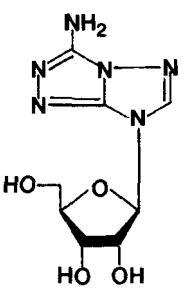
ABSTRACT: The first chemical synthesis of 3-amino-1-β-D-ribofuranosyl-s-triazolo[5,1-c]-s-triazole (6) is described. Direct glycosylation of 3-amino-5(7)H-s-triazolo[5,1-c]-s-triazole (2) with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (3) in the presence of TMS-triflate gave 3-amino-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-s-triazolo[5,1-c]-s-triazole (4) which, on ammonolysis, gave 6. The absolute structure of 6 is determined by X-ray diffraction techniques employing Mo Kα radiation. The structure is solved by direct methods and refined to the R value of 0.044 by using a full-matrix least-squares method. The sugar of 6 has a $^3T_2$ configuration. The torsion angles about the C5'-C4' bond are both gauche and the torsion angle about the glycosidic bond is in the anti range. Each azole ring of the aglycon is planar and the dihedral angle between the planes of the rings is 3.6°.

In the course of a program designed to synthesize novel azapentalene nucleosides[2] as potential chemotherapeutic agents, it became desirable to attempt the preparation of the previously undescribed s-triazolo[5,1-c]-s-triazole nucleoside (1), which is structurally similar to adenosine. Azapentalene ring systems, which contain two heteroaromatic five-membered rings fused together, can be construed to mimic purine



Adenosine



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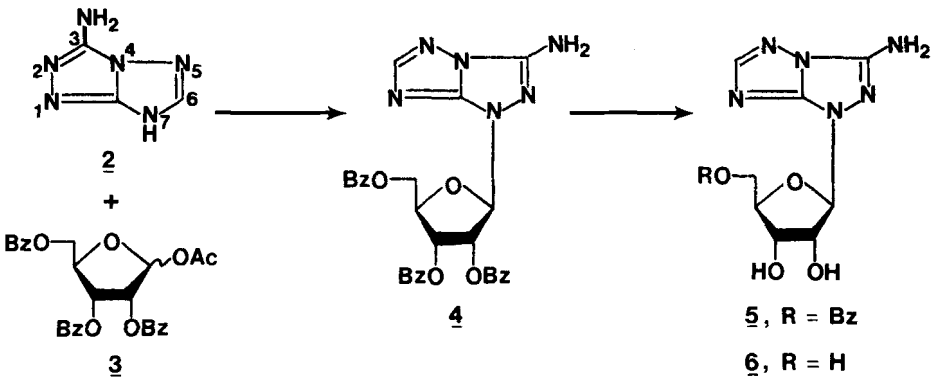
analogs in which the pyrimidine ring has been contracted in size by one member. Replacement of the adenine moiety in adenosine with an appropriately substituted azapentalene ring will result in an adenosine analog with an altered geometry. Although the geometric configuration of the ring possessing the glycon moiety will presumably be similar to that of adenosine, the exocyclic amino group will assume a slightly different spatial relationship with respect to the natural product. Such a nucleoside could be expected to have altered substrate binding characteristics toward certain nucleic acid enzymes.

In an attempt to prepare 1, 3-amino-5(7)H-s-triazolo[5,1-c]-s-triazole (2)[3] was selected for glycosylation studies. Attachment of the β-D-ribofuranosyl moiety to 2, using the general trimethylsilyl-Lewis acid procedure,[4] met with little success. However, direct glycosylation of the unsilylated 2 with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (3) in the presence of the catalyst, trimethylsilyl trifluoromethanesulfonate (TMS-triflate)[5] in acetonitrile at room temperature gave a nucleoside product identified as 3-amino-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-s-triazolo[5,1-c]-s-triazole (4) (SCHEME 1). The reaction is essentially over within 20 min and with higher temperature or prolonged period of time, considerable degradation of the nucleoside product occurred. The isolated yield of 4 by this method was 89%. Debenzoylation of 4 with methanolic ammonia at room temperature overnight, gave a minor amount of partially deblocked material 3-amino-1-(5-O-benzoyl-β-D-ribofuranosyl)-s-triazole (5), along with 3-amino-1-β-D-ribofuranosyl-s-triazolo[5,1-c]-s-triazole (6). Due to the lability of the glycosidic bond, the isolated yield of 6 is only 18.3%. The absolute structural assignment of 6 was made by single crystal X-ray analysis.

