

Synthesis and Single-Crystal X-ray Diffraction Studies of 1- β -D-Ribofuranosyl-1,2,4-triazole-3-sulfonamide and Certain Related Nucleosides

Naeem B. Hanna, Slobodan D. Dimitrijević, Steven B. Larson,
Roland K. Robins and Ganapathi R. Revankar*

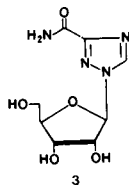
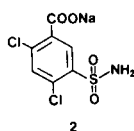
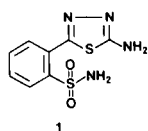
Nucleic Acid Research Institute, 3300 Hyland Avenue,
Costa Mesa, California 92626

Received May 19, 1988

1- β -D-Ribofuranosyl- **21**, 1-(2-deoxy- β -D-*erythro*-pentofuranosyl)- **27** and 1- β -D-arabinofuranosyl- **29** derivatives of 1,2,4-triazole-3-sulfonamide (**19**) have been prepared. Glycosylation of the silylated **19** with 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose (**5**) in the presence of trimethylsilyl triflate gave the corresponding blocked nucleoside (**20**), which on ammonolysis afforded 1- β -D-ribofuranosyl-1,2,4-triazole-3-sulfonamide (**21**). Stereospecific glycosylation of the sodium salt of **19** with either 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl- α -D-*erythro*-pentofuranose (**22**) or 1-chloro-2,3,5-tri-*O*-benzyl- α -D-arabinofuranose (**23**) provided the corresponding protected nucleosides **26** and **28**. Deprotection of **26** and **28** furnished 1-(2-deoxy- β -D-*erythro*-pentofuranosyl)-1,2,4-triazole-3-sulfonamide (**27**) and 1- β -D-arabinofuranosyl-1,2,4-triazole-3-sulfonamide (**29**), respectively. 2- β -D-Ribofuranosyl-1,2,4-triazole-3(4*H*)-thione (**7**) and 4- β -D-ribofuranosyl-1,2,4-triazole-3(2*H*)-thione (**9**) were also prepared utilizing either an acid catalyzed fusion of 1,2,4-triazole-3(1*H*,2*H*)-thione (**4**) with **5**, the reaction of **5** with silylated **4** in the presence of trimethylsilyl triflate, or by ring closure of 4-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)thiosemicarbazide (**10**) with mixed anhydride and subsequent deacylation. The synthesis of 1- β -D-ribofuranosyl-3-benzylthio-1,2,4-triazole (**15**) has also been accomplished by the silylation procedure employing 3-benzylthio-1,2,4-triazole (**13**) and **5** to give 1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-3-benzylthio-1,2,4-triazole (**14**). Deacetylation of **14** furnished **15**. The structural assignments of **7**, **14** and **21** were made by single-crystal X-ray diffraction analysis and their hydrogen bonding characteristics have been studied. The sulfonamido-1,2,4-triazole nucleosides are devoid of any significant antiviral or antitumor activity in cell culture.

J. Heterocyclic Chem., **25**, 1857 (1988).

The development of sulfonamides is one of the most fascinating and informative chapters in medicinal chemistry, highlighting the roles of skillful planning and serendipity in drug research [1]. Since the initial dramatic results obtained with sulfonamides in the treatment of streptococcal infections, studies with these drugs have been extended to viruses. It has been found that some "large viruses" of *Lymphogranuloma venereum* in mice were susceptible to the action of sulfonamides [2] and in almost all cases their action is related to PAB antagonism. Efforts have been devoted in recent years to the synthesis of compounds having the sulfonamide group as antiviral agents. Such compounds of interest are, 2-amino-5-(2-sulfamoylphenyl)-1,3,4-thiadiazole (**1**) [3] and sodium 5-sulfamoyl-2,4-dichlorobenzoate (**2**) [4]. Compound **1** is effective in inhibiting the replication of several DNA and RNA viruses *in vitro* at concentrations which do not exhibit any toxic effects on cells [3]. Compound **2** has been found to possess a broad-spectrum of activity against RNA viruses *in vitro* as well as *in vivo*, selective toxicity and a large margin of safety [4].



Ribavirin (1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamide, **3**) [5], a synthetic nucleoside analog of guanosine [6,7] synthesized and reported from our laboratory, is singular in its broad-spectrum of activity against both DNA and RNA viruses [8,9]. Ribavirin has been developed clinically [10] and approved for human use in an aerosol form for the treatment of lower respiratory disease caused by respiratory syncytial virus [11-14]. Ribavirin has also shown considerable efficacy in the treatment of influenza A and B by a small-particle aerosol route of administration [15-19]. Administered intravenously, ribavirin is effective in the treatment of Lassa fever [20,21] and epidemic hemorrhagic fever with renal syndrome caused by Hantaan virus [22]. Although a sindbis viral mutant has recently been shown to be resistant to ribavirin [23], its failure in general to induce viral resistance and its lack of toxicity are of particular interest.

In view of ribavirin's proven potential for therapeutic use, the synthesis of certain sulfonamide analogs of ribavirin appeared of particular interest. We now report the synthesis of 1- β -D-ribofuranosyl-1,2,4-triazole-3-sulfonamide (**21**), and the corresponding 2-deoxy- β -D-*erythro*-pentofuranosyl- **27** and β -D-arabinofuranosyl- **29** analogs.

Results and Discussion.

Several methods have been described in the literature

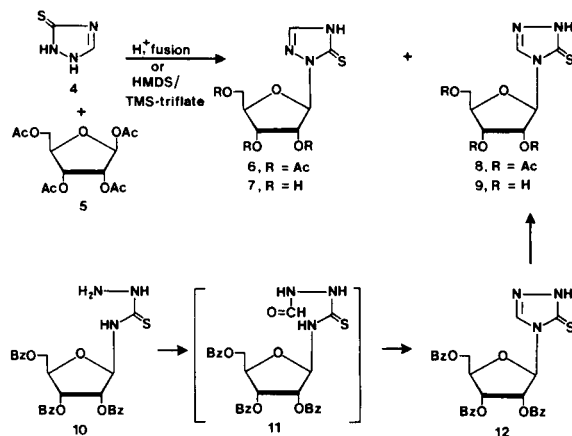
Table 1
Positional and Equivalent Isotropic Thermal Parameters [a] for Non-hydrogen Atoms in Compounds 7, 14 and 21

Atom	x/a	y/b	z/c	U _{eq}	Atom	x/a	y/b	z/c	U _{eq}
Compound 7									
S	.21914(9)	-.00705(6)	.88430(3)	.0425(2)	N1	.2131(3)	.3846(2)	.98833(11)	.0393(6)
N2	.2215(3)	.2917(2)	.92467(10)	.0305(5)	C3	.2099(3)	.1430(2)	.94327(12)	.0294(5)
N4	.1917(3)	.1445(2)	1.02095(11)	.0374(6)	C5	.1940(4)	.2906(3)	1.04490(13)	.0422(7)
C1'	.2469(3)	.3538(2)	.84807(11)	.0271(5)	C2'	.1229(3)	.4904(3)	.83173(11)	.0318(5)
C3'	.2404(3)	.5752(3)	.77151(13)	.0353(6)	C4'	.4406(3)	.5442(2)	.79734(11)	.0300(6)
C5'	.5187(3)	.6671(3)	.84810(14)	.0356(6)	O1'	.4361(2)	.4024(2)	.83996(9)	.0343(4)
O2'	-.0532(2)	.4389(2)	.80488(10)	.0444(5)	O3'	.2151(3)	.5091(3)	.69772(9)	.0467(6)
O5'	.6913(2)	.6140(2)	.88096(11)	.0407(5)	OW	.3671(3)	.6809(3)	1.03514(12)	.0544(6)
Compound 14									
N1	.6616(4)	.1168(4)	.24470(15)	.0452(11)	N2	.6204(5)	.2372(4)	.2232(2)	.0494(12)
C3	.5253(5)	.1982(5)	.1866(2)	.0508(14)	N4	.4986(5)	.0617(4)	.1845(2)	.0537(13)
C5	.5869(6)	.0153(5)	.2218(2)	.052(2)	S6	.4458(2)	.31715(14)	.14427(6)	.0636(4)
C7	.2806(9)	.2244(7)	.1236(3)	.094(3)	C8	.1936(5)	.3037(5)	.0856(2)	.067(2)
C9	.0767(5)	.3855(5)	.1040(2)	.095(3)	C10	-.0087(5)	.4629(5)	.0695(2)	.149(5)
C11	.0229(5)	.4585(5)	.0166(2)	.142(5)	C12	.1398(5)	.3767(5)	-.0019(2)	.177(7)
C13	.2251(5)	.2993(5)	.0327(2)	.135(5)	C1'	.7567(5)	.1102(5)	.2897(2)	.0462(13)
C2'	.8851(5)	.2157(5)	.2897(2)	.0446(13)	C3'	.8315(5)	.3171(5)	.3305(2)	.0468(13)
C4'	.7391(5)	.2291(5)	.3674(2)	.0449(13)	C5'	.6235(7)	.3070(7)	.3982(2)	.060(2)
O1'	.6654(4)	.1370(4)	.33399(13)	.0628(12)	O2'	1.0161(3)	.1425(4)	.30843(14)	.0525(10)
O3'	.9511(4)	.3781(4)	.36005(12)	.0549(10)	O5'	.5749(6)	.2193(7)	.4397(2)	.110(2)
C6'	1.1532(5)	.1828(7)	.2894(2)	.060(2)	C7'	1.2728(6)	.0869(8)	.3077(3)	.082(2)
O6'	1.1697(5)	.2806(5)	.2630(2)	.077(2)	C8'	1.0157(6)	.4912(5)	.3405(2)	.056(2)
C9'	1.1342(7)	.5431(7)	.3769(3)	.079(2)	O8'	.9819(5)	.5388(4)	.2999(2)	.078(2)
C10'	.4424(11)	.1913(11)	.4503(4)	.110(4)	C11'	.4197(12)	.0926(13)	.4931(3)	.151(5)
O10'	.3412(9)	.2411(11)	.4228(4)	.166(4)					
Compound 21									
N1	.3726(2)	.8517(2)	.2894(2)	.0247(5)	N2	.2183(3)	.7519(2)	.2623(2)	.0276(5)
C3	.2458(3)	.6840(2)	.1439(2)	.0261(5)	N4	.4079(3)	.7330(2)	.0936(2)	.0340(6)
C5	.4837(4)	.8395(3)	.1881(3)	.0320(6)	S6	.08409(6)	.538112	.05734(5)	.0284(2)
O7	.1365(3)	.5095(2)	-.0803(2)	.0439(6)	O8	-.1224(3)	.5781(2)	.0573(2)	.0471(6)
N9	.1481(3)	.3998(2)	.1623(2)	.0318(6)	C1'	.4043(3)	.9549(2)	.4146(2)	.0244(5)
C2'	.2046(3)	1.0374(3)	.4142(2)	.0247(5)	C3'	.1152(3)	.9434(2)	.5181(2)	.0231(5)
C4'	.3121(3)	.8966(2)	.6368(2)	.0230(5)	C5'	.2933(3)	.7569(3)	.7161(2)	.0282(5)
O1'	.4652(2)	.8776(2)	.5525(2)	.0285(4)	O2'	.2515(3)	1.1725(2)	.4890(2)	.0358(5)
O3'	-.0352(2)	1.0144(2)	.5764(2)	.0322(5)	O5'	.4913(2)	.7132(2)	.8088(2)	.0310(5)

