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Nucleosides, Nucleotides and Nucleic Acids

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NUCLEOSIDES, XL¹
SYNTHESIS AND PROPERTIES OF lin-NAPHTHIMIDAZOLE-RIBONUCLEOSIDES

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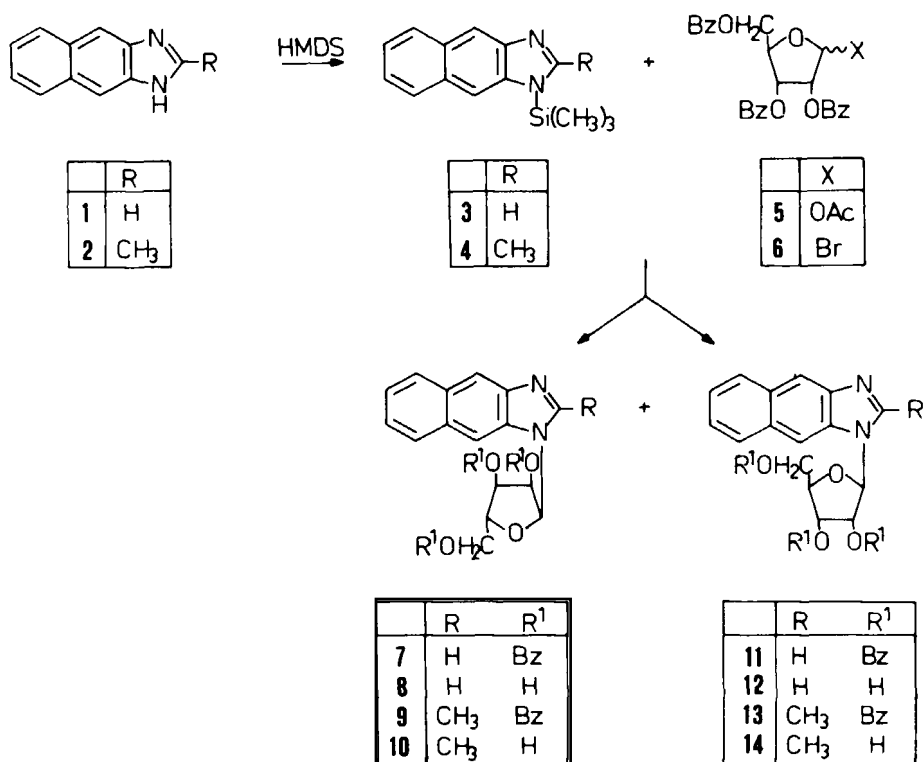
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Abstract. The fusion reaction between 1-trimethylsilyl-naphth[2,3-d]imidazole (3) and its 2-methyl derivative (4) with 2,3,5-tri-O-benzoyl-1-bromo-D-ribofuranose (6) leads to anomeric mixtures of the corresponding 2',3',5'-tri-O-benzoyl-1 α - and β -D-ribofuranosylnaphth[2,3-d]imidazoles (7,11 and 9,13). Separation of the anomers was achieved by chromatographical means and debenzoylation yielded the corresponding nucleosides (8,12 and 10,14). Structural proofs are based on elementary analysis, UV- and ¹H-NMR spectra.

The isolation of a lin-naphthimidazole-cobalamine analog² from vitamin B₁₂ concentrates, the investigations of a biosynthetic utility of naphth[2,3-d]imidazole (1)³ and the observation of a slight antibacterial activity of 2-amino-naphth[2,3-d]imidazole⁴ against *Strep. pyogenes*, *Staph. aureus*, *E. coli* and *Pr. vulgaris* encouraged us to synthesize chemically various lin-naphthimidazole nucleosides for subsequent biological testing.

The starting materials naphth[2,3-d]imidazole (1)³ and its 2-methyl derivative (2)⁵ have been obtained by known procedures from 2,3-diaminonaphthalene and formic and acetic acid respectively. First attempts to achieve a direct ribosylation with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (5) under the catalysis of BF₃-etherate⁶ and SnCl₄⁷ respectively in various solvents turned out so far to be unsuccessful. The modified fusion method, however, developed in the benzimidazole series⁸ worked quite well and led on fusion of 1-trimethylsilylnaphth[2,3-d]imidazole (3) with 2,3,5-tri-O-benzoyl-1-bromo-D-ri-

bofuranose (6)¹⁵ at 130°C and in presence of catalytic amounts of potassium iodide to the expected α,β -anomeric mixture of 7 and 11 in 90% yield. Analogous treatment of 2-methyl-naphth[2,3-d]imidazole (2) first with hexamethyldisilazane (HMDS) to form the trimethylsilyl derivative 4 and followed by fusion condensation with 6 again yielded over 90 % of the α,β -anomeric ribosides 9 and 13.