In an effort to obtain the desired 7-glycosyl isomer 1, two additional glycosylation procedures were attempted. First, the sodium salt glycosylation procedure, developed recently in our laboratory,[6,7] was employed. It was hoped that the anion formed would reside on the ring not bearing the electron-donating amino group. Thus, the sodium salt of 2, produced *in situ* by sodium hydride in acetonitrile, was treated with 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide at 50-55°C. However, this reaction furnished a blocked nucleoside identical with 4. Secondly, the high temperature glycosylation procedure[8] using 2 and 3 in nitromethane with BF_3 etherate as the catalyst gave similar results.



SCHEME 1

It appears that under the conditions used in this study the glycon moiety prefers the electron rich ring bearing the amino function. The Lewis acid catalyzed glycosylation procedures are known to form acyloxonium ions at the C-1 position of the carbohydrate.[9] This intermediate carbonium ion would be expected to react with the most nucleophilic site on the heterocycle, which would eventually give rise to the observed product. The sodium salt should form on the ring nitrogen not bearing the exocyclic amino function, thus giving rise to a different isomer. Whether or not such an isomer forms as an intermediate which spontaneously rearranges to the isolated N-1 isomer (4) is not known.

X-Ray Crystallographic Study. Slow crystallization of 6 from MeOH: CH_2Cl_2 (1:9) gave X-ray quality crystals. A suitable single crystal (0.2 X 0.4 X 0.1 mm) was mounted on a Nicolet P3 auto-diffractometer and the diffraction data for the determination of both the lattice parameters and the structural study were collected using Mo Kα graphite monochromated radiation (λ = 0.71069 Å). The lattice parameters were obtained using a least-squares procedure of 15 centered 2θ values. Crystal data are listed in TABLE 1. Single crystal data was collected using a θ-2θ scan mode to a sinθ/λ limit of 0.756. A variable scan rate was employed with total background time being equal to the scan time. The three standard reflections measured every 97 reflections showed no noticeable changes. A total of 2067 unique data were measured with 1714 considered observed, $I > 2\sigma(I)$. No corrections for extinction or absorption were made.

TABLE 1

SPACE GROUP	P1	γ	106.70(4)°
a	4.901(2) Å	Z	1
b	7.240(3) Å	V	265.8 Å^3
c	8.170(3) Å	ρ_x	1.60 g/cc
α	102.57(4)°	μ	0.86 cm^{-1}
β	96.97(3)°	Fooo	134.0

The structure was solved using the direct methods program of SHELX-76.[10] All nonhydrogen atoms were located in the E-map and the structure was refined using a full-matrix least-squares procedure. The nonhydrogen atoms were refined anisotropically while the hydrogen atoms, which were located in a difference map, were refined isotropically. The final R values were R = 0.044 and Rw = 0.032. The weights were calculated from counting statistics and the quantity minimized was $\Sigma w(/Fo/ - /Fc/)^{\frac{1}{2}}$.[11] The final difference map did not show any significant peaks.

RESULTS AND DISCUSSION

The structural formula, conformation and atom labels of compound 6 as well as the interatomic bond lengths are shown in FIGURE 1. The study established that glycosylation occurred at the N-1 position, indicating that the compound is not similar to adenosine. It also showed that the compound is the β-anomer. To the best of our knowledge, this study is the first X-ray structure determination of the s-triazolo-[5,1-c]-s-triazole ring system. Each five-membered ring of the heterocycle is planar within experimental error. The dihedral angle between the planes of the rings is 3.6°. This is significantly larger than the angle reported in other studies of fused five-membered rings. For example, the values of this dihedral angle in the N-1 and N-5 glycosyl derivatives of imidazo[1,2-b]pyrazole-7-carbonitrile are 0.84° and 0.87°, respectively.[2] The value for the corresponding dihedral angle in 1,6-dimethyl-7-ethoxycarbonylpyrazolo[1,5-d]tetrazole is 1.6°.[12] The five- and six-membered rings in adenosine are coplanar.

