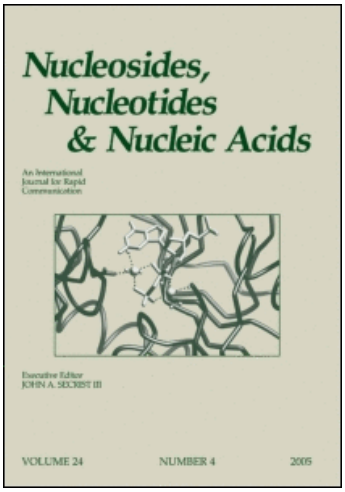

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Nucleosides, III[1] Synthesis and Properties of 2-Trifluoromethyl-Naphthimidazole-Ribonucleoside

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NUCLEOSIDES, III[1]

SYNTHESIS AND PROPERTIES OF 2-TRIFLUOROMETHYL-NAPHTHIMIDAZOLE-RIBONUCLEOSIDE

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Abstract. The fusion reaction between 2-trifluoromethyl--naphth[2,3-d]imidazole (1) and 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (2) leads to 2',3',5'-tri-O-benzoyl-1-β-D-ribofuranosylnaphth[2,3-d]imidazole (3). Debenzoylation of (3) gives the corresponding nucleoside 1-β-D-ribofuranosyl -2-trifluoromethylnaphth[2,3-d]imidazole (4). Structural proofs are based on elementary analysis, UV-and ^{1}H-NMR spectra.

Considerable interest has been evinced in recent years in studying the effect of altering the heterocyclic moiety of a biologically active nucleoside. Antibacterial[2] as well as antiviral[3] properties of some 2-trifluoromethylbenzimidazole-derivatives have been described. These derivatives are

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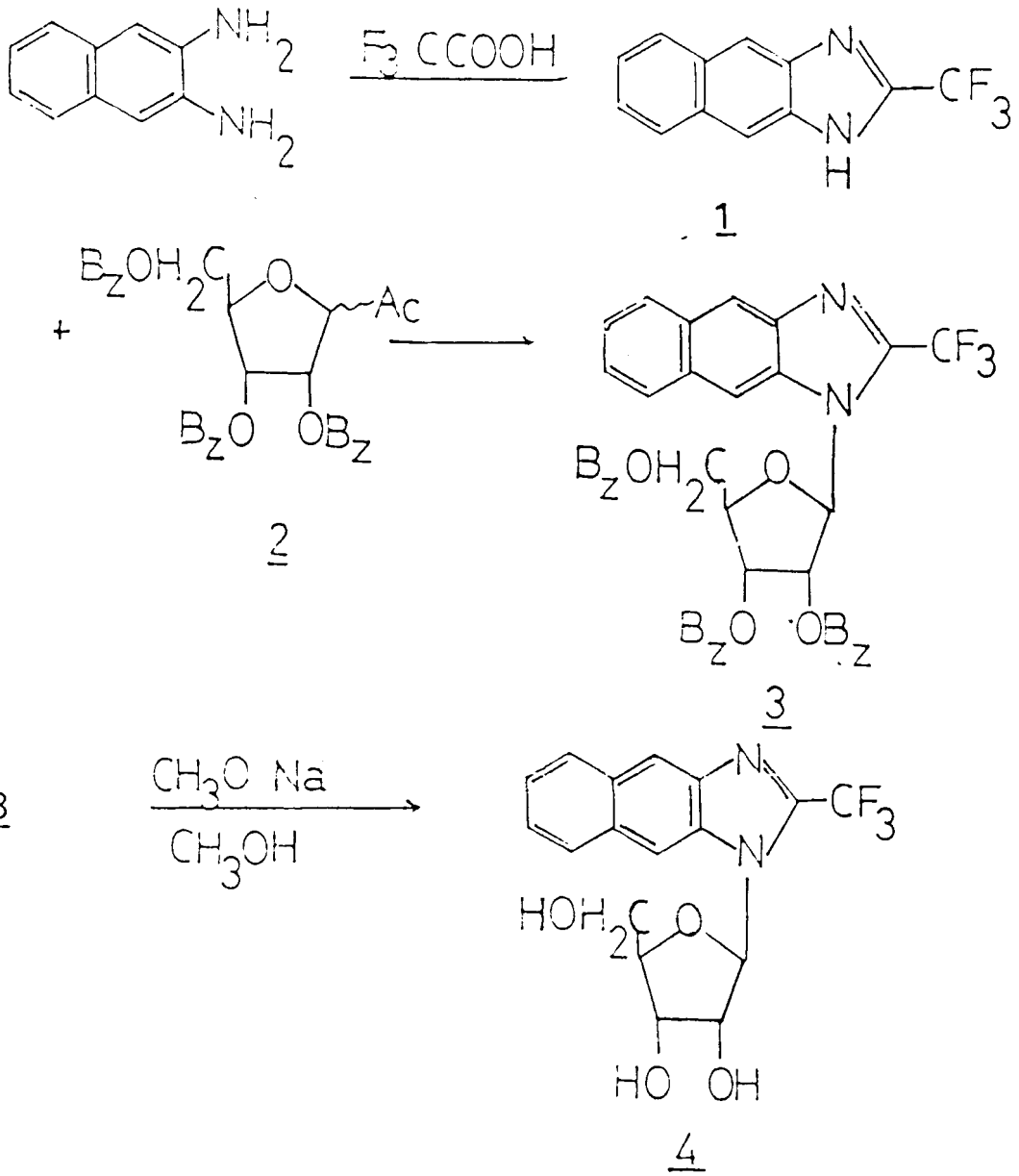
known as inhibitors of photosynthetic processes[4]; some of them also exhibit appreciable herbicidal and insecticidal activities[5]. It was, therefore, of interest to study the ribosylation of the 2-trifluoromethyl-lin-naphth[2,3-d]-imidazole system. The present study is, in fact, an extension of our former investigations with lin-naphth[2,3-d]imidazole[6].

