Synthesis of Certain Exocyclic Thiazole Nucleosides Related to Tiazofurin. Formation of a Unique Acycloaminonucleoside

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Several thiazole nucleosides structurally related to tiazofurin (**1**) and ARPP (**2**) were prepared, in order to determine whether these nucleosides had enhanced antitumor/antiviral activities. Ring closure of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiourea (**4**) with ethyl bromopyruvate (**5a**) gave ethyl 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylamino)thiazole-4-carboxylate (**6a**). Treatment of **6a** with sodium methoxide furnished methyl 2-(β-D-ribopyranosylamino)thiazole-4-carboxylate (**9**). Ammonolysis of the corresponding methyl ester of **6a** gave a unique acycloaminonucleoside 2-[(1*R*, 2*R*, 3*R*, 4*R*)(1-benzamido-2,3,4,5-tetrahydroxypentane)amino]-thiazole-4-carboxamide (**7a**). Direct glycosylation of the sodium salt of ethyl 2-mercaptothiazole-4-carboxylate (**12**) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**11**) gave the protected nucleoside **10**, which on ammonolysis provided 2-(β-D-ribofuranosylthio)thiazole-4-carboxamide (**3b**). Similar glycosylation of **12** with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride (**13**), followed by ammonolysis gave 2-(2-deoxy-β-D-ribofuranosylthio)thiazole-4-carboxamide (**3c**). The structural assignments of **3b**, **7a**, and **9** were made by single-crystal X-ray analysis and their hydrogen bonding characteristics have been studied. These compounds are devoid of any significant antiviral/antitumor activity *in vitro*.

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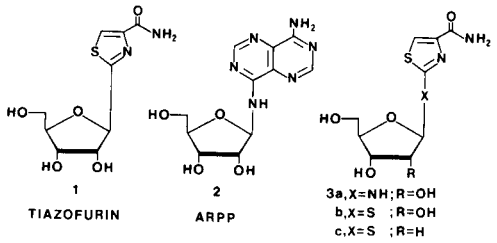
Introduction.

A large number of thiazole derivatives have been found as metabolic products [1] and a few of them exhibit a variety of pharmacological properties [2,3]. The synthetic oncolytic thiazole *C*-nucleoside, 2-β-D-ribofuranosylthiazole-4-carboxamide (tiazofurin, **1**) reported from our laboratory [4], is a promising antitumor agent [5], currently undergoing phase II clinical trials [6,7]. In preclinical trials in experimental murine tumor systems, tiazofurin was found to be very efficacious against P388 and L1210 leukemias and Lewis lung carcinoma [8,9], the later neoplasm being refractory to many chemotherapeutic agents. Tiazofurin was also active against four human lymphoid tumors in culture [10], *i.e.* CCRF-CEM, MOLT-4, HUT-8 (all T-cell leukemias) and NALM-1 (B-cell leukemia).



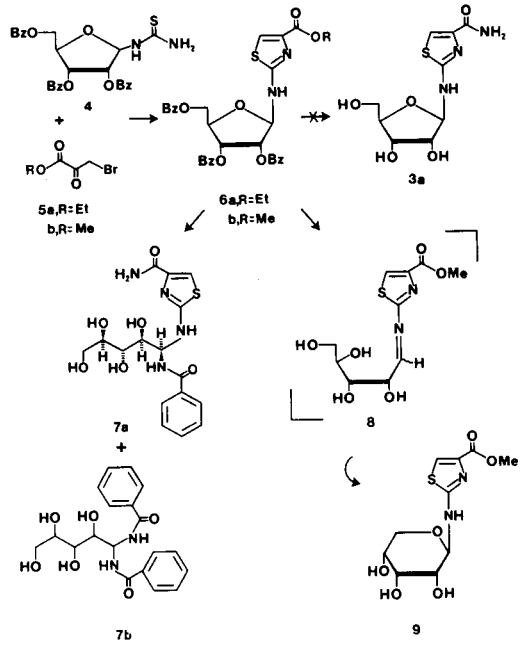
We have also reported [11,12] the synthesis of a novel *N*-nucleoside, 4-amino-8-(β-D-ribofuranosylamino)-pyrimido[5,4-*d*]pyrimidine (ARPP, **2**). The nucleoside **2** has shown some interesting broad spectrum antiviral activity against both DNA and RNA viruses in cell culture [12]. ARPP also showed immunosuppressive activity and inhibited the growth of L1210 leukemia in mice [13]. Considering the potent biological properties exhibited by the two structurally different nucleoside analogues, it was deemed desirable to understand the substrate specificity of enzymes involved in the mechanism of action of **1** and **2**. Therefore, the synthesis of 2-amino- and 2-thiothiazole nucleosides **3a-c** as biochemical probes, having structural resemblance to both tiazofurin and ARPP, is of particular interest. We now report details of our unusual results obtained during the synthesis of these novel 2-amino- and 2-thiothiazole nucleoside analogues related to **1** and **2**.

Results and Discussion.

Several methods have been described in the literature for the syntheses of *N*-glycosyl nucleoside derivatives [14,15]. Foye and An [16] synthesized 2-(β-D-glucopyranosylamino)thiazole-4-carboxamide from *N*-β-D-glycopyranosylthiourea and ethyl bromopyruvate to give ethyl 2-(β-D-glucopyranosylamino)thiazole-4-carboxylate in good yield, which on ammonolysis provided the corresponding 4-carboxamide derivative. Recently, Mota and coworkers [17] reported several 5-substituted-glycosylaminothiazoles prepared by ring closure of phenacylglycosylthioureas. Studies from our own laboratory [12] on the synthesis of **2**, by the treatment of ammonia with 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine-6-carbonitrile, indicated the stability of such β-*N*-glycosidic linkage towards base.

A logical extension of these findings was the use of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiourea [18] (**4**) with ethyl bromopyruvate (**5a**) to obtain the desired blocked *N*-nucleoside **6a**. When **4** was allowed to react with **5a** in ethanol at reflux temperature, it gave a complex mixture of products from which, after extensive column chromatography over silica gel, ethyl 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylamino)thiazole-4-carboxylate (**6a**) was obtained in 40% yield (Scheme I). Treatment of **6a** with sodium methoxide in methanol at room temperature, to debenzoylate the glycon moiety, furnished a crystalline polar product. Proton nmr of the product revealed a singlet at δ 3.75 (3 protons for $COOCH_3$ group) indicating transesterification had occurred. Surprisingly, the anomeric proton appeared as a multiplet at δ 4.87, which on deuterium exchange collapsed to a doublet ($J_{1',2'}$ = 8.5 Hz). It is rather unusual for an anomeric proton of a β-*N*-ribofuranosyl nucleoside to appear so very upfield. However, it it quite possible for the β-*N*-ribopyranosyl derivative to have an anomeric proton signal in this region. Such base-mediated rearrangements of ribosylamino to pyranosylamino derivatives have been reported recently by Nakanishi and coworkers [19]. Single-crystal X-ray diffraction analysis unambiguously confirmed the structure of this compound as methyl 2-(β-D-ribopyranosylamino)thiazole-4-carboxylate (**9**). The formation of **9** may be visualized as occurring by extraction of the N*H* proton by methoxide ion followed by the rapid ring opening of the β-D-ribofuranosyl moiety *via* the imine **8** and subsequent ring closure to give **9**. Compound **9** is the only nucleoside product that could be isolated from the reaction mixture. Further ammonolysis studies with **9** to obtain the corresponding 4-carboxamide derivative resulted in glycosidic cleavage and gave rise to an unseparable mixture of compounds. Therefore, an easily ammonolysable methyl ester **6b** was chosen and prepared by reacting **4** with methyl bromopyruvate [20]. The reaction was much cleaner and furnished the desired **6b** in modest yield. Ammonolysis of **6b** with liquid ammonia did result in a smoother conversion of the methyl ester to an amide at room temperature, but the ^1H nmr spectrum of the isolated crystalline product (51% yield) was rather unusual. The ^1H nmr spectrum revealed two deuterium exchangeable $CONH_2$ protons (2 broad singlets at δ 7.35 and 7.52), a benzamide group (multiplet at δ 7.48-7.83) and four exchangeable OH protons. The anomeric proton appeared as a multiplet centered at δ 5.82 and displayed coupling constants of $J_{1',2'}$ = 7.7 Hz, $J_{1',NH}$ = 8.3 Hz and $J_{1',NHCO}$ = 7.3 Hz, which are in good agreement with the values reported [21] for acyclic pentose derivatives. On the basis of these ^1H nmr results and single-crystal X-ray diffraction studies, the structure of this unique ring opened product was assigned as 2-[(1*R*, 2*R*, 3*R*, 4*R*)(1-benzamido-2,3,4,5-tetrahydroxypentane)-amino]thiazole-4-carboxamide (**7a**). A small amount (<3%) of an acyclic product was also isolated from the reaction mixture and found to be 1,1-bis(benzamido)-1-deoxypentitol [22] (**7b**). A plausible mechanism of the reaction would be the addition of ammonia to the carbohydrate moiety at $C_{1'}$, and the nitrogen of the amino group thus introduced into the glycon approaches the carboxylate carbon of a neighboring acyl group, resulting in a cyclic orthoamide. The labile orthoamide rearranges with migration of the acyl group to the nitrogen, resulting in a benzamido group at C_1, of the newly formed acyclic sugar. Similar migrations are documented [22] in the literature, where methanolic ammonia reacts with benzoylated D-ribose to give 1,1-bis(benzamido)-1-deoxyribitol. Similar treatment of **6b** with methanolic ammonia gave **7b** in 35% yield. Further attempts towards synthesis of **3a**, by the direct glycosylation of 2-aminothiazole-4-carboxamide (**16b**) by the sodium salt [23] or the trimethylsilyl [24] procedures, failed in our hands.

Scheme I



In view of the structural similarity of the thionucleosides **3b** and **3c** to tiazofurin, it was of interest to prepare these and compare their biological activity with **1**. Such *S*-ribofuranosides are generally prepared by the reaction of the anion of a thio substituted aglycon with a halogenose [25]. Ethyl 2-mercaptothiazole-4-carboxylate (**12**) required for the glycosylation studies was prepared as reported [26] by reacting ethyl bromopyruvate with ammonium dithiocarbamate in acetonitrile. Glycosylation of the sodium salt of **12**, produced *in situ* [23] by sodium hydride

in acetonitrile, with freshly prepared 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide [27] (**11**) gave the protected nucleoside ethyl 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylthio)-thiazole-4-carboxylate (**10**) (Scheme II). Ammonolysis of **10** furnished a mixture of two products. Proton nmr of the less polar compound **15** revealed two deuterium exchangeable signals at δ 7.61 and 7.73 for the amide protons, anomeric proton at δ 5.67 (suggesting the sugar is in the fur-

Table I

Positional and Equivalent Isotropic Thermal Parameters [a] for Non-hydrogen Atoms in Compounds **3b**, **7a**, and **9**

Atom	x/a	y/b	z/c	U_{eq}	Atom	x/a	y/b	z/c	U_{eq}
					3b				
S1	−.0024(2)	.41067(13)	.71437(3)	.0360(3)	C2	.2816(8)	.5351(4)	.71050(11)	.0282(9)
N3	.3894(7)	.5737(4)	.74971(9)	.0298(8)	C4	.2406(9)	.5034(5)	.78485(11)	.0301(10)
C5	.0262(9)	.4148(5)	.77240(13)	.0346(11)	C6	.3127(9)	.5331(5)	.83369(11)	.0323(10)
O7	.1721(8)	.4721(4)	.86398(9)	.0465(10)	N8	.5222(10)	.6255(6)	.84147(12)	.0462(12)
S9	.4078(2)	.61001(14)	.65868(3)	.0336(3)	C1′	.1163(8)	.5858(5)	.62294(11)	.0284(9)
C2′	.1405(9)	.6862(5)	.57746(12)	.0322(11)	C3′	.1959(9)	.5417(5)	.54344(11)	.0290(10)
C4′	.0419(8)	.3912(5)	.56333(11)	.0282(10)	C5′	.1234(10)	.2126(5)	.54978(13)	.0361(12)
O1′	.0743(7)	.4100(3)	.61186(8)	.0394(9)	O2′	−.1052(8)	.7603(4)	.56696(9)	.0434(10)
O3′	.1085(6)	.5752(4)	.49813(8)	.0361(8)	O5′	.3973(8)	.1876(4)	.56012(10)	.0443(10)
					7a				
S1	−.0363(2)	.394464	.17501(6)	.0425(2)	C2	.2394(6)	.4568(3)	.2242(2)	.0316(9)
N3	.3751(5)	.3652(3)	.2660(2)	.0334(8)	C4	.2577(7)	.2382(3)	.2590(2)	.0344(9)
C5	.0412(7)	.2344(4)	.2138(2)	.0399(10)	C6	.3690(7)	.1168(3)	.3035(2)	.0383(10)
O7	.2727(6)	.0016(3)	.2932(2)	.0462(9)	N8	.5712(7)	.1382(4)	.3533(3)	.0510(11)
N9	.2962(6)	.5900(3)	.2139(2)	.0370(9)	C1′	.5151(6)	.6533(3)	.2560(2)	.0283(8)
C2′	.5058(6)	.6762(3)	.3480(2)	.0279(8)	C3′	.7390(6)	.7369(3)	.3929(2)	.0297(8)
C4′	.7131(7)	.7837(4)	.4815(2)	.0370(10)	C5′	.9527(9)	.8012(5)	.5357(3)	.0588(15)
C6′	.7009(6)	.7983(3)	.1584(2)	.0316(8)	C7′	.6854(6)	.9309(3)	.1104(2)	.0292(8)
C8′	.5048(7)	1.0279(4)	.1119(2)	.0387(10)	C9′	.5015(8)	1.1477(4)	.0649(3)	.0492(12)
C10′	.6766(9)	1.1693(5)	.0151(3)	.0508(13)	C11′	.8564(8)	1.0739(5)	.0123(2)	.0482(13)
C12′	.8611(8)	.9548(4)	.0590(2)	.0423(11)	O2′	.3004(4)	.7523(3)	.3612(2)	.0351(7)
O3′	.9086(5)	.6281(3)	.3936(2)	.0391(7)	O4′	.5929(5)	.9137(3)	.4805(2)	.0430(8)
O5′	1.1022(6)	.9007(4)	.5060(3)	.0718(13)	N6′	.5461(5)	.7825(3)	.2137(2)	.0322(8)
O7′	.8443(5)	.7096(3)	.1461(2)	.0455(8)					
					9				
S1	1.01140(10)	.2251	.37500(10)	.034(1)	C2	1.0414(2)	−.0191(7)	.2627(3)	.028(2)
N3	1.1353(2)	−.1058(7)	.2926(3)	.030(2)	C4	1.1893(2)	.0232(8)	.4106(3)	.030(2)
C5	1.1364(2)	.2076(10)	.4682(3)	.034(2)	C6	1.2992(3)	−.0506(11)	.4597(3)	.038(2)
O7	1.3478(2)	−.1742(7)	.3929(2)	.065(2)	O8	1.3380(2)	.0459(8)	.5855(2)	.053(2)
C10	1.4463(2)	−.0135(11)	.6437(4)	.068(3)	N9	.9705(2)	−.1073(7)	.1497(3)	.034(2)
C1′	.8681(2)	−.0075(8)	.1097(3)	.029(2)	C2′	.8170(2)	−.1236(7)	−.0317(3)	.026(2)
C3′	.7036(2)	−.0432(8)	−.0717(3)	.030(2)	C4′	.6512(2)	−.1111(8)	.0429(3)	.037(2)
C5′	.7102(2)	.0168(9)	.1787(3)	.042(2)	O1′	.8132(2)	−.0880(7)	.2106(2)	.039(1)
O2′	.8738(2)	−.0538(5)	−.1296(2)	.037(1)	O3′	.6943(2)	.2429(6)	−.0978(2)	.034(1)
O4′	.54620(10)	−.0335(6)	.0152(2)	.049(2)					

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

anosyl form) and the presence of a 5′-*O*-benzoyl group. This was another unexpected observation where an ester function at position-4 of the thiazole ring undergoes ammonolysis faster than the deblocking of 5′-*O*-benzoyl moiety of the glycon portion. The more polar compound was found to be the desired 2-(β-D-ribofuranosylthio)thiazole-4-carboxamide (**3b**), the structure of which is confirmed by X-ray diffraction studies.

In a similar manner, glycosylation of the sodium salt of **12** with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride [28] (**13**) in acetonitrile at room temperature gave the protected nucleoside ethyl 2-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosylthio)thiazole-4-carboxylate (**14**) in 48% yield. Formation of other nucleoside products was not detected. Treatment of **14** with methanolic ammonia led to extensive decomposition, which on purification on a silica gel column furnished the desired **3c**, albeit in low yield, along with the partially deprotected 2-(2-deoxy-5-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosylthio)-

Scheme II

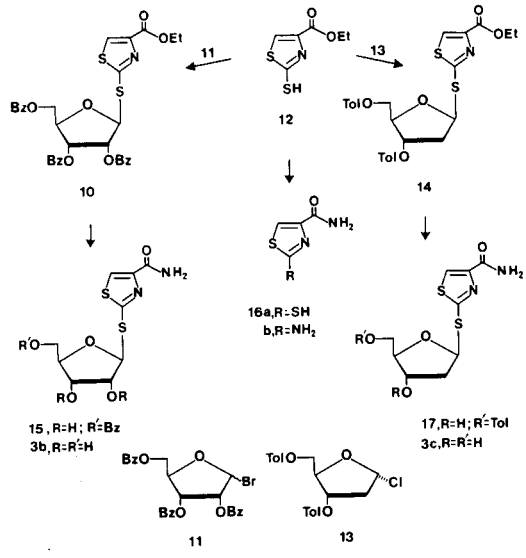


Table II

Bond Lengths (Å) in Compounds **3b**, **7a**, and **9**

1	2	**3b**	**7a**	**9**
C2	S1	1.747(4)	1.759(3)	1.746(3)
C5	S1	1.705(4)	1.710(3)	1.720(3)
N3	C2	1.308(4)	1.303(4)	1.294(4)
S9;N9;N9	C2	1.747(4)	1.346(4)	1.367(4)
C4	N3	1.390(5)	1.395(4)	1.385(4)
C5	C4	1.344(6)	1.340(5)	1.353(5)
C6	C4	1.494(5)	1.477(5)	1.484(5)
O7	C6	1.235(5)	1.244(4)	1.194(5)
N8;N8;O8	C6	1.308(6)	1.324(5)	1.329(4)
C1′	S9;N9;N9	1.828(4)	1.465(4)	1.423(4)
C2′	C1′	1.548(5)	1.526(5)	1.528(4)
C3′	C2′	1.528(5)	1.534(4)	1.529(4)
C4′	C3′	1.525(6)	1.542(5)	1.502(5)
C5′	C4′	1.503(6)	1.522(6)	1.536(4)
O1′;N6′;O1′	C1′	1.422(4)	1.452(4)	1.425(4)
O2′	C2′	1.414(6)	1.418(4)	1.404(4)
O3′	C3′	1.423(4)	1.425(4)	1.431(5)
O1′;O4′;O4′	C4′	1.438(4)	1.431(4)	1.419(3)
O5′;O5′;O1′	C5′	1.443(7)	1.411(7)	1.436(4)
C10	O8	—	—	1.461(4)

Additional bond lengths in compound **7a**

C7′	C6′	1.502(4)	N6′	C6′	1.349(5)	O7′	C6′	1.218(4)
C8′	C7′	1.391(5)	C12′	C7′	1.405(5)	C9′	C8′	1.390(6)
C10′	C9′	1.381(7)	C11′	C10′	1.380(7)	C12′	C11′	1.382(6)

thiazole-4-carboxamide (**17**) in respectable yield. Isolation and characterization of **17** is yet another instance in which the ethyl ester group on the thiazole ring undergoes ammonolysis faster than complete deblocking of the carbohydrate moiety. The low yield of **3c** was due to glycosidic cleavage during crystallization, to give 2-mercaptothiazole-4-carboxamide (**16a**).

Single-Crystal X-ray Diffraction Analyses of Compounds **3b**, **7a**, and **9**.

Atomic coordinates for compounds **3b**, **7a**, and **9** are listed in Table I. Bond lengths and bond angles involving only non-hydrogen atoms are given in Tables II and III. The conformations of each are illustrated in Figures 1, 2 and 3, respectively. In all figures, non-hydrogen atoms are

Table III

Bond Angles (°) in Compounds **3b**, **7a**, and **9**.

1	2	3	**3b**	**7a**	**9**
C2	S1	C5	89.0(2)	88.7(2)	88.6(2)
N3	C2	S9; N9; N9	122.0(3)	125.8(3)	122.7(3)
N3	C2	S1	114.8(3)	115.2(2)	115.4(2)
S9; N9; N9	C2	S1	123.1(2)	118.9(2)	121.8(2)
C4	N3	C2	109.2(3)	108.6(3)	109.7(3)
C5	C4	C6	122.6(3)	122.9(3)	126.6(3)
C5	C4	N3	116.5(3)	117.3(3)	116.3(2)
C6	C4	N3	120.8(4)	119.8(3)	117.1(3)
S1	C5	C4	110.5(3)	110.2(3)	110.0(2)
O7	C6	N8; N8; O8	124.1(3)	123.3(3)	124.0(3)
O7	C6	C4	119.0(4)	120.0(3)	124.2(3)
N8; N8; O8	C6	C4	116.9(3)	116.7(3)	111.7(3)
C1′	S9; N9; N9	C2	99.3(2)	123.0(3)	124.4(3)
C2′	C1′	O1′; N6′; O1′	107.5(3)	111.4(2)	110.5(3)
C2′	C1′	S9; N9; N9	112.0(3)	112.3(3)	109.3(3)
O1′; N6′, O1′	C1′	S9; N9; N9	110.6(3)	106.8(2)	108.8(3)
C3′	C2′	O2′	108.8(3)	113.4(3)	114.5(2)
C3′	C2′	C1′	101.8(3)	112.4(3)	110.7(3)
O2′	C2′	C1′	108.8(3)	111.4(2)	110.3(2)
C4′	C3′	O3′	109.6(3)	111.2(3)	108.6(3)
C4′	C3′	C2′	102.7(3)	111.9(3)	110.4(2)
O3′	C3′	C2′	114.5(3)	104.7(2)	110.0(3)
C5′	C4′	O1′; O4′; O4′	108.8(3)	107.0(3)	110.5(3)
C5′	C4′	C3′	117.7(3)	112.6(3)	109.9(3)
O1′; O4′; O4′	C4′	C3′	103.9(3)	110.8(3)	113.7(2)
O5′; O5′; O1′	C5′	C4′	109.7(3)	113.8(4)	108.9(3)
C1′	O1′; N6′, O1′	C4′, C6′; C5′	109.9(3)	123.2(3)	111.3(2)
C10	O8	C6	—	—	116.3(3)

Additional angles in compound **7a**

C7′	C6′	N6′	116.7(3)	C7′	C6′	O7′	120.7(3)
N6′	C6′	O7′	122.7(3)	C8′	C7′	C12′	118.7(3)
C8′	C7′	C6′	124.0(3)	C12′	C7′	C6′	117.2(3)
C9′	C8′	C7′	120.6(4)	C10′	C9′	C8′	119.7(4)
C11′	C10′	C9′	120.6(4)	C12′	C11′	C10′	120.0(4)
C7′	C12′	C11′	120.4(4)				

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

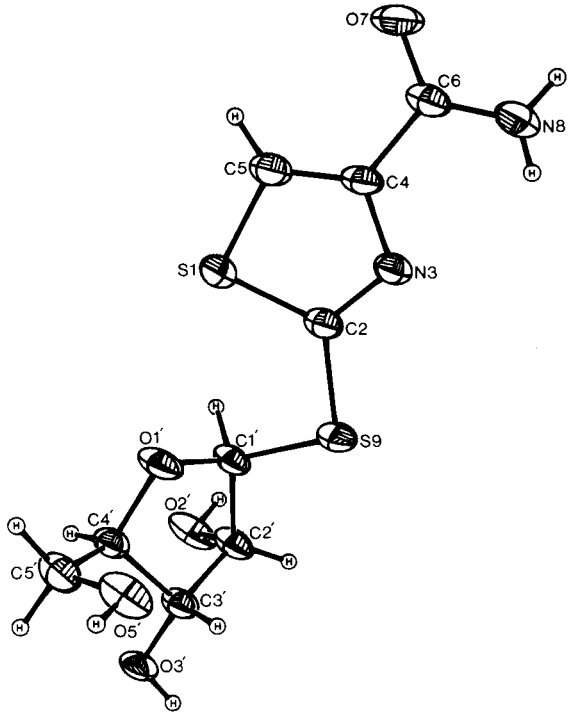


Figure 1. Perspective drawing of 3b

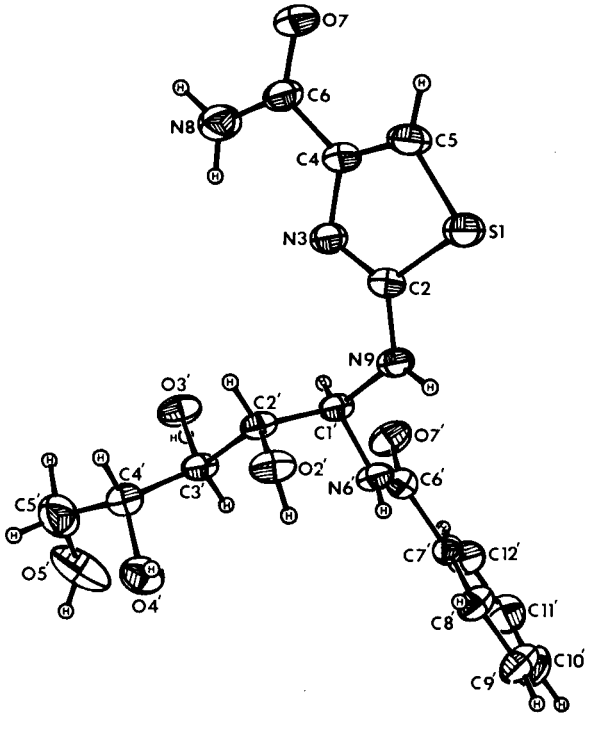


Figure 2. Perspective drawing of 7a

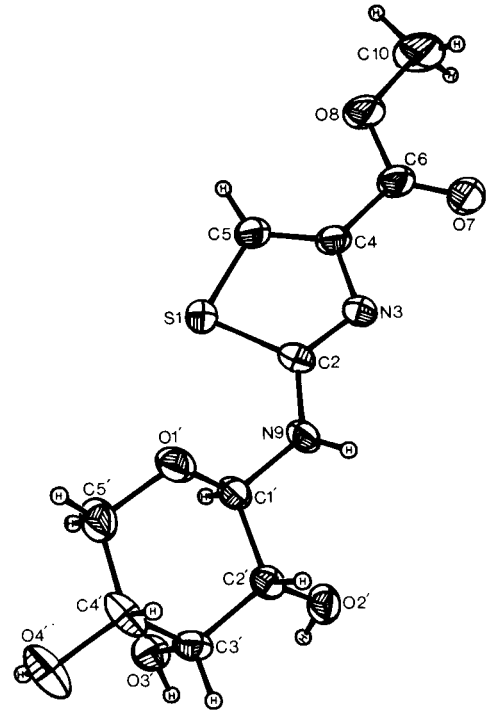


Figure 3. Perspective drawing of 9

The thiazole rings in the three structures are essentially equivalent in both bond lengths and interior angles. However, the C2-S1 bonds are consistently and significantly longer than observed in tiazofuran (**1**) and its analogues [29]. The rings are planar having rms deviations of 0.005, 0.001 and 0.003 Å for **3b**, **7a**, and **9**, respectively.

The carboxamide groups in **3b** and **7a** are planar. In **3b**, the thiazole ring-carboxamide dihedral angle is 2.0(2)° with C6, O7 and N8 on the same side of the thiazole plane. In **7a**, this angle is 6.4(2)° and represents a rotation about the C4-C6 bond. In both compounds, N8 is *cis* to the ring nitrogen as is observed in tiazofurin (**1**) and its analogues [29]. The entire methyl ester moiety in **9** is planar and rotated 12.79(13)° with respect to the thiazole plane.

The ribose in **3b** remained in the furanose form. The sugar conformation is type N, C_3, endo-C_4, exo of form $^3T_4$ with pseudorotation of 27.7° and amplitude of pucker of 37.3°. This conformation is outside the narrow range of most purine and pyrimidine *N*-β-nucleosides [30]. The side chain is gg [torsion angles: O1', −62.3(4)°; C3', 55.4(4)°]. In **9**, the ribose moiety rearranged to the pyranose form which exists in a slightly twisted chair conformation [C4' is −0.079(4) Å from the plane of C1', C3' and O1']. Atoms N9, O2' and O4' are in equatorial positions and O3' is in an axial position. The rearrangement of the sugar in forming **7a** results in a straight carbon chain ribose moiety having a completely non-eclipsed zigzag conformation, in contrast to the sickle conformation (obtained by rotation of a

Table IV

Hydrogen Bonding in Compounds **3b**, **7a**, and **9**

D	H	A	Symmetry of A relative to D			d(D···A) (Å)	d(H···A) (Å)	(D-H··A) (°)
			3b					
N8	H8A	N3	x,	y,	z,	2.799(4)	2.43(5)	109(4)
N8	H8B	O5′	1.0−x,	0.5 + y,	1.5−z	2.949(5)	2.12(6)	168(6)
O2′	HO2′	O7	−x,	0.5+y,	1.5−z	2.630(4)	1.79(8)	166(8)
O3′	HO3′	O2′	0.5+x,	1.5−y,	1.0−z	2.721(4)	1.96(5)	155(5)
O5′	HO5′	O3′	0.5+x,	0.5−y,	1.0−z	2.872(4)	2.11(7)	164(7)
			7a					
N8	HN8A	N3	x,	y,	z	2.768(5)	2.32(6)	111(4)
N8	HN8B	O4′	x,	y−1,	z	2.998(5)	2.17(5)	151(4)
N9	HN9	O7′	x−1,	y,	z	2.884(4)	2.00(5)	165(5)
O2′	HO2′	O7	x,	y+1,	z	2.655(4)	1.84(5)	162(5)
O3′	HO3′	O2′	x+1,	y,	z	2.639(4)	1.77(9)	168(8)
O4′	HO4′	O5′	x−1,	y,	z	2.866(4)	1.85(5)	171(5)
O5′	HO5′	O3′	2−x,	0.5+y,	1-z	2.752(5)	1.96(6)	163(6)
N6′	HN6′	O7	x,	1+y,	z	3.023(4)	2.27(4)	157(4)
			9					
O2′	HO2′	N3	2−x,	0.5+y,	−z	2.721(4)	1.94(3)	149(3)
O3′	HO3′	O7	2-x,	0.5+y,	−z	2.888(4)	2.03(4)	175(4)
O4′	HO4′	O4′	1-x,	y-0.5,	−z	2.736(3)	1.98(3)	150(2)

terminal carbon, C1′ or C5′, out of the zigzag form) found in the ribose chain of riboflavin in the solid state as determined by X-ray diffraction [31]. It has been determined by ^{1}H nmr that the predominant conformation of acyclic ribose derivatives in solution is also the sickle form [32,33].

The bridging between base and sugar is characterized by nonequivalent bonds involving the bridging atom. The C2-X9 (X = S in **3b** and X = N in **7a** and **9**) bond is shorter than C1′-X9 by 0.081, 0.119 and 0.056 Å for **3b**, **7a**, and **9**, respectively, suggesting conjugation of the bridging atom with the thiazole ring. This conjugation, which is absent in tiazofurin and its analogues, may account for longer C2-S1 bond distances noted above. The torsion angle about the bridging bonds are: for C1′-S9-C2-S1, 18.4(3)° in **3b**, 176.4(3)° in **7a** and 1.8(5)° in **9**; for O1′-C1′-S9-C2 (corresponding to the glycosidic torsion angle, X), −75.2(3)° in **3b** and −67.3(4)° in **9** [the analogous angle in **7a** in which N6′ replaces O1′ is 165.0(3)°]. Thus, the bridging conformations in **3b** and **9** are very similar to those of the exocyclic aminonucleosides, 4-amino-8-(β-D-ribofuranosyl)aminopyrimido[5,4-*d*]pyrimidine, **2** (torsion angles: 14.0° and −99.2°) [34] and 6-amino-5-nitro-4-(β-D-ribofuranosylamino)pyrimidine (clitocine, torsion angles: 9.8° and −99.2°) [35].

Besides the already noted similarities of **3b** to tiazofurin (**1**), the S1···O1′ distance of 3.026(2)Å is only slightly longer than the 2.958(1)Å [29] found in **1** despite the long C-S9 bonds composing the glycosyl linkage. The narrow angle characteristic of divalent sulfur in conjunction with the bridging conformation allows for this short S···O contact which supports the postulation that an electrostatic interaction exists between S1 and O1′ in **3b** as well as in tiazofurin and its analogues [29]. Similarly in **9**, the S1···O1′ distance is 3.179(2)Å. The torsion angle S1-C2···C1′-O1′ is −50.4(2)° in **3b** and 60.1(2)° in **9**, corresponding to a nearly ideal *gauche* conformation about the C2-C1′ vector.

Hydrogen bonding parameters in the three structures are listed in Table IV. All hydroxyl groups in **3b** and **7a** act as both donors and acceptors in hydrogen bonding, while in **9** only O4′ participates as both; O2′ and O3′ in **9** are donors only. The N3 nitrogens in **3b** and **7a** are not involved in hydrogen bonding unless there is some interaction with the interior amide hydrogen (Table IV); otherwise, steric effects from these same hydrogens presumably prevent participation of N3 in hydrogen bonding. N3 is in-

Table V

Crystal and Experimental Data for Compounds **3b**, **7a**, and **9**

Empirical formula	$C_9H_{12}N_2O_5S_2$	$C_{16}H_{20}N_4O_6S$	$C_{10}H_{20}N_4O_6S$
Formula wt	292.32	396.42	290.29
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	$P2_12_12_1$	$P2_1$	$P2_1$
a (Å) [a]	5.1040(4)	5.655(1)	13.354(4)
b (Å)	7.774(1)	9.692(2)	4.917(1)
c (Å)	29.266(3)	16.314(4)	9.939(2)
β (°)	90.	97.95(2)	102.99(2)
V (Å^3)	1161.3(2)	885.7(3)	636.0(3)
Z	4	2	2
σ_{calcd} (g cm^{-3})	1.67	1.49	1.52
F(000) (electrons)	608	416	304
Radiation, λ (Å)	CuKα, 1.54178	CuKα, 1.54178	MoKα, 0.71073
Crystal dimensions (mm)	$0.29\times0.18\times0.105$	$0.37\times0.17\times0.035$	$0.12\times0.15\times0.21$
μ (cm^{-1})	42.8	19.7	2.3
max 2Θ (°)	152	152	55
Total refls, measd, unique	1462, 1462	4052, 3536	1590, 1590
Observed refls	1391 ($F\geq\sigma_F$)	3268 ($F\geq3\sigma_F$)	1450 ($F\geq3\sigma_F$)
No. of variables	212	324	230
S (goodness of fit)	2.81	2.27	—
R, wR[d]	0.032, 0.057	0.046, 0.68	0.036, 0.025
Extinction parameter	$1.4(2)\times10^{-6}$	$1.0(3)\times10^{-6}$	—
Max Δ/σ	0.0012	0.0024	2.2 (Hydrogen)
Max, min in $\Delta\varphi$ map	0.45, −0.45	1.00, −0.48	0.31, −0.28

[a] Unit-cell parameters were obtained by least-squares refinement of the setting angles as follows: for **3b**, 25 reflections with $55.1<2\Theta60.0°$; for **7a**, 25 reflections with $49.5<2\Theta<60.1°$; for **9**, 15 reflections with $8.3<2\Theta<18.0°$. [b] Intensity measurement 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 were reduced with the SDP-Plus program package and included Lorentz, polarization, decay and absorption corrections [42]. [c] Data were collected on a Nicolet P3 automatic diffractometer equipped with a graphite monochromator using an ω-2Θ scan procedure and variable scan speeds. Data were corrected for Lorentz, polarization and decay effects [43]. [d] Function minimized was $^s\mathrm{w}(F_o - F_c)^2$, where $w = (\sigma_F^2 + 0.0002F^2)^{-1}$ for **3b**, $w = (\sigma_F^2 + 0.0004F^2)^{-1}$ for **7a** and $w = \sigma_F^{-2}$ for **9**.

volved in hydrogen bonding in **9** in which there is no amide group. The carbonyl oxygens in all structures are involved in at least one hydrogen bond.

In summary, the ribofuranose moiety when attached to a 2-amino group of the thiazole ring is rather unstable and rearranges to either the ribopyranose form or the open-chain form in the presence of base. This phenomenon is in contrast to the stability of **2** towards ammonia [12]. Similarly, 5′-*O*-protecting groups on ribofuranosyl and 2′-deoxyribofuranosyl sugars attached to a 2-thiothiazole system are surprisingly stable in comparison to other thioglycosides [25]. Partially deprotected compounds **15** and **17** could prove useful in the synthesis of other sugar-modified nucleosides.

The formation of the unique acycloaminonucleoside **7a** is also noteworthy, as it constitutes a model for the acyclic-sugar side chain of riboflavin and the oxidation-reduction coenzyme flavine adenine dinucleotide (FAD). Enzymatic studies suggest that riboflavin involves a ribitylamino derivative in its biosynthesis, and recently such intermediates have been the subject of considerable synthetic interest [36]. The favored position of this ribitylamino chain in **7a** may have significant synthetic applications in addition to providing insight into certain biological processes.

All compounds prepared during this study have been evaluated *in vitro* for their ability to inhibit the growth of L1210-leukemia, WI-L2 and CCRF-CEM (for antitumor effects), as well as against HSV-1, Para-3, VV, and Cox B-1 viruses (for antiviral effects). These compounds are devoid of any significant biological effects in these systems.

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 (uv) spectra with a Beckman DU-50 spectrophotometer. Nuclear magnetic resonance (^{1}H nmr) spectra were recorded at 300 MHz with an IBM NR/300 spectrometer. The chemical-shift values are expressed in δ values (parts per million) relative to tetramethylsilane as the internal standard. The signals are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The presence of water and methanol of solvation as indicated by elemental analysis was verified by ^{1}H nmr spectroscopy. Preparative hplc was performed utilizing the Waters Delta prep 3000 system.

Ethyl 2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosylamino)thiazole-4-carboxylate (**6a**).

To a solution of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiourea [18] (**4**, 10.0 g, 19.23 mmoles) in dry ethanol (85 ml) was added ethyl bromopyruvate (**5a**, 5.27 g, 27 mmoles) over a period of 30 minutes, and the mixture was heated to reflux for 45 minutes. The reaction mixture was cooled and concentrated to a syrup. The syrup was purified by silica gel chromatography. Pooling and concentration of the appropriate fractions eluted with acetone:hexanes (3:7, v/v) furnished 5.0 g (40%) of **6a** as foam; mp 58°; uv λ max (methanol): 228 nm (ϵ 40,100), 273 (7,100); ^{1}H nmr (DMSO-d_6): δ 1.24 (t, 3, CH_2CH_3), 4.23 (m, 2, CH_2CH_3), 4.62 (m, 2, $C_5'CH_2$), 5.80 (q, 1, $C_1'H$), 7.44-8.20 (m, 16, Ar-*H* and C_5H).

Anal. Calcd. for $C_{32}H_{28}N_2O_9S$: C, 62.33; H, 4.58; N, 4.54; S, 5.20. Found: C, 62.51; H, 4.73; N, 4.38; S, 5.05.

Methyl 2-(β-D-Ribopyranosylamino)thiazole-4-carboxylate (**9**).

To a solution of **6a** (0.616 g, 1 mmole) in anhydrous methanol (10 ml) was added 1*N* solution of sodium methoxide in methanol until the *p*H 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. The colored solution was neutralized with Dowex-50 (H^+) resin and filtered. The filtrate was evaporated to dryness, the residue triturated with anhydrous ether (3 × 10 ml) and crystallized from ethanol as white needles, 0.225 g (78%), mp 192-193°; uv λ max (*p*H 1): 248 nm (ϵ, 10,700); (*p*H 7): 240 nm (ϵ 6,700); (*p*H 11): 240 nm (ϵ 6,700), 275 (3,500); ^{1}H nmr (DMSO-d_6): δ 3.75 (s, 3, CH_3), 4.87 (q, 1, $C_1'H$, collapsed to a d after deuterium oxide addition, J = 8.5 Hz), 7.62 (s, 1, C_5H), 8.39 (d, 1, J = 8.8 Hz, N*H*) and other sugar protons.

Anal. Calcd. for $C_{10}H_{14}N_2O_6S$: C, 41.38; H, 4.86; N, 9.65; S, 11.05. Found: C, 41.56; H, 4.70; N, 9.42; S, 11.07.

Methyl 2-(2,3,5-Tri-*O*-benzoyl-β-*D*-ribofuranosylamino)thiazole-4-carboxylate (**6b**).

To a solution of **4** (5.20 g, 10 mmoles) in dry acetonitrile (100 ml) cooled to 0°, a solution of methyl bromopyruvate [20] (**5b**, 5.43 g, 30 mmoles) in dry acetonitrile (40 ml) was added dropwise over a period of 1 hour. The solution was stirred at room temperature for 3 hours and then stored at 4° for 48 hours. The reaction mixture was neutralized by addition of sodium bicarbonate (10 g) and filtered. The filtrate was concentrated, and the residue purified by silica gel chromatography as described for the purification of **6a**, to furnish 2.40 g (40%) of **6b**, mp 65° (foam); uv λ max (methanol): 249 nm (ϵ 36,700); ^{1}H nmr (deuteriochloroform): δ 3.86 (s, 3, CH_3), 5.80 (q, 1, $C_1'H$, collapsed to a d on deuterium oxide addition), 7.48-7.92 (m, 16, 3 Ar-*H* and C_5H) and other sugar protons.

Anal. Calcd. for $C_{31}H_{26}N_2O_9S.1/4\ H_2O$: C, 61.32; H, 4.40; N, 4.61; S, 5.28. Found: C, 61.11; H, 4.50; N, 4.56; S, 5.33.

2-[(1*R*, 2*R*, 3*R*, 4*R*) (1-Benzamido-2,3,4,5-tetrahydroxypentane)amino]-thiazole-4-carboxamide (**7a**).

A mixture of **6b** (1.65 g, 2.74 mmoles) and ammonia (40 ml) was stirred at room temperature in a pressure vessel for 18 hours. After removal of excess ammonia, the residue was dissolved in methanol and adsorbed onto silica gel (5 g), and was loaded on top of a flash silica gel column (3 × 45 cm) packed in ethyl acetate:water:methanol:acetone (7:1:1:1, v/v) and eluted with the same solvent mixture. Fractions containing the pure product were pooled and evaporated to dryness. Crystallization of the residue from ethanol gave 0.55 g (51%) of **7a**, mp 203-205°; uv λ max (*p*H 1): 233 nm (ϵ 15,200); (*p*H 7): 240 nm (sh) (ϵ 13,500), 268 (sh) (4,000); (*p*H 11): 230 nm (sh) (ϵ 11,900), 270 (3,300); ^{1}H nmr (DMSO-d_6): δ 4.50 (t, 1, $C_5'OH$), 4.76, 4.90 and 5.38 (3 d, 3, $C_{2',3',4'}OH$), 5.82 (m, 1, $C_1'H$), 7.24 (s, 1, C_5H), 7.35 and 7.52 (2 br s, 2, $CONH_2$), 8.00 and 8.42 (2 d, 2, $J_{1',NH}$ = 8.3 Hz and $J_{1',NHCO}$ = 7.3 Hz, 2 N*H*), 7.48-7.83 (m, 5, Ar-*H*), and other C*H* protons).

Anal. Calcd. for $C_{16}H_{20}N_4O_6S$: C, 48.47; H, 5.08; N, 14.13; S, 8.08. Found: C, 48.56; H, 5.01; N, 14.01; S, 7.94.

1,1-Bis(benzamido)-1-deoxypentitol (**7b**).

A mixture of **6b** (1.0 g, 1.66 mmoles) in methanolic ammonia (50 ml, saturated at 0°) was kept in a pressure bottle at 25° for 16 hours. The solvent was removed and the residue purified by chromatography in a similar way as described for **7a**, to furnish 0.218 g (35%) of **7b** as amorphous powder; mp 172° dec [Lit [22] mp 190°]; uv λ max (*p*H 1, 7 and 11): 230 nm (ϵ 21,900); ^{1}H nmr (DMSO-d_6): δ 4.42 (t, 1, C_5OH), 4.73, 4.93 and 5.39 (3 d, 3, $C_{2,3,4}OH$), 6.21 (t, 1, C_1H), 7.45-7.87 (m, 10, 2, Ar-*H*), 8.24 and 8.47 (2 d, 2, $J_{1,NH}$ = 7.8 Hz, $J_{1,NH}$ = 8.2 Hz, 2 N*H*), and other C*H* protons.

Anal. Calcd. for $C_{19}H_{22}N_2O_6.1/4\ H_2O$: C, 60.22; H, 5.98; N, 7.39. Found: C, 60.20; H, 6.02; N, 7.28.

Ethyl 2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosylthio)thiazole-4-carboxylate (**10**).

To a solution of ethyl 2-mercaptothiazole-4-carboxylate [26] (**12**, 3.8 g, 20 mmoles) in dry acetonitrile (200 ml) was added sodium hydride (60% in oil, 0.88 g, 22 mmoles) and the solution was stirred under nitrogen at room temperature for 30 minutes. A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide [27] (**11**, prepared from 11.08 g, 22 mmoles of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose) in dry acetonitrile (150 ml) was added dropwise over a period of 15 minutes. The reaction mixture was stirred for 3 hours before it was filtered through a celite pad. The filtrate was evaporated to dryness and the residue purified by silica gel column chromatography using toluene:ethyl acetate (95:5, v/v) as the solvent giving 4.8 g (38%) of crystalline **10** (from methanol), mp 113°; uv λ max (methanol): 230 nm (ϵ 25,700), 267 (14,600); ^{1}H nmr (DMSO-d_6): δ 1.24 (t, 3, CH_2CH_3), 4.24 (m, 2, CH_2CH_3), 4.60 (m, 2, $C_5'CH_2$), 4.87 (m, 1, $C_4'H$), 5.90 (m, 2, $C_{2',3'}H$), 6.20 (d, 1, J = 3.4 Hz, $C_1'H$), 7.42-8.00 (m, 15, 3 Ar-*H*), 8.48 (s, 1, C_5H).

Anal. Calcd. for $C_{32}H_{27}NO_9S_2$: C, 60.65; H, 4.29; N, 2.21; S, 10.11. Found: C, 60.51; H, 4.21; N, 2.05; S, 9.97.

2-(5-*O*-Benzoyl-β-D-ribofuranosylthio)thiazole-4-carboxamide (**15**) and 2-(β-D-Ribofuranosylthio)thiazole-4-carboxamide (**3b**).

A mixture of **10** (4.50 g, 7.1 mmoles) and liquid ammonia (50 ml) was stirred at room temperature in a steel reaction vessel for 18 hours. The excess ammonia was evaporated and the residue was purified on a silica gel column (2.5 × 40 cm) using chloroform:methanol (9:1, v/v) as solvent giving two compounds in the order described. The less polar **15** (R_f 0.46, chloroform:methanol, 9:1), crystallized from ethanol to give 1.26 g (45%), mp 168°; uv λ max (methanol): 271 nm (ϵ 13,100); ^{1}H nmr (DMSO-d_6): δ 4.18-4.54 (m, 5, $C_{2',3',4'}H$, $C_5'CH_2$), 5.40 and 5.81 (2 d, 2, J = 4.5 Hz, $C_{2',3'}OH$), 5.67 (d, 1, J = 2.2 Hz, $C_1'H$), 7.51-8.00 (m, 7, $CONH_2$, Ar-*H*), 8.17 (s, 1, C_5H).

Anal. Calcd. for $C_{16}H_{16}N_2O_6S_2$: C, 48.47; H, 4.06; N, 7.06; S, 16.17. Found: C, 48.23; H, 3.99; N, 6.92; S, 15.89.

The polar compound **3b** (R_f 0.15, chloroform:methanol, 9:1), crystallized from water to give 0.31 g (15%), mp 154°; uv λ max (*p*H 1): 305 nm (ε 11,100); (*p*H 7): 219 nm (ε 16,600), 274 (8,900); (*p*H 11): 218 nm (ε 19,000), 274 (9,200); ^{1}H nmr (DMSO-d_6): δ 3.36-3.50 (m, 2, C_5-C*H*$_2$), 3.85-4.09 (m, 3, $C_{2',3',4'}$-*H*), 4.86 (t, 1, C_5-O*H*), 5.15 and 5.64 (2 d, 2, J = 5.7 Hz, $C_{2',3'}$-O*H*), 5.55 (d, 1, J = 4.2 Hz, C_1-*H*), 7.76 and 7.87 (br s, 2, CON*H*$_2$), 8.19 (s, 1, C_5-*H*).

Anal. Calcd. for $C_9H_{12}N_2O_5S_2$: C, 36.97; H, 4.13; N, 9.58; S, 21.93. Found: C, 36.99; H, 4.07; N, 9.49; S, 21.66.

Ethyl 2-(2-Deoxy-3,5,-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosylthio)thiazole-4-carboxylate (**14**).

To a solution of **12** (1.9 g, 10 mmoles) in dry acetonitrile (100 ml) was added sodium hydride (60% in oil, 0.44 g, 11 mmoles) and the solution was stirred at room temperature under nitrogen for 1 hour. Finely powdered 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride [28] (**13**, 4.3 g, 11 mmoles) was added portionwise, over a period of 15 minutes. The reaction mixture was stirred at room temperature for 3 hours before it was filtered through a celite pad. The filtrate was evaporated to dryness and purified by silica gel chromatography using toluene:ethyl acetate (95:5, v/v) as eluant giving 2.6 g (48%) of crystalline (from ethanol) **14**, mp 140°; uv λ max (methanol): 242 nm (ε 44,800); ^{1}H nmr (deuteriochloroform): δ 1.39 (t, 3, CH_2-C*H*$_3$), 2.42 (s, 6, 2 Ph-C*H*$_3$), 2.52-2.75 (m, 2, C_2-C*H*$_2$), 4.39 (m, 2, C*H*$_2$-CH$_3$), 4.55 (m, 2, C_5-C*H*$_2$), 4.62 (m, 1, C_4-*H*), 5.62 (m, 1, C_3-*H*), 6.11 (t, 1, C_1-*H*), 7.22-7.95 (m, 8, 2 Ar-*H*), 8.10 (s, 1, C_5-*H*).

Anal. Calcd. for $C_{27}H_{27}NO_7S_2$: C, 59.88; H, 5.02; N, 2.58; S, 11.84. Found: C, 59.83; H, 5.08; N, 2.44; S, 11.71.

2-(2-Deoxy-5-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosylthio)thiazole-4-carboxamide (**17**) and 2-(2-Deoxy-β-D-*erythro*-pentofuranosylthio)thiazole-4-carboxamide (**3c**).

A mixture of **14** (0.41 g, 0.75 mmole) and methanolic ammonia (saturated at 0°, 20 ml) was stirred at room temperature in a pressure bottle for 12 hours. The solution was evaporated and the residue purified by silica gel chromatography using chloroform:methanol (9:1, v/v) as eluant furnishing two compounds in the order described. The less polar **17** (R_f 0.5, chloroform:methanol, 9:1), crystallized from ethanol to give 58 mg (20%), mp 145°; uv λ max (methanol): 238 nm (ε 13,600); ^{1}H nmr (DMSO-d_6): δ2.40 (s, 3, Ph-C*H*$_3$), 2.30-2.51 (m, 2, C_2-C*H*$_2$), 4.16-4.42 (m, 4, $C_{3',4'}$-*H*, C_5-C*H*$_2$), 5.50 (d, 1, J = 4.5 Hz, C_3-O*H*), 6.07 (t, 1, C_1-*H*), 7.58 and 7.74 (2 br s, 2, CON*H*$_2$), 7.31-7.87 (m, 4, Ar-*H*), 8.17 (s, 1, C_5-*H*).

Anal. Calcd. for $C_{17}H_{18}N_2O_5S_2$: C, 51.76; H, 4.59; N, 7.10; S, 16.25. Found: C, 51.70; H, 4.65; N, 7.00; S, 15.99.

The polar compound **3c** (R_f 0.3, chloroform:methanol, 9:1), proved to be unstable on crystallization from methanol, giving undesirable cleaved product **16a** (56 mg) (identical with a sample prepared by an unambiguous route, see below) and 11 mg (5.3%) of desired **3c**, mp 94°; uv λ max (*p*H 1): 305 nm (ε 16,300); (*p*H 7): 259 nm (ε 7,500); (*p*H 11): 260 nm (ε 7,300); ^{1}H nmr (DMSO-d_6): δ 6.04 (t, 1, C_1-*H*), 7.60 (s, 1, C_5-*H*), 7.60 and 7.88 (2 br s, 2, CONH_2).

Anal. Calcd. for $C_9H_{12}N_2O_4S_2$.1/2 MeOH): C, 39.02; H, 4.82; N, 9.58; S, 21.93. Found: C, 38.64; H, 4.54; N, 9.79; S, 21.89.

2-Mercaptothiazole-4-carboxamide (**16a**).

A mixture of **12** (3.78 g, 20 mmoles) and methanolic ammonia was treated as described above for the preparation of **3c** to furnish 1.70 g (51%) of **16a**, mp 175°; uv λ max (*p*H 1): 305 nm (ε 5,300); (*p*H 7): 274 nm (ε 4,000); (*p*H 11): 274 nm (ε 4,200); ^{1}H nmr (DMSO-d_6): δ 7.57 (s, 1, C_5-*H*), 7.68 and 7.93 (2 br s, 2, CONH_2), 13.37 (br s, 1, S*H*).

Anal. Calcd. for $C_4H_4N_2OS_2$: C, 30.01; H, 2.52; N, 17.50; S, 40.05. Found: C, 30.14; H, 2.68; N, 17.28; S, 40.19.

2-Aminothiazole-4-carboxamide (**16b**).

Methyl 2-aminothiazole-4-carboxylate was heated with ammonia (50 ml) in a steel reaction vessel at 110° for 12 hours. Following the workup as described for **15**, and purification by silica gel chromatography using chloroform:methanol (6:1, v/v) as the solvent, furnished 0.85 g (47%) of **16b**, mp 206°; uv λ max (*p*H 1): 245 nm (ε 8,800); (*p*H 7): 232 nm (ε 5,300), 274 (3,100); (*p*H 11): 234 nm (ε 5,200), 273 (3,000); ^{1}H nmr (DMSO-d_6): δ 7.07 (br s, 2, NH_2), 7.17 (s, 1, C_5-*H*), 7.13 and 7.36 (2 br s, 2, CONH_2).

Anal. Calcd. for $C_4H_5N_3OS$: C, 33.55; H, 3.52; N, 29.35; S, 22.39. Found: C, 33.56; H, 3.44; N, 29.37; S, 22.50.

X-Ray Crystallography.

Crystal and experimental data for **3b**, **7a**, and **9** are summarized in Table V. The structure of **3b** was developed from Fourier maps phased by sulfur positions derived from a sharpened Patterson map. The atomic positions of **7a**, and **9** were determined by direct methods using the programs SHELXS-86 [37] and SHELX-76 [38], respectively. All structures were refined by a full-matrix least-squares procedure (SHELX-76) [38]. All positional and thermal parameters were refined (only non-hydrogen atoms were treated anisotropically). Atomic scattering factors and anomalous-dispersion corrections for non-hydrogen atoms were taken from the International Tables for X-ray Crystallography [39]. For hydrogen, these parameters were taken from Stewart, Davidson and Simpson [40]. Figures were drawn with ORTEPII [41].

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