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Synthesis of Some Nucleoside Analogs of Substituted 1,2,3-Triazole

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1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (**4**) and 4-amino-1-(β-D-ribofuranosyl)-1,2,3-triazole-5-carboxamide (**7**) have been synthesized as an approach to obtain bioisosteres of pyrazomycin, an antiviral agent. The synthesis has been accomplished by condensation of blocked triazoles with tri-*O*-benzoyl-D-ribofuranosyl chloride in the presence of mercuric cyanide in nitromethane. UV spectral studies revealed the orientation of *N*-glycosidation in the substituted triazoles.

Current research in nucleoside antibiotics has stimulated an interest in synthesizing nucleoside analogs of a variety of heterocyclic bases. We interested in synthesizing some compounds related to pyrazomycin which was recently discovered by Gerzon *et al.*[1] Pyrazomycin (3-(β-D-ribofuranosyl)-4-hydroxypyrazole-5-carboxamide) is one of the rare *C*-nucleosides and an inhibitor of virus multiplication.

In this paper the syntheses of 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (**4**) and 4-amino-1-(β-D-ribofuranosyl)-1,2,3-triazole-5-carboxamide (**7**) are described. In these compounds, the CH= group in pyrazomycin is replaced by ring nitrogen (an isosteric ring equivalent).

In the present synthesis, the coupling of blocked triazoles with a poly-*O*-acylribosyl halide was effected with mercuric cyanide in nitromethane[2] to give the blocked nucleosides. Another purpose of the present investigation was to study the orientation of *N*-glycosidation in substituted 1,2,3-triazole.

Condensation of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[3] (**2**) with 4-ethoxycarbonyl-1,2,3-triazole[4] (**1**) or 5-acetamido-1,2,3-triazole-4-carboxamide[5] (**5**) in the presence of mercuric cyanide in nitromethane gave 1-(β-D-2′,3′,5′-tri-*O*-benzoylribofuranosyl)-4-ethoxycarbonyl-1,2,3-triazole (**3**) or 4-acetamido-1-(β-D-2′,3′,5′-tri-*O*-benzoylribofuranosyl)-1,2,3-triazole-5-carboxamide (**6**).

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2) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965).

3) H. M. Kissman, C. Pidacks, and B. R. Baker, *J. Amer. Chem. Soc.*, **77**, 18 (1955).

4) S. Yamada, T. Mizoguchi, and A. Ayata, *J. Pharm. Soc. Japan, Yakugaku Zasshi*, **77**, 452 (1957).

5) S. Yamada, T. Mizoguchi, and A. Ayata, *ibid.*, **77**, 455 (1957).

Treatment of **3** with methanolic ammonia gave 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (**4**). This compound proved to be identical to that recently prepared by G. Alonso *et al.*[6] by an alternative synthesis from a glycosyl azide and methyl propiolate.

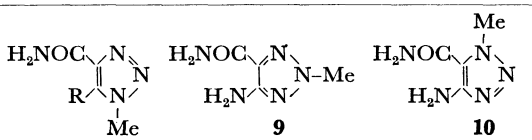
Similar treatment of **6** with methanolic ammonia gave crude 4-acetamido-1-(β-D-ribofuranosyl)-1,2,3-triazole-5-carboxamide (**7'**). Further hydrolysis of crude **7'** with methanolic ammonia in a sealed tube at 80°C for 20 hr afforded 4-amino-1-(β-D-ribofuranosyl)-1,2,3-triazole-5-carboxamide (**7**).

