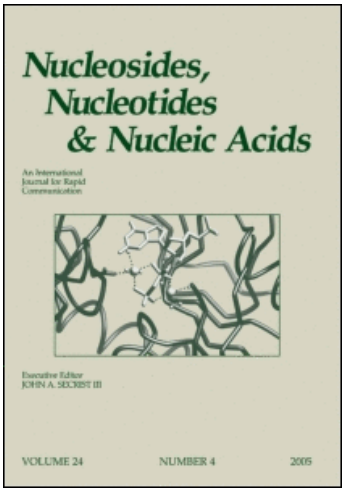

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Nucleosides, XLII. Synthesis and Properties of Lin-Naphthotriazole-Ribosides

Abdullah Hijazi[a]; Wolfgang Pfleiderer[b]
[a] Dept. of Chemistry, King Saud University, Riyadh, Saudi-Arabia [b] Fakultät für Chemie, Universität Konstanz, Konstanz, West Germany

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NUCLEOSIDES, XLII[1]

SYNTHESIS AND PROPERTIES OF lin-NAPHTHOTRIAZOLE-RIBOSIDES

Abdullah Hijazi[Δ] and Wolfgang Pfleiderer[#*]

[Δ]Dept. of Chemistry, King Saud University, Riyadh/Saudi-Arabia,
[#]Fakultät für Chemie, Universität Konstanz, Postfach 5560,
D-7750 Konstanz/West Germany

Abstract. Fusion of 1-trimethylsilylnaphtho[2,3-d]-1,2,3-triazole (4) and 2,3,5-tri-O-benzoyl-1-bromo-D-ribofuranose (5) in presence of KI leads at 130°C to an anomeric mixture of the corresponding 1-(2,3,5-tri-O-benzoyl-α- and -β-D-ribofuranosyl)-naphtho-[2,3-d]-1,2,3-triazoles (6 and 8). Separation of the anomers was achieved by chromatographical means. Debenzoylation led to the free nucleosides 7 and 9 respectively. Structural proofs are based on elementary analyses, UV- and ^{1}H-NMR-spectra.

Considerable interest has been shown in recent years in studying the effects of altering the heterocyclic moiety of a biologically active compound. Since various benzotriazole derivatives are used as chemotherapeutic agents[2-4] and synthetic nucleosides often exhibit enhanced biochemical activity compared to the corresponding aglycon[5,6] it was of interest to ribosylate the lin-naphtho[2,3-d]-1,2,3-triazole system as an extension of former investigations with lin-naphth[2,3-d]imidazole[7]. The structural features of these systems are closely related and reveal therefore some potential significance due to the fact that the lin-naphthimidazole-cobalamine analog[8] has been isolated as a minor vitamin B_{12} component.

The starting material lin-naphtho[2,3-d]-1,2,3-triazole (1)[9] has been obtained by a known procedure from 2,3-diamino naphthalene and nitrous acid. The ribosylation of this heterocycle was successfully achieved by the modified fusion

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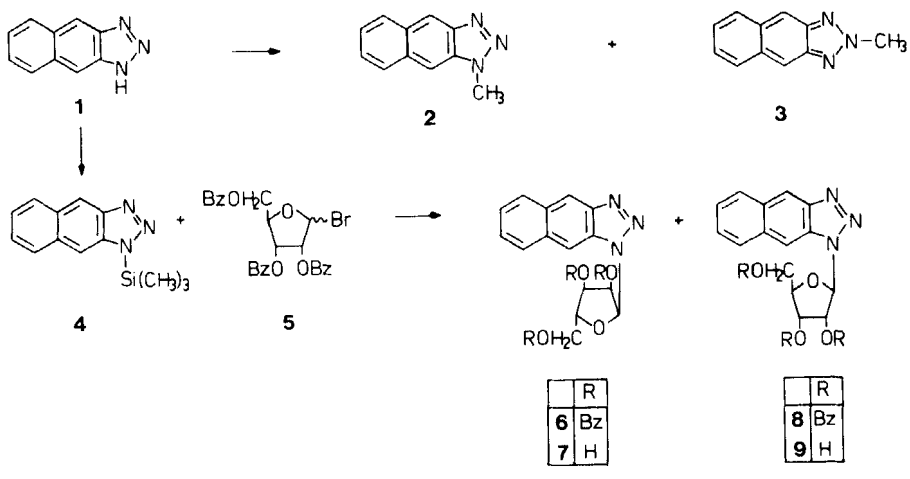
method developed some time ago in the benzimidazole series[10]. The fusion of 1-trimethylsilylnaphtho[2,3-d]-1,2,3-triazole (4) with 2,3,5-tri-O-benzoyl-1-bromo-D-ribofuranose (5) at 130°C and in presence of catalytic amounts of potassium iodide led to the formation of a mixture of mainly two compounds in 85 % yield, which turned out to be the N-1 α-(6) and β-anomers (8). Their separation into the pure compounds was achieved by silica gel chromatography in the solvent system 1,2-dichloroethane/ethyl acetate (20/1). Debenzoylation to the free ribosides 7 and 9 was performed by Zemplen's method[11] applied to the purified anomers.



