Synthesis of Nucleosides of 5-Substituted-1,2,4-Triazole-3-Carboxamides

S. R. Naik, J. T. Witkowski, and Roland K. Robins*

ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute,
2727 Campus Drive, Irvine, California 92664

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Nucleosides of 5-substituted-1,2,4-triazole-3-carboxamides were prepared by the acid-catalyzed fusion procedure and by glycosylation of the appropriate trimethylsilyl derivative. The following nucleosides were obtained in two steps starting from methyl 5-substituted-1,2,4-triazole-3-carboxylates: 5-chloro-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**6**), 3-chloro-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (**5**), 3-nitro-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (**12**), 3-amino-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (**13**), 5-methyl-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**15**), and 3-methyl-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (**16**). In addition, 5-amino-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**7**), and 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide-5-thiol (**8**) were prepared from **6**.

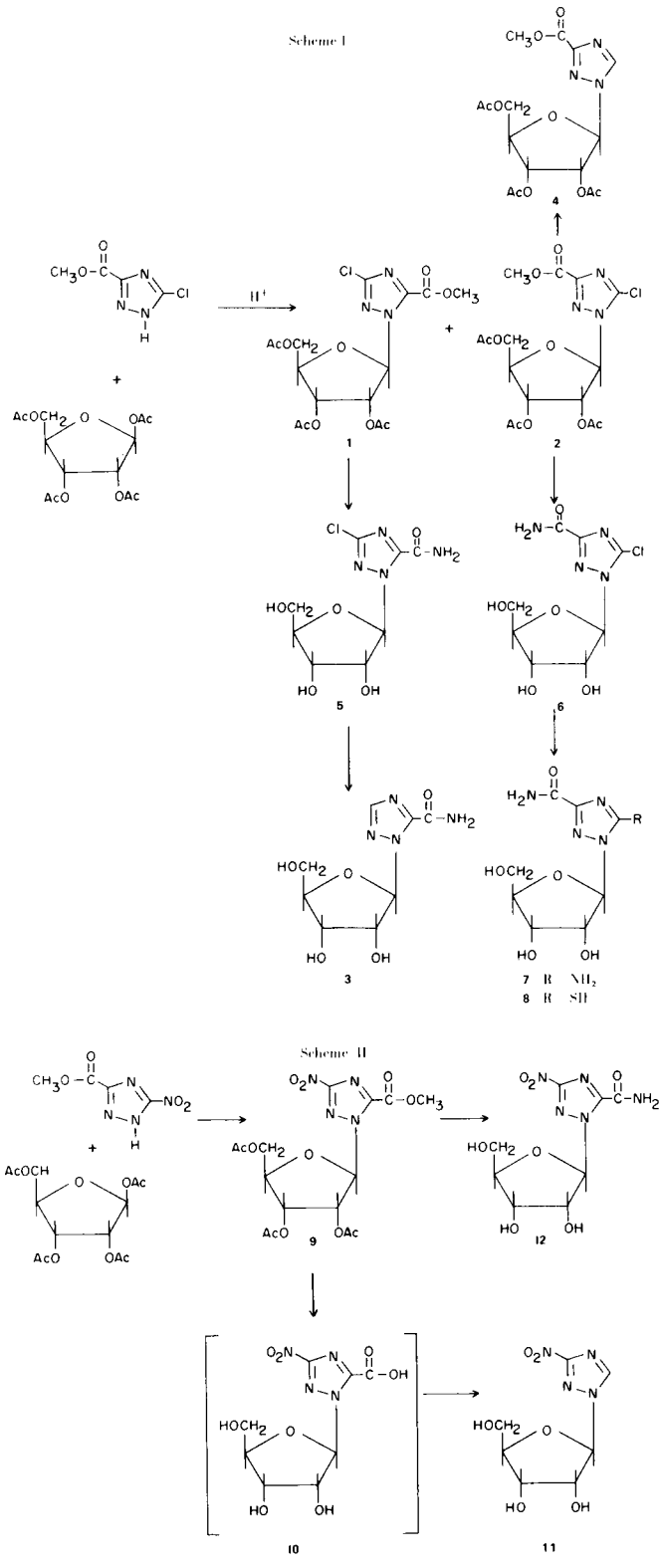
The broad-spectrum antiviral activity (1) of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (VIRAZOLE) (2) has prompted us to investigate the synthesis of related 1,2,4-triazole nucleosides. The present work reports the synthesis of nucleosides of 5-substituted-1,2,4-triazole-3-carboxamides.

