

Stereospecific Synthesis by the Sodium Salt Glycosylation Method of Halogeno Benzimidazole 2'-Deoxyribose Analogues of the Inhibitor of hnRNA Synthesis, 5,6-Dichloro-1-(β -D-ribofuranosyl)benzimidazole (DRB)

Z. Kazimierzczuk^a, R. Stolarski^{a,b}, and D. Shugar^{a,c}

^a Department of Biophysics, Institute of Experimental Physics, University of Warsaw, 02-089 Warszawa

^b Institut für Biophysikalische Chemie, Klinikum der Universität, 6000 Frankfurt am Main 70, GFR

^c Institute of Biochemistry and Biophysics, Academy of Sciences, 02-532 Warszawa, Poland

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The recently developed stereospecific sodium salt glycosylation procedure has been successfully applied to the synthesis of the β -D-2'-deoxyribofuranosides of benzimidazole, 5,6-dihalogeno benzimidazoles, and some 2-substituted analogues in high yield. The 5,6-dibromo analogue was obtained by bromination of the parent nucleoside. These have all been characterized by spectroscopic methods, including ¹H NMR, which permitted analyses of their solution conformations and comparison with those of the corresponding ribofuranosides. Some biological aspects, including preliminary results on cytotoxicity and antiviral activity, are briefly considered.

Introduction

The synthetic nucleoside analogue 5,6-dichloro-1- β -D-ribofuranosylbenzimidazole (DRB) is widely employed as a selective and reversible inhibitor of transcription of a number of hnRNA producing genes [1, 2]. While these events have been well characterized, relatively little is known about the mode of action of DRB at the molecular level [1, 3]. The results of one study with some structural analogues of DRB [4] suggested the utility of synthesizing some of the corresponding 2'-deoxyribosides, and a comparison of their activities with that of the parent DRB.

Synthesis of 2'-deoxyribonucleosides of purines and purine analogues is usually achieved by condensation methods which normally furnish a mixture of α - and β -anomers, and occasionally positional isomers, followed by separation procedures which are frequently tedious and may result in a low yield of the desired product. More recent approaches have been based on multi-step deoxygenation of the 2'-

phenoxythiocarbonyl or 2'-imidazolylthiocarbonyl derivatives of the corresponding β -D-ribonucleosides [5–9]. A procedure was recently developed which leads to stereoselective formation of the β -D-2'-deoxyribosides of purines and purine analogues. This involves use of the sodium salt of the appropriate heterocyclic base which, following its formation *in situ*, is condensed directly with 1-chloro-2-deoxy-3,5-di-O-*p*-toluoyl- α -D-erythropentofuranose [10].

The 2'-deoxyribonucleosides of some benzimidazole derivatives have been previously prepared by fusion of the desired base with 1,3,5-tri-O-acetyl-2-deoxy-D-ribofuranose and separation of the two resulting anomers with the aid of column chromatography and fractional crystallization [11]. We now describe the use of the forementioned sodium salt glycosylation procedure [10] to the stereoselective synthesis of the β -D-2'-deoxyribose analogues of several halobenzimidazoles, and their solution conformations with the aid of ¹H NMR spectroscopy.

While the foregoing procedure furnishes exclusively the normally desired biologically active β -anomers of nucleosides, it should nonetheless be noted that there are now numerous examples of α -anomers of nucleosides with marked antimetabolic activities [12–14]. For example, it has been shown that the α -D-arabinofuranosyl analogue of DRB is almost 50% as active as DRB itself in inhibition of hnRNA transcription [4]. Furthermore, there are a few known

Abbreviations: DRB, 5,6-dichloro-1- β -D-ribofuranosylbenzimidazole; hnRNA, heterogeneous nuclear RNA.

Reprint requests to Dr. Z. Kazimierzczuk, Department of Biophysics, Institute of Experimental Physics, University of Warsaw, 93 Zwirki i Wigury St., 02-089 Warszawa, Poland.

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instances of the existence of α -anomeric nucleosides in biological systems *e.g.* 5,6-dimethyl-1- α -D-ribofuranosylbenzimidazole, which is a constituent of vitamin B₁₂. Consequently the availability of a procedure for obtaining uniquely the β -anomers should also prove of utility in distinguishing the mixture of two anomers resulting from the use of classical methods.