In accord with expectation based on participation[7] of the *C*-2 benzoyl group of the halogenosugar (**2**), the above-mentioned condensations afforded β-anomers (**3** and **6**) respectively. The anomeric nature was established by their NMR spectra. The anomeric protons of **3** and **6** appeared as doublets with $J_{1',2'}$ values of 2.8 and 1.8 (in DMSO-d_6) respectively, indicating their β-configuration.[8]

Positions of substitution of the ribosyl moiety in the triazole bases were established by comparison of the ultraviolet spectra of **4** and **7** with those of *N*-methyl derivatives **12**, **8**, **9**, **10** of 1,2,3-triazole-4-carboxamide and 5-amino-1,2,3-triazole-4-carboxamide. The former *N*-methyl derivative (**12**) was prepared from 4-carboxy-1-*N*-methyl-1,2,3-triazole which was reported by Pedersen.[9] The latter three *N*-methyl derivatives (**8**, **9**, **10**) were prepared by the method reported by Albert and Tratt[10] and their UV spectra have here been determined. The absorption maxima and extinctions of **4** and **7** were compatible with those of 1-*N*-methyl-1,2,3-triazole-4-carboxamide (**12**) and 5-amino-3-*N*-methyl-1,2,3-triazole-4-carboxamide (**10**), respectively, as shown in Table 1. It should be noted that the ribosyl group is introduced to *N*-1 of the triazole ring in case of **1**, whereas, in case of **5**, the sugar group is introduced to *N*-3 of the triazole ring.

Table 1. Ultraviolet spectral data

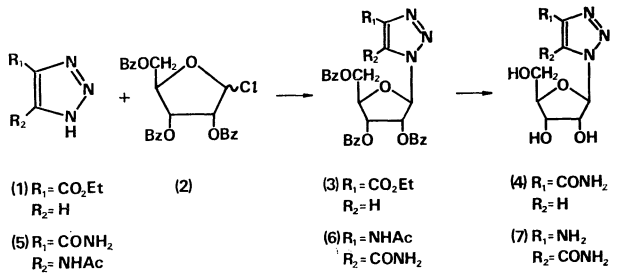
Compd No.	Solvents, absorption spectra: 0.1N-HCl λ_{max}	0.1N-HCl λ_{min}	pH 7 water λ_{max}	pH 7 water λ_{min}	0.1N-NaOH λ_{max}	0.1N-NaOH λ_{min}
12[a]	215 (11400)		212 (10400)		221 (9000)	
4	213 (12200)		211 (12700)		220 (11100)	
8[a]	228 (7990)	242 (4620)	228 (8630)	242 (5040)	228 (7770)	242 (4550)
	262 (7560)		262 (8180)		262 (7480)	
9[a]	218 (6700)	240 (1970)	218 (6310)	240 (1790)	228 (5250)	240 (1550)
	274 (5840)		274 (6350)		274 (6280)	
10[a]	206 (7620)	243 (2020)	201 (9400)	241 (2250)	221 (4370)	240 (2220)
	275 (4280)		273 (5020)		273 (5070)	
7	206 (10500)	239 (2800)	200 (11000)	241 (1900)	220 (6600)	240 (1800)
	277 (6400)		279 (6200)		280 (6400)	

a) 

8: R=NH_2
12: R=H

9

10



(1) R_1=CO_2Et, R_2=H
(2)
(3) R_1=CO_2Et, R_2=H
(4) R_1=$CONH_2$, R_2=H
(5) R_1=$CONH_2$, R_2=NHAc
(6) R_1=NHAc, R_2=$CONH_2$
(7) R_1=NH_2, R_2=$CONH_2$

Chart 1.

Experimental

Thin-layer chromatography (tlc) was carried out on microscope slides coated with silica gel, and the spots were visualized with sulfuric acid. The NMR spectra were measured with a Varian A-60D spectrometer. Tetramethylsilane (τ 10.00; for the solution of deuteriodimethylsulfoxide) and sodium 4,4-dimethyl-4-silapentane-1-sulfonate (τ 10.00; for the solution of deuterium oxide) were used as internal standards.