Separation of the chemically and physically very similar anomers was a difficult task and could be achieved with the 7 + 11 mixture by preparative thick layer chromatography in the solvent system 1,2-dichloroethane/ethylacetate (20/1), whereas 9 and 13 separated on silica gel column chromatography in chloroform/acetone (13/1) to give the pure components.

Debenzoylation to the free ribosides 8, 10, 12 and 14 was performed by Zemplen's method⁹ either by use of the purified anomers or by treatment of the anomeric mixture (7+11) and subsequent separation of the deprotected nucleosides into 8 and 12 by fractional crystallization.

The empirical formula of the newly synthesized compounds were determined by elementary analyses and the structural assignments could be derived unambiguously from UV and ¹H-NMR spectra. The UV spectra (TAB. 1) are not too informative with regard to fine structural problems but show a characteristic splitting of the long wavelength band due to the planar and rigid structure of the aglycon.

Constitution and assignment of the configuration of the glycosidic linkages can be depicted nicely from the ¹H-NMR spectra taken in CDCl₃ and D₆-DMSO respectively (TAB. 2). There is agreement with earlier findings¹⁰⁻¹⁴ on other ribofuranosides that in an anomeric pair the chemical shift of the anomeric proton 1'-H of the α-D-riboside appears at lower field compared to the corresponding β-form. It is furthermore noticed that there is in almost all cases a very distinct separation and coupling of the sugar protons proving the assigned constitutions additionally.

EXPERIMENTAL

UV Spectra were recorded on a Cary Recording Spectrophotometer, Model 118, from Appl. Physics Corp. - NMR spectra were obtained from Bruker WM 250 and Jeol JNM-MH-100 high resolution spectrometers with tetramethylsilane as an internal standard and 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 40 x 20 cm coated with a 0.2 cm layer of silica gel PF₂₅₄ 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.

Naphth[2,3-d]imidazole (1)³. 2,3-Diaminonaphthalene (4.74 g, 0.03 mol) is refluxed in formic acid (30 ml) for 4.5 hr. It is evapo-

Table 1. UV-Absorption Spectra of Naphth[2,3-d]imidazole Derivatives in MeOH

-naphth[2,3-d]- imidazole	λ_{max} (nm)		lg ϵ	
unsubstituted (1)	236	313 323 339	4.82	3.87 3.90 3.79
1-(2,3,5-Tri-O-benzoyl- α -D-ribofuranosyl)- (7)	237 275 283	314 326 341	4.95 3.61 3.62	3.85 3.80 3.68
1-(2,3,5-Tri-O-benzoyl- β -D-ribofuranosyl)- (11)	237 275 282	313 [322] 339	4.96 3.61 3.63	3.88 [3.82] 3.68
1- α -D-ribofuranosyl- (8)	241 [258][306]	317 [322] 338	4.84 [3.52][3.80]	3.91 [3.89] 3.75
1- β -D-ribofuranosyl- (12)	238 [257][302]	314 324 341	4.83 [3.31][3.70]	3.87 3.89 3.71
2-Methyl- (2)	238 [306]	317 326 335	4.85 [3.82]	3.95 3.86 3.80
2-Methyl-1-(2,3,5-tri-O-benzoyl- α -D-ribofuranosyl)- (9)	235 275 282	316 [321] 335	4.89 3.62 3.64	3.87 [3.84] 3.70
2-Methyl-1-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)- (13)	240 275 283	[304] 314 335	4.96 3.66 3.68	[3.84] 3.94 3.74
2-Methyl-1- α -D-ribofuranosyl- (10)	242 [257][306]	316 [322] 337	4.84 [3.50][3.80]	3.92 [3.90] 3.76
2-Methyl-1- β -D-ribofuranosyl- (14)	241 [257][305]	316 [321] 336	4.84 [3.54][3.82]	3.92 [3.92] 3.75

[] = Shoulder

Table 2. $^1\text{H-NMR}$ Spectra of Naphth[2,3-d]imidazoles in $\text{D}_6\text{-DMSO}$ and CDCl_3 :