Results and Discussion

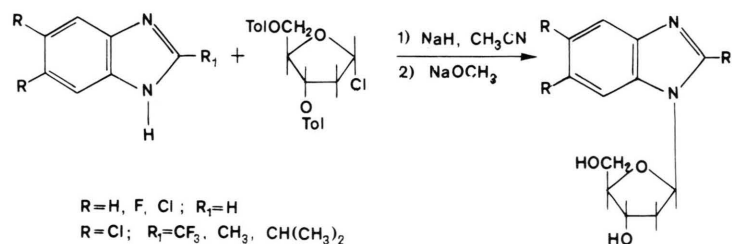
The stereospecific sodium salt glycosylation procedure [10] was applied to the synthesis of 2'-deoxyribosides of benzimidazole analogues as previously described, and the results testify to the general applicability of this method. In the present case the condensation procedure is facilitated by the ease with which benzimidazoles form sodium salts, while the symmetry of 5,6-disubstituted analogues of benzimidazole excludes possible formation of positional isomers.

The sodium salts of the various benzimidazoles were prepared *in situ* by treatment with NaH in acetonitrile. The condensation procedure then involved portionwise addition, with continuous stirring at room temperature, of 1-chloro-2-deoxy-3,5-di-O-*p*-toluoyl- α -D-erythropentofuranose. This was followed by isolation of the blocked nucleosides by column chromatography in excellent yields, and deblocking with sodium methoxide, as shown in Scheme 1, and described in Experimental, below.

The one exception to the foregoing was the 5,6-dibromo analogue, which was obtained by bromination of 1-(2'-deoxy- β -D-ribofuranosyl)benzimidazole, as elsewhere described for bromination of the riboside and α -arabinoside of benzimidazole [15].

The structures of the synthesized deoxyribonucleosides were established by means of: (a) Elementary analysis (data in Experimental section, below); (b) UV absorption spectroscopy (data in Table I), which showed that the absorption spectra are similar to those for the corresponding ribonucleosides [15, 16]; (c) ¹H NMR spectroscopy (data

Scheme 1



Benzimidazole	pH 1	249 (4500)	262 (4800)	275 (5700)	
	pH 12	246 (6600)	265 (3400)	280 (3700)	
5,6-Difluoro-	pH 1	241 (4900)	271 (6700)	276 (6900)	281 (6700)
	pH 12	243 (6400)	274 (5100)	279 (5300)	286 (4900)
5,6-Dichloro-	pH 1	246 (5300)	285 (7500)	294 (7300)	
	pH 12	254 (6800)	287 (5500)	296 (5400)	
5,6-Dibromo-	pH 1	—	288 (6700)	296 (6300)	
	pH 12	256 (5700)	289 (4900)	297 (4700)	
5,6-Dichloro-2-trifluoromethyl-	pH 1	256 (4700)	289 (7100)	298 (6700)	
	pH 12	259 (7200)	292 (5700)	301 (5200)	
5,6-Dichloro-2-methyl-	pH 1	249 (4700)	285 (6900)	295 (6900)	
	pH 12	253 (6400)	287 (5300)	297 (5400)	
5,6-Dichloro-2-isopropyl-	pH 1	245 (4500)	286 (8100)	295 (8400)	
	pH 12	254 (6500)	288 (6100)	297 (6400)	

Table I. Ultraviolet spectral data for 1-(2'-deoxy- β -D-ribofuranosyl)benzimidazole, and analogues with substituted benzimidazole rings, in aqueous medium at pH 1 (protonated forms) and pH 12 (neutral forms). Values in brackets are molar extinction coefficients.

Table II. Proton chemical shifts (in ppm vs internal Me₄Si) for 1-(2'-deoxy-β-D-ribofuranosyl) derivatives of benzimidazole and substituted benzimidazoles.