Attempts to introduce substituents into the 5-position of 1,3-disubstituted-1,2,4-triazoles by electrophilic substitution (*e.g.*, bromination, chlorination, nitration) generally have not been successful (3). We have, therefore, approached the synthesis of these nucleosides *de novo via* the acid-catalyzed fusion procedure (4) utilizing 3,5-disubstituted-1,2,4-triazoles.

Fusion of methyl 3-chloro-1,2,4-triazole-5-carboxylate (5) with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of an acidic catalyst provided a mixture of two isomeric nucleosides which were separated by chromatography over silica gel. These blocked nucleosides were identified as 3-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (**1**) and 5-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (**2**) by conversion of each isomer to nucleosides of known structure and anomeric configuration. Thus, catalytic dehalogenation of **2** provided 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (**4**). The structure and anomeric configuration of **4**, as the deblocked nucleoside, 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (2), have previously been established by pmr and ^{13}C nmr studies (6) and x-ray crystallography (7). Treatment of the blocked nucleosides **1** and **2** with methanolic ammonia provided 3-chloro-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (**5**) and 5-chloro-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**6**), respectively. Dehalogenation of **5** afforded the known 1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (**3**) (2,6).

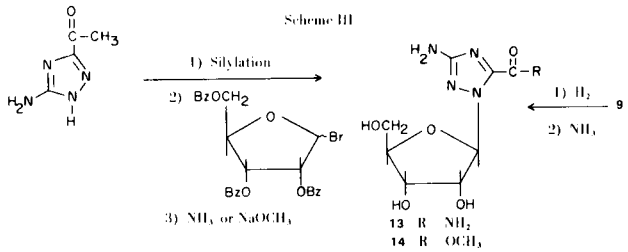
Nucleophilic displacement of the chloro group in 5-chloro-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**6**) provided a convenient route to the corresponding 5-substituted nucleosides (Scheme I). Treatment of **6** with liquid ammonia at 100° thus gave 5-amino-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**7**). Similarly, 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide-5-thiol (**8**) was obtained on treatment of **6** with sodium hydrosulfide.

Use of the fusion procedure with methyl 3-nitro-1,2,4-triazole-5-carboxylate (5) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the absence of an acidic catalyst gave a nucleoside product which was identified as 3-nitro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (**9**) as follows (Scheme II). Treatment of **9** with dilute sodium hydroxide hydrolyzed both the methyl ester and acetyl groups to afford, after acidification with Dowex 50 (H), the carboxylic acid **10**, which was not isolated. Decarboxylation of **10** by heating an aqueous solution at 100° gave the known 3-nitro-1-β-D-ribofuranosyl-1,2,4-triazole (**11**) (8), thus establishing the structure of the nucleoside **9** obtained from the fusion reaction. It is of interest to note that alkylation of methyl 3-nitro-1,2,4-triazole-5-carboxylate has been reported (9) to give only the 1-substituted product corresponding to **9**. Treatment of **9** with methanolic ammonia provided 3-nitro-1-β-D-ribofuranosyl-1,2,4-triazole-5-carb-



oxamide (**12**).

Glycosylation of the appropriate trimethylsilyl derivative was investigated as an alternate route to these triazole nucleosides. Treatment of the trimethylsilyl derivative of methyl 3-amino-1,2,4-triazole-5-carboxylate (10) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile at room temperature afforded, after treatment of the blocked nucleoside with methanolic ammonia, a 3-amino-1,2,4-triazole-5-carboxamide nucleoside (**13**) which was different from the 5-amino-1,2,4-triazole-3-carboxamide nucleoside **7**. The structure of **13** was established by reduction of the nitro-1,2,4-triazole nucleoside **9** to the corresponding amino product followed by deblocking and amide formation. The nucleoside from this route was identical to **13**, which is thus established as 3-amino-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (Scheme III). The methyl ester **14** was obtained by treatment of the blocked nucleoside from the silylation procedure with sodium methoxide.