1-(2',3',5'-Tri-O-benzoyl-β-D-ribofuranosyl)-4-ethoxycarbonyl-1,2,3-triazole (3). 2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl chloride (**2**) (prepared[3] from 4.63 g (9.2 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose) was dissolved in nitromethane (25 m*l*) and the solution was added to a hot mixture of 4-ethoxycarbonyl-1,2,3-triazole (**1**) (1.31 g, 9.29 mmol), mercuric cyanide (2.33 g, 9.2 mmol), and Drierite (5 g) in nitromethane (70 m*l*). The mixture was refluxed for 2.5 hr with stirring. The hot suspension was filtered and the filter cake was washed thoroughly with ethylacetate. The filtrate and washings were combined and evaporated to dryness. The residue was dissolved in ethylacetate (5 m*l*) and silica gel (5 g) was added; the mixture was evaporated and the residue was chromatographed on a column of silica gel (150 g) with benzene and benzene–ethylacetate (19:1). The main portion eluted with the latter solvent system was evaporated to give **3**. Recrystallization from benzene, colorless needles, 2.99 g (54.9%); mp 168—170°C; $[\alpha]_D^{22}$ −74.8° (*c* 1.47, chloroform); UV: λ_{max} (methanol) 229 mμ (ε 48800); IR (KBr): 1730 (C=O), 710 cm^{-1} (phenyl); NMR (DMSO-d_6, τ): 0.93 (s, H-5), 3.17 (d, $J_{1',2'}$ 2.8 Hz, H-1'), 5.61 (q, *J* 7.0 Hz, $CO_2C\underline{H}_2CH_3$), 8.68 (t, *J* 7.8 Hz, $CO_2CH_2C\underline{H}_3$).

Found: C, 63.80; H, 4.62; N, 7.32%. Calcd for $C_{31}H_{27}$-

6) G. Alonso, M. T. Garcia-Lòpez, G. Garcia-Munoz, R. Madronero, and M. Rico, *J. Heterocycl. Chem.*, **7**, 1269 (1970).

7) B. R. Baker, *Ciba Foundation Symposium, Chem. and Biol. of Purines*, **1957**, 120; J. J. Fox and I. Wempen, *Advances in Carbohydrate Chem.*, **14**, 283 (1959); J. A. Montgomery and H. J. Thomas, *ibid.*, **17**, 301 (1962).

8) R. U. Lemieux and D. R. Lineback, *Ann. Rev. Biochem.*, **32**, 155 (1963).

9) C. Pedersen, *Acta Chem. Scand.*, **13**, 888 (1959).

10) A. Albert and K. Tratt, *J. Chem. Soc.*, **1968**, 344; A. Albert, *ibid.*, **1968**, 2076.

O_9N_3: C, 63.58; H, 4.65; N, 7.18%.

1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (4). A solution of **3** (0.96 g, 1.6 mmol) in absolute methanol (40 ml) saturated with ammonia was kept at 0°C for 3 days. The solution was evaporated and the resulting syrup was chromatographed on a column of 40 g of silica gel (2.1×30 cm) with benzene–ethanol (10: 1), (6: 1), (4: 1), (1: 2), and ethanol. The last fraction gave a chromatographically homogeneous **4**. Recrystallization from water, colorless needles; 0.32 g (80%); mp 208°C (lit,[6] mp 204°C); $[\alpha]_D^{20}$ −57.3° (*c* 1.43, water) (lit,[6] $[\alpha]_D$ −51.5° (*c* 0.45, water)); UV: λ_{max} (water) 211 mμ (ε 12700); IR (KBr): 3420, 3300 (OH), 1637, 1615, 1560 cm^{-1} (amide); NMR (D_2O, τ): 1.17 (s, H-5), 3.92 (d, $J_{1',2'}$ 3.9 Hz, H-1').

Found: C, 39.23; H, 4.82; N, 22.41%. Calcd for $C_8H_{12}O_5N_4$: C, 39.34; H, 4.95; N, 22.94%.