Base analogue	H(2)	H(4)	H(5) H(6)	H(7)	CH ₃ CH	H(1')	H(2')	H(2'')	H(3')	H(4')	H(5')	H(5'')	5'-OH 3'-OH
Benzimidazole	8.457	7.659	7.220 7.252	7.698		6.360	2.604	2.298	4.394	3.869	3.577	3.537	4.954 5.340
5,6-Difluoro-	8.537	7.732	—	7.966	—	6.349	2.555	2.282	4.406	3.884	3.601	3.569	5.050 5.350
5,6-Dichloro-	8.593	7.957	—	8.171	—	6.379	2.562	2.309	4.407	3.887	3.598	3.562	5.037 5.344
5,6-Dibromo-	8.559	8.083	—	8.287	—	6.368	2.553	2.304	4.395	3.875	3.585	3.548	5.013 5.326
5,6-Dichloro-2-trifluoromethyl-	—	8.205	—	8.722	—	6.346	2.515	2.094	4.464	3.959	3.75 ^a	3.75 ^a	5.356 5.450
5,6-Dichloro-2-methyl-	—	7.787	—	8.252	2.592 ^b	6.254	2.428	2.187	4.419	3.852	3.70 ^a	3.70 ^a	5.162 5.370
5,6-Dichloro-2-isopropyl	—	7.844	—	8.284	1.299 ^c 1.337 3.367	6.323	2.494	2.151	4.441	3.867	3.71 ^a	3.71 ^a	5.190 5.380

^a Deceptively simple H(4'), H(5'), H(5'') system; values are for the centre of the H(5'), H(5'') doublet.^b Signal of CH₃ group.^c CH and CH₃ signals of isopropyl group.

Table III. Coupling constants in Hz and conformational parameters for the sugar rings and exocyclic groups of the 1-(2'-deoxy-D-ribofuranosyl) derivatives of benzimidazole and substituted benzimidazoles.

Base analogue	<i>J</i> (H,H)														Conformer population (%)		
	4,5	5,6	6,7	4,6 5,7	1,2'	1',2''	2',2''	2',3'	2'',3'	3',4'	4',5'	4',5''	5',5''	<i>C</i> (2') <i>endo</i>	<i>gg</i>	<i>gt</i>	<i>tg</i>
Benzimidazole	7.8	7.0	7.8	1.7 1.7	7.6	6.0	−13.2	6.2	3.2	3.1	4.2	4.6	−12.0	71	49	30	21
5,6-Difluoro-	11.1	—	11.0	7.5 7.4	7.7	6.0	−13.2	6.1	3.1	3.0	2.8	4.8	−11.8	72	59	37	4
5,6-Dichloro-	—	—	—	—	7.3	6.0	−13.3	6.2	3.4	3.2	3.5	4.4	−11.8	70	57	30	13
5,6-Dibromo-	—	—	—	—	7.3	6.0	−13.3	6.4	3.5	3.2	3.7	4.3	−11.9	70	56	29	15
5,6-Dichloro-2-trifluoro-methyl-	—	—	—	—	8.6	5.8	−13.3	7.3	1.8	3.6	2.6 ^a	2.6 ^a	a	70 ^b	84	a	a
5,6-Dichloro-2-methyl-	—	—	—	—	8.7	6.0	−13.3	6.9	2.3	3.8	3.0 ^a	3.0 ^a	a	70 ^b	76	a	a
5,6-Dichloro-2-isopropyl-	—	—	—	—	8.8	5.9	−13.2	7.2	2.0	3.6	3.1 ^a	3.1 ^a	a	71 ^b	75	a	a

^a The deceptively simple H(4'), H(5'), H(5'') system see Table II makes possible determination of only the mean value of *J*(4',5') and *J*(4',5''), and not of *J*(5',5''). This permits of assignment of only the *gauche-gauche* population.^b The sugar conformation in these derivatives differs from that of ordinary 2'-deoxynucleosides. The values for the *C*(2')*endo* populations are therefore approximate.

in Tables II and III). The NMR data were also employed to evaluate the conformation in solution of the various compounds, as described in the following section.

Somewhat surprising was the observation that the 2-trifluoromethyl congener of 5,6-dichlorobenzimidazol 2'-deoxyriboside was unstable in aqueous medium. It underwent cleavage of the glycosidic bond at a rate of 20–30% per day at room temperature, readily placed in evidence by chromatography. In anhydrous medium, *e.g.* dimethyl sulfoxide, it was fully stable, as shown by NMR spectroscopy. By contrast, the corresponding ribofuranoside is stable in both aqueous and non-aqueous media [17]. While no interpretation is available for the lability of the deoxyriboside in aqueous medium, it will have to be taken into consideration when employed in biological experiments.