The pmr data for the anomeric proton of these triazole carboxamide nucleosides are given in Table I. A large difference in the position of the signal for the anomeric proton in the 3-carboxamide *vs.* 5-carboxamide nucleosides is consistently observed. The downfield shift of the anomeric protons of the latter compounds is attributed to the anisotropy of the carboxamide group (6). Similar effects have been observed with other carboxamide nucleosides (11).

The above pmr data was of value in the assignment of structure of an additional pair of isomeric triazole nucleosides. Fusion of methyl 3-methyl-1,2,4-triazole-5-carboxylate (12) with the appropriate acyl ribofuranose followed by separation of the resulting isomers and treatment of each with methanolic ammonia provided the triazole carboxamide nucleosides **15** and **16** (Scheme

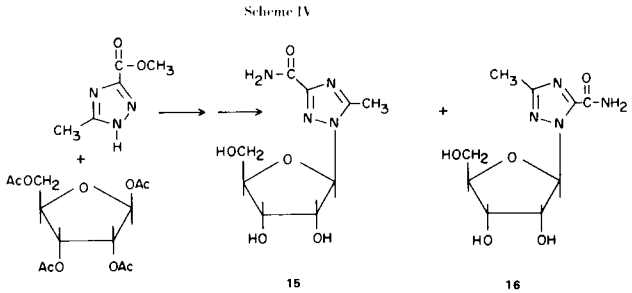
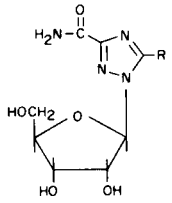


TABLE I

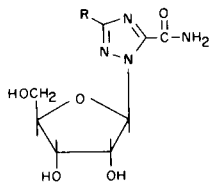
Pmr Data

5-Substituted-1,2,4-triazole-3-carboxamide Nucleosides



Cpd. No.	R	δ (a) H-1′	$J_{1',2'}$
	H (b)	5.85	3.8
6	Cl	5.82	3.9
7	NH_2	5.70	4.0
15	CH_3	5.79	3.9

3-Substituted-1,2,4-triazole-5-carboxamide Nucleosides



Cpd. No.	R	δ (a) H-1′	$J_{1',2'}$
	H (b)	6.77	3.0
5	Cl	6.75	3.5
13	NH_2	6.62	3.2
16	CH_3	6.74	3.5

(a) Determined in DMSO-d_6. (b) References 2 and 6.

IV). Evidence for the structures of these products as 5-methyl-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**15**) and 3-methyl-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (**16**) is given in Table I by comparison of the δ values for the anomeric protons with those of the triazole carboxamide nucleosides of known structures. Assignment of the anomeric configuration of **15** and **16** as beta is supported by the data in Table I. The H-1′ signal for 1′,2′-*cis* nucleosides has been shown (13) to appear at lower field than the H-1′ signal of the corresponding 1′,2′-*trans* nucleosides. Formation of the α-anomers corresponding to **15** and **16** was not detected in this procedure. However, the chemical shifts of the H-1′ signal of **15** and **16** are in good agreement with those of similar nucleosides (Table I) of known β-configuration. It may be noted that the H-1′ signal for 1-α-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, synthesized by a different route, occurs at δ 6.14 (DMSO-d_6) compared with the H-1′ signal for the β-anomer at δ 5.85 (14).

In contrast to 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (1,2), the 5-substituted-1,2,4-triazole-3-carboxamide nucleosides obtained in this work did not exhibit significant antiviral activity (15).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Evaporations were accomplished with a Buchler rotating evaporator under reduced pressure with a bath temperature of $< 35°$. The nmr spectra were recorded at 60 MHz on a Perkin-Elmer Hitachi R20A spectrometer and chemical shifts are reported in parts per million (δ) with DDS or TMS as an internal reference. Specific rotations were determined with a Perkin-Elmer Model 141 Polarimeter. Purity of products was determined by thin layer chromatography on silica gel. Chromotograms were visualized under uv light and with a spray of 10% sulfuric acid in methanol followed by heating the plate at 110°. Analytical results were determined by MHW Laboratories, Garden City, Michigan and Galbraith Laboratories, Inc., Knoxville, Tennessee.