	R
6	Bz
7	H

	R
8	Bz
9	H

The site of ribosylation was concluded from UV-spectral comparisons with the modelsubstances 1-(2) and 2-methylnaphtho[2,3-d]-1,2,3-triazole (3) which resulted from the methylation of 1 with dimethylsulfate in basic medium. The separation of these two isomers was again achieved by chromatography and the structural assignment based on the fact that 1-methylnaphtho[2,3-d]-1,2,3-triazole (2) should absorb at lower wavelengths than the 2-methylisomer with its quinonoid-type electron distribution. Since there is close spectral similarity between 2 and the newly synthesized nucleo-

sides, the N-1 substitution obviously represents the correct molecular structure (Tab. 1).

Constitution and assignment of the configuration of the glycosidic linkages can be depicted from the ^{1}H-NMR-spectra taken in $CDCl_3$ and D_6-DMSO respectively (Tab. 2). According to earlier findings [12-16], there is good agreement with the other ribonucleosides, proving that in an anomeric pair the chemical shift of the anomeric 1'-H of the α-riboside tends to appear at lower field compared to that of the corresponding β-form. Furthermore, the coupling constants of the former type of compounds are mostly larger than in the β-series. All newly synthesized nucleosides except 6 reveal a normal ^{1}H-NMR spectrum with the aromatic protons at low field and rising chemical shifts of the sugar protons in the order 1',2',3',4' and 5'-H. The 1-(2,3,5-tri-O-benzoyl-α-D-ribofuranosyl)-naphtho[2,3-d]-1,2,3-triazole (6), however, shows some anomaly by the separation of 2 aromatic protons from the broad multiplet and their shift to higher field at 6.97 ppm. The pseudo-triplet consists of 2 protons, one of which appears in form of a singlet and the other as a doublet according to decoupling experiments. It is very much likely that the singlet is derived from 9-H and the doublet with an ortho-coupling constant of 6.2 Hz from 8-H, which are shifted to higher field by the influence of the 2'- and 3'-O-benzoyl groups at the sugar moiety. The anomeric proton in 6 is hidden under the aromatic multiplet around 7.3 ppm as indicated from a double resonance experiment irradiating the 2'-H signal.

Biological Screening. - The deprotected nucleosides 7 and 9 have been applied to antiviral screening and cytotoxicity studies, but no activity could be detected.

E X P E R I M E N T A L

UV-Spectra were recorded on a Cary Recording Spectrophotometer, Model 118, from Appl. Physics Corp. - NMR-

Table 1 - UV-Absorption Spectra of Naphtho[2,3-d]-1,2,3-triazole Derivatives in MeOH

-naphtho[2,3-d]-1,2,3-triazole	λ_{max} (nm)					lg ε				
Unsubstituted (1)	[218]	229	[294]	308	321	[4.58]	4.71	[3.31]	3.64	3.83
	[344]	353	[369]			[3.70]	3.74	[3.53]		
1-Methyl- (2)	[219]	231	[296]	308	322	[4.53]	4.74	[3.28]	3.61	3.80
	[346]	359	[376]			[3.70]	3.74	[3.57]		
2-Methyl- (3)	[221]	232	303	310	317	[4.52]	4.70	3.32	3.44	3.71
	325	332	370	390		3.66	3.94	3.72	3.56	
1-(2,3,5-Tri-O-benzoyl-α-D-Ribofuranosyl)-(6)	[219]	230	280	307	321	[4.71]	4.82	3.57	3.57	3.72
	[344]	356				[3.57]	3.62			
1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-(8)	219	233	280	307	320	4.66	4.81	3.44	3.57	3.73
	[344]	356				[3.54]	3.60			
1-α-D-Ribofuranosyl-(7)	219	234	[294]	307	321	4.56	4.72	[3.37]	3.65	3.81
	[344]	358	[376]			[3.67]	3.72	[3.52]		
1-β-D-Ribofuranosyl-(9)	218	234	[293]	307	321	4.56	4.73	[3.34]	3.67	3.83
	[346]	356	[375]			[3.67]	3.76	[3.54]		