NMR data and conformational analysis

The ^1H chemical shifts for all the foregoing nucleosides are listed in Table II. The values of the proton-proton vicinal coupling constants, and the results of the conformational analyses, are presented in Table III.

Sugar ring conformation. This was determined from the two-state $\text{N} \rightleftharpoons \text{S}$ model of Altona and Sundaralingam [18] and conformer populations calculated from the equation

$$\% \text{C}(2')_{\text{endo}} = J(1',2'') / \{J(1',2') + J(3',4')\} \cdot 100$$

Values thus found are close to those obtained by accurate comparisons of the measured coupling constants with the values determined theoretically from the relationship of Haasnoot *et al.* [19] with the aid of a program devised by Dr. B. Lesyng. For those nucleosides with bulky substituents at C(2), the conformational parameters N_p , S_p , $\text{S}_{\text{r}_\text{m}}$ and $\text{N}_{\text{r}_\text{m}}$ are somewhat modified, testified to by the increase by about 2 Hz of the sums of the coupling constants $J(1',2') + J(3',4')$, and by about 1 Hz the values of the *cisoidal* coupling constants $J(2',3')$. This is most likely due to partial flattening of the sugar rings, as in the case of the corresponding benzimidazole ribonucleosides [16, 21].

Exocyclic group conformations were determined on the assumption of the existence of an equilibrium between three classical rotamers, *gauche-gauche*, *gauche-trans* and *trans-gauche*, as for furanose rings

and nucleosides [20]. Rotamer populations were calculated from the relationship of Haasnoot *et al.* [19]. It will be noted (Table II) that the *gauche-gauche* population is predominant, and increases appreciably on introduction of a bulky C(2) substituent.

Glycosidic bond conformation. It has been previously shown that, in the case of benzimidazole nucleosides, the values of the chemical shifts of the sugar protons, and principally that of H(2'), together with the chemical shift of the heterocyclic ring H(7), provide information about the conformation at the glycosidic bond [21]. This applies also, as regards the chemical shift of H(7), to analogues with similar substituents at the ring C(5) and C(6). Since for benzimidazole nucleosides with bulky substituents at C(2) the conformation *syn* is predominant [21], it may be concluded that this also prevails for the 2'-deoxynucleosides examined here, as in the case of ribofuranosides [16, 21].

Biological aspects

The biological activities of the foregoing compounds are presently under investigation, and will be reported on elsewhere. They do not appear to be substrates, or inhibitors, of adenosine kinase and purine nucleoside phosphorylase (unpublished data). The results of previous studies [4, 22] suggest that several of them should mimic the inhibitory effects of DRB on hnRNA transcription.

The reported antiviral activities of DRB and some of its analogues, reviewed elsewhere [1] are, however, in apparent conflict with the results of others [23, 24], who concluded that these activities were due to secondary effects on metabolic processes of the host cells. In preliminary tests on HSV-1 infected Vero cells, under conditions where viral replication was effectively inhibited by 25 μM of 5-iodo-2'-deoxyuridine, it was found that DRB and several of its analogues exhibited comparable activities only at concentrations of 100–200 μM . Further examination showed that the apparent activities of these compounds were, in fact, due to cytotoxicity *vs* the host cells. This is being further examined, using other host cells.

Experimental

Melting points (uncorr.) were measured on a Boetius microscope hot stage. UV absorption spec-

tra were run on a Zeiss (Jena, GDR) VSU-2 spectrophotometer. Elementary analyses were performed with a Perkin-Elmer Model 240 instrument at the Institute of Organic Chemistry, PAN.

¹H NMR spectra were recorded on a Bruker AM 270, using 0.04 M solutions of the compounds in DMSO-d₆ with Me₄Si as internal standard. Values of chemical shifts are given to ± 0.005 ppm, and of coupling constants to ± 0.2 Hz.