The sugar of the nucleoside has a $^3T_2$ configuration. The torsion angles about the C(5')-C(4') bond are both gauche with the value of

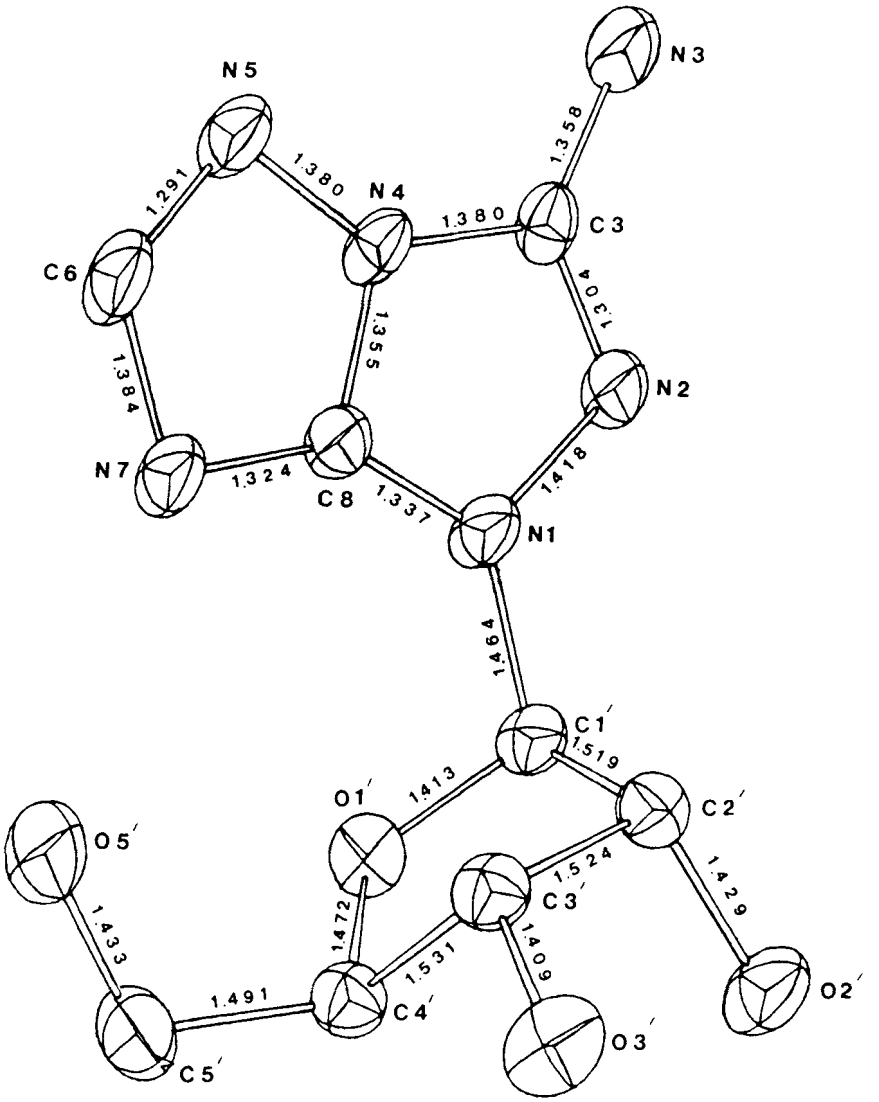


FIGURE 1. ORTEP drawing of 6

O(5')-C(5')-C(4')-O(1') torsion angle being -75.3° and that of O(5')-C(5')-C(4')-C(3') is 41.5°. The torsion angle about the glycosidic bond is in the anti range (16.2°).

There are five hydrogen bonds in the structure, one being intramolecular. The intramolecular hydrogen bond, O(5')-HO(5')...N-7, is an attractive force between the base and the sugar which reduces the volume occupied by the molecule and accounts for the rather large density re-

TABLE 2

Donor Atom	Hydrogen Atom	Acceptor Atom	Unit cell Translation of Acceptor atom †	D...A(Å) distance	H...A(Å) distance	D-H...A(°) angle
O5'	HO5'	N7	0,0,0	2.70	1.93	166
N3	H1N3	O2'	1,0,1	3.00	2.23	154
N3	H2N3	O3'	1,1,1	3.10	2.15	173
O2'	HO2'	O5'	0,1,0	2.73	1.91	147
O3'	HO3'	N5	-1,0,-1	2.78	1.95	152

† relative to parameters of atom in asymmetric unit

ported in TABLE 1. H bonds link the molecule to four others in different unit cells. These data are summarized in TABLE 2.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on either a Varian EM-390 or on a Jeol FX-90 Q spectrometer. The chemical-shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. Infrared spectra (IR) were obtained on a Beckman Acculab 2 spectrophotometer and are expressed in reciprocal centimeters. Ultraviolet spectra (UV; sh = shoulder) were recorded on a Cary Model 15 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Thin-layer chromatography (TLC) was run on silica gel 60 F-254 (EM Reagents) plates. J. T. Baker silica gel (70-230 mesh) was used for column chromatography. Detection of components on TLC was by UV light and with 10% H_2SO_4 in MeOH spray followed by heating. Evaporations were carried out under reduced pressure with the bath temperature below 30°C.