3-Chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic Acid Methyl Ester (**1**) and 5-Chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylic Acid Methyl Ester (**2**).

A mixture of methyl 3-chloro-1,2,4-triazole-5-carboxylate (5) (2.44 g., 15.0 mmoles) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (4.62 g., 15.0 mmoles) was heated at 185° in the presence of bis(*p*-nitrophenyl)phosphate (15 mg.) under reduced pressure for 15 minutes. Chromatography of the resulting mixture on a silica gel column (5 x 85 cm) with chloroform:acetone (30:1) provided two products in the following order: **1)** 3-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (3.2 g., 50%) with m.p. 89-90°; $[\alpha]_D^{25}$ -15.7° (C 1.00, chloroform) and **2)** 5-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (2.3 g., 36%) as a syrup.

Anal. for **1)** Calcd. for $C_{15}H_{18}ClN_3O_9$: C, 42.91; H, 4.32; Cl, 8.44; N, 10.01. Found: C, 42.73; H, 4.57; Cl, 8.35; N, 10.11.

3-Chloro-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (**5**).

A solution of 3-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2.5 g.) in methanol (200 ml.) saturated at 0° with ammonia was kept in a pressure flask at 25° for 48 hours. The solvent was removed and the residue was chromatographed on a column of silica gel (4.5 x 40 cm) with ethyl acetate:methanol (19:1) to provide the nucleoside (1.09 g., 71%). Crystallization from ethyl acetate-methanol afforded pure **5** with m.p. 167.5-168.5°; $[\alpha]_D^{25}$ -36.6° (C 1.00, water).

Anal. Calcd. for $C_8H_{11}ClN_4O_5$: C, 34.47; H, 3.97; Cl, 12.72, N, 20.10. Found: C, 34.19; H, 4.14; Cl, 12.50; N, 20.00.

5-Chloro-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**6**).

A solution of 5-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (2.00 g.) in methanol

(125 ml.) saturated at 0° with ammonia was kept in a pressure bottle at 25° for 16 hours. The solvent was removed and the residue was triturated with methanol to give the nucleoside (0.60 g.). Column chromatography of the filtrate on silica gel with ethyl acetate:methanol (19:1) afforded additional product (0.45 g.). Recrystallization from methanol provided pure **6** with m.p. 191-192°; $[\alpha]_D^{25}$ -45.7° (C 1.00, water). The total yield was 68%.

Anal. Calcd. for $C_8H_{11}ClN_4O_5$: C, 34.47; H, 3.97; Cl, 12.72; N, 20.10. Found: C, 34.30; H, 3.97; Cl, 12.50; N, 20.09.

1-β-D-Ribofuranosyl-1,2,4-triazole-5-carboxamide (**3**).

A solution of **5** (0.20 g.) in a mixture of ethanol (10 ml.) and water (5 ml.) containing sodium acetate (0.10 g.) was shaken with 10% palladium on carbon (50 mg.) on a Parr hydrogenation apparatus at 50 psi for 16 hours at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to dryness. Crystallization of the product from ethyl acetate-methanol provided **3** which was identical with an authentic sample (2) as shown by comparison of ir and nmr spectra, melting points and by tlc.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylic Acid Methyl Ester (**4**).

Catalytic dehalogenation of **2** by the same procedure used above afforded **4** which was identical with an authentic sample (2) as above.

5-Amino-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**7**).

A mixture of 5-chloro-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**6**) (350 mg.) and liquid ammonia (20 ml.) was heated in a steel pressure vessel at 100° for 24 hours. Evaporation of the ammonia and crystallization of the product from aqueous ethanol provided 300 mg. (92%) of **7** with m.p. 188-190°; $[\alpha]_D^{25}$ -69.10° (C 1.00, water).