1-(2'-deoxy-β-D-ribofuranosyl)benzimidazole. A mixture of 480 mg (4.06 mmol) benzimidazole and 200 mg (4.16 mmol) of 50% NaH (in oil) in 30 ml anhydrous acetonitrile was stirred for 15 min at room temperature, leading to formation of a white precipitate of the sodium salt of benzimidazole. To this mixture was added, portionwise, 1.55 g (3.96 mmol) of 1-chloro-3,5-di-*o*-*p*-toluoyl-α-D-erythropentofuranose and stirring continued for an additional 2 hrs. The mixture was then passed through a Celite pad and the filtrate brought to an oil under reduced pressure. The oil was dissolved in a small volume of chloroform, which was deposited on a 3.5 × 20 cm column of silica gel, and eluted with ethylene chloride (1 l) and ethylene chloride-ethyl acetate (5:1, v/v, 1 l). The pooled fractions of product were brought to a dry foam (1.6 g, 86%), which was taken up in 30 ml anhydrous methanol containing 4 ml of 1 N sodium methoxylate, and left for two days at room temperature. The solution was neutralized with acetic acid, brought to dryness several times from water to remove the ester. The final residue was crystallized from water to yield 683 mg (85%) of the nucleoside in the form of cubic crystals, m.p. 155 °C, liter. 153.5–154.5 °C [11].

1-(2'-deoxy-β-D-ribofuranosyl)-5,6-difluorobenzimidazole. This was prepared as described in the previous paragraph with the use of 5,6-difluorobenzimidazole [16] as base. The nucleoside was crystallized from water in the form of microscopic needles, m.p. 184–185 °C (total yield 91%). Elementary analysis: Calculated for C₁₂H₁₂N₂O₃F₂: C, 53.34%; H, 4.48%; N, 10.37%; Found: C, 53.13%; H, 4.41%; N, 10.15%.

1-(2'-deoxy-β-D-ribofuranosyl)-5,6-dichlorobenzimidazole. Prepared as above with use the 5,6-dichlorobenzimidazole as base, and the final product crystallized from aqueous ethanol in the form of small platelets (total yield 84%), m.p. 169–170 °C, previously reported 168–169 °C [11].

1-(2'-deoxy-β-D-ribofuranosyl)-5,6-dichloro-2-trifluoromethylbenzimidazole. Prepared from 5,6-dichloro-2-trifluoromethylbenzimidazole [25], as above, and crystallized from a small volume of ethanol on addition of water in the form of fine needles (total yield 57%), m.p. 153–154 °C. The nucleoside was found to be unstable in aqueous medium in which it underwent cleavage of the glycosidic bond. Elementary analysis: Calculated for C₁₃H₁₁N₂O₃F₃Cl₂: C, 42.07%; H, 2.99%; N, 7.55%; Found: C, 42.31%; H, 2.89%; N, 7.73%.

1-(2'-deoxy-β-D-ribofuranosyl)-5,6-dichloro-2-methylbenzimidazole. Prepared as above from 5,6-dichloro-2-methylbenzimidazole [26] as base. The final product crystallized from aqueous ethanol in the form of small needles (total yield 72%), m.p. 218–220 °C. Elementary analysis: Calculated for C₁₃H₁₄N₂O₃Cl₂: C, 49.20%; H, 4.45%; N, 8.83%; Found: C, 49.42%; H, 4.31%; N, 9.02%.

1-(2'-deoxy-β-D-ribofuranosyl)-5,6-dichloro-2-isopropylbenzimidazole. Prepared as above from 5,6-dichloro-2-isopropylbenzimidazole, and crystallized from ethyl acetate in the form of platelets (total yield 49%), m.p. 90–92 °C. Elementary analysis: Calculated for C₁₅H₁₈N₂O₃Cl₂: C, 52.19%; H, 5.26%; N, 8.11%; Found: C, 52.35%; H, 5.15%; N, 8.36%.

1-(2'-deoxy-β-D-ribofuranosyl)-5,6-dibromobenzimidazole. To a solution of 235 mg (1 mmol) of 1-(2'-deoxy-β-D-ribofuranosyl)-benzimidazole and 500 mg Na₂HPO₄ in 30 ml water was added portionwise over a period of 3 hrs with stirring, 35 ml (~ 7 mmol) bromine water. Stirring was continued for an additional 3 hrs at room temperature. The reaction mixture was then concentrated, under reduced pressure, to an oil, which was taken up in a minimal volume of methanol and chromatographed on two plates of silica gel with chloroform–methanol (1:1, v/v), brought to dryness under reduced pressure, and crystallized from aqueous ethanol to yield 192 mg (49%) in the form of tiny needles, m.p. 110–112 °C. Calculated for C₁₂H₁₂N₂O₃Br₂: C, 36.76%; H, 3.09%; N, 7.15%. Found C, 36.51%; H, 3.01%; N, 7.32%.

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- [1] P. B. Seghal and I. Tamm, *Antibiotics Chemother.* **27**, 93 (1980).
- [2] B. Mittleman, R. Zandomeini, and R. Weinmann, *J. Mol. Biol.* **165**, 461 (1983).
- [3] K. A. Tweeten and G. R. Molloy, *Arch. Biochem. Biophys.* **217**, 332 (1982).
- [4] E. Eghazi, A. Ossoinak, U. Tayip, Z. Kazimierczuk, and D. Shugar, *Biochim. Biophys. Acta* **697**, 213 (1982).
- [5] M. J. Robins and J. S. Wilson, *J. Am. Chem. Soc.* **103**, 932 (1981).
- [6] M. J. Robins, J. S. Wilson, and F. Hansske, *J. Am. Chem. Soc.* **105**, 4059 (1983).
- [7] R. A. Lessor and N. J. Leonard, *J. Org. Chem.* **46**, 4300 (1981).
- [8] K. Pankiewicz, A. Matsuda, and K. A. Watanabe, *J. Org. Chem.* **47**, 485 (1982).
- [9] K. Furukawa, T. Ueda, and T. Hirano, *Chem. Pharm. Bull.* **31**, 1842 (1983).
- [10] Z. Kazimierczuk, H. B. Cottam, G. R. Revankar, and R. K. Robins, *J. Am. Chem. Soc.* **106**, 6379 (1984).
- [11] Ch. P. Whittle and R. K. Robins, *J. Am. Chem. Soc.* **87**, 4940 (1965).
- [12] D. Shugar, *FEBS Lett.* **40** (Suppl.), 548 (1974).
- [13] L. L. Bennett Jr., P. W. Allan, D. L. Hill, H. J. Thomas, and J. W. Carpenter, *Mol. Pharmacol.* **12**, 242 (1976).
- [14] W. M. Shannon and F. M. Schabel Jr., *Pharmacol. Ther.* **11**, 263 (1980).
- [15] Z. Kazimierczuk, R. Stolarski, L. Dudycz, and D. Shugar, *Z. Naturforsch.* **35c**, 30 (1980).
- [16] Z. Kazimierczuk, L. Dudycz, R. Stolarski, and D. Shugar, *J. Carbohydr. Nucleosides Nucleotides* **8**, 101 (1981).
- [17] Z. Kazimierczuk, R. Stolarski, L. Dudycz, and D. Shugar, *Nucleosides Nucleotides* **1**, 275 (1982).
- [18] C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.* **95**, 2333 (1973).
- [19] C. A. G. Haasnoot, F. A. A. M. de Leeuw, and C. Altona, *Tetrahedron* **36**, 2783 (1980).
- [20] B. J. Blackburn, A. A. Grey, I. P. C. Smith, and F. E. Hruska, *Can. J. Biochem.* **48**, 2866 (1970).
- [21] Z. Kazimierczuk, R. Stolarski, L. Dudycz, and D. Shugar, *Z. Naturforsch.* **36c**, 126 (1981).
- [22] I. Tamm and P. B. Seghal, *Adv. Virus Res.* **22**, 187 (1977).
- [23] H. M. Kissman, R. G. Child, and M. J. Weiss, *J. Am. Chem. Soc.* **79**, 1185 (1957).
- [24] A. Diwan, N. C. Gowdy, R. K. Robins, and W. C. Prusoff, *J. Gen. Virol.* **3**, 393 (1968).
- [25] K. H. Büchel, *Z. Naturforsch.* **25b**, 934 (1970).
- [26] H. Antaki and V. Petrov, *J. Chem. Soc.*, 2873 (1951).