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

for the synthesis of *N*-nucleoside derivatives of substituted 1,2,4-triazoles [9]. We envisioned that the synthesis of target *N*-glycosyl derivatives of 1,2,4-triazole-3-sulfonamide might be realized by selective oxidative amination of the requisite 1- β -D-ribofuranosyl-1,2,4-triazole-3-thione. The synthesis of such a nucleoside precursor seemed propitious by the direct glycosylation of 1,2,4-triazole-3(1*H*, 2*H*)-thione (**4**) [24]. Acid-catalyzed [bis(*p*-nitrophenyl) phosphate] fusion of **4** with 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose (**5**) at 150° for 20 minutes however, provided a

Scheme I



mixture of two isomeric protected nucleosides, which were separated by column chromatography over silica gel. These nucleosides were identified as 2-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole-3(4*H*)-thione (**6**), and the isomeric 4-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole-3(2*H*)-thione (**8**), by conversion of each of these isomers with methanolic ammonia at 4° for 20 hours to furnish the free nucleosides **7** and **9**, respectively. The structure of 2- β -D-ribofuranosyl-1,2,4-triazole-3(4*H*)-thione (**7**) was established by single-crystal X-ray diffraction analysis, and the structure of 4- β -D-ribofuranosyl-1,2,4-triazole-3(2*H*)-thione (**9**) was confirmed by direct comparison with an authentic sample prepared by the ring closure of 4-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)thiosemicarbazide (**10**) [25]. Treatment of **10** with a mixture of acetic anhydride and formic acid in the presence of 4-dimethylaminopyridine gave crystalline 4-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-1,2,4-triazole-3(2*H*)-thione (**12**) in 69% yield. The ring closure probably proceeds *via* the formyl intermediate **11**, which was not isolated. Debenzoylation of **12** with sodium methoxide in methanol at room temperature readily gave **9** in over 85% yield, which was identical in all respects with **9** prepared by the fusion procedure.

As depicted in Scheme I, compound **4** was also silylated with hexamethyldisilazane (HMDS) in the presence of ammonium sulfate to give the bis-silylated triazole. Reaction of this bis-TMS derivative with one molar equivalent of **5**

Table 2
Bond Lengths (Å) in **7**, **14** and **21**

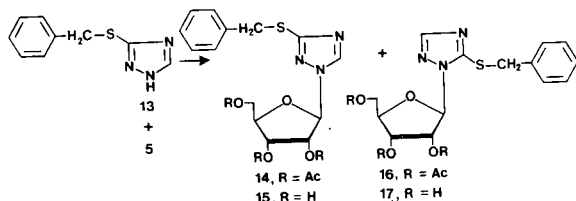
1	2	1-2	1	2	1-2
7					
C3	S	1.675(2)	N2	N1	1.379(3)
C5	N1	1.294(3)	C3	N2	1.353(3)
C1'	N2	1.453(3)	N4	C3	1.359(3)
C5	N4	1.353(4)	C2'	C1'	1.520(3)
O1'	C1'	1.419(2)	C3'	C2'	1.535(3)
O2'	C2'	1.412(3)	C4'	C3'	1.519(3)
O3'	C3'	1.422(3)	C5'	C4'	1.504(3)
O1'	C4'	1.454(3)	O5'	C5'	1.433(3)
14					
N2	N1	1.362(5)	C5	N1	1.338(6)
C1'	N1	1.435(6)	C3	N2	1.321(6)
N4	C3	1.369(6)	S6	C3	1.751(5)
C5	N4	1.320(7)	C7	S6	1.805(8)
C8	C7	1.472(9)	C9	C8	1.395(6)
C13	C8	1.395(6)	C10	C9	1.395(6)
C11	C10	1.395(6)	C12	C11	1.395(6)
C13	C12	1.395(6)	C2'	C1'	1.541(7)
O1'	C1'	1.425(6)	C3'	C2'	1.529(7)
O2'	C2'	1.448(6)	C4'	C3'	1.526(7)
O3'	C3'	1.436(6)	C5'	C4'	1.506(8)
O1'	C4'	1.411(6)	O5'	C5'	1.444(8)
C6'	O2'	1.367(6)	C8'	O3'	1.351(6)
C10'	O5'	1.235(11)	C7'	C6'	1.496(9)
O6'	C6'	1.191(8)	C9'	C8'	1.498(8)
O8'	C8'	1.186(7)	C11'	C10'	1.487(15)
O10'	C10'	1.243(13)			
21					
N2	N1	1.352(2)	C5	N1	1.345(3)
C1'	N1	1.468(3)	C3	N2	1.314(3)
N4	C3	1.361(3)	S6	C3	1.774(2)
C5	N4	1.321(3)	O7	S6	1.430(2)
O8	S6	1.424(2)	N9	S6	1.590(2)
C2'	C1'	1.531(3)	O1'	C1'	1.421(2)
C3'	C2'	1.527(3)	O2'	C2'	1.419(3)
C4'	C3'	1.529(2)	O3'	C3'	1.417(3)
C5'	C4'	1.504(3)	O1'	C4'	1.449(3)
O5'	C5'	1.425(2)			

in anhydrous acetonitrile in the presence of 1.44 molar equivalent of trimethylsilyl trifluoromethanesulfonate (trimethylsilyl triflate) according to the general procedure of Vorbrüggen *et al.* [26] again gave a mixture of **6** (36% yield) and **8** (17% yield). Although the yield of **6** obtained

by this procedure was considerably higher than that obtained (8.3%) by the fusion method, no formation of the desired *N*-1 glycosyl derivative was observed.

Since neither of these precursors **6** and **8** could be converted to the desired ribavirin sulfonamide **21**, we extended our glycosylation studies with 3-benzylthio-1,2,4-triazole (**13**) in the hope that the viable precursor 1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-3-benzylthio-1,2,4-triazole (**14**) thus obtained could be converted to **21** by reductive cleavage of the thiobenzyl ether function, followed by manipulation of the functional groups. Compound **13** was prepared as reported [27], and silylated with HMDS in the presence of ammonium sulfate. Treatment of this trimethylsilyl derivative with 1 molar equivalent of **5** in acetonitrile in the presence of 1.44 molar equivalent of trimethylsilyl triflate gave a mixture of two isomeric protected nucleosides. After separation on a silica gel column, these nucleosides were identified as 1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-3-benzylthio-1,2,4-triazole (**14**, 41% yield) and the positional isomer 1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-5-benzylthio-1,2,4-triazole (**16**, 15% yield). However, acid [bis(*p*-nitrophenyl)phosphate] catalyzed fusion of **13** and **5** increased the yield of **14** and **16** to 48%

Scheme II

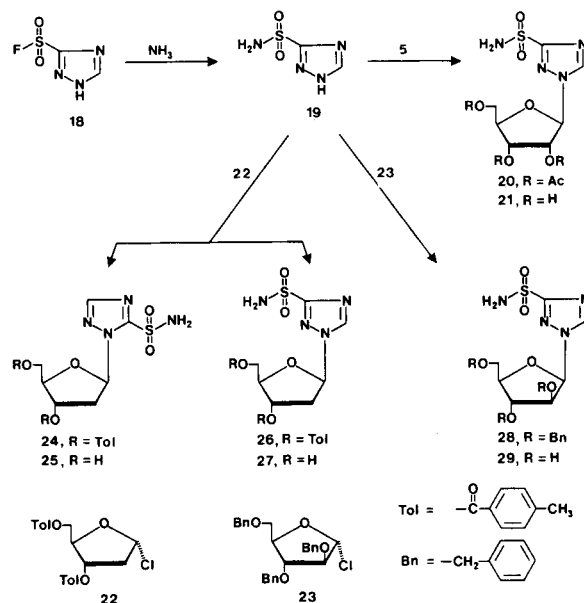


and 35%, respectively. Subsequent deacetylation of **14** and **16** with methanolic ammonia by the conventional procedure furnished 1- β -D-ribofuranosyl-3-benzylthio-1,2,4-triazole (**15**, 76% yield) and 1- β -D-ribofuranosyl-5-benzylthio-1,2,4-triazole (**17**, 64% yield), respectively. The purity of these nucleosides was assured by elemental analysis and by ^1H nmr spectroscopy. The structural assignment of **14** was on the basis of single-crystal X-ray diffraction analysis. However, reductive cleavage of the thiobenzyl ether group of **14** with either sodium in liquid ammonia or sodium naphthalene [28] in tetrahydrofuran gave an intractable reaction mixture from which the desired product could not be isolated.