4-Acetamido-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,3-triazole-5-carboxamide (6). To a hot mixture of 5-acetamido-1,2,3-triazole-4-carboxamide (**5**) (0.97 g, 5.7 mmol), mercuric cyanide (1.45 g, 5.7 mmol) and Drierite (5.5 g) in nitromethane (140 ml), a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (**2**) (prepared from 2.87 g (5.7 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose) in nitromethane (30 ml) was added and the mixture was refluxed for 3 hr with stirring. The hot mixture was filtered, the filter cake was thoroughly washed with ethylacetate, and the filtrate and washings were combined and evaporated to dryness. The resulting gum was dissolved in methanol (5 ml), silica gel (5 g) was added and the suspension was evaporated to dryness. The residue was placed on a column of silica gel (140 g) and eluted successively with benzene–ethylacetate (19: 1, 440 ml), (9: 1, 960 ml), (4: 1, 1330 ml), and (2: 1, 1560 ml). Evaporation of the last fraction gave **6**, colorless glass, 1.63 g (48%). The product could not be crystallized, but it was chromatographycally homogeneous; $[\alpha]_D^{20}$ −73.0° (*c* 1.54, chloroform); UV: λ_{max} (methanol) 231 mμ (ε 10400); IR (KBr): 1730 (C=O, benzoyl), 1673, 1603, 1561 (amide), 713 cm^{-1} (phenyl); NMR (DMSO-d_6, τ): 3.32 (d, $J_{1',2'}$ 1.8 Hz, H-1').

Found: C, 60.59; H, 4.82; N, 11.26%. Calcd for $C_{31}H_{27}O_9N_5$: C, 60.68; H, 4.44; N, 11.42%.

4-Amino-1-(β-D-ribofuranosyl)-1,2,3-triazole-5-carboxamide (7). A solution of **6** (1.38 g, 2.25 mmol) in absolute methanol (200 ml) was saturated with ammonia at 0°C, kept at the same temperature for 3 days, and evaporated under diminished pressure at 40°C. A mixture of the residue and silica gel (1 g) in methanol was placed on a column of silica gel (40 g, 2.1×30 cm) and eluted successively with benzene and benzene–ethanol (9: 1). The latter fraction was evaporated to dryness. A solution of the residue (crude **7'**) in absolute methanol (10 ml) saturated with ammonia was placed in a sealed tube and kept at 80°C for 20 hr. After removal of the solvent under diminished pressure, the residue was taken in methanol and silica gel (500 mg) was added. The mixture was placed on a column of silica gel (30 g, 2.0×25 cm; packed with ethylacetate) and successively eluted with ethylacetate (70 ml) and ethylacetate–acetone (1: 1, 100 ml). Evaporation of the latter fraction gave **7**, colorless glass, chromatographycally homogeneous, 0.309 g (54%); $[\alpha]_D^{23}$ −52.4° (*c* 1.29, water); UV: λ_{max} (water) 200, 270 mμ (ε 11000, 6200); λ_{min} (water) 241 mμ (ε 1900); IR (KBr): 3340 (OH), 1660, 1605 cm^{-1} (amide); NMR (D_2O, τ): 4.27 (d, $J_{1',2'}$ 3.8 Hz, H-1').

Found: C, 36.92; H, 5.54; N, 26.55%. Calcd for $C_8H_{13}O_5N_5$: C, 37.07; H, 5.06; N, 27.02%.

1-Methyl-4-ethoxycarbonyl-1,2,3-triazole (11). A solution of 1-methyl-4-carboxy-1,2,3-triazole[6] (2.50 g, 16.1 mmol) in absolute ethanol (40 ml) saturated with dry hydrogen chloride was refluxed for 4 hr. After removal of the solvent, the resulting syrup was triturated with water (5 ml). Filtration yielded colorless powder, 2.00 g (65.4%). Recrystallization from water; mp 93—94.5°C.

Found: C, 46.50; H, 5.74; N, 27.22%. Calcd for $C_6H_9O_2N_3$: C, 46.44; H, 5.85; N, 27.08%.

1-Methyl-1,2,3-triazole-4-carboxamide (12). A suspension of **11** (1.01 g, 6.52 mmol) in absolute methanol (40 ml) saturated with ammonia was placed in a sealed tube and kept at 90°C for 5 hr. After cooling, the precipitate was filtered, 616 mg (75.0%). Recrystallization from 50% aqueous ethanol; sublimes at 150—220°C.

Found: C, 38.02; H, 4.45; N, 44.27%. Calcd for $C_4H_6ON_4$: C, 38.09; H, 4.80; N, 44.43%.

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