	2-H(1) 2-CH ₃ (3)	Aromatic Protons	$J_{1',2'}$ (Hz)	1'-H(1)	2'-H (1)	3'-H (1)	4'-H (1)	5'-H (2)	2'-OH (1)	3'-OH (1)	5'-OH (1)
1	8.30	7.95s(2) 7.18q(2)									
7	8.84	7.25 - 8.42m(21)		6.97d 2.3	6.38pt	6.23q	5.18q	5.91d ³			
11	8.52	7.40 - 8.43m(21)		6.63d 2.6	6.35pt	6.20q	4.90 - 5.10m				
8	8.64	7.90 - 8.20m(4) 7.40m(2)		6.39d 2.0	4.40dd	4.21pt	4.11dd	3.58m	5.56d	5.35d	4.91t
12	8.71	8.26s(2) 7.42m(2)		5.99d 2.5	4.51dd	4.17dd	4.01dd	3.70m	5.55d	5.27d	5.20t
2	2.57s	7.96m(4)									
9	2.77s	6.90pt(1) 7.20 - 8.10m(20)		6.73d 2.0	6.21pt	6.01pt	5.25dd	4.80d ³			
13	2.87s	7.00 - 8.24m(21)		6.40d 3.0	6.19pt	6.10dd	4.80dd	4.93d ³			
10	2.66s	8.02s(2) 7.35m(2)		6.34d 1.0		4.23s(3H)		3.68dd	5.37d	5.13bs	4.88t
14	2.68s	8.39s(1) 7.96m(2)		5.85d 3.0	4.54dd	4.20bs	4.02dd	3.80bs	5.38d	5.25	5.33m

s = singlet; bs = broad singlet; d = doublet; dd = double doublet; d³ = doublet of doublet of doublet; t = triplet; pt = pseudotriplet; q = quadruplet; m = multiplet. () number of protons.

rated to dryness, the residue dissolved in boiling water (80 ml), treated with charcoal and filtered. The hot filtrate is treated with conc. ammonia and on cooling the precipitate collected. On crystallization from water/methanol (3/1) are obtained slightly brownish coloured needles (4.8 g, 95 %) of m.p. 211°C. Lit.³ m.p. 220°C.

2-Methyl-naphth[2,3-d]imidazole (2)⁵. 2,3-Diaminonaphthalene (3.16 g, 0.02 mol) is heated under reflux in acetic acid (30 ml) for 18 hr. Evaporation to dryness, suspension in water and treatment with conc. ammonia yielded a crude material which was recrystallized from ethanol to give yellowish crystals (3.52 g, 97 %) of m.p. 286-287°C. Lit.⁵ m.p. 286°C.

1-Trimethylsilyl-naphth[2,3-d]imidazole (3). A suspension of 1 (3.36 g, 0.02 mol) and a few crystals of ammonium sulfate in hexamethyldisilazane (15 ml) is refluxed under anhydrous conditions with stirring for 30 min. to form a clear solution. The excess of HMDS is distilled off in vacuum to yield 3 quantitatively. The material is pure enough for further reactions.

2-Methyl-1-trimethylsilyl-naphth[2,3-d]imidazole (4). A suspension of 2 (3.64 g, 0.02 mol) and a few crystals of ammonium sulfate in hexamethyldisilazane (30 ml) has to be refluxed under anhydrous conditions in an oil-bath of 160°C with stirring for 3 days. The excess of HMDS is distilled off in vacuum and the residue used for further reactions.

1-(2,3,5-Tri-O-benzoyl- α -D-) (7) and 1-(2,3,5-Tri-O-benzoyl- β -D-ribofuranosyl)-naphth[2,3-d]imidazole (11). A solution of 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose (5) (10.08 g, 0.02 mol) in dichloromethane (60 ml) is 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. followed by evaporation in vacuum to a sirup. Subsequent evaporation with absol. dichloromethane (25 ml) and absol. toluene (25 ml) yielded acid-free 6¹⁵ which was dissolved in absol. benzene (30 ml). The crude material of 3 was also dissolved in absol. benzene (30 ml), both solutions united and then again evaporated in vacuum to a sirupous 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 co-evaporated with methanol (200 ml) to yield an amorphous foam (11.5 g, 90 %) of the anomeric mixture 7 + 11. Separation into the pure components is difficult, but can be achieved by preparative silica gel chromatography of 0.18 g of the mixture on a 40 x 20 x 0.2 cm plate and development in 1,2-dichloroethane/ethyl acetate (20/1) for five times. The lower part of the main band is cut out and eluted by chloroform to yield on evaporation a colourless foam of 7.