Anal. Calcd. for $C_8H_{13}N_5O_5$: C, 37.07; H, 5.06; N, 27.02. Found: C, 36.90; H, 5.18; N, 27.16.

1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide-5-thiol (**8**).

Hydrogen sulfide was bubbled into a solution of sodium methoxide (prepared from 0.60 g. of sodium and 20 ml. of methanol) for 20 minutes and 5-chloro-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**6**) (0.65 g.) was added to this solution with stirring. The solution was refluxed for 5½ hours with continuous addition of hydrogen sulfide. After the solution was cooled and diluted with methanol (50 ml.), it was neutralized with Bio-Rad AG50W-X8 (H). The resin was removed by filtration and thoroughly washed with methanol. The filtrates were evaporated to dryness. The residue was triturated with carbon disulfide and collected by filtration. Crystallization of the product from water provided pure **8** (0.51 g., 78%) with m.p. 228-230°; $[\alpha]_D^{25}$ -74.6° (C 1.00, water); pmr (DMSO-d_6): δ 6.18 (d, 1, $J_{1',2'}$ 3.5 Hz, 1'-H).

Anal. Calcd. for $C_8H_{12}N_4O_5S$: C, 34.78; H, 4.38; N, 20.28; S, 11.60. Found: C, 34.89; H, 4.34; N, 20.26; S, 11.60.

3-Nitro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic Acid Methyl Ester (**9**).

A mixture of methyl 3-nitro-1,2,4-triazole-5-carboxylate (5) (1.00 g., 5.8 mmoles) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (1.85 g., 5.8 mmoles) was heated at 135° under reduced pressure for 30 minutes. The mixture was cooled and triturated with ether-methylene chloride to provide 1.92 g. (77%) of product. Recrystallization from ether provided pure **9** with m.p. 100-101°; $[\alpha]_D^{25}$ -49.5° (C 1.00, chloroform).

Anal. Calcd. for $C_{15}H_{18}N_4O_{11}$: C, 41.86; H, 4.21; N, 13.02. Found: C, 41.81; H, 4.06; N, 12.88.

3-Nitro-1-β-D-ribofuranosyl-1,2,4-triazole (**11**).

A mixture of **9** (0.86 g., 2.0 mmoles) and 1*N* aqueous sodium hydroxide (10 ml.) was stirred at room temperature for 24 hours. The solution was then treated with excess Bio-Rad AG 50W-X8 (H) and filtered. The acidic solution was heated on the steam bath for 1 hour. Partial hydrolysis of the nucleoside was observed by thin-layer chromatography (silica gel, 9:2 acetonitrile:0.1*N* aqueous ammonium chloride). An acidic product (carboxylic acid) was removed by passing the solution through a column of Amberlite IR 45 (OH) (10 ml.). The solution was evaporated to dryness and the residue was applied to a silica gel chromatography plate (2mm x 20 cm x 20 cm). The chromatogram was developed with 2-propanol and the major band afforded **11** (60 mg.) which was identical with an authentic sample (8).

3-Nitro-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (**12**).

A solution of 3-nitro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (**9**) (0.60 g.) in methanol (30 ml.) saturated at 0° with ammonia was kept in a pressure flask at 25° for 48 hours. The solvent was removed and chromatography of the residue on a silica gel column (2 x 20 cm) with ethyl acetate:methanol (19:1) provided the carboxamide. Crystallization from methanol gave pure **12** (100 mg., 24%) with m.p. 160-161°; R_f on silica gel, 0.43, ethyl acetate:methanol (10:1); $[\alpha]_D^{25}$ -34.9° (C 0.50, water); pmr (DMSO-d_6) δ 6.86 (d, 1, $J_{1',2'}$ = 3.0 Hz, H-1').

Anal. Calcd. for $C_8H_{11}N_5O_7$: C, 33.22; H, 3.83; N, 24.22. Found: C, 32.98; H, 3.90; N, 24.15.

3-Amino-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (**13**).

Method A.