Such compounds have a potential biological significance, due to the fact that the lin-naphthimidazole-cobalamine analog[7] has been isolated as a minor vitamin B_{12} component. The starting material 2-trifluoromethylnaphth[2,3-d] imidazole (1) was obtained from 2,3-diaminonaphthalene and trifluoroacetic acid by a known procedure[8].

The first attempt to achieve ribosylation of (1), using the modified fusion method, developed in the benzimidazole series[9], was a failure and the expected nucleoside was not formed. A second attempt carried out using trimethylsilyl triflate, a new catalyst described by Vorbruggen et al[10], also failed.

After the failing of the two previous attempts, we decided to examine the fusion of (1) with (2) at 180°C under reduced pressure. This proved to be successful and gave 1-(2,3,5-tri-O-benzoyl)-β-D-ribofuranosyl-2-(trifluoromethyl)-naphth[2,3-d]imdidazole (3) in 63% yield. Debenzoylation to the free riboside (4) was performed by Zemplen's method[11], using the pure anomer.



The empirical formulas of the newly synthesized compounds were determined by elementary analyses and the structural assignments could be derived unambiguously from UV and ^{1}H-NMR spectra.

Table 1. UV-Absorption Spectra of 2-Trifluoromethylnaphthimidazole Derivatives in MeOH.

2-Trifluoromethylnaphth [2,3-d]-imidazole	λ_{max} (nm)	log ε
unsubstituted (1)	[302] 317 335 349	[3.63] 3.86 3.71 3.5
1-(2,3,5-Tri-O-benzoyl β-D-ribofuranosyl)-(3)	221 236 274 281 [306] 316 338, [352]	[4.77] 4.87 3.60 3.60 [3.78] 3.95 3.71 [3.59]
1-β-D-Ribofuranosyl(4)	219 239, [286][306]317 337.5 [352]	4.61 4.77 [3.40] [3.80] 3.96 3.78 [3.63]

Table 2. ^{1}H-NMR Spectra of Naphth[2,3-d]imidazole Derivatives in D_6-DMSO and $CDCl_3$*