[ ] = Shoulder

Tab. 2 - ^{1}H-NMR Spectra of Naphtho[2,3-d]-1,2,3-triazoles in D_6DMSO* or $CDCl_3$ (δ -values in ppm).

	Aromatic Protons			Sugar Protons						N-H N-CH_3
				1'H(1H)	$J_{1,2}$ (Hz)	2'-H(1H) 2'-OH	3'-H(1H) 3'-OH	4'-H (1H)	5'-H(2H) 5'-OH	
1*	8.60bs(2H)	8.13m (2H)	7.50m (2H)							15.86s
2	8.60s (1H)	8.00m (3H)	7.45m (2H)							4.37s
3	8.40s (2H)	7.90m (2H)	7.33m (2H)							4.64s
6	8.60s (1H) 6.97pt(2H)	8.15-7.80m (7H)	7.60-7.20m (12H)	-a)	-	6.18pt	6.60m	5.41m	4.82ddd	
8	8.60s (1H)	7.98m (8H)	7.60-7.24m (12H)	6.90d	1.0	6.67pt	6.34pt	4.96m	4.70ddd	
7*	8.74s (1H) 7.50m (2H)	8.43s (1H)	8.11m (2H)	6.86d	1.7	4.46m 5.46d	5.21d	4.27m	3.70m 4.94t	
9*	8.80s (1H) 7.54m (2H)	8.63s (1H)	8.15m (2H)	6.44d	2.3	4.91d 5.62d	4.34d 5.36d	4.09m	3.62m 5.05t	

s = Singlet; bs = broad singlet; d = doublet; ddd = doublet of doublet of doublet;

t = triplet; pt = pseudotriplet; m = multiplet.

a) Covered by aromatic protons.

Spectra were obtained from Bruker WM 250 and Jeol JNM-MH-100 high resolution spectrometers with tetramethylsilane as an internal standard on a δ-scale in ppm. - Thin layer chromatography was performed on silica gel sheets F 1550 LS 254 of Schleicher & Schüll, preparative thick layer chromatography on glass plates 40x20 cm coated with a 0.2 cm layer of silica gel PF 254 of Merck/Darmstadt and column chromatography on Merck silica gel 60 (particle size 0.063-0.2 mm). - Drying of the substances was achieved in a vacuum desiccator or in a Büchi-TO 50 drying oven under vacuum at room temp. and slightly elevated temp. respectively. - Melting points are determined in a Tottoli apparatus and are uncorrected.

Naphtho[2,3-d]-1,2,3-triazole (1)[9]. The slow addition of 50 ml of 10 % sodium nitrite solution to a cold solution of 2,3-diaminonaphthalene (2.373 g, 0.015 mol) in 50 ml of water and 10 ml of conc. hydrochloric acid gave a slightly yellowish product. The collected solid was washed with water, recrystallized from water and gave after drying in a vacuum desiccator over P_4O_{10} (2.0 g, 80 %) crystals of m.p. 187°C. Lit.[9] m.p. 187°C.

1-Trimethylsilyl-naphtho[2,3-d]-1,2,3-triazole (4). A suspension of 1 (1.6 g, 0.01 mol) and a few crystals of ammonium sulfate in hexamethyldisilazane (15 ml) was refluxed under anhydrous conditions with stirring for 30 min. to form a clear solution. The excess of HMDS was distilled off in vacuum to yield 4 quantitatively. The material is pure enough for further reactions.