3-Amino-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-s-triazolo[5,1-c]-s-triazole (4). To a suspension of 3-amino-5(7)H-s-triazolo[5,1-c]-s-triazole[3] (2, 4.0 g, 32 mmol) and 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (3, 16.15 g, 32 mmol) in anhydrous CH_3CN (200 ml) was added trimethylsilyl trifluoromethanesulfonate (10.0 g, 8.2 ml, 45 mmol) and the

mixture was stirred at room temperature for 15 min. The mixture was carefully poured into cold, saturated aqueous $NaHCO_3$ solution (200 ml) and stirred for 20 min. The aqueous mixture was extracted with EtOAc (3 X 100 ml). The combined, dried (Na_2SO_4), organic phase was evaporated to dryness and the residue was purified by prep LC using acetone: methylene chloride (8:92, v/v) as the solvent. Evaporation of the solvent gave 16.3 g (89%) of homogeneous foam; mp 85-87°C; IR (KBr) ν 1725 (C=O) cm^{-1}; UV λ_{max} (nm) (ε X 10^{-3}) MeOH, 280 sh (3.1), 270 sh (3.7), 230 (48.3); NMR ($CDCl_3$) δ 6.62 (d, 1, $J_{1',2'}$ = 5.0 Hz, C_1',H), 7.40 to 8.30 (m, 16, $3COC_6H_5$, C_6H), and other sugar protons. Anal. Calcd for $C_{29}H_{24}N_6O_7$: C, 61.26; H, 4.25; N, 14.78. Found: C, 61.24; H, 4.41; N, 14.72.

3-Amino-1-(5-O-benzoyl-β-D-ribofuranosyl)-s-triazolo[5,1-c]-s-triazole (5), and 3-Amino-1-β-D-ribofuranosyl-s-triazolo[5,1-c]-s-triazole (6). A solution of 4 (18.2 g, 32 mmol) in MeOH/NH_3 (saturated at 0°C, 100 ml) was stirred at room temperature for 18 hr in a pressure bottle. The solvent was evaporated and the residue was purified on a silica gel column (2.5 X 60 cm) using MeOH:CH_2Cl_2 (5:95, v/v) as the solvent. The following two nucleosides were isolated in the order listed: 3-Amino-1-(5-O-benzoyl-β-D-ribofuranosyl)-s-triazolo[5,1-c]-s-triazole (5) was obtained as crystalline solid, 0.89 g (7.7%); mp 185-187°C; IR (KBr) ν 1720 (C=O), 3300-3500 (OH, NH_2) cm^{-1}; UV λ_{max} (nm) (ε X 10^{-3}) pH 1 and 11, 232 (16.9); pH 7, 232 (18.7). Anal. Calcd for $C_{15}H_{16}N_6O_5$: C, 50.00; H, 4.47; N, 23.32. Found: C, 50.03; H, 4.46; N, 23.28.

3-Amino-1-β-D-ribofuranosyl-s-triazolo[5,1-c]-s-triazole (6) was obtained as white crystals (from H_2O), 1.50 g (18.3%); mp 144-145°C; IR (KBr) ν 1650, 3300-3500 (OH, NH_2) cm^{-1}; UV λ_{max} (nm) (ε X 10^{-3}) pH 1, 238 (6.8); pH 7, 238 (8.0); pH 11, 238 (7.6); NMR (Me_2SO-d_6) δ 5.50 (d, 1, $J_{1',2'}$ = 4.0 Hz, C_1',H), 6.80 (b s, 2, NH_2), 8.02 (s, 1, C_6H), and other sugar protons. Anal. Calcd for $C_8H_{12}N_6O_4$: C, 37.50; H, 4.72; N, 32.80. Found: C, 37.49; H, 4.78; N, 32.83.

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