Methyl 3-amino-1,2,4-triazole-5-carboxylate (10) (2.34 g., 16.5 mmoles) was converted to the trimethylsilyl derivative by refluxing the triazole with excess hexamethyldisilazane for 20 hours according to the procedure of Wittenburg (16). Excess hexamethyldisilazane was removed under reduced pressure and the resulting product was used without further purification. An acetonitrile solution (100 ml.) of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (17), prepared from 7.56 g. (15.0 mmoles) of the 1-*O*-acetyl derivative, was added to the trimethylsilyl derivative of the triazole. The resulting solution was stirred in a stoppered flask at room temperature for 3 days. The solution was then evaporated to dryness and ethanol was added to the residue. The mixture was evaporated to a syrup which was dissolved in chloroform and chromatographed on a silica gel column (3.5 x 80 cm) using 3% acetone in chloroform. Evaporation of homogenous fractions from the column provided 5.7 g. (65%) of 3-amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester as a syrup. A portion (1.0 g., 1.7 mmoles) of this product was kept in a pressure bottle at room temperature for 36 hours with 100 ml. of methanol saturated at 0° with ammonia. The solution was evaporated to dryness, and the residue was dissolved in 5 ml. of ethyl acetate:methanol (9:1) and chromatographed on a silica gel column (2 x 20 cm) using the same solvent mixture as the eluant. Fractions containing the benzamide were rejected. Fractions containing the product were collected and evaporated to dryness. Crystallization of the product from aqueous ethanol gave **13** (0.29 g., 66%) with m.p. 206-208°; $[\alpha]_D^{25}$ -39.7° (C 1.00, water).

Anal. Calcd. for $C_8H_{13}N_5O_5$: C, 37.07; H, 5.06; N, 27.02.

Found: C, 37.11; H, 5.10; N, 26.96.

Method B.

A solution of **9** (0.86 g., 2.0 mmoles) in ethanol (100 ml.) was shaken with 10% palladium on carbon (0.10 g.) on a Parr hydrogenation apparatus at 40 psi for 4 hours at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to dryness. This product was treated with saturated methanolic ammonia (20 ml.) at room temperature for 24 hours. The solvent was removed and the product was crystallized from ethanol to afford **13** (0.40 g., 77%). All properties of this product were identical with those of **13** prepared by Method A.

3-Amino-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxylic Acid Methyl Ester (**14**).

3-Amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (1.76 g., 3.0 mmoles) was treated with a solution of 23 mg. of sodium in 50 ml. of anhydrous methanol at room temperature for 4 hours. The solution was neutralized with Bio-Rad AG50W-X2 (H) and filtered. The filtrate was evaporated to dryness. The oily residue was partitioned between water (20 ml.) and chloroform (70 ml.). The aqueous layer was evaporated to dryness and the product was crystallized from ethyl acetate containing a few drops of methanol to give **14** (0.62 g., 76%) with m.p. 153-154° dec.; $[\alpha]_D^{25}$ -43.2° (C 1.00, water).

Anal. Calcd. for $C_9H_{14}N_4O_6$: C, 39.41; H, 5.14; N, 20.43. Found: C, 39.51; H, 5.00; N, 20.34.

5-Methyl-1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**15**) and 3-Methyl-1-β-D-ribofuranosyl-1,2,4-triazole-5-carboxamide (**16**).

A mixture of methyl 3-methyl-1,2,4-triazole-5-carboxylate (12) (1.3 g., 9.2 mmoles) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (2.9 g., 9.2 mmoles) was heated with *bis*(*p*-nitrophenyl)phosphate (15 mg.) at 175-180° for 30 minutes under reduced pressure. The resulting mixture was chromatographed on a silica gel column (2.5 x 50 cm) using 20:1 chloroform:acetone. Two homogenous fractions were obtained; each was treated with a saturated methanolic ammonia solution at room temperature for 24 hours. The faster-migrating component (0.50 g.) afforded compound **16** (0.20 g., 8.4%) with m.p. 183-184°; $[\alpha]_D^{25}$ -44.5° (C 1.00, water) (crystallized from ethyl acetate-methanol).