Anal. Calc. for $C_{37}H_{28}N_2O_7$ (612.6): C, 72.54; H, 4.61; N, 4.57. Found: C, 72.33; H, 4.49; N, 4.44.

The front part of the main band gave on elution and evaporation the chromatographically pure β -anomer 11.

Anal. Calc. for $C_{37}H_{28}N_2O_7$ (612.6): C, 72.54; H, 4.61; N, 4.57. Found: C, 72.24; H, 4.60; N, 4.48.

1- α - (8) and 1- β -D-Ribofuranosyl-naphth[2,3-d]imidazole (12).
Anomeric mixture of 7+11 (2.2 g) was added to methanolic sodium methoxide solution [from sodium (40 mg) in methanol (200 ml)]. After stirring for 3 hr. at room temp. the solution is neutralized with acetic acid, evaporated to dryness and then coevaporated three times with water. The residue is recrystallized from methanol (30 ml) to yield in the first fraction pure β -anomer 12 (0.25 g) as colourless crystals of m.p. 197-199°C.

Anal. Calc. for $C_{16}H_{16}N_2O_4$ (300.3): C, 63.99; H, 5.37; N, 9.33. Found: C, 63.79; H, 5.38; N, 9.07.

Partial evaporation leads to the separation of a mixture, but from the mother liquid crystallizes a small amount of the α -anomer 8 (20 mg) as colourless crystals of m.p. 198-202°C.

Anal. Calc. for $C_{16}H_{16}N_2O_4$ (300.3): C, 63.99; H, 5.37; N, 9.33.

Found: C, 63.81; H, 5.29; N, 9.20.

2-Methyl-1-(2,3,5-tri-O-benzoyl- α -D-) (9) and 2-Methyl-1-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)-naphth[2,3-d]imidazole (13). Analogously to the preceding procedure of 7 + 11 2-methyl-1-trimethylsilyl-naphth[2,3-d]imidazole (4) (5.1 g, 0.02 mol) and 2,3,5-tri-O-benzoyl-1-bromo-D-ribofuranose (6)¹⁵ (0.02 mol) are fused at 130°C for 1 hr. with magnetic stirring. After the same work-up the anomeric mixture 9 + 13 is obtained as an amorphous, solid foam (11.5 g, 92 %). The mixture was separated on two silica gel columns (50 x 4 cm) by chromatography in chloroform/acetone (13/1) to yield as the faster running fraction the β -anomer 13 (5.1 g, 41 %) as an amorphous solid.

Anal. Calc. for $C_{38}H_{30}N_2O_7$ (626.6): C, 72.83; H, 4.83; N, 4.47. Found: C, 72.98; H, 4.80; N, 4.33.

Collection of the slower running fraction and evaporation yielded the α -anomer 9 (2.0 g, 16 %) as a solid foam.

Anal. Calc. for $C_{38}H_{30}N_2O_7$ (626.6): C, 72.83; H, 4.83; N, 4.47. Found: C, 72.63; H, 4.70; N, 4.46.

2-Methyl-1- α -D-ribofuranosyl-naphth[2,3-d]imidazole (10). Compound 9 (1.88 g, 0.003 mol) was added to methanolic sodium methoxide solution [from sodium (60 mg) in methanol (200 ml)] and then stirred for 3 hr. at room temp. After dilution with water (20 ml) the solution is neutralized by acetic acid and evaporated to dryness. The residue is co-evaporated three times with water (10 ml), twice with methanol (20 ml) and then crystallized from ethyl acetate to give 10 (0.64 g, 68 %) in colourless crystals of m.p. 204°C.

Anal. Calc. for $C_{17}H_{18}N_2O_4$ (314.3): C, 64.96; H, 5.77; N, 8.91. Found: C, 64.54; H, 5.82; N, 8.91.

2-Methyl-1- β -D-ribofuranosyl-naphth[2,3-d]imidazole (14). The preceding procedure is used analogously for deacylation of 13 (1.88 g, 0.003 mol) to yield on crystallization from water 0.68 g (72 %) colourless crystals of m.p. 204-206°C.

Anal. Calc. for $C_{17}H_{18}N_2O_4$ (314.3): C, 64.96; H, 5.77; N, 8.91. Found: C, 64.97; H, 5.69; N, 8.60.

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