1-(2,3,5-Tri-O-benzoyl-α-) (6) and 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl-naphtho[2,3-d]-1,2,3-triazole (8). A solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (5.04 g, 0.01 mol) in dichloromethane (60 ml) was saturated with HBr-gas under ice cooling for 15 min. The mixture is stirred for 1 hr at 0°C and then 15 min at room temp. fol-

lowed by evaporation in vacuum to a sirup. Subsequent evaporation with absol. dichloromethane (25 ml) and absol. toluene (25 ml) yielded acid-free 5, which was dissolved in dry benzene (30 ml). The crude material of 4 was also dissolved in dry benzene (30 ml), both solutions unified and then again evaporated in vacuum to a sirupy residue. Potassium iodide (30 mg) is added and then the mixture heated in an oil-bath to 130°C for 1 hr with magnetic stirring and under a slightly reduced pressure. The cold melt is dissolved in warm chloroform (250 ml), a precipitate of unreacted 1 filtered off and then the filtrate treated subsequently three times with 1 N sodium bicarbonate solution (100 ml) and twice with water. The organic layer is dried over sodium sulfate, evaporated to dryness and then coevaporated with methanol (200 ml) to yield an amorphous foam (5.2 g, 85 %) of the anomeric mixture 6 + 8. The mixture was separated on two silica gel columns (50x4 cm) by chromatography in 1,2-dichloroethane/ethyl acetate (20/1) to yield as the faster running fraction the ß-anomer 8 (2.9 g, 47 %) as an amorphous solid.

Anal. Calc. for $C_{36}H_{27}N_3O_7$ (613.6): C, 70.46; H, 4.43; N, 6.85. Found: C, 69.86; H, 4.44; N, 6.94.

Collection of the slower running fraction and evaporation yielded the α-anomer 6 (0.67 g, 11 %) as a solid foam.

Anal. Calc. for $C_{36}H_{27}N_3O_7$ (613.6): C, 70.46; H, 4.43; N, 6.85. Found: C, 70.37; H, 4.55; N, 6.52.

1-ß-D-Ribofuranosyl-naphtho[2,3-d]-1,2,3-triazole (9). Compound 8 (2.0 g, 0.0033 mol) was added into a methanolic sodium methoxide solution (60 mg sodium in 200 ml of methanol) and then stirred for 4 hr at room temp.. After addition of water (20 ml) the solution was neutralized with acetic acid and evaporated to dryness. The residue was coevaporated three times with water (10 ml), twice with methanol (20

ml) and then the residue crystallized from water (30 ml) to give a yellowish powder (0.72 g, 73 %) of m.p. 187°C (decomp.).

Anal. Calc. for $C_{15}H_{15}N_3O_4$ (301.3): C, 59.79; H, 5.02; N, 13.95. Found: C, 59.42; H, 5.28; N, 13.63.

1-α-D-Ribofuranosyl-naphtho[2,3-d]-1,2,3-triazole (7). The preceding procedure is used analogously for deacylation of 6 (0.35 g, 0.0006 mol) to yield a brownish product (0.05g, 30 %) of m.p. 186-190°C (decomp.).

Anal. Calc. for $C_{15}H_{15}N_3O_4$ (301.3): C, 59.79; H, 5.02; N, 13.95. Found: C, 59.65; H, 5.15; N, 13.86.

1-(2) and 2-Methyl-naphtho[2,3-d]-1,2,3-triazole (3). To a solution of lin-naphthotriazole (1) (0.5 g, 0.003 mol) in 5 % aqueous sodium-hydroxide (3 ml, 5 %), dimethylsulfate (1 ml) was added dropwise at 30-35°C with stirring. A yellow precipitate separates out and is filtered after 1 hr, dried in a vacuum desiccator to yield 0.5 g (92 %) of the crude mixture with m.p. 160-180°C. Tlc showed two spots of the two isomers 2 and 3, which were separated on preparative silica gel plates (40x20x0.2 cm) using 1,2-dichloroethane/ethyl acetate (20/1) as solvent system. The two bands were eluted separately with chloroform/methanol (4/1). From the faster running zone 2-methylnaphtho[2,3-d]-1,2,3-triazole (3) was crystallized from n-hexane/methanol (2/1) to give yellow crystals of m.p. 240°C (decomp.).

Anal. Calc. for $C_{11}H_9N_3$ (183.2): C, 72.11; H, 4.95; N, 22.94. Found: C, 71.86; H, 4.90; N, 22.77.

The extract of the slower moving band gave on crystallization from n-hexane/ethanol (4/1) colourless crystals of m.p. 175°C.

Anal. Calc. for $C_{11}H_9N_3$ (183.2): C, 72.11; H, 4.95; N, 22.94. Found: C, 71.84; H, 4.81; N, 22.74.

A C K N O W L E D G E M E N T

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