In an effort to obtain the desired 1- β -D-ribofuranosyl-1,2,4-triazole-3-sulfonamide (**21**), direct glycosylation of the preformed 1,2,4-triazole-3-sulfonamide (**19**) itself was next considered. A low yield (20%) synthesis of **19** has been described by Roblin and Clapp [29] from the unstable 1,2,4-triazole-3-sulfonyl chloride. Since sulfonyl fluorides are considerably more stable than sulfonyl chlorides [30], the synthesis of **19** via the intermediate 1,2,4-triazole-

3-sulfonyl fluoride (**18**) was considered. Thus, when a suspension of **4** in methanol, aqueous hydrofluoric acid and potassium fluoride was treated with chlorine gas at 0° , compound **18** was obtained in good yield. As expected, compound **18** was found to be quite stable with a mp of $68-70^\circ$ and could be crystallized from boiling absolute ethanol. The hydrofluoric acid-potassium fluoride mixture seems to provide a buffered reaction medium which keeps the acidity low, thus preventing acid-catalyzed nucleophilic replacement of the fluorosulfonyl group. This procedure was originally employed in our laboratory [30] for the synthesis of purine-6-sulfonyl fluoride. Treatment of **18** with liquid ammonia at room temperature gave **19** in good yield and was found to be identical with the one reported by Roblin and Clapp [29]. Glycosylation of the trimethylsilyl derivative of **19** with 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose (**5**) in the presence of 1.44 molar equivalent of trimethylsilyl triflate in anhydrous acetonitrile gave 1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole-3-sulfonamide (**20**). Compound **20** was the only nucleoside product which could be isolated from the reaction mixture

Scheme III



and no formation of other isomeric nucleosides was detected by tlc procedures. Ammonolysis of **20** with methanolic ammonia gave the desired ribavirin congener 1- β -D-ribofuranosyl-1,2,4-triazole-3-sulfonamide (**21**) in 93% yield. The structure of **21** was established by single-crystal X-ray diffraction studies.

In an effort to prepare the 2'-deoxyribofuranosyl (2-deoxy- β -D-*erythro*-pentofuranosyl) derivative of **19**, we examined the stereospecific sodium salt glycosylation procedure [31-33], developed and reported recently from our laboratory. Thus, treatment of the sodium salt of **19**, gen-

Table 3
Bond Angles ($^{\circ}$) in **7**, **14** and **21**

1	2	3	1-2-3	1	2	3	1-2-3
7							
N2	N1	C5	103.7(2)	N1	C5	N4	112.0(2)
C3	N2	C1'	126.3(2)	C3	N2	N1	112.3(2)
C1'	N2	N1	121.3(2)	N4	C3	S	128.5(2)
N4	C3	N2	103.5(2)	S	C3	N2	128.0(2)
C5	N4	C3	108.4(2)	C1'	O1'	C4'	109.3(2)
C2'	C1'	O1'	107.1(2)	C2'	C1'	N2	113.4(2)
O1'	C1'	N2	108.9(2)	C3'	C2'	O2'	114.4(2)
C3'	C2'	C1'	101.4(2)	O2'	C2'	C1'	108.8(2)
C4'	C3'	O3'	108.2(2)	C4'	C3'	C2'	102.8(2)
O3'	C3'	C2'	110.4(2)	C5'	C4'	O1'	109.1(2)
C5'	C4'	C3'	113.0(2)	O1'	C4'	C3'	106.6(2)
O5'	C5'	C4'	108.4(2)				
14							
N2	N1	C5	109.9(4)	N2	N1	C1'	121.8(4)
C5	N1	C1'	127.8(4)	C3	N2	N1	102.0(4)
N4	C3	S6	124.4(4)	N4	C3	N2	115.2(4)
S6	C3	N2	120.4(4)	C5	N4	C3	102.1(4)
N1	C5	N4	110.8(4)	C7	S6	C3	99.8(3)
C8	C7	S6	110.5(5)	C9	C8	C13	120.0(4)
C9	C8	C7	117.9(5)	C13	C8	C7	122.1(5)
C10	C9	C8	120.0(4)	C11	C10	C9	120.0(4)
C12	C11	C10	120.0(4)	C13	C12	C11	120.0(4)
C8	C13	C12	120.0(4)	C2'	C1'	O1'	106.9(4)
C2'	C1'	N1	113.7(4)	O1'	C1'	N1	108.0(4)
C3'	C2'	O2'	110.2(4)	C3'	C2'	C1'	102.4(4)
O2'	C2'	C1'	104.7(4)	C4'	C3'	O3'	107.6(4)
C4'	C3'	C2'	102.9(4)	O3'	C3'	C2'	114.3(4)
C5'	C4'	O1'	109.7(4)	C5'	C4'	C3'	113.7(4)
O1'	C4'	C3'	103.4(4)	O5'	C5'	C4'	106.7(5)
C1'	O1'	C4'	110.4(4)	C6'	O2'	C2'	116.4(4)
C8'	O3'	C3'	117.3(4)	C10'	O5'	C5'	125.5(7)
C7'	C6'	O6'	127.4(5)	C7'	C6'	O2'	109.3(5)
O6'	C6'	O2'	123.4(5)	C9'	C8'	O8'	126.5(5)
C9'	C8'	O3'	110.1(5)	O8'	C8'	O3'	123.4(5)
C11'	C10'	O10'	125.9(10)	C11'	C10'	O5'	116.0(9)
O10'	C10'	O5'	118.0(10)				
21							
N2	N1	C5	110.3(2)	N2	N1	C1'	122.0(2)
C5	N1	C1'	127.8(2)	C3	N2	N1	102.1(2)
N4	C3	S6	122.6(2)	N4	C3	N2	115.2(2)
S6	C3	N2	122.2(2)	C5	N4	C3	102.7(2)
N1	C5	N4	109.7(2)	O7	S6	O8	120.87(12)
O7	S6	N9	107.72(11)	O7	S6	C3	106.09(11)

Table 3 (continued)
 Bond Angles (°) in **7**, **14** and **21**

1	2	3	1-2-3	1	2	3	1-2-3
O8	S6	N9	108.04(12)	O8	S6	C3	105.87(11)
N9	S6	C3	107.61(9)	C2'	C1'	O1'	106.9(2)
C2'	C1'	N1	112.24(14)	O1'	C1'	N1	109.1(2)
C3'	C2'	O2'	105.4(2)	C3'	C2'	C1'	101.6(2)
O2'	C2'	C1'	110.96(15)	C4'	C3'	O3'	114.6(2)
C4'	C3'	C2'	101.91(14)	O3'	C3'	C2'	114.2(2)
C5'	C4'	O1'	108.7(2)	C5'	C4'	C3'	115.0(2)
O1'	C4'	C3'	103.94(15)	O5'	C5'	C4'	110.5(2)
C1'	O1'	C4'	110.37(15)				

Table 4

Sugar Conformational Parameters for Compounds **7**, **14** and **21**

Parameter	7	14	21
P (°)	170.0	36.8	13.1
τ (°)	35.2	37.1	38.4
Conformation	² T ₃	⁴ T	³ T ₂
	C _{2'} , <i>endo</i>	C _{3'} , <i>endo</i> -C _{4'} , <i>exo</i>	C _{3'} , <i>endo</i>
χ_{CN} (°) O1'-C1'-N _x -Y	x = 2, Y = N1	x = 1, Y = C5	x = 1, Y = C5
	73.8(2)	-91.9(6)	-114.0(2)
ϕ_{∞} (°) O1'-C4'-C5'-O5'	50.6(2)	79.4(5)	56.1(2)
ϕ_{co} (°) C3'-C4'-C5'-O5'	169.0(2)	-165.3(4)	172.1(2)
	gt	gt	gt

erated *in situ* by the addition of sodium hydride in anhydrous acetonitrile, with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl- α -D-erythro-pentofuranose (**22**) [34] gave a mixture of two nucleoside products. After silica gel column chromatography (methylene chloride:ethyl acetate, 85:15 as the solvent), the lower *R_f* product 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl- β -D-erythro-pentofuranosyl)-1,2,4-triazole-3-sulfonamide (**26**) in 40% yield and a higher *R_f* product 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl- β -D-erythro-pentofuranosyl)-1,2,4-triazole-5-sulfonamide (**24**) in 13% yield, were obtained. Ammonolysis of **24** and **26** with methanolic ammonia at room temperature for 15 hours gave the deblocked nucleosides **25** and **27**, respectively. The ¹H nmr studies provided unequivocal proof for the assignment of structures for **25** and **27** when compared with the ¹H nmr spectra of appropriate triazoles as reported previously from our laboratory [35]. In the ¹H nmr spectrum of **27**, the C-5 ring proton (δ 8.89 ppm) had a comparable chemical shift to the C-5 proton resonance (δ 8.91 ppm) of ribavirin [35]. Similarly, the C-3 ring proton resonance (δ 8.21 ppm) of **25** was very similar to that of 1- β -D-ribofuranosyl-1,2,4-triazole-5-carboxamide (δ 8.16 ppm) [35]. The anomeric configuration of **25** and **27** was

also assigned as β by ¹H nmr data, where the characteristic triplet for the anomeric proton was observed at δ 6.60 and δ 6.24 ppm, respectively. This pattern is similar to that observed for the anomeric proton of other 2'-deoxy- β -D-ribonucleosides [36,37]. The site of glycosylation in **27** was further corroborated as *N*-1 by comparison of the uv spectrum of **21** and **27**, which are identical.