	Aromatic Protons	1'-H(1) $J_{1',2'}$(Hz)	2'-H (1)	3'-H (1)	4'-H (1)	5'-H (2)	2'-OH (1)	3'-OH (1)	5'-OH (1)
1	8.3bs(2) 8.03 dd(2) 7.49 dd(2)								
*3	7.30-8.12 m (21)	6.6 d 7.94	6.3pt	6.15dd	4.8dd	4.97m			
4	8.83S(1) 8.49(1) 8.08dd(2)7.50m(2)	5.91d 7.63	4.72q	4.26m	4.07d	3.83m	5.47pt	5.47pt	5.29d

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

The configuration of the glycosidic linkages can be assigned readily from the ^{1}H-NMR spectra taken in $CDCl_3$ and D_6-DMSO, respectively (TAB. 2). As expected[12], the direct fusion reaction method resulted exclusively in the formation of β-anomer as indicated by an upfield chemical shift of 1'-H. However, this is different from the chemical shift observed in the lower field which was recognized for α-anomer of similar system[6]. Again this result is in agreement with earlier report for β-anomer on very similar system[12], and other ribofuranosides[13-17], 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 that of 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 configuration conclusively. A comprehensive study is currently underway to determine the biological characteristics of the newly synthesized compound. Initial results from this study are very encouraging and a separate report is intended upon its completion.

Experimental

UV spectra were recorded on a Carey Recording Spectrophotometer, Model 118, from Appl. Physics Corp.'H-NMR spectra were obtained from Brucker WM 250. Thin layer chromatography was performed on silica gel sheets F1550 LS

254 of Schleicher & Schull, preparative thick layer chromatography on glass plates 40 x 20 cm coated with a 0.2 cm layer of silica gel PF_{254} of Merck/Darmstadt and colum 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 Buchi-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.

2-Trifluoromethylnaphth[2,3-d]imidazole (1). 2,3-Diaminonaphthalene (1.58 g, 0.01 mol) was refluxed with 10 ml of trifluoroacetic acid, resulting in the formation of a brownish precipitate. This precipitate was filtered and washed throughly with water before it was suspended again in water, and heated until boiling. Ethanol was then added gradually until the suspension was converted to a clear solution. Active charcoal was then added to the boiling solution and the entire contents were kept at boiling temp. for 10 min. The solution was then filtered and cooled to give colourless crystals (2.1 g, 89%) of m.p. 270°C. Lit. m.p. 273°C.

Anal. Calc. for $C_{12}H_7N_2F_3$ (236.2): C_1 61.2; H, 2.99; N, 11.86 Found: C, 60.67; H, 2.93; N,11,81.

1-(2,3,5-Tri-O-benzoyl-β-D-)-2-trifluoromethylnaphth [2,3-d]imidazole (3).

A finely ground mixture (0.95 g 0.004 mol) of 2-trifluoromethylnaphth[2,3-d]imidazole and (2.4 g, 0.0047 mol) of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (2) was heated for two hours at 180-185^0 under reduced pressure (20 mm Hg, water pump). The mixture was then taken in 50 ml methanol and refluxed for ½ hr and filtered. The separation into the pure component (3) was achieved by preparative silica gel chromatography of 0.13 g from residue on a 40 x 20 x 0.2 cm plate and development in 1,2-dichloroethane/ethyl acetate (25/1) three times. The lower part was cut out and eluted by chloroform to yield, on evaporation, a colourless foam which was crystallized from ethanol to give the pure β-anomer (0.082 g, 63%) of m.p. 211^{0}C.

Anal. Calc. for $C_{38}H_{27}N_2O_7F_3$ (680.59): C 67.05; H, 3.99; N, 4.11 Found C, 66.86; H,3,81; N,4,07.

1-β-D-Ribofuranosyl-2-trifluoromethylnaphth[2,3-d] imidazole (4). Compound (3) (0.0 82 g, 0.00012 mol) was added to methanolic sodium methoxide solution (40 mg sodium in 100 ml of absol. methanol) and then stirred for 4 h at room temp. After addition of water (15 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 was crystallized

from water (10 ml) to give a colourless product (0.038g, 84%) of m.p. 188-9^0.

Anal. Calc. for $C_{17}H_{15}N_2F_3O_4$ (370.41): C, 55.12; H, 4.08 N, 7.59. Found: C, 55.38; H, 4.16; N, 7.28.

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