Anal. Calcd. for $C_9H_{14}N_4O_5$: C, 41.86; H, 5.46; N, 21.70. Found: C, 41.73; H, 5.26; N, 21.56.

The slower-migrating product (0.60 g.) similarly afforded **15** (0.26 g., 11%) with m.p. 209-211°; $[\alpha]_D^{25}$ -50.4° (C 1.00, water), (crystallized from methanol).

Anal. Calcd. for $C_9H_{14}N_4O_5$: C, 41.86; H, 5.46; N, 21.70. Found: C, 41.59; H, 5.25; N, 21.81.

REFERENCES

(1) R. W. Sidwell, J. H. Huffman, G. P. Khare, L. B. Allen, J. T. Witkowski, and R. K. Robins, *Science*, **177**, 705 (1972).

(2) J. T. Witkowski, R. K. Robins, R. W. Sidwell, and L. N. Simon, *J. Med. Chem.*, **15**, 1150 (1972).

(3a) C. F. Kroeger and R. Miethchen, *Chem. Ber.*, **100**, 2250 (1967); (b) 1,2,4-Triazolin-3-one and derivatives are readily brominated and nitrated in the 5-position; see, for example, C. F. Kroeger, R. Miethchen, H. Frank, M. Siemer, and S. Pilz, *ibid.*, **102**, 755 (1969); (c) Bromination of 1-phenyl-1,2,4-triazole with *N*-bromosuccinimide was reported to afford 5-bromo-1-phenyl-1,2,4-triazole: E. G. Kovalev, and I. Ya. Postovskii, *Khim. Geterotsikl. Soedin.* (Eng. Trans), **4**, 544 (1968).

(4) T. Sato, T. Shimidato, and Y. Ishido, *Nippon Kagaku Zasshi*, **81**, 1440, 1442 (1960).

(5) L. I. Bagal, M. S. Pevzner, and V. A. Lopyrev, *Khim. Geterotsikl. Soedin., Sb. 1: Azotsoderzhashchie Geterotsikly*, 180 (1967); *Chem. Abstr.*, **70**, 77876t (1969).

(6) G. P. Kreishman, J. T. Witkowski, R. K. Robins, and M. P. Schweizer, *J. Am. Chem. Soc.*, **94**, 5894 (1972).

(7) P. Prusiner and M. Sundaralingam, *Nature New Biology*, **244**, 116 (1973).

(8) J. T. Witkowski and R. K. Robins, *J. Org. Chem.*, **35**, 2635 (1970).

(9) L. I. Bagal, M. S. Pevzner, N. I. Sheludyakova, and V. M. Kerusov, *Khim. Geterotsikl. Soedin.* (Eng. Trans.), **6**, 245 (1970).

(10) G. E. Cipens and V. Grinsteins, *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.*, 204 (1965); *Chem. Abstr.*, **63**, 13243f (1965).

(11) G. R. Revankar and L. B. Townsend, *J. Heterocyclic Chem.*, **7**, 1329 (1970).

(12) T. N. Vereshchagina and V. A. Lopyrev, *Khim. Geterotsikl. Soedin.*, 1695 (1970).

(13) C. A. Dekker and L. Goodman in "The Carbohydrates" Vol. IIA, W. Pigman and D. Horton, Eds., Academic Press, New York, N. Y., 1970, Chapter 29, p. 53.

(14) J. T. Witkowski and R. K. Robins, unpublished results.

(15) J. T. Witkowski, F. A. Lehmkuhl, S. R. Naik, R. W. Sidwell, and R. K. Robins, Abstracts, "Twelfth Interscience Conference on Antimicrobial Agents and Chemotherapy", Sept. 1972, No. 55.

(16) E. Wittenburg, *Z. Chem.*, **4**, 303 (1964).

(17) J. D. Stevens and H. G. Fletcher, Jr. in "Synthetic Procedures in Nucleic Acid Chemistry", Vol. 1, W. W. Zorbach and R. S. Tipson, Eds., Interscience Publishers, New York, N. Y., 1968, p. 532.