The preparation of the β -D-arabinofuranosyl derivative of **19** was also accomplished in a manner similar to that of **27**. Glycosylation of the sodium salt of **19** (generated *in situ* by the addition of sodium hydride in anhydrous acetonitrile) with 1-chloro-2,3,5-tri-*O*-benzyl- α -D-arabinofuranose (**23**) [38] at ambient temperature and subsequent purification of the reaction product by flash chromatography on silica gel gave 1-(2,3,5-tri-*O*-benzyl- β -D-arabinofuranosyl)-1,2,4-triazole-3-sulfonamide (**28**) in good yield. Nucleoside **28** was the only nucleoside product which could be detected in the reaction mixture by tlc or column chromatography procedures. Debenzylation of **28** with boron trichloride at low temperature gave the desired 1- β -D-arabinofuranosyl-1,2,4-triazole-3-sulfonamide (**29**) in 71% yield. The site of glycosyl attachment in **29** was established as *N*-1 by comparison of the uv spectrum of **29** (266 nm) with that of **21** (266 nm), which are identical. The anomeric configuration of **29** was again assigned as β on the basis of *J*_{1',2'} coupling constant (5.73 Hz) observed for the anomeric proton in the ¹H nmr spectra, which is within the region of 3.5-8.0 Hz as expected for a vicinal, *cis* arrangement of the C_{1'} and C_{2'} protons [39].

Single-Crystal X-ray Diffraction Analyses of Compounds **7**, **14** and **21**.

Atomic coordinates for compounds **7**, **14** and **21** are listed in Table 1. Bond lengths and bond angles involving only non-hydrogen atoms are given in Tables 2 and 3. The conformations of each are illustrated in Figures 1, 2 and 3, respectively. In all Figures, non-hydrogen atoms are repre-

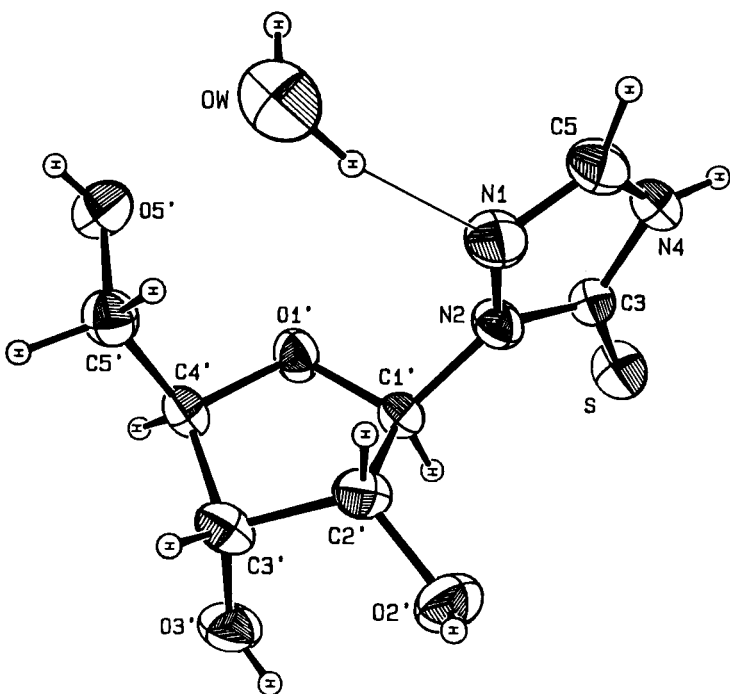


Figure 1. Perspective drawing of 7.

sented by thermal ellipsoids drawn at the 50% probability level and hydrogens are drawn with arbitrary radii.

Compound 7 exists in the thione form possessing a very short C3-S bond length of 1.675(2) Å. Comparing 7 with 2- and 4- β -D-ribofuranosyl-1,2,4-triazolin-3-one [40] analogs, shows a general similarity in bond length and bond angle patterns. The N1-C5 bond is a predominant double bond in all three. However, in 7, the C3-N2 and C3-N4 bonds are equivalent whereas in the oxo analogs C3-N2 is 0.05-0.06 Å shorter than C3-N4. The bonding patterns in the triazole rings of 14, 21 and the two forms of ribavirin (3) [6,7] are likewise similar; the predominant double bond character occurs in N2-C3, N4-C5 and N1-C5. As expected, the fully oxidized S in 21 compared to 14 results in a longer C3-S6 bond length. The sulfonamide nitrogen, N9, is 1.467(2) Å out of the triazole plane unlike the carboxamide nitrogens in the two forms of ribavirin which are nearly coplanar with the triazole rings. The triazole rings of 7, 14 and 21 are planar with rms deviations of 0.003, 0.002 and 0.009 Å, respectively. The dihedral angle between the triazole and phenyl rings in 14 is 70.1(2)°. The planar C3-S6-C7-C8 fragment (rms deviation 0.009 Å) makes a dihedral angle of 22.4(3)° and 87.5(3)° with the triazole and phenyl rings respectively.

The ribose conformational parameters are summarized

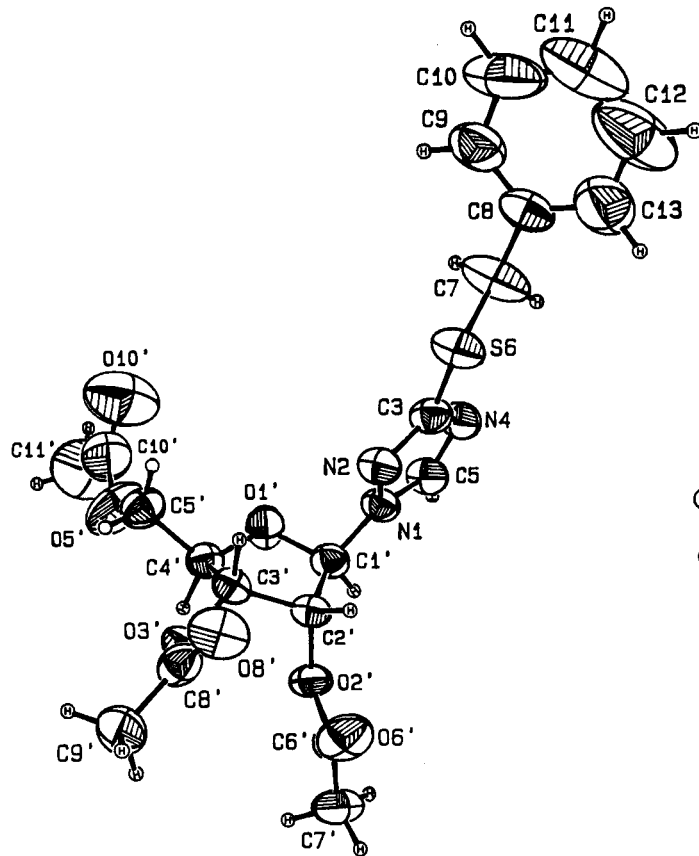


Figure 2. Perspective drawing of 14.

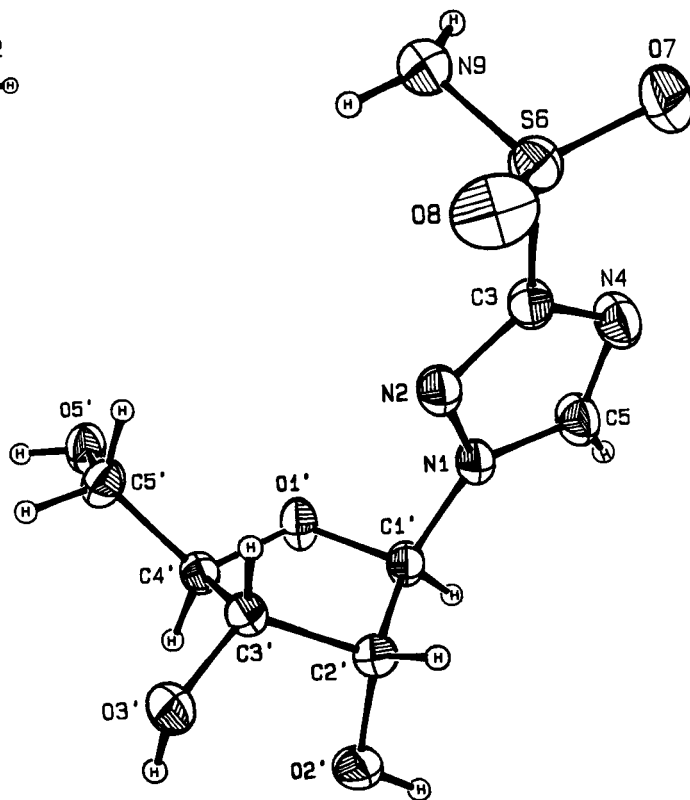


Figure 3. Perspective drawing of 21.

Table 5
Hydrogen Bonding in **7** and **21**.

D	H	A	Symmetry of A relative to D	d(H...A) (Å)	d(D...A) (Å)	$\angle(\text{D}-\text{H}\cdots\text{A})$ (°)
7						
N4	H4	O5'	$x-0.5, 0.5-y, 2.0-z$	2.04(4)	2.848(3)	169.(4)
O2'	HO2'	O5'	$x-1.0, \quad y, \quad z$	1.94(3)	2.728(3)	158.(3)
O3'	HO3'	S	$-x, y+0.5, 1.5-z$	2.64(4)	3.408(2)	159.(3)
O3'	HO3'	O2'	$x, \quad y, \quad z$	2.35(4)	2.741(2)	110.(3)
O5'	HO5'	OW	$x+0.5, 1.5-y, 2.0-z$	1.94(5)	2.640(3)	166.(5)
OW	HW1A	N1	$x, \quad y, \quad z$	1.95(4)	2.948(3)	167.(4)
OW	HW1B	S	$x+0.5, 0.5-y, 2.0-z$	2.25(4)	3.255(2)	173.(3)
21						
N9	HN9A	O3'	$-x, y-0.5, 1.0-z$	2.10(3)	2.912(2)	161.(3)
N9	HN9B	O5'	$1.0-x, y-0.5, 1.0-z$	2.00(3)	2.908(3)	160.(3)
O2'	HO2'	O1'	$1.0-x, 0.5+y, 1.0-z$	1.96(4)	2.771(2)	156.(4)
O3'	HO3'	N2	$-x, 0.5+y, 1.0-z$	2.51(7)	3.080(2)	124.(5)
O5'	HO5'	N4	$x, \quad y, 1.0+z$	2.07(4)	2.836(2)	158.(4)

in Table 4. The sugar rings in **7** and **21** fall into the conformational ranges frequently observed in β -purine and β -pyrimidine nucleosides [41] while in **14**, the blocked sugar does not. The conformation of **21** is the same as form I of ribavirin. However, the glycosidic linkages are much different with **21** (and **14**) in the *syn* region and form I of **3** in the *anti* region. The side chain is *gt* in each structure. Bond lengths and thermal parameters suggest orientational disorder in the O5' acetyl and the benzyl groups in **14**.

Hydrogen bonding geometries in the structures **7** and **21** are listed in Table 5; there is no hydrogen bonding in the fully blocked nucleoside **14**. All hydroxyl groups in **7** and **21** act as donors. Only O5' in **7** and O3' and O5' in **21** are acceptors in hydrogen bonding. In **7**, the water molecule is involved in three hydrogen bonds and there appears to be a weak intramolecular hydrogen bond between O3' and O2'. Compound **21** exhibits the unusual feature of a hydrogen bond involving O1'.

EXPERIMENTAL

Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting-point apparatus. Elemental analyses were performed by Robertson Laboratory, Madison, NJ. 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 with a Perkin-Elmer 1420-spectrophotometer and ultraviolet spectra (uv) were recorded on a Beckman DU-50 spectrophotometer. Nuclear

magnetic resonance (^1H 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. The signals are described as s (singlet), d (doublet), t (triplet), and m (multiplet).

2-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole-3(4*H*)-thione (**6**) and 4-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole-3(2*H*)-thione (**8**).

Method A.

A mixture of 1,2,4-triazole-3(1*H*,2*H*)-thione (**4**, 4.04 g, 40 mmoles) [24] and 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose (**5**, 12.72 g, 40 mmoles) was heated in an oil bath maintained at 150°. Bis(*p*-nitrophenyl) phosphate (0.10 g) was added with stirring, and heating at 150° under diminished pressure was continued for 20 minutes. The reaction mixture was cooled, dissolved in chloroform (250 ml) and the organic phase was washed with 5% sodium bicarbonate solution (2 x 100 ml), followed by water (3 x 50 ml). The dried (sodium sulfate) organic extracts were evaporated, and the residue was purified on a silica gel column (5 x 20 cm) using chloroform-methanol (99:1, v/v) as the solvent. The following two nucleosides were isolated in the order listed: 4-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole-3(2*H*)-thione (**8**), amorphous solid, 2.60 g (18%); uv λ max (methanol): 257 nm (ϵ 10,400); ^1H nmr (DMSO- d_6): δ 2.05-2.11 (3 s, 9, 3COCH₃), 6.10 (d, 1, J_{1',2'} = 6.0 Hz, C_{1'*H*}), 8.72 (s, 1, C_{5'*H*}) and 13.98 (br s, 1, N₂H, exchanged with deuterium oxide).

Anal. Calcd. for C₁₃H₁₇N₃O₇S (mw 359.33): C, 43.45; H, 4.77; N, 11.69; S, 8.92. Found: C, 43.64; H, 4.69; N, 11.42; S, 8.70.

2-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole-3(4*H*)-thione (**6**) was an amorphous solid, 1.20 g (8.3%); uv λ max (methanol): 253 nm (ϵ 12,100); ^1H nmr (DMSO- d_6): δ 2.01-2.08 (3 s, 9, 3COCH₃), 6.31 (d, 1, J_{1',2'} = 3.81 Hz, C_{1'*H*}), 8.50 (s, 1, C_{5'*H*}) and 13.80 (br s, 1, N₄H, exchanged with deuterium oxide).

Anal. Calcd. for C₁₃H₁₇N₃O₇S (mw 359.33): C, 43.45; H, 4.77; N, 11.69; S, 8.92. Found: C, 43.22; H, 4.63; N, 11.50; S, 8.69.

Method B.

A mixture of **4** (4.04 g, 40 mmoles), hexamethyldisilazane (HMDS, 90

Table 6
Crystal and Experimental Data [a] [b] for Compounds **7**, **14** and **21**

	7	14	21
Empirical formula	C ₇ H ₁₁ N ₃ O ₄ S·H ₂ O	C ₂₀ H ₂₃ N ₃ O ₇ S	C ₇ H ₁₂ N ₄ O ₆ S
Formula weight	251.26	449.49	280.26
Crystal system	orthorhombic	orthorhombic	monoclinic
Space group	P2 ₁ 2 ₁ 2 ₁	P2 ₁ 2 ₁ 2 ₁	P2 ₁
a (Å)	7.1211(7)	8.8428(7)	6.6598(5)
b (Å)	8.8197(11)	9.8670(12)	9.2240(6)
c (Å)	17.430(2)	25.812(4)	9.2328(9)
β (°)	90.0	90.0	105.538(15)
V (Å ³)	1094.7(2)	2252.2(5)	546.44(9)
Z	4	4	2
ρ_{calcd} (g cm ⁻³)	1.52	1.33	1.70
F(000) (electrons)	488	944	584
Radiation, λ (Å)	CuK α , 1.54178	CuK α , 1.54178	CuK α , 1.54178
Crystal dimensions (mm)	0.44 x 0.12 x 0.06	0.40 x 0.29 x 0.075	0.40 x 0.34 x 0.13
μ (cm ⁻¹)	27.36	16.33	29.16
max 2θ (°)	152	152	152
Total refls, measd, unique	1329, 1329	2686, 2686	1312, 1220
Observed refls ($F \geq 4\sigma_F$)	1249	2215	1215
No. of variables	209	324	211
S (goodness of fit)	1.478	2.58	1.72
R, wR [c]	0.027, 0.039	0.059, 0.083	0.024, 0.036
Extinction parameter	$2.7(2) \times 10^{-6}$	$3.9(12) \times 10^{-7}$	$8.0(5) \times 10^{-6}$
Max Δ/σ	0.050	0.001	0.022
Max, min in $\Delta\rho$ map (e/Å ³)	0.16, -0.22	0.51, -0.35	0.24, -0.22

[a] Unit-cell parameters were obtained by least-squares refinement of the setting angles of 25 reflections in the ranges: for **7**, $53.1 < 2\theta < 59.5^\circ$; for **14**, $52.5 < 2\theta < 58.7^\circ$; for **21**, $51.6 < 2\theta < 59.5^\circ$. [b] Intensity measurements were made on an Enraf-Nonius CAD4 automatic diffractometer equipped with a graphite monochromator using an ω - 2θ scan procedure and variable scan speeds. Data reduction was accomplished with the SDP-Plus program package and included Lorentz, polarization, decay and absorption corrections [42]. [c] Function minimized was $\sum w(|F_o| - |F_c|)^2$, where $w = (\sigma_F^2 + 0.0004F^2)^{-1}$ for all three structures. $\sigma_F = F\sigma/2I$ and $\sigma_I = (N_{pk} + N_{bg} + N_{bg2})^{1/2}$.

ml) and ammonium sulfate (0.2 g) was heated under reflux at 150° (oil bath temperature) for 18 hours. The excess of HMDS was evaporated at 55 – 60° under diminished pressure. The residue was co-evaporated with dry toluene (2 x 50 ml) and dried for 30 minutes at 50° *in vacuo* to give the bis-silylated triazole. To a stirred solution of the silylated triazole in anhydrous acetonitrile (80 ml) was added **5** (12.72 g, 40 mmol) followed by trimethylsilyl triflate (13.12 ml, 57.6 mmol) and the mixture was stirred at room temperature. After 1 hour the reaction mixture was evaporated. The residue was dissolved in ethyl acetate (300 ml) and washed with 5% sodium bicarbonate solution (300 ml). The organic layer was separated, washed with water (2 x 100 ml), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed on a silica gel column as described in Method A to yield 1.8 g (17%) of **8** and 5.2 g (36%) of **6**. The products **6** and **8** were identical in all respects with **6** and **8** obtained by Method A.

2- β -D-Ribofuranosyl-1,2,4-triazole-3(4H)-thione (**7**).

A solution of **6** (0.61 mmol) in methanolic ammonia (saturated at 0° , 20 ml) was kept at 4° for 20 hours. The solvent was removed and the

residue was purified on a silica gel column (1.5 x 20 cm) using chloroform:methanol (9:1 and 8:2, v/v) as the eluent to provide 0.11 g of **7**. Crystallization from ethanol afforded 0.10 g (71%) of analytical sample, mp 186 – 188° ; uv λ max (pH 1): 256 nm (ϵ 18,500); (pH 7): 257 nm (ϵ 17,100); (pH 11): 250 nm (ϵ 16,400); ^1H nmr (DMSO- d_6): δ 6.09 (d, 1, $J_{1,2'} = 3.75$ Hz, C₁H), 8.39 (s, 1, C₅H) and 13.61 (s, 1, N₄H, exchanged with deuterium oxide).

Anal. Calcd. for C₇H₁₁N₃O₄S (mw 233.24): C, 36.04; H, 4.75; N, 18.02; S, 13.75. Found: C, 35.89; H, 4.72; N, 17.87; S, 13.59.

4- β -D-Ribofuranosyl-1,2,4-triazole-3(2H)-thione (**9**).

Method A.

In the same manner as for **7**, the title compound was prepared using **8** (0.27 g, 0.75 mmol) and methanolic ammonia (25 ml). The product was crystallized from ethanol to yield 0.16 g (91%) of **9**, mp 135 – 137° ; uv λ max (pH 1): 252 nm (ϵ 11,000); (pH 7): 249 nm (ϵ 9,600); (pH 11): 238 nm (ϵ 8,700); ^1H nmr (DMSO- d_6): δ 5.81 (d, 1, $J_{1,2'} = 5.01$ Hz, C₁H), 8.68 (s, 1, C₅H) and 13.81 (s, 1, N₂H, exchanged with deuterium oxide).

Anal. Calcd. for C₇H₁₁N₃O₄S (mw 233.24): C, 36.04; H, 4.75; N, 18.02; S, 13.75. Found: C, 35.95; H, 4.79; N, 17.76; S, 13.53.

Method B.

To a solution of **12** (5.4 g, 10 mmol) in anhydrous methanol (100 ml) was added a 1*N* solution of sodium methoxide in methanol until the pH of the solution was 9. The alkaline solution was stirred at room temperature for 5 hours. Complete conversion of the starting material to a new product was indicated by tlc (silica gel, chloroform:methanol, 9:1, v/v). The solution was neutralized with Dowex-50 (H⁺) resin and filtered. The filtrate was evaporated to dryness and the residue was crystallized from *iso*-propyl alcohol to yield 2.0 g (86%) of **9**, mp 136–137°.

Anal. Calcd. for C₇H₁₁N₃O₄S (mw 233.24): C, 36.04; H, 4.75; N, 18.02; S, 13.75. Found: C, 35.98; H, 4.60; N, 18.10; S, 14.07.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole-3(2*H*)-thione (**12**).

Acetic anhydride (10 ml) was cooled to 0° and to this was added dropwise with stirring formic acid (99%, 5 ml). The mixture was heated at 50° for 15 minutes and then cooled to 0°. To the cold mixture was added 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiosemicarbazide (**10**, 3.0 g, 5.6 mmol) [25] and 4-dimethylaminopyridine (DMAP, 50 mg). The resulting solution was stirred at room temperature for 15 hours. The reaction mixture was evaporated to dryness and the residue was co-evaporated with methanol (5 x 50 ml). Crystallization of the residue with hot methanol gave 2.1 g (69%) of the title compound, mp 179–180°.

Anal. Calcd. for C₂₈H₂₃N₃O₇S (mw 545.54): C, 61.64; H, 4.25; N, 7.70; S, 5.88. Found: C, 61.75; H, 3.99; N, 7.58; S, 5.95.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-3-benzylthio-1,2,4-triazole (**14**) and 1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-5-benzylthio-1,2,4-triazole (**16**).

Method A.

In a similar manner as for **6** and **8** (Method B), silylation of 3-benzylthio-1,2,4-triazole (**13**, 1.34 g, 7 mmol) [27] with HMDS (20 ml) in the presence of ammonium sulfate (0.10 g) and subsequent glycosylation with **5** (2.33 g, 7 mmol) in the presence of trimethylsilyl triflate (2 ml, 10.1 mmol) gave crude products. Purification of the products on a silica gel column (3 x 20 cm) using successively 200 ml portions of methylene chloride:methanol (98:2 and 96:4, v/v) gave two nucleosides, which were isolated in the following order: 1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-3-benzylthio-1,2,4-triazole (**14**), 1.30 g (41%) as syrup; ¹H nmr (DMSO-*d*₆): δ 1.96–2.09 (3 s, 9, 3COCH₃), 4.34 (s, 2, CH₂C₆H₅), 6.21 (d, 1, J_{1',2'} = 2.04 Hz, C₁H), 7.22–7.74 (m, 5, CH₂C₆H₅) and 8.73 (s, 1, C₃H).

Anal. Calcd. for C₂₀H₂₃N₃O₇S (mw 449.49): C, 53.44; H, 5.16; N, 9.35; S, 7.13. Found: C, 53.37; H, 5.34; N, 9.26; S, 7.06.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-5-benzylthio-1,2,4-triazole (**16**) was a syrup (0.46 g, 15%); ¹H nmr (DMSO-*d*₆): δ 2.00–2.09 (3 s, 9, 3COCH₃), 4.47 (s, 2, CH₂C₆H₅), 5.92 (d, 1, J_{1',2'} = 2.28 Hz, C₁H), 7.25–7.38 (m, 5, CH₂C₆H₅) and 8.20 (s, 1, C₃H).

Anal. Calcd. for C₂₀H₂₃N₃O₇S (mw 449.49): C, 53.44; H, 5.16; N, 9.35; S, 7.13. Found: C, 53.22; H, 5.09; N, 9.19; S, 7.10.

Method B.

A mixture of **13** (0.96 g, 5 mmol) and **5** (1.59 g, 5 mmol) was heated at 185° in the presence of bis(*p*-nitrophenyl) phosphate (0.10 g) under diminished pressure for 15 minutes. Chromatography of the resulting reaction mixture on a silica gel column as described for **6** and **8** (Method A), gave **14** (48%) and **16** (35%), identical with the ones prepared by Method A.

1-β-D-Ribofuranosyl-3-benzylthio-1,2,4-triazole (**15**).

In the same manner as for **7**, the title compound was prepared using **14** (0.67 g, 1.5 mmol) and methanolic ammonia (40 ml). The product was crystallized from diethyl ether to yield 0.37 g (76%) of **15**, mp 110–112°; ¹H nmr (DMSO-*d*₆): δ 4.32 (s, 2, CH₂C₆H₅), 5.73 (d, 1, J_{1',2'} = 3.75 Hz, C₁H), 7.22–7.41 (m, 5, CH₂C₆H₅) and 8.78 (s, 1, C₃H).

Anal. Calcd. for C₁₄H₁₇N₃O₄S (mw 323.36): C, 52.00; H, 5.30; N, 13.00; S, 9.91. Found: C, 51.94; H, 5.31; N, 13.03; S, 10.18.

1-β-D-Ribofuranosyl-5-benzylthio-1,2,4-triazole (**17**).

In a similar manner as for **7**, compound **17** was prepared using **16** (0.45 g, 1 mmol) and methanolic ammonia (30 ml). The product was crystallized from diethyl ether to yield 0.20 g (64%) of **17**, mp 100°; ¹H nmr (DMSO-*d*₆): δ 4.47 (s, 2, CH₂C₆H₅), 5.60 (d, 1, J_{1',2'} = 4.20 Hz, C₁H), 7.28–7.42 (m, 5, CH₂C₆H₅) and 8.09 (s, 1, C₃H).

Anal. Calcd. for C₁₄H₁₇N₃O₄S (mw 323.36): C, 52.00; H, 5.30; N, 13.00; S, 9.91. Found: C, 51.76; H, 5.41; N, 13.27; S, 9.76.

1,2,4-Triazole-3-sulfonyl Fluoride (**18**).

To a polyethylene beaker, cooled in an ice-salt bath, were added methanol (70 ml), 48% hydrofluoric acid (7.5 ml) and potassium fluoride dihydrate (7.5 g). The solution was cooled to 10° and 1,2,4-triazole-3(1*H*,2*H*)-thione (**4**, 9.2 g, 91 mmol) [24] was added. The mixture was cooled to 0° and with stirring a fast stream of chlorine gas was bubbled into the reaction mixture. The rate of chlorine introduction was adjusted so that a reaction temperature of <5° was maintained. The time required for the reaction to complete was 4 hours, as judged by tlc. The reaction mixture was poured slowly with stirring onto crushed ice (200 g). The mixture was stirred for 5 minutes (excess ice must always be present), and the pale-yellow solid was collected by filtration, washed thoroughly with ice-cold water, pressed dry and air-dried. The dry residue was crystallized from boiling absolute ethanol to yield 4.3 g (32%) of **18**, mp 68–70°; ir (potassium bromide): ν max 1160 (S=O), 1260 (SO₂ sym), 1380 (SO₂, antisym) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 9.21 (s, 1, C₃H) and 12.10 (br s, 1, NH).

Anal. Calcd. for C₂H₂FN₃O₂S·½ H₂O (mw 151.1): C, 15.00; H, 1.25; N, 26.26; F, 20.00; S, 11.88. Found: C, 15.24; H, 1.24; N, 26.01; F, 19.74; S, 11.82.

1,2,4-Triazole-3-sulfonamide (**19**).

To liquid ammonia (50 ml) was added, with stirring, finely powdered **18** (3.0 g, 20 mmol) in small portions over a period of 10 minutes. The ammonia was allowed to evaporate, with stirring, over a period of 30 minutes at room temperature. The resulting moist solid was dissolved in ice cold water (50 ml), and the pH of the solution adjusted to 5 with glacial acetic acid. After allowing the mixture to stand at 0° overnight, the precipitated **19** was collected by filtration and dried to yield 1.20 g (40%), mp 227–230° [lit [3] mp 224.5–225.5°]; ir (potassium bromide): ν max 1160, 1370 (SO₂) and 3200–3600 (NH₂) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 7.78 (br s, 2, SO₂NH₂), 8.75 (s, 1, C₃H) and 14.66 (br s, 1, NH).

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-3-sulfonamide (**20**).

A mixture of dry **19** (1.48 g, 10 mmol), HMDS (20 ml) and ammonium sulfate (100 mg) was heated under reflux at 150° (oil bath temperature) for 18 hours with the exclusion of moisture. The excess of HMDS was evaporated at 50–55° (bath temperature) under diminished pressure to give the silylated sulfonamide. To a solution of the silylated sulfonamide in acetonitrile (35 ml) was added dry **5** (3.18 g, 10 mmol), followed by trimethylsilyl triflate (2.78 ml, 14.4 mmol), and the mixture was stirred at room temperature for 1 hour, at which time tlc (silica gel, methylene chloride:methanol, 96:4, v/v) indicated complete conversion of the starting material to a new product. The reaction mixture was evaporated to dryness and the residue was dissolved in ethyl acetate (150 ml). The organic layer was washed with a 5% sodium bicarbonate solution (2 x 75 ml), followed by water (2 x 100 ml), before it was dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by flash chromatography over silica gel using successively methylene chloride (200 ml), and methylene chloride:methanol [98:2 (500 ml), 96:4 (500 ml), v/v] as the eluent. The homogeneous fractions were pooled together and evaporated to give 2 g (50%) of **20** as a semisolid; ir (potassium bromide): ν max 1060 (SO), 1235, 1370 (SO₂), 1750 (C=O) and 3200–3500 (NH₂) cm⁻¹; uv (ethanol): λ max 266 nm (ε 8,800); ¹H nmr (DMSO-*d*₆): δ 2.02–2.10 (3 s, 9, 3COCH₃), 6.36 (d, 1, J_{1',2'} = 3.35 Hz, C₁H), 7.95 (s, 2, SO₂NH₂) and 8.97 (s, 1, C₃H).

Anal. Calcd. for $C_{13}H_{18}N_4O_7S$ (mw 406.36): C, 38.42; H, 4.46; N, 13.79; S, 7.89. Found: C, 38.27; H, 4.34; N, 13.59; S, 7.63.

1- β -D-Ribofuranosyl-1,2,4-triazole-3-sulfonamide (**21**).

In the same manner as for **7**, treatment of **20** (2.03 g, 5 mmoles) with methanolic ammonia (100 ml, saturated at 0°) gave the crude product. Purification of the crude product by flash chromatography over silica gel using methylene chloride:methanol (9:1, 8:2, v/v) gave 1.5 g of homogeneous product, which after crystallization from methanol afforded 1.30 g (93%) of **21** as needles, mp 128-130°; ir (potassium bromide): ν max 1050 (SO), 1160, 1350 (SO₂) and 3000-3600 (NH₂, OH) cm⁻¹; uv (ethanol): λ max 266 nm (ϵ 2,400); ¹H nmr (DMSO-d₆): δ 5.83 (d, 1, J_{1',2'} = 4.5 Hz, C₁H), 7.86 (s, 2, SO₂NH₂) and 8.98 (s, 1, C₅H).

Anal. Calcd. for $C_7H_{12}N_4O_6S$ (mw 280.26): C, 30.00; H, 4.32; N, 19.99; S, 11.44. Found: C, 29.97; H, 4.26; N, 19.86; S, 11.22.

1-(2-Deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)-1,2,4-triazole-3-sulfonamide (**26**) and 1-(2-Deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)-1,2,4-triazole-5-sulfonamide (**24**).

A mixture of **19** (1.48 g, 10 mmoles) and sodium hydride (60% in oil, 0.5 g, 12.5 mmoles) in anhydrous acetonitrile (60 ml) was stirred at ambient temperature under a nitrogen atmosphere for 30 minutes. Dry, powdered 1-chloro-2-deoxy-3,5-di-O-p-toluoyl- α -D-erythro-pentofuranose (**22**, 3.88 g, 10 mmoles) [34] was added portionwise with stirring during 5 minutes, and stirring was continued for 20 hours. A small amount of insoluble material was removed by filtration. Evaporation of the filtrate gave an oily residue, which was purified on a silica gel column (2 x 20 cm) packed in methylene chloride, using methylene chloride:ethyl acetate (85:15, 8:2, v/v) as the eluent. The following two nucleosides were isolated in the order listed: 1-(2-deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)-1,2,4-triazole-5-sulfonamide (**24**), homogenous foam, 0.65 g (13%); ir (potassium bromide): ν max 1100, 1270, 1360 (SO₂), 1720 (C=O of ester) and 3200-3500 (NH₂) cm⁻¹; uv λ max (ethanol): 262 nm (ϵ 4,100); ¹H nmr (DMSO-d₆): δ 2.30 (s, 3, CH₃), 2.41 (s, 3, CH₃), 6.87 (t, 1, J_{1',2'} = 6.15 Hz, C₁H), 7.30-7.37 (m, 4, Ph), 7.85-7.90 (m, 4, Ph), 8.30 (s, 1, C₃H) and 8.51 (s, 2, SO₂NH₂).

Anal. Calcd. for $C_{23}H_{24}N_4O_7S$ (mw 500.51): C, 55.19; H, 4.83; N, 11.19; S, 6.41. Found: C, 54.97; H, 4.86; N, 10.95; S, 6.17.

1-(2-Deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)-1,2,4-triazole-3-sulfonamide (**26**) was a homogenous foam, 2.0 g (40%); ir (potassium bromide): ν max 1100, 1270, 1360 (SO₂), 1720 (C=O of ester) and 3200-3500 (NH₂) cm⁻¹; uv (ethanol): λ max 264 nm (ϵ 3,700); ¹H nmr (DMSO-d₆): δ 2.41 (s, 3, CH₃), 2.43 (s, 3, CH₃), 6.57 (t, 1, J_{1',2'} = 6.06 Hz, C₁H), 7.87 (s, 2, SO₂NH₂), 7.27-7.37 (m, 4, Ph), 7.86-7.92 (m, 4, Ph) and 9.00 (s, 1, C₅H).

Anal. Calcd. for $C_{23}H_{24}N_4O_7S$ (mw 500.51): C, 55.19; H, 4.83; N, 11.19; S, 6.41. Found: C, 54.92; H, 4.80; N, 10.93; S, 6.61.

1-(2-Deoxy- β -D-erythro-pentofuranosyl)-1,2,4-triazole-3-sulfonamide (**27**).

A solution of **26** (0.34 g, 0.67 mmole) in methanolic ammonia (saturated at 0°, 30 ml) was stirred at room temperature in a pressure bottle for 15 hours and then evaporated to dryness. The residue was purified by flash chromatography over silica gel using methylene chloride:methanol (9:1, 8:2, v/v) as the eluent. The homogeneous fractions were pooled and evaporated to dryness. The residue was crystallized from methanol to yield 0.10 g (40%) of **27**, mp 100°; ir (potassium bromide): ν max 1370, 1450 (SO₂) and 2700-3500 (NH₂, OH) cm⁻¹; uv (ethanol): λ max 266 nm (ϵ 3,800); ¹H nmr (DMSO-d₆): δ 6.24 (t, 1, J_{1',2'} = 5.94 Hz, C₁H), 7.82 (s, 2, SO₂NH₂) and 8.89 (s, 1, C₅H).

Anal. Calcd. for $C_7H_{12}N_4O_6S$ (mw 264.26): C, 31.82; H, 4.55; N, 21.21; S, 12.12. Found: C, 31.96; H, 4.62; N, 20.97; S, 11.91.

1-(2-Deoxy- β -D-erythro-pentofuranosyl)-1,2,4-triazole-5-sulfonamide (**25**).

The title compound was prepared in a similar manner as described for **27**, using **24** (0.40 g, 0.8 mmole) and methanolic ammonia (25 ml). The

product was isolated as an amorphous solid in 46% yield (0.12 g); ir (potassium bromide): ν max 1370, 1450 (SO₂) and 2700-3500 (NH₂, OH) cm⁻¹; uv (ethanol): λ max 264 nm (ϵ 3,900); ¹H nmr (DMSO-d₆): δ 6.67 (t, 1, J_{1',2'} = 6.0 Hz, C₁H), 7.74 (s, 2, SO₂NH₂) and 8.21 (s, 1, C₅H).

Anal. Calcd. for $C_7H_{12}N_4O_6S$ (mw 264.26): C, 31.82; H, 4.55; N, 21.21; S, 12.12. Found: C, 32.05; H, 4.79; N, 20.94; S, 11.88.

1-(2,3,5-Tri-O-benzyl- β -D-arabinofuranosyl)-1,2,4-triazole-3-sulfonamide (**28**).

To a stirred solution of **19** (1.48 g, 10 mmoles) in dry acetonitrile (50 ml) was added sodium hydride (60% in oil, 0.50 g, 12.5 mmoles) in small portions at room temperature. After the addition of sodium hydride, the mixture was stirred for 30 minutes, and then 1-chloro-2,3,5-tri-O-benzyl- α -D-arabinofuranose (**23**, 4.39 g, 10 mmoles) [38] in dry acetonitrile (50 ml) was added. The reaction mixture was stirred at room temperature for 20 hours under a nitrogen atmosphere, and filtered to remove a small amount of insoluble material. Evaporation of the filtrate gave an oily residue which was purified by flash chromatography using methylene chloride:methanol [98:2 (400 ml), 97:3 (400 ml), v/v] as the eluent to yield 2.2 g (40%) of **28** as syrup; ir (neat): ν max 1120, 1160, 1350 (SO₂) and 3000-3500 (NH₂) cm⁻¹; uv (ethanol): λ max 268 nm (ϵ 3,900); ¹H nmr (DMSO-d₆): δ 4.37, 4.44 and 4.54 (3 s, 6, 3CH₂C₆H₅), 6.46 (d, 1, J_{1',2'} = 5.76 Hz, C₁H), 7.28-7.31 (m, 15, 3CH₂C₆H₅), 7.92 (s, 2, SO₂NH₂) and 8.81 (s, 1, C₅H).

Anal. Calcd. for $C_{28}H_{30}N_4O_6S$ (mw 550.61): C, 61.07; H, 5.49; N, 10.18; S, 5.82. Found: C, 61.21; H, 5.44; N, 9.81; S, 5.71.

1- β -D-Arabinofuranosyl-1,2,4-triazole-3-sulfonamide (**29**).

To a cooled (-78°) and stirred solution of **28** (0.55 g, 1 mmole) in dry methylene chloride (100 ml) under an argon atmosphere was added 1M boron trichloride in methylene chloride (10 ml) dropwise during 15 minutes. The stirring was continued at -78° for 4 hours and at -25° for an additional 2 hours. To the reaction mixture methanol:methylene chloride (1:1, 40 ml) was added and stirred at room temperature for 1 hour, and then diluted with methanol (40 ml). The cooled (0-5°) solution was neutralized with concentrated ammonium hydroxide and stirred for 1 hour. The precipitated solid was collected by filtration and washed with methanol (20 ml), followed by methylene chloride (20 ml). The combined filtrates were evaporated, the residue was dissolved in methanol and adsorbed onto silica gel (2 g). The excess of the solvent was evaporated and the dry residue was placed on top of a silica gel column (1.5 x 15 cm) packed in methylene chloride. The column was eluted successively with (100 ml portions) methylene chloride:methanol (9:1 and 8:2, v/v). The homogeneous fractions were pooled and evaporated. The residue was crystallized from methanol to yield 0.20 g (71%) of **29**, mp 80°; ir (potassium bromide): ν max 1060, 1160, 1350 (SO₂) and 3000-3500 (NH₂, OH) cm⁻¹; uv (ethanol): λ max 266 nm (ϵ 2,600); ¹H nmr (DMSO-d₆): δ 6.06 (d, 1, J_{1',2'} = 5.73 Hz, C₁H), 7.82 (br s, 2, SO₂NH₂) and 8.79 (s, 1, C₅H).

Anal. Calcd. for $C_7H_{12}N_4O_6S$ (mw 280.26): C, 30.00; H, 4.32; N, 19.99; S, 11.44. Found: C, 30.24; H, 4.57; N, 19.69; S, 11.28.

X-Ray Crystallography.

Crystal and experimental data for **7**, **14** and **21** are summarized in Table 6. Crystals were obtained from evaporated methanol/dichloromethane solutions (8:2, v/v for **7** and **21**; 9:1, v/v for **14**). Six of the sixteen non-hydrogen atomic positions for **7** and 16 of the 18 non-hydrogen positions for **21** were obtained with MULTAN-82 [43]. A subsequent Fourier map for **7** and a difference Fourier map for **21** revealed the positions of the remaining non-hydrogen positions. Twenty-five non-hydrogen positions for **14** were obtained with SHELXS-86 [44] and the remaining six positions were found in a ΔF map. All structures were refined by a full-matrix least-squares procedure (SHELX-76) [45]. All positional and thermal parameters were refined for compounds **7** and **21** (only non-hydrogen atoms were treated anisotropically); in **14** the phenyl ring was treated as a rigid group and the phenyl, benzyl and methyl hydrogens were idealized with d(C-H)=1.00 Å. Atomic scattering factors and anomalous-dispersion corrections for non-hydrogen atoms were taken from the In-

ternational Tables for X-ray Crystallography [46]. For hydrogen, these parameters were taken from Stewart, Davidson and Simpson [47]. Figures were drawn with ORTEPII [48]; least-squares planes program was obtained from Cordes [49].

Acknowledgement.

The authors wish to thank Ms. Sandy Young for her very competent and meticulous typing of this manuscript.

REFERENCES AND NOTES

- [1] N. Anand in "Burger's Medicinal Chemistry", Pt. II, M. E. Wolff, ed, Wiley-Interscience Publication, New York, 1979, pp 1-40.
- [2] F. O. McCallum and G. M. Findlay, *Lancet*, 136 (1938).
- [3] L. Bonina, G. Orzalesi, R. Merendino, A. Arena and P. Mastroeni, *Antimicrob. Agents Chemother.*, **22**, 1067 (1982).
- [4] H. Ohnishi, K. Yamaguchi, S. Shinada, S. Himuro and Y. Suzuki, *Antimicrob. Agents Chemother.*, **22**, 250 (1982).
- [5] J. T. Witkowski, R. K. Robins, R. W. Sidwell and L. N. Simon, *J. Med. Chem.*, **15**, 1150 (1972).
- [6] P. Prusiner and M. Sundaralingam, *Nature New Biol.*, **244**, 116 (1973).
- [7] P. Prusiner and M. Sundaralingam, *Acta Cryst.*, **B32**, 419 (1976).
- [8] "Ribavirin, A Broad-Spectrum Antiviral Agent", R. A. Smith and W. Kirkpatrick, eds, Academic Press, New York, 1980.
- [9] R. W. Sidwell, G. R. Revankar and R. K. Robins in "Viral Chemotherapy", Vol 2, D. Shugar, ed, Pergamon Press, New York, 1985, pp 49.
- [10] "Clinical Applications of Ribavirin", R. A. Smith, V. Knight and J. A. D. Smith, eds, Academic Press, New York, 1984.
- [11] L. H. Taber, V. Knight, B. E. Gilbert, H. W. McClung, S. Z. Wilson, H. J. Norton, J. M. Thurson, W. H. Gordon, R. L. Atmar and W. R. Schlaudt, *Pediatr.*, **72**, 613 (1983).
- [12] C. B. Hall, J. T. McBride, E. E. Walsh, D. M. Bell, C. L. Gala, S. Hildreth, L. G. Ten Eyck and W. J. Hall, *New Eng. J. Med.*, **308**, 1443 (1983).
- [13] C. G. Prober, *Hospital Therapy*, 45 (1987).
- [14] P. A. Brunell, R. S. Daum, G. S. Giebink, C. B. Hall, M. L. Lepow, G. H. McCracken, Jr., A. J. Nahmias, C. F. Phillips, S. A. Plotkin and H. T. Wright, *Pediatr.*, **79**, 475 (1987).
- [15] V. Knight, S. Z. Wilson, J. M. Quarles, S. E. Greggs, H. W. McClung, B. K. Waters, R. W. Cameron, J. M. Zerwas and R. B. Couch, *Lancet*, 945 (1981).
- [16] H. W. McClung, V. Knight, B. E. Gilbert, S. Z. Wilson, J. M. Quarles and G. Divine, *J. Am. Med. Assoc.*, **249**, 2671 (1983).
- [17] S. Z. Wilson, B. E. Gilbert, J. M. Quarles, V. Knight, H. W. McClung, R. V. Moore and R. B. Couch, *Antimicrob. Agents Chemother.*, **26**, 200 (1984).
- [18] B. E. Gilbert, S. Z. Wilson, V. Knight, R. B. Couch, J. M. Quarles, L. Dure, N. Hayes and G. Willis, *Antimicrob. Agents Chemother.*, **27**, 309 (1985).
- [19] V. Knight, B. E. Gilbert and S. Z. Wilson in "Studies with a Broad-Spectrum Antiviral Agent", T. Stapleton ed, Royal Society of Medicine Services, London, 1986, pp 37.
- [20] J. B. McCormick, P. A. Webb, K. M. Johnson and C. S. Scribner in "Clinical Applications of Ribavirin", R. A. Smith, V. Knight and J. A. D. Smith, eds, Academic Press, New York, 1984, pp 187.
- [21] J. B. McCormick, I. J. King, P. A. Webb, C. S. Scribner, R. B. Craven, K. M. Johnson, L. H. Elliott and R. Belmont-Williams, *New Engl. J. Med.*, **314**, 20 (1986).
- [22] J. W. Huggins, G. R. Kim, O. M. Brand and K. T. McKee, Jr., *J. Infect. Dis.*, **153**, 489 (1986).
- [23] L. M. Scheidel, R. K. Durbin and V. Stollar, *Virology*, **158**, 1 (1987).
- [24] Commercially available from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin.
- [25] M. Hohnjec, J. Kobe, U. Valcavi and M. Japelj, *J. Heterocyclic Chem.*, **12**, 909 (1975).
- [26] H. Vorbrüggen, K. Krolikiewicz and B. Bennua, *Chem. Ber.*, **114**, 1234 (1981).
- [27] H. Becke and K. Wehner, British Patent, 1,157,256 (July 1969).
- [28] K. D. Phillips and J. P. Horwitz, *J. Org. Chem.*, **40**, 1856 (1975).
- [29] R. O. Roblin, Jr. and J. W. Clapp, *J. Am. Chem. Soc.*, **72**, 4890 (1950).
- [30] A. G. Beaman and R. K. Robins, *J. Am. Chem. Soc.*, **83**, 4038 (1961).
- [31] Z. Kazimierczuk, H. B. Cottam, G. R. Revankar and R. K. Robins, *J. Am. Chem. Soc.*, **106**, 6379 (1984).
- [32] K. Ramasamy, R. K. Robins and G. R. Revankar, *Tetrahedron*, **42**, 5869 (1986).
- [33] K. Ramasamy, N. Imamura, R. K. Robins and G. R. Revankar, *Tetrahedron Letters*, **28**, 5107 (1987).
- [34] M. Hoffer, *Chem. Ber.*, **93**, 2777 (1960).
- [35] G. P. Kreishman, J. T. Witkowski, R. K. Robins and M. P. Schweizer, *J. Am. Chem. Soc.*, **94**, 5894 (1972).
- [36] M. J. Robins and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 4934 (1965).
- [37] K. Ramasamy, R. K. Robins and G. R. Revankar, *J. Heterocyclic Chem.*, **24**, 863 (1987).
- [38] C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 3004 (1963).
- [39] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
- [40] D. R. Haines, N. J. Leonard and D. F. Wiemer, *J. Org. Chem.*, **47**, 474 (1982).
- [41] C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.*, **94**, 8205 (1972).
- [42] B. A. Frenz, "Enraf-Nonius SDP-Plus Structure Determination Package. Version 3.0", Enraf-Nonius, Delft, The Netherlands, 1985.
- [43] P. Main, H. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq and M. M. Woolfson, *MULTAN-82*. "A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data", Univs. of York, England and Louvain, Belgium (1982).
- [44] G. M. Sheldrick, SHELXS-86. "Program for crystal structure determination", Univ. of Göttingen, Federal Republic of Germany (1986).
- [45] G. M. Sheldrick, SHELX-76. "Program for crystal structure determination", Univ. of Cambridge, England (1976).
- [46] "International Tables for X-ray Crystallography", Vol IV, J. A. Ibers and W. C. Hamilton, eds., Kynoch Press: Birmingham, England, 1974, pp 99, 149.
- [47] R. F. Stewart, E. R. Davidson and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).
- [48] C. K. Johnson, "ORTEPII. A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations", Oak Ridge National Laboratory ORNL-5138 Third Revision, March 1976.
- [49] A. W. Cordes, Personal Communication.