Preparation of 1-α-D-Arabinofuranosylbenzimidazole and Its 5,6-Dichloro Derivative, and the Direct Bromination of Benzimidazole Nucleosides

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The 1-α-D-arabinofuranosides of benzimidazole and 5,6-dichlorobenzimidazole, analogues of the biologically active 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole, have been synthesized by condensation of the trimethylsilyl derivative of the appropriate benzimidazole in the presence of $SnCl_4$ with 1-O-methyl-2,3,5-tribenzoyl-α-D-arabinoside.

The 5(6)-monobromo and the 5,6-dibromo derivatives of 1-β-D-ribofuranosylbenzimidazole and 1-α-D-arabinofuranosylbenzimidazole were then prepared by direct bromination of the latter. With 1-β-D-ribofuranosylbenzimidazole, the initial product of bromination was a 1:1 mixture of the 5-bromo and 6-bromo derivatives; the final product was the desired 5,6-dibromo analogue. In the case of 1-α-D-arabinofuranosylbenzimidazole, the initial product of bromination was the 5-(*or* 6-)bromo derivative, and the 5,6-dibromo derivative the final product. The monobromo derivatives were easily separated from the dibromo by chromatography on Amberlite XAD-4. Identification of all of these was based on several criteria, including detailed analyses of the ^{1}H NMR spectra.

The benzimidazole nucleoside are considerably more resistant to acid hydrolysis than the corresponding purine nucleosides. The effects of halogenation on the ultraviolet absorption spectra of the benzimidazole nucleosides are described.

Introduction

The biological properties of halogenated benzimidazole nucleosides [1] have taken on added significance in the light of the demonstration that 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole (DRB) is a selective and reversible inhibitor of hnRNA production in mammalian cells [2, 3 a, 3 b], reviewed in ref. [4] . Under appropriate conditions DRB also leads to a marked enhancement of interferon production in mammalian cells [2, 3 a, 3 b], reviewed in ref. [4]. Under appropriate conditions DRB also ical properties of this class of analogues are their antiviral and cytotoxic activities, exhibited also to an appreciable extent by the α-anomers of some benzimidazole nucleosides [4]. It is of interest in this connection that 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole is a constituent of vitamin B_{12} .

As the initial part of a program to study the antimetabolic properties of new benzimidazole and halogenated benzimidazole nucleosides, we report here on the preparation of the α-D-arabinofuranosyl nucleosides of benzimidazole and 5,6-dichlorobenzimidazole, as well as the bromo derivatives of the β-D-ribosides and α-D-arabinosides of benzimidazole *via* a new route involving direct bromination of the parent nucleosides. Syntheses of the latter have hitherto been based on direct condensation reactions of the halogenated aglycone with the appropriate protected halogeno sugar [5, 6]. The desirability of a simple procedure for preparation of the bromo derivatives is underlined by the fact that bromo derivatives of some benzimidazole nucleosides are as active, in some instances even more so, than the corresponding chloro derivatives [4].

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Results and Discussion

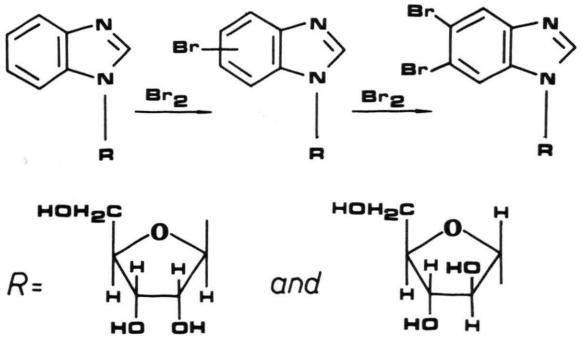
The 1-α-D-arabinofuranosides of benzimidazole and 5,6-dichlorobenzimidazole were prepared essentially according to the general procedure of Niedballa and Vorbrüggen [7]. The trimethylsilyl derivative of the appropriate benzimidazole was condensed in the presence of $SnCl_4$ with 1-O-methyl-2,3,5-tribenzoyl-α-D-arabinofuranose. The resulting benzoylated nucleosides were purified by chromatography on silica gel, and debenzoylated by treatment with $NaOCH_3$ in methanol to give the free nucleo-

sides, which were crystallized from aqueous ethanol (for the benzimidazole nucleoside), or water (for the 5,6-dichloro derivative). Identification was based on elementary analysis, ^{1}H NMR spectroscopy and UV spectrum. The same procedure was followed for the synthesis of 1-β-D-ribofuranosylbenzimidazole.

The monobromo and *ortho*-5,6-dibromo derivatives of the benzimidazole nucleosides were then obtained by direct treatment with bromine water in aqueous medium. In the case of 1-β-D-ribofuranosylbenzimidazole, the initial product of the reaction was an approximately equimolar mixture of the 5- and 6-monobromo derivatives, as shown by analysis of the ^{1}H NMR spectrum (see below). By contrast, the initial product in the case of 1-α-D-arabinofuranosylimidazole appeared to be the 5- *or* 6-monobromo derivative; in this case it did not prove feasible with the aid of NMR spectroscopy to establish unequivocally the position of bromination (see below).

Further prolonged treatment with bromine water led, for both nucleosides systems, to appearance of the 5,6-dibromo derivatives. The products were all identified on the basis of elementary analyses, ^{1}H NMR spectroscopy, as well as by acid hydrolysis to release the aglycone. In the case of the dibromo derivatives, this led to release of dibromobenzimidazole, identical with an authentic sample obtained according to Weygand *et al.* [8]. It is of interest that the benzimidazole nucleosides were much more stable in acid than purine nucleosides, *e. g.* under conditions where the latter undergo complete hydrolysis, the former exhibit only traces of hydrolysis products.

Bromination consequently proceeds stepwise as illustrated in Scheme 1. These results are reminiscent of those reported by Büchel [9] for bromination of 2-



Scheme 1.

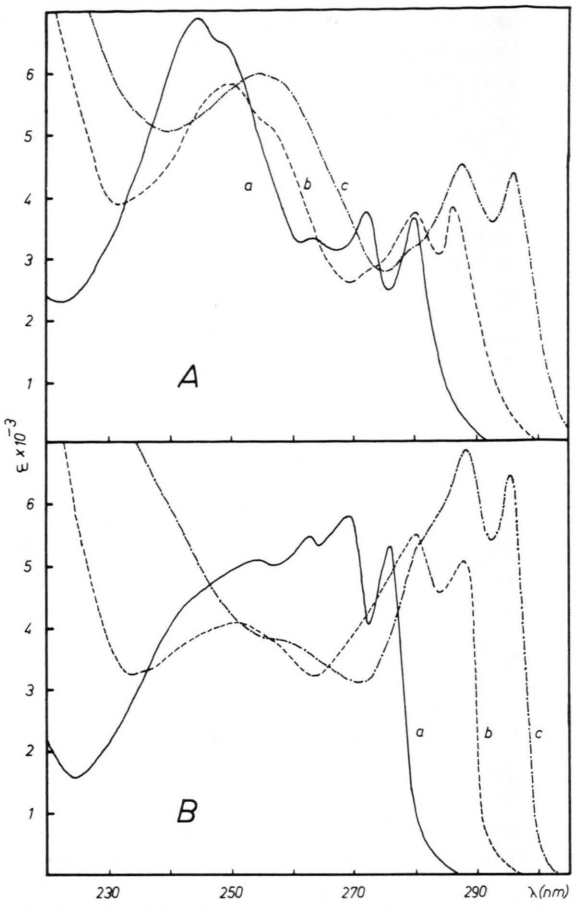


Fig. 1. Ultraviolet absorption spectra in aqueous medium of (A) the neutral forms, at pH 8, and (B) the cationic forms, at pH 1, of: (a) 1-β-D-ribofuranosylbenzimidazole; (b) the 5(6)-monobromo derivative; (c) the 5,6-dibromo derivative.

trifluorobenzimidazole, where the initial products are the 5(6)-monobromo derivatives. Somewhat different results were reported by Dandegonker and Shastri [10] for bromination of 2-methylbenzimidazole, the order of bromination being the 5-monobromo, followed by 5,7 [4, 6]; the evidence for this latter result is, however, rather weak.

Fractionation of the mono- and dibromo derivatives was considerably facilitated with the aid of Servachrom (Heidelberg, GFR) XAD-4, hitherto profited from mainly with lipidic compounds. The potential use of this resin for fractionation of nucleic acid derivatives was pointed out by Zaika [11] and Uematsu and Suhadolnik [12]. It very effectively separated the monobromo and dibromo nucleosides of benzimidazole, the latter of which are more

lipophilic. However, it did not prove feasible in this way to separate the isomeric monobromo nucleosides. Attempts to separate these by fractional crystallization were equally unsuccesful.

The ultraviolet absorption spectra of the brominated nucleosides exhibit certain regularities with respect to the parent compound (Fig. 1 and Table I). Introduction of a bromine atom leads to a bathochromic shift of the long-wavelength absorption bands, both for the neutral and cationic forms. Furthermore the spectra of the 5,6-dichloro and 5,6-dibromo nucleosides are quite similar, the latter being shifted somewhat bathochromically relative to the former.

^1H NMR analyses

Final identification of the various products was achieved with the aid of ^1H NMR spectroscopy. The appropriate data for the chemical shifts and vicinal coupling constants of the base protons of benzimidazole, 5,6-dibromobenzimidazole, and the various nucleosides are listed in Table II. Analysis of the signals of the various protons, and the changes in chemical shifts resulting from bromination, permitted of complete assignments of the individual proton signals and the position(s) of attachment of bromine in the benzimidazole ribosides: the initial product(s) of bromination are the 5-bromo and 6-bromo derivatives, which crystallizes as a 1 : 1 mixture; the second bromine then adds *ortho* to the first, so that the final unique product is the 5,6-dibromo derivative. By contrast, the initial product in the case of the arabinoside is the 5-bromo *or* 6-bromo derivative, and the final product the 5,6-dibromo as for the riboside.

The monobromo derivative of the β-riboside exhibits two pairs of signals characteristic for bromine substitution at C(5) and C(6). Each of these consists of two singlets and two coupled AB doublets, with coupling constants of about 8.5 Hz. One of these corresponds to the 5-bromo derivative, the other to the 6-bromo. The most highly shielded singlets, located close to each other, originate from the H(2) proton of each monobromo derivative. The coupled doublets correspond to the protons H(6) and H(7) in the 5-bromo derivative, and the H(4) and H(5) in the 6-bromo analogue. The non-coupled (or very weakly coupled) singlets at 7.85 ppm and 8.07 ppm correspond to protons separated by four bonds, H(4) in the 5-bromo derivative and H(7) in the 6-bromo derivative.

By contrast, the monobromo derivative of the α-arabinoside exhibits only one set of signals, corresponding to either the 5-bromo or 6-bromo, with other possibilities excluded. The product of further bromination exhibits three singlets, as in the case of the β-riboside (see Table II), hence must be the 5,6-dibromo derivative.

Table I. Principal absorption bands (and extinction coefficients) in the ultraviolet absorption spectra of benzimidazole nucleosides and their halogenated derivatives in aqueous medium at pH 8 (neutral forms) and pH 2 (cationic forms).

Nucleoside	λ_{max} ($\varepsilon_{max} \times 10^{-3}$)							
	pH 8 (neutral forms)				pH 2 (cationic forms)			
1-β-D-ribofuranosyl-benzimidazole	245 (6.80)	273 (3.70)	281 (3.52)	– –	254 (5.05)	262 (5.45)	270 (5.75)	276 (5.35)
1-β-D-ribofuranosyl-5(6)-bromobenzimidazole	250 (5.80)	280 (3.65)	287 (3.70)	– –	255 (4.10)	279 (5.51)	287 (5.10)	– –
1-β-D-ribofuranosyl-5,6-dibromobenzimidazole	255 (5.90)	288 (4.40)	297 (4.30)	– –	288 (6.80)	296 (6.40)	– –	– –
1-β-D-ribofuranosyl-5,6-dichlorobenzimidazole	254 (6.40)	287 (4.90)	296 (4.95)	– –	253 (3.55)	285 (6.05)	294 (5.95)	– –
1-α-D-arabinofuranosyl-benzimidazole	245 (8.50)	265.5 (4.19)	273 (4.69)	280 (4.38)	254 (6.19)	262 (6.58)	268.5 (7.94)	275 (6.94)
1-α-D-arabinofuranosyl-5(6)-bromobenzimidazole	250 (6.25)	283 (3.87)	– –	– –	217 (13.5)	249 (4.70)	280 (5.92)	– –
1-α-D-arabinofuranosyl-5,6-dibromobenzimidazole	251 (6.05)	289 (4.29)	297 (3.95)	– –	288 (6.20)	296 (5.65)	– –	– –
1-α-D-arabinofuranosyl-5,6-dichlorobenzimidazole	255 (7.67)	287 (5.83)	296 (5.83)		254 (5.83)	286 (7.58)	295 (7.33)	

Table II. Chemical shifts (in ppm vs internal TMS) and coupling constants (in Hz) for the benzimidazole protons of benzimidazole, 5,6-dibromobenