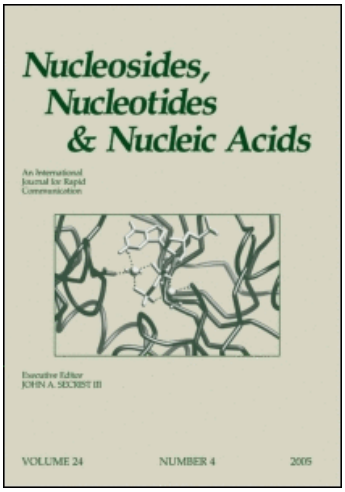

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Naeem B. Hanna[a]; Krishna G. Upadhya[a]; Charles R. Petrie[a]; Roland K. Robins[a]; Ganapathi R. Revankar[a]
[a] Nucleic Acid Research Institute, Costa Mesa, California

To cite this Article Hanna, Naeem B. , Upadhya, Krishna G. , Petrie, Charles R. , Robins, Roland K. and Revankar, Ganapathi R.(1986) 'Synthesis of Certain 5'-Substituted Derivatives of Ribavirin and Tiazofurin', Nucleosides, Nucleotides and Nucleic Acids, 5: 4, 343 — 362
To link to this Article: DOI: 10.1080/07328318608068678
URL: http://dx.doi.org/10.1080/07328318608068678

NUCLEOSIDES & NUCLEOTIDES, 5(4), 343-362 (1986)

SYNTHESIS OF CERTAIN 5'-SUBSTITUTED DERIVATIVES OF RIBAVIRIN AND TIAZOFURIN

Naeem B. Hanna,† Krishna G. Upadhya, Charles R. Petrie, Roland K. Robins, and Ganapathi R. Revankar*

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

ABSTRACT: The synthesis of several 5'-substituted derivatives of ribavirin (1) and tiazofurin (3) are described. Direct acylation of 1 with the appropriate acyl chloride in pyridine-DMF gave the corresponding 5'-O-acyl derivatives (4a-h). Tosylation of the 2',3'-O-isopropylidene-ribavirin (6) and tiazofurin (11) with p-toluenesulfonyl chloride gave the respective 5'-O-p-tolylsulfonyl derivatives (7a and 12a), which were converted to 5'-azido-5'-deoxy derivatives (7b and 12b) by reacting with sodium/lithium azide. Deisopropylidenation of 7b and 12b, followed by catalytic hydrogenation afforded 1-(5-amino-5-deoxy-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (10b) and 2-(5-amino-5-deoxy-ß-D-ribofuranosyl)thiazole-4-carboxamide (16), respectively. Treatment of 6 with phthalimide in the presence of triphenylphosphine and diethyl azodicarboxylate furnished the corresponding 5'-deoxy-5'-phthaloylamino derivative (9). Reaction of 9 with n-butylamine and subsequent deisopropylidenation provided yet another route to 10b. Selective 5'-thioacetylation of 6 and 11 with thiolacetic acid, followed by saponification and deisopropylidenation afforded 5'-deoxy-5'-thio derivatives of 1-ß-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (8a) and 2-ß-D-ribofuranosylthiazole-4-carboxamide (15), respectively.

1-ß-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide (ribavirin, 1) prepared and reported from our laboratory[1] in 1972 has shown significant broad spectrum antiviral activity against both DNA and RNA viruses in vitro and in vivo.[2] The antiviral activity of 1 has been reviewed.[3-5] In early 1986, FDA has approved use of ribavirin aerosol for treating severe infections of respiratory syncytial virus (RSV), a disease often fatal to infants and children. However, administered parenterally, ribavirin has had little or no

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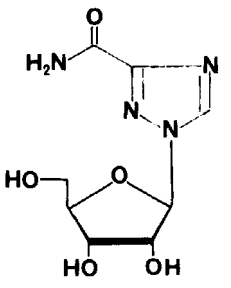
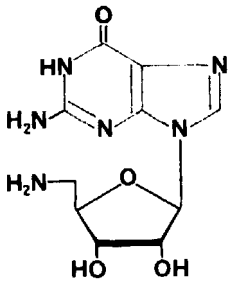
effect upon virus infections of the central nervous system (CNS). Mice inoculated intracerebrally with viruses causing primary encephalitis (rhabdo-), Western or Venezuelan equine encephalitis (alpha-), Japanese B encephalitis (flavi-) and yellow fever viruses, regardless of the viral nucleic acid type,[6] displayed little protection following i.p., s.c., p.o. or i.v. ribavirin therapy.[2,7-9] These results are attributed to failure of ribavirin to adequately pass the blood-brain barrier. The low lipid solubility of ribavirin would contribute significantly to this failure. In an attempt to overcome this problem, a number of selected 5'-O-acyl derivatives of ribavirin (4a-h) have now been prepared. Such a form of ribavirin should offer a range of solubility, transport characteristics and lipophilic nature differing from ribavirin itself. Similar rationale has been used in prodrug design for a number of pharmaceuticals.[10,11]

Efforts have been directed, in recent years, toward the synthesis of 5'-amino-5'-deoxy-pyrimidine and purine nucleosides that are more selective in their antiviral effects. The highly selective antiviral activity of 5'-amino-2',5'-dideoxy-5-iodouridine against HSV in vitro has been well documented.[12,13] Although this 5'-amino-5'-deoxypyrimidine nucleoside is incorporated into both viral and cellular DNA,



1

ribavirin



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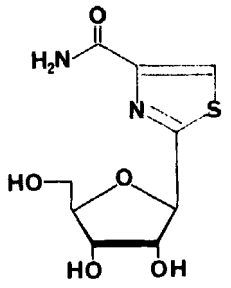


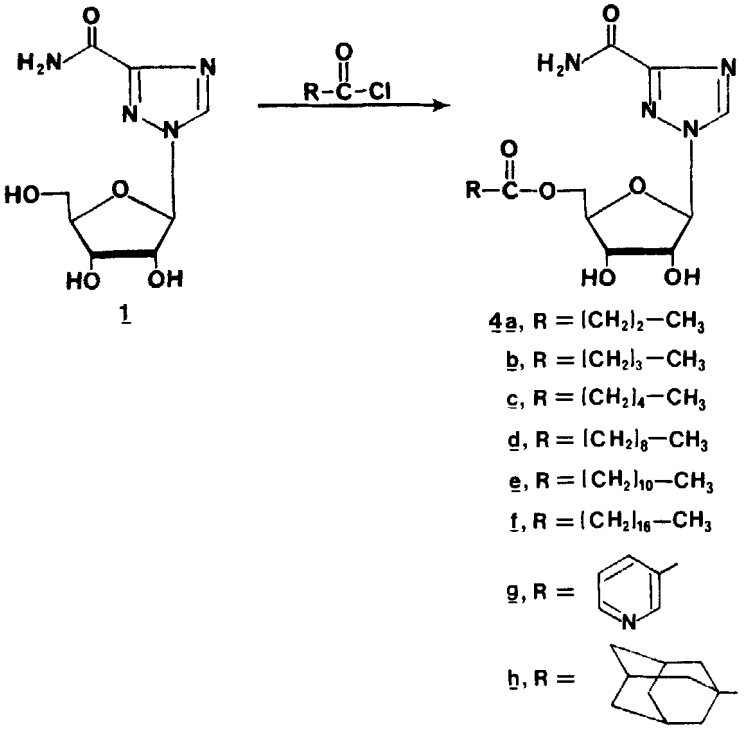
3

tiazofurin

such incorporation is restricted to the infected cells only.[14,15] The increase of the antiviral therapeutic index of 5-trifluoromethyl-2'-deoxyuridine by a factor of 10 by replacement of the 5'-hydroxyl with an amino group is another convincing example.[16] 5'-Amino-5'-deoxyguanosine[17]

(2) also produced a highly significant inhibition (>80%) of a number of RNA virus replication at concentrations as low as 6.4 μg/ml. No cytotoxicity was observed with 2 even at concentrations as high as 1000 μg/ml. Compound 2, which exhibited significant inhibition of MLV replication *in vitro* at a concentration of 0.64 μg/ml, gave a "selectivity ratio" of >1500.[18] The structure of ribavirin as noted by single crystal X-ray studies,[19] is strikingly similar to that of guanosine with the carbonyl oxygen and the amide nitrogen occupying stereochemically similar positions to the carbonyl oxygen (O^6) and the amide ring nitrogen (N^1) in guanosine. In view of these findings we have now prepared the 5'-amino-5'-deoxy derivatives of ribavirin, as well as the synthetic oncolytic C-nucleoside tiazofurin (2-ß-D-ribofuranosylthiazole-4-carboxamide, 3). Tiazofurin, synthesized and reported simultaneously from our laboratory[20] and by Fuertes et al.,[21] is a promising antitumor agent[22-24] currently undergoing Phase II clinical trials. Tiazofurin shows potent activity against several murine tumors, including Lewis lung carcinoma.[25-27]

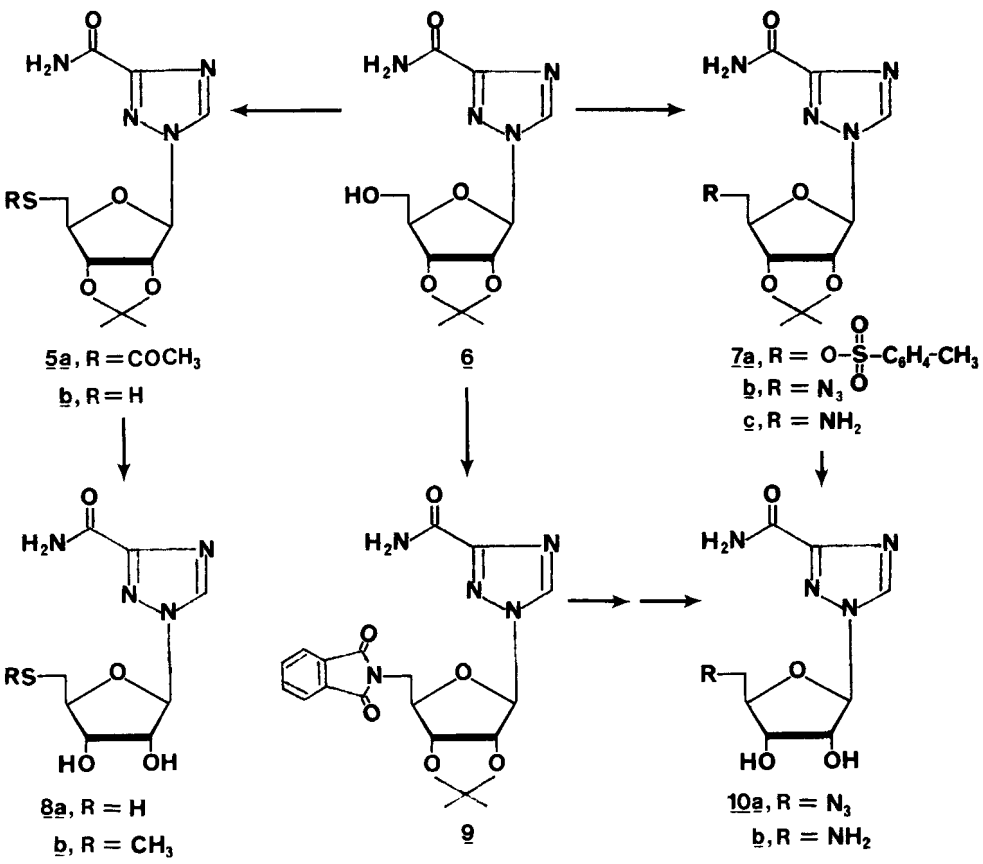
Direct acylation (Scheme I) of ribavirin was accomplished by adding 1.1 molar equivalent of the appropriate acyl chloride to a solution of 1 in 1:1 mixture of pyridine:N,N-dimethylformamide. This solvent mixture was found to greatly facilitate the selectivity of the acylation of the primary hydroxyl group over either of the secondary hydroxyl groups.[28] This could be a consequence of having the acylating agent in a charged species (like N-acylpyridinium chloride) in an aprotic, polar solvent, such as DMF.[29,30] The 5'-O-acylated nucleosides (4a-f) were isolated in over 60% yield as crystalline solids after column chromatography over silica gel to separate minor, peracylated contaminants and unreacted ribavirin. 5'-O-Nicotinoyl (4g) and 5'-O-adamantoyl (4h) derivatives were isolated in 44% and 42% yield, respectively. That the carbamoyl function on the aglycon remained unacylated was confirmed by their ^{1}H NMR spectra in Me_2SO-d_6, that typically showed the carbamoyl protons at δ 7.60 and 7.80 ppm. The ^{1}H NMR spectra also revealed an expected downfield shift[28] (multiplet at δ 4.20-



Scheme I

4.40) for the 5'-methylene function that was consistent with 5'-O-acylation of 1.

The synthesis of 5'-amino-5'-deoxyribavirin (10b) via the intermediate 5'-iodo-5'-deoxyribavirin is unsatisfactory due to poor yields.[31] Further studies in our laboratory resulted in the successful synthesis of 10b by two different routes (Scheme II). Tosylation of 2',3'-O-isopropylidene ribavirin[32] (6) with p-toluenesulfonyl chloride in dry pyridine at 0-4°C[33] gave 1-(2,3-O-isopropylidene-5-O-p-tolylsulfonyl-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (7a) in 89% yield. The 5'-O-p-tolylsulfonyl group of 7a was selectively displaced by the 5'-azido function (7b) by reacting with sodium azide in dry DMF at 85-90°C for 10 hr, according to the general procedure of Horwitz et al.[34] Deisopropylidenation of 7b with 80% acetic acid gave 10a, which on further catalytic (Pd/C) hydrogenation[35] in EtOH-H_2O



Scheme II

(1:1) at room temperature and 37 psi of hydrogen pressure afforded the desired 10b in 70% yield. Alternatively, when compound 6 was allowed to react with diethyl azodicarboxylate, triphenylphosphine and phthalimide in THF at room temperature overnight,[36] 1-(2,3-O-isopropylidene-5-deoxy-5-phthaloylamino-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (9) was obtained in a 60% yield. On treatment of 9 with methanolic n-butylamine under reflux for 12 hr, afforded the corresponding 5'-amino-5'-deoxy derivative (7c), which on subsequent deisopropylideanation provided yet another route to 10b.

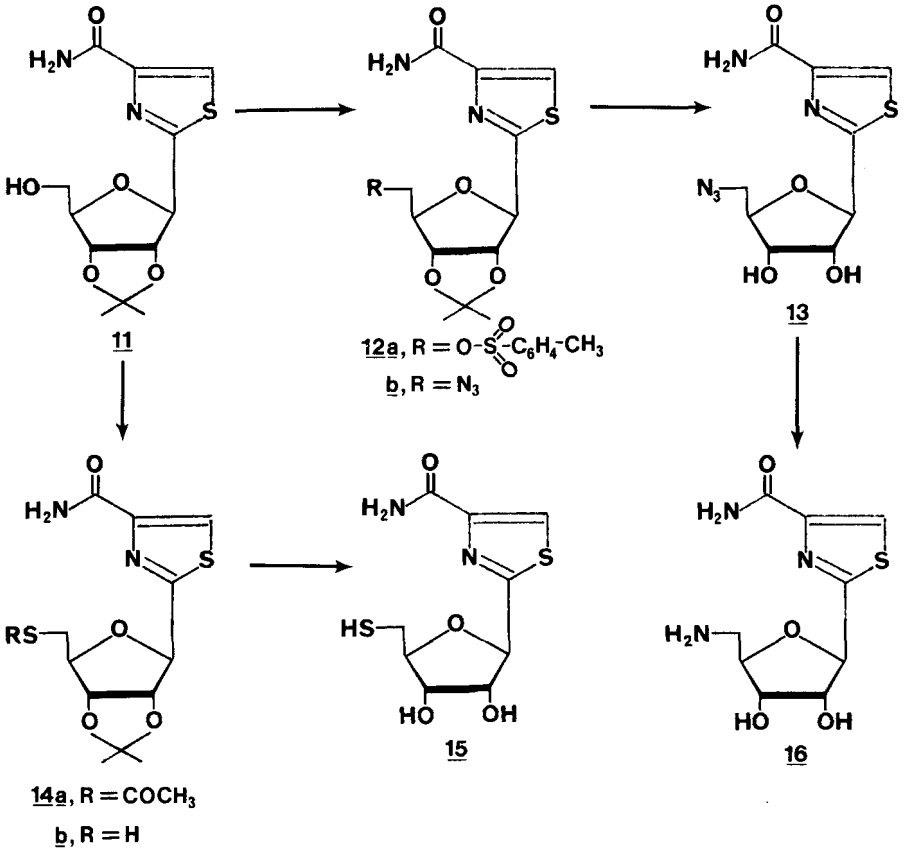
A highly efficient method for the conversion of alcohols to thiolesters and thiols has recently been described.[37] Application of this procedure to 2',3'-O-

isopropylidene ribavirin (6) by treatment with diisopropyl azodicarboxylate, triphenylphosphine and thiolacetic acid in THF at 0-5°C readily gave 1-(2,3-O-isopropylidene-5-deoxy-5-acetylthio-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (5a) in excellent yield. That the carbamoyl function on the aglycon remained unacylated was again confirmed by its ^{1}H NMR spectrum, which revealed the carbamoyl protons at δ 7.68 and 7.88 ppm. The free thiol (5b) was obtained by saponification (NaOMe) of 5a. Acid catalyzed deisopropylidenation of 5b provided 1-(5-deoxy-5-thio-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (8a).

A similar selective 5'-thioacetylation of ribavirin with thiolacetic acid in the presence of triphenylphosphine and diisopropyl azodicarboxylate in dry dioxane gave 5'-deoxy-5'-acetylthioribavirin, which on subsequent methylation with methyl iodide in alkaline conditions furnished 5'-deoxy 5'-methylthioribavirin (8b) in 67% yield.

Studies were extended to provide several 5'-substituted tiazofurin derivatives (Scheme III). Treatment of 2-(2,3-O-isopropylidene-ß-D-ribofuranosyl)thiazole-4-carboxamide[21] (11) with triphenylphosphine, diisopropyl azodicarboxylate and thiolacetic acid in dry THF gave an 84% yield of the corresponding 5'-deoxy-5'-acetylthio derivative (14a). Saponification of 14a with sodium methoxide in MeOH afforded 14b, which on acid catalyzed deisopropylidenation furnished 5'-deoxy-5'-thiotiazofurin [2-(5-deoxy-5-thio-ß-D-ribofuranosyl)thiazole-4-carboxamide, 15] in a 84% yield.

5'-Amino-5'-deoxytiazofurin (16) was prepared by employing the procedure that was used to obtain 5'-amino-5'-deoxyribavirin (10b). Thus, tosylation of 11 with p-toluenesulfonyl chloride in dry pyridine gave 2-(2,3-O-isopropylidene-5-O-p-tolylsulfonyl-ß-D-ribofuranosyl)thiazole-4-carboxamide (12a) in 69.3% yield, which on treatment with lithium azide in DMF at 85-90°C for 20 hr furnished the corresponding 5'-azido-5'-deoxy derivative (12b). Removal of the 2',3'-O-isopropylidene blocking groups of 12b with hot 80% acetic acid gave 5'-azido-5'-deoxytiazofurin (13). Hydrogenation of 13 in 50% aqueous ethanol at room temperature and 35 psi of hydrogen pressure in the presence of 10%



Scheme III

Pd/C afforded the desired 2-(5-amino-5-deoxy-ß-D-ribofuranosyl)thiazole-4-carboxamide (16) in 66% yield.

The site of glycosyl attachment and ß-anomeric configuration of all nucleosides synthesized in this study were confirmed, since the structure of the starting azole nucleosides was already established.

EXPERIMENTAL SECTION

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR) spectra were determined at 89.6 MHz with a JEOL FX-90Q spectrometer. The chemical shift

values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. The presence of solvent as indicated by elemental analysis was verified by ^{1}H NMR. Infrared spectra (IR in KBr) were obtained on a Beckman Acculab 2 spectrophotometer and ultraviolet spectra (UV; sh = shoulder) were recorded on a Cary Model 15 spectrophotometer. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ. Thin-layer chromatography (tlc) was run on silica gel 60 F-254 plates (EM Reagents). E. Merck silica gel (230-400 mesh) was used for column chromatography. All solvents used were reagent grade. Detection of nucleoside components on tlc was by UV light and with 10% H_2SO_4 in MeOH spray followed by heating. Evaporations were carried out under reduced pressure with the bath temperature below 30°C.

General Procedure for the Synthesis of 1-(5-O-Acyl-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamides (4a-h). To a stirred solution of dry 1-ß-D-ribofuranosyl-1,2,4-triazole-3-carboxamide[1] (ribavirin, 1, 3.66 g, 15 mmol) in pyridine: N,N-dimethylformamide (1:1, v/v, 150 ml), cooled to 0°C in an ice bath was added, dropwise, freshly distilled appropriate acyl chloride (15.15 mmol). The clear reaction mixture was stirred at 0°C for 15-20 hr at the end of which time water (15 ml) was added, and the solvents were evaporated at 50°C. The residue was dissolved in MeOH (50 ml) and adsorbed onto silica gel (10 g). The excess solvent was evaporated under reduced pressure. Co-evaporation with toluene (3 x 50 ml) from the solid mass gave dry residue, which was loaded onto a silica gel column (4 x 40 cm) packed in $CHCl_3$. The column was eluted with $CHCl_3$-MeOH (9:1, v/v). The appropriate homogeneous fractions were combined and the solvents evaporated. The residue was crystallized from MeOH to yield the title compound.

1-(5-O-Butyryl-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (4a) was isolated in 61.6% yield (2.90 g); mp 160°C; IR: ν 1650, 1725 (C=O), 2920-3420 (OH, NH_2)cm^{-1}; ^{1}H NMR (Me_2SO-d_6): δ 0.80-2.40 (m, 7, 5'-$(CH_2)_2$-CH_3), 5.90 (d, 1, J = 2.5 Hz, C_1'H), 7.60 and 7.80 (2 br s, 2, $CONH_2$), 8.80 (s, 1, C_5H), and other sugar protons.

Anal. Calcd for $C_{12}H_{18}N_4O_6$ (314.3): C, 45.86; H, 5.77; N, 17.82. Found: C, 45.90; H, 5.89; N, 17.83.

1-(5-O-Valeryl-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (4b) was isolated in 64% yield (3.15 g); mp 181-182°C; IR: ν 1645, 1725 (C=O), 2960-3420 (OH, NH_2)cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 0.80-2.40 (m, 9, 5'-(CH_2)$_3$-CH_3), 5.90 (d, 1, J = 2.5 Hz, C_1,H), 7.56 and 7.76 (2 br s, 2, $CONH_2$), 8.77 (s, 1, C_5H), and other sugar protons.
Anal. Calcd for $C_{13}H_{20}N_4O_6$ (328.3): C, 47.56; H, 6.14; N, 17.06. Found: C, 47.60; H, 6.25; N, 16.96.

1-(5-O-Caproyl-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (4c) was isolated in 62.4% yield (3.20 g); mp 168-169°C; IR: ν 1655, 1730 (C=O), 2960-3420 (OH, NH_2)cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 0.80-2.40 (m, 11, 5'-(CH_2)$_4$-CH_3), 5.95 (d, 1, J = 2.5 Hz, C_1,H), 7.60 and 7.78 (2 br s, 2, $CONH_2$), 8.80 (s, 1, C_5H), and other sugar protons.
Anal. Calcd for $C_{14}H_{22}N_4O_6$ (342.3): C, 49.12; H, 6.48; N, 16.36. Found: C, 49.21; H, 6.54; N, 16.16.

1-(5-O-Decanoyl-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (4d) was isolated in 61% yield (3.67 g); mp 158°C; IR: ν 1645, 1725 (C=O), 2850-3420 (OH, NH_2)cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 0.80-2.40 (m, 19, 5'-(CH_2)$_8$-CH_3), 5.92 (d, 1, J = 2.5 Hz, C_1,H), 7.58 and 7.76 (2 br s, 2, $CONH_2$), 8.79 (s, 1, C_5H), and other sugar protons.
Anal. Calcd for $C_{18}H_{30}N_4O_6$ (398.4): C, 54.26; H, 7.59; N, 14.06. Found: C, 54.45; H, 7.51; N, 13.94.

1-(5-O-Lauroyl-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (4e) was isolated in 64% yield (4.13 g); mp 165°C; IR: ν 1645, 1725 (C=O), 2850-3420 (OH, NH_2)cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 0.80-2.40 (m, 23, 5'-(CH_2)$_{10}$-CH_3), 5.88 (d, 1, J = 2.5 Hz, C_1,H), 7.56 and 7.74 (2 br s, 2, $CONH_2$), 8.78 (s, 1, C_5H), and other sugar protons.
Anal. Calcd for $C_{20}H_{34}N_4O_6$ (426.5): C, 56.32; H, 8.03; N, 13.14. Found: C, 56.05; H, 8.35; N, 13.24.

1-(5-O-Stearoyl-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (4f) was isolated in 62% yield (4.80 g); mp 195°C

(dec.); IR: ν 1650, 1730 (C=O), 2860-3430 (OH, NH_2)cm^{-1}; ^1H NMR (Me_2SO-$\underline{d}_6$): δ 0.90-1.50 (m, 35, 5'-($C\underline{H}_2$)$_{16}$-$C\underline{H}_3$), 5.88 (d, 1, J = 3.0 Hz, C_1'$\underline{H}$), 7.60 and 7.78 (2 br s, 2, $CON\underline{H}_2$), 8.78 (s, 1, $C_5\underline{H}$), and other sugar protons.

Anal. Calcd for $C_{26}H_{46}N_4O_6 \cdot 1.5\ H_2O$ (537.7): C, 58.08; H, 9.18; N, 10.42. Found: C, 58.09; H, 9.09; N, 10.28.

1-(5-O-Nicotino-3-yl-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (4g) was isolated in 44% yield (2.30 g); mp 178°C; IR: ν 1660, 1700 (C=O), 3100-3500 (OH, NH_2)cm^{-1}; UV: λ_{max} (pH 1) 258 nm (ϵ 8,000); λ_{max} (pH 7) 260 nm (ϵ 5,200); λ_{max} (pH 11) 259 nm (ϵ 5,200); ^1H NMR (Me_2SO-$\underline{d}_6$): δ 5.95 (d, 1, J = 2.5 Hz, C_1'$\underline{H}$), 7.50-9.05 (m, 7, $CON\underline{H}_2$, $C_5\underline{H}$ and pyridyl protons), and other sugar protons.

Anal. Calcd for $C_{14}H_{15}N_5O_6$ (349.3): C, 48.14; H, 4.32; N, 20.04. Found: C, 48.09; H, 4.60; N, 19.84.

1-(5-O-Adamantoyl-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (4h) was isolated in 42% yield (2.60 g); mp 105°C; IR: ν 1590, 1680 (C=O), 2920-3420 (OH, NH_2)cm^{-1}; ^1H NMR (Me_2SO-$\underline{d}_6$): δ 1.62-2.50 and 5.36-5.70 (5'-adamantoyl protons), 5.86 (d, 1, J = 2.7 Hz, C_1'$\underline{H}$), 7.65 and 7.82 (2s, 2, $CON\underline{H}_2$), 8.80 (s, 1, $C_5\underline{H}$), and other sugar protons.

Anal. Calcd for $C_{19}H_{26}N_4O_6 \cdot 1/4\ H_2O$ (410.9): C, 55.53; H, 6.50; N, 13.63. Found: C, 55.45; H, 6.79; N, 13.44.

1-(2,3-O-Isopropylidene-5-deoxy-5-acetylthio-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (5a). Triphenylphosphine (5.25 g, 20 mmol) and diisopropyl azodicarboxylate (4.16 g, 20 mmol) were dissolved in anhydrous cold (0-5°C) THF (50 ml). To the solution was added a mixture of 2',3'-O-isopropylidene ribavirin[32] (6, 2.84 g, 10 mmol) and thiolacetic acid (1.43 ml, 20 mmol) in THF (25 ml), dropwise, with stirring. The reaction mixture was stirred at ice bath temperature for 1 hr and then at ambient temperature for an additional 1 hr. A clear yellow solution was obtained, which was evaporated to dryness. The residue was triturated with MeOH (50 ml) and filtered. The filtrate was adsorbed onto silica gel (20 g). The excess solvent was evaporated. Co-evaporation with toluene (3 x 50 ml) from

the solid mass gave dry residue, which was loaded onto a silica gel column (4 x 40 cm) packed in CH_2Cl_2 . The column was eluted with CH_2Cl_2-MeOH (9:1, v/v). The homogeneous fractions were pooled and evaporated to yield 3.13 g (91.5%) of the title compound; mp 105-110°C; IR: ν 1590, 1680 (C=O), 2980, 3440 $(NH_2)cm^{-1}$; ^1H NMR (Me_2SO-$\underline{d}_6$): δ 1.32 and 1.48 (2s, 6, $2C\underline{H}_3$), 2.32 (s, 3, $SCOC\underline{H}_3$), 6.32 (d, 1, J = 0.5 Hz, $C_1,\underline{H}$), 7.68 and 7.88 (2 br s, 2, $CON\underline{H}_2$), 8.84 (s, 1, $C_5\underline{H}$), and other sugar protons.

Anal. Calcd for $C_{13}H_{18}N_4O_5S \cdot 1/2\ H_2O$ (351.3): C, 44.44; H, 5.45; N, 15.94; S, 9.12. Found: C, 44.48; H, 5.21; N, 15.71; S, 8.96.

1-(2,3-O-Isopropylidene-5-deoxy-5-thio-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (5b). A solution of 5a (17.12 g, 50 mmol) in absolute MeOH (500 ml) was adjusted to pH 9 with 1N NaOMe in MeOH and the resulting mixture was stirred at room temperature for 3 days with the exclusion of moisture. The reaction mixture was neutralized with Amberlite-IRC 120(H^+) ion-exchange resin. The resin was removed by filtration and the filtrate evaporated to dryness. The residual foam was purified on a silica gel column (4 x 40 cm) using $CHCl_3$-MeOH (6:1, v/v) as the eluent. The desired homogeneous fractions were pooled, solvent evaporated and the residue was crystallized from MeOH to yield 7.20 g (48%) of 5b; mp >85°C (foams); IR: ν 1670, 1685 (C=O), 3200-3400 $(NH_2)cm^{-1}$; ^1H NMR (Me_2SO-$\underline{d}_6$): δ 1.32 and 1.48 (2s, 6, $2C\underline{H}_3$), 6.32 (d, 1, J = 0.5 Hz, $C_1,\underline{H}$),7.68 and 7.82 (2 br s, 2, $CON\underline{H}_2$), and other sugar protons.

Anal. Calcd for $C_{11}H_{16}N_4O_4S$ (300.3): C, 43.99; H, 5.37; N, 18.66; S, 10.69. Found: C, 43.72; H, 5.10; N, 18.46; S, 10.50.

1-(5-Deoxy-5-thio-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (8a). A suspension of compound 5b (3.0 g, 10 mmol) in 80% acetic acid (100 ml) was heated on a steam bath for 2 hr. A clear solution thus obtained was evaporated to dryness and the residue was purified on a silica gel column (2.5 x 40 cm) using $CHCl_3$-MeOH (6:1, v/v) as the eluent. Crystallization of the homogeneous product from MeOH gave

2.10 g (80%) of the title compound; mp >100°C (foams); IR: ν 1670 (C=O), 3420 (NH_2)cm^{-1}; ^1H NMR (Me_2SO-$\underline{d}_6$): δ 5.90 (d, 1, J = 3.5 Hz, C_1,$\underline{H}$), 7.66 and 7.90 (2 br s, 2, CON$\underline{H}_2$), 8.88 (s, 1, $C_5\underline{H}$), and other sugar protons.
Anal. Calcd for $C_8H_{12}N_4O_4S$ (260.2): C, 36.92; H, 4.65; N, 21.53; S, 12.32. Found: C, 36.93; H, 4.64; N, 21.31; S, 12.06.

1-(5-Deoxy-5-methylthio-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (8b). To a cold (0-5°C) solution of triphenylphosphine (10.48 g, 40 mmol) and diisopropyl azodicarboxylate (8.32 g, 40 mmol) in anhydrous dioxane (200 ml) were added ribavirin (4.90 g, 20 mmol) and thiolacetic acid (2.84 ml, 40 mmol) in DMF (30 ml). The resulting solution was stirred at room temperature for 15 hr and then evaporated to dryness. The residual DMF was removed by co-evaporation with water (3 x 50 ml). The residue was suspended in water (100 ml) and extracted with ether (3 x 100 ml). The aqueous phase was evaporated to dryness; the residue dissolved in MeOH (50 ml) and adsorbed onto silica gel (20 g). The silica gel was loaded on top of a flash silica gel column (3 x 20 cm) and eluted with $CHCl_3$-MeOH (6:1, v/v/). Fractions containing the pure material were pooled and evaporated to dryness. Crystallization of the residue from MeOH gave 3.80 g (64%) of 1-(5-deoxy-5-acetylthio-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide; mp 58-62°C IR: ν 1590, 1670 (C=O), 2940-3330 (NH_2)cm^{-1}; ^1H NMR (Me_2SO-$\underline{d}_6$): δ 2.34 (s, 3, SCOC$\underline{H}_3$), 5.84 (d, 1, J = 3.5 Hz, C_1,$\underline{H}$), 7.62 and 7.84 (2 br s, 2, CON$\underline{H}_2$), 8.84 (s, 1, $C_5\underline{H}$), and other sugar protons.
Anal. Calcd for $C_{10}H_{14}N_4O_5S \cdot 1/2\ H_2O$ (311.3): C, 38.58; H, 4.82; N, 18.00; S, 10.28. Found: C, 38.49; H, 5.07; N, 18.05; S, 10.30.

To the above 5'-acetylthio compound (1.50 g, 5 mmol) in aqueous MeOH (1:1, 100 ml) was added CH_3I (2.22 g, 10 mmol), followed by 2N NaOH. The solution was stirred at room temperature for 4 hr, and then treated with Dowex-50 (H^+) resin, followed by Dowex-1 (HCO_3) resin. The resin was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in hot MeOH (20 ml) and

adsorbed onto silica gel (10 g). The silica gel was loaded on the top of a flash silica gel column (3 x 25 cm) and eluted with EtOAc-acetone-MeOH-H_2O (15:1:1:1, v/v) to give 0.90 g (67%) of analytically pure 8b; mp 158-160°C; IR: ν 1650 (C=O), 3100-3330 (OH, NH_2)cm^{-1}; ^{1}H NMR (Me_2SO-d_6): δ 2.04 (s, 3, SCH_3), 5.82 (d, 1, J = 3.5 Hz, C_1H), 7.58 and 7.80 (2 br s, 2, $CONH_2$), 8.80 (s, 1, C_5H), and other sugar protons.

Anal. Calcd for $C_9N_{14}N_4O_4S$: C, 39.41; H, 5.14; N, 20.43; S, 11.69. Found: C, 39.34; H, 5.21; N, 20.61; S, 11.50.

1-(2,3-O-Isopropylidene-5-O-p-tolylsulfonyl-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (7a). A suspension of 6 (2.84 g, 10 mmol) in anhydrous pyridine (35 ml) was cooled to 0°C in an ice bath, p-toluenesulfonyl chloride (2.10 g, 11 mmol) was added, and the mixture was stirred for 22 hr while being cooled in an ice bath. The solution was concentrated to one-third of its original volume, and the resulting syrup was poured, with stirring, into ice-water (200 ml). The resulting gummy precipitate was extracted with EtOAc (200 ml), the organic phase was dried (Na_2SO_4) and evaporated to dryness. Crystallization of the residue from benzene gave colorless needles; yield 3.90 g (89%); mp 132-134°C; IR: ν 1160, 1350 (SO_2), 1680 (C=O), 3350-3460 (NH_2)cm^{-1}; ^{1}H NMR (Me_2SO-d_6): δ 1.28 and 1.46 (2s, 6, $2CH_3$), 2.40 (s, 1, CH_3), 6.32 (d, 1, J = 0.5 Hz, C_1,H), 7.32-7.80 (m, 6, aromatic protons and $CONH_2$), 8.72 (s, 1, C_5H), and other sugar protons.
Anal. Calcd for $C_{18}H_{22}N_4O_7S$ (438.4): C, 49.32; H, 5.06; N, 12.78; S, 7.30. Found: C, 49.32; H, 5.09; N, 13.07; S, 7.47.

1-(2,3-O-Isopropylidene-5-azido-5-deoxy-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (7b). A solution of 7a (4.38 g, 10 mmol) and sodium azide (1.95 g, 30 mmol) in dry DMF (150 ml) was stirred for 10 hr at 85-90°C and evaporated to dryness at 50°C. The residue was co-evaporated several times with EtOH and then triturated with cold water (150

ml). The solid that separated was collected by filtration and crystallized from MeOH to yield 2.70 g (87.4%) of 7b; mp 184-186°C (dec.); IR: ν 1710 (C=O), 2100 (CH_2N_3), 3300-3480 (NH_2)cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 1.32 and 1.50 (2s, 6, $2CH_3$), 6.38 (d, 1, J = 1.8 Hz, C_1,H), 7.70 and 7.92 (2s, 2, $CONH_2$), 8.87 (s, 1, C_5H), and other sugar protons.

Anal. Calcd for $C_{11}H_{15}N_7O_4$ (309.3): C, 42.72; H, 4.89; N, 31.70. Found: C, 42.56; H, 4.79; N, 31.47.

1-(5-Azido-5-deoxy-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (10a). In a similar manner as for 8a, deisopropylidenation of 7b (6.18 g, 20 mmol) with 80% acetic acid (200 ml) gave 4.40 g (83.6%) of 10a; mp 124-125°C; IR: ν 1650 (C=O), 1270 and 2100 (CH_2N_3), 2920-3420 (OH, NH_2)cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 5.92 (d, 1, J = 2.0 Hz, C_1,H), 7.63 and 7.83 (2 br s, 2, $CONH_2$), 8.85 (s, 1, C_5H), and other sugar protons.

Anal. Calcd for $C_8H_{11}N_7O_4$ (269.23): C, 35.69; H, 4.12; N, 36.42. Found: C, 35.82; H, 3.99; N, 36.20.

1-(2,3-O-Isopropylidene-5-deoxy-5-phthaloylamino-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (9). To a cold (0-5°C) solution of triphenylphosphine (3.0 g, 12 mmol) and diisopropyl azodicarboxylate (2.50 g, 12 mmol) in anhydrous THF (50 ml) were added 6 (2.84 g, 10 mmol) and phthalimide (1.47 g, 10 mmol). After stirring at room temperature for 15 hr under anhydrous conditions, the reaction mixture was worked up as described for 5a to yield 2.50 g (60%) of the title compound as amorphous foam; IR: ν 1700 (C=O of amide), 1760 (C=O of phthalimide), 3200-3500 (NH_2)cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 1.32 and 1.48 (2s, 6, $2CH_3$), 6.38 (d, 1, J = <0.5 Hz, C_1,H), 7.70-7.88 (m, 6, $CONH_2$ and aromatic protons), 8.84 (s, 1, C_5H), and other sugar protons.

Anal. Calcd for $C_{19}H_{19}N_5O_6$ (413.4): C, 55.20; H, 4.63; N, 16.94. Found: C, 54.97; H, 4.74; N, 16.77.

1-(5-Amino-5-deoxy-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (10b). Method A. A mixture of 9 (1.03 g, 2.5 mmol) and n-butylamine (2 ml) in MeOH (10 ml) was heated under reflux for 12 hr, and then evaporated to dryness. The

residue was purified on a silica gel column (2.5 x 25 cm) using $CHCl_3$-MeOH (9:1, v/v) as the eluent, and crystallized from MeOH to yield 0.35 (50%) of 1-(2,3-O-isopropylidene-5-amino-5-deoxy-ß-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (7c); mp >70°C (dec.); IR: ν 1690 (C=O), 3120-3380 (NH_2) cm^{-1}; ^1H NMR (Me_2SO-d_6); δ 1.32 and 1.49 (2s, 6, $2CH_3$), 6.22 (d, 1, J = 2.0 Hz, C_1H), 7.66 and 7.88 (2 br s, 2, $CONH_2$), 8.85 (s, 1, C_5H), and other sugar protons.

Anal. Calcd for $C_{11}H_{17}N_5O_4 \cdot 1/2H_2O$ (292.3): C, 45.20; H, 6.20; N, 23.96. Found: C, 45.47; H, 6.24; N, 23.68.

Deisopropylidenation of 7c with 80% acetic acid as described for 8a gave 5'-amino-5'-deoxy-ribavirin (10b) as hygroscopic solid in 80% yield; mp >130°C (dec.); IR: ν 1670 (C=O), 3100-3400 (OH, NH_2) cm^{-1}; ^1H NMR (Me_2SO-d_6): δ 3.16 (br s, 2, C_5-NH_2, exchanged with D_2O), 5.84 (d, 1, J = 3.7 Hz, C_1H), 7.63 and 7.84 (2 br s, 2, $CONH_2$), 8.89 (s, 1, C_5H), and other sugar protons.

Anal. Calcd for $C_8H_{13}N_5O_4 \cdot 1/2H_2O$+EtOH (275.2): C, 39.27; H, 6.22; N, 25.44. Found: C, 39.35; H, 5.98; N, 25.44.

Method B. A mixture of compound 10a (2.69 g, 10 mmol) and 10% Pd/C (2.0 g) in EtOH-H_2O (1:1, v/v, 200 ml) was hydrogenated for 3 hr at room temperature at 37 psi. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated to a small volume. To the concentrate was added ether and the solid that separated was collected by filtration. The solid was washed with a small amount of cold 50% aqueous EtOH (2 x 10 ml), followed by ether and crystallized from aqueous ethanol as hygroscopic solid, 1.70 g (70%); mp >130°C (dec.). This compound was identical in all respects to 10b prepared by Method A.

2-(2,3-O-Isopropylidene-5-deoxy-5-acetylthio-ß-D-ribofuranosyl)thiazole-4-carboxamide (14a). In a similar manner as for 5a, treatment of 2-(2,3-O-isopropylidene-ß-D-ribofuranosyl)thiazole-4-carboxamide[21] (11, 3.0 g, 10 mmol) with triphenylphosphine (5.25 g, 20 mmol), diisopropyl azodicarboxylate (4.16 g, 20 mmol) and thiolacetic acid (1.43 ml, 20 mmol) in anhydrous THF (50 ml) gave 3.0 g (84%) of 14a as colorless needles; mp 159-161°C (dec.); IR: ν 1660 (C=O),

3340-3460 (NH_2)cm^{-1}; UV: λ_{max} (pH 1) 229 nm (ϵ 14,500); λ_{max} (pH 7) 228 nm (ϵ 14,700); λ_{max} (pH 11) 228 nm (ϵ 15,400); ^{1}H NMR (Me_2SO-d_6): δ 1.30 and 1.48 (2s, 6, $2CH_3$), 2.36 (s, 3 $SCOCH_3$), 5.26 (d, 1, J = 3.5 Hz, C_1,H), 7.58 and 7.66 (2 br s, 2, $CONH_2$), 8.26 (s, 1, C_8H), and other sugar protons.
Anal. Calcd for $C_{14}H_{18}N_2O_5S_2$ (358.3): C, 46.91; H, 5.06; N, 7.82; S, 17.89. Found: C, 47.17; H, 5.07; N, 7.88; S, 18.02.

2-(2,3-O-Isopropylidene-5-deoxy-5-thio-ß-D-ribofuranosyl)-thiazole-4-carboxamide (14b). In a similar manner as for 5b, treatment of 14a (1.07 g, 3 mmol) with 1N NaOMe in MeOH gave 0.50 g (53%) of 14b as amorphous solid; IR: ν 1670 (C=O), 3340-3450 (NH_2)cm^{-1}; UV: λ_{max} (pH 1) 236 nm (ϵ 3,600); λ_{max} (pH 7) 236 nm (ϵ 3,800); λ_{max} (pH 11) 236 nm (ϵ 4,700); ^{1}H NMR (Me_2SO-d_6): δ 1.33 and 1.52 (2s, 6, $2CH_3$), 5.30 (d, 1, J = 3.5 Hz, C_1,H), 7.60 and 7.80 (2 br s, 2, $CONH_2$), 8.28 (s, 1, C_8H), and other sugar protons.
Anal. Calcd for $C_{12}H_{16}N_2O_4S_2$ (316.4): C, 45.55; H, 5.10; N, 8.85; S, 20.27. Found: C, 45.55; H, 4.86; N, 8.77; S, 20.16.

2-(5-Deoxy-5-thio-ß-D-ribofuranosyl)thiazole-4-carboxamide (15). In a similar manner as for 8a, treatment of 14b (0.94 g, 3 mmol) with 80% aqueous acetic acid (50 ml) at 100°C for 2 hr gave 0.70 g (84%) of 15 as needles (from aqueous EtOH); mp 236-238°C; IR: ν 1660 (C=O), 3200-3400 (NH_2)$^{-1}$; UV: λ_{max} (pH 1) 238 nm (ϵ 6,600); λ_{max} (pH 7) 238 nm (ϵ 6,900); λ_{max} (pH 11) 238 nm (ϵ 7,200); ^{1}H NMR (Me_2SO-d_6): δ 5.50 (d, 1, J = 5.5 Hz, C_1,H), 7.56 and 7.68 (2 br s, 2, $CONH_2$), 8.21 (s, 1, C_8H), and other sugar protons.
Anal. Calcd for $C_9H_{12}N_2O_4S_2$ (276.3): C, 39.12; H, 4.38; N, 10.14; S, 23.20. Found: C, 30.34; H, 4.10; N, 10.10; S, 22.92.

2-(2,3-O-Isopropylidene-5-O-p-tolylsulfonyl-ß-D-ribofuranosyl)thiazole-4-carboxamide (12a). In a similar manner as for 7a, treatment of 11 (6.0 g, 20 mmol) with p-toluenesulfonyl chloride (4.20 g, 22 mmol) in anhydrous pyridine, and purification of the reaction product on a silica gel

column (4 x 50 cm) using $CHCl_3$-MeOH (6:1, v/v) gave 6.30 g (69.3%) of 12a as homogeneous foam; IR: ν 1175, 1360 (SO_2), 1670 (C=O), 3440 (NH_2)cm^{-1}; UV: λ_{max} (pH 1 and 7) 224 nm (ϵ 21,000), 266 sh (9,000); λ_{max} (pH 11) 222 nm (ϵ 21,300), 266 sh (9,500); ^{1}H NMR (Me_2SO-d_6): δ 1.36 and 1.58 (2s, 6, $2CH_3$), 2.44 (s, 1, CH_3), 5.22 (d, 1, J = 3.5 Hz, C_1,H), 6.40, 7.30-7.70 (m, 6, $CONH_2$ and aromatic protons), 8.12 (s, 1, C_5H), and other sugar protons.

Anal. Calcd for $C_{19}H_{22}N_2O_7S_2$ (454.5): C, 50.21; H, 4.88; N, 6.16; S, 14.10. Found: C, 50.36; H, 5.07; N, 6.31; S, 13.89.

2-(2,3-O-Isopropylidene-5-azido-5-deoxy-ß-D-ribofuranosyl)-thiazole-4-carboxamide (12b). A solution of 12a (5.91 g, 13 mmol) and lithium azide (1.90 g, 39 mmol) in dry DMF (120 ml) was stirred at 85-90°C for 20 hr and evaporated to dryness at 50°C. The residue was co-evaporated several times with EtOH and then triturated with cold water (150 ml). The gummy residue was extracted with EtOAc, dried (Na_2SO_4) and evaporated to dryness. The residue was purified on a silica gel column (2.5 x 40 cm) using $CHCl_3$-MeOH (6:1, v/v) as the eluent to give 3.50 g (82.7%) of 12b as homogeneous foam: IR: ν 1685 (C=O), 2110 (CH_2N_3), 3080-3480 (NH_2)cm^{-1}; UV: λ_{max} (pH 1) 238 nm (ϵ 6,800); λ_{max} (pH 7 and 11) 238 nm (ϵ 6,900); ^{1}H NMR (Me_2SO-d_6): δ 1.32 and 1.52 (2s, 6, $2CH_3$), 5.28 (d, 1, J = 3.5 Hz, C_1,H), 7.58 and 7.76 (2 br s, 2, $CONH_2$), 8.30 (s, 1, C_5H), and other sugar protons.

Anal. Calcd for $C_{12}H_{15}N_5O_4S$ (325.3): C, 44.30; H, 4.65; N, 21.53; S, 9.85. Found: C, 44.60; H, 4.73; N, 21.37; S, 9.63.

2-(5-Azido-5-deoxy-ß-D-ribofuranosyl)thiazole-4-carboxamide (13). In a similar manner as for 8a, deisopropylidenation of 12b (3.57 g, 11 mmol) with 80% acetic acid (100 ml) gave 2.50 g (81.5%) of 13; mp 119-120°C; IR; ν 1280 and 2100 (CH_2N_3), 1665 (C=O), 3080-3400 (OH, NH_2)cm^{-1}; UV: λ_{max} (pH 1 and 7) 237 nm (ϵ 7,700); λ_{max} (pH 11) 237 nm (ϵ 7,100); ^{1}H NMR (Me_2SO-d_6): δ 5.02 (d, 1, J = 3.5 Hz, C_1,H), 7.56 and 7.68 (2 br s, 2, $CONH_2$), 8.25 (s, 1, C_5H), and other sugar protons.

Anal. Calcd for $C_9H_{11}N_5O_4S$ (285.3): C, 37.89; H, 3.89; N, 24.55; S, 11.24. Found: C, 37.84; H, 3.92; N, 24.35; S, 11.17.

2-(5-Amino-5-deoxy-ß-D-ribofuranosyl)thiazole-4-carboxamide (16). A mixture of compound 13 (2.56 g, 9 mmol) and 10% Pd/C (2.0 g) in EtOH-H_2O (1:1, v/v, 200 ml) was hydrogenated for 6 hr at room temperature at 35 psi. The catalyst was removed by filtration through a Celite pad, and the filtrate was evaporated to dryness. The residue was crystallized from MeOH to yield 1.50 g (66%) of 16 as colorless needles; mp 189-190°C; IR: ν 1650, 1670 (C=O), 3100-3500 (OH, NH_2)cm^{-1}; UV: λ_{max} (pH 1) 238 nm (ϵ 6630); λ_{max} (pH 7) 238 nm (ϵ 6,900); λ_{max} (pH 11) 237 nm (ϵ 6,400); ^{1}H NMR (Me_2SO-d_6): δ 3.28 (br s, 1, C_5,NH_2, exchanged with D_2O), 4.96 (d, 1, J = 5.5 Hz, C_1,H), 7.60 and 7.70 (2 br s, 2, CONH_2), 8.24 (s, 1, C_6H), and other sugar protons.

Anal. Calcd for $C_9H_{13}N_3O_4S$ (259.3): C, 41.69; H, 5.05; N, 16.21; S, 12.37. Found: C, 41.92; H, 5.33; N, 15.97; S, 12.48.

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Received March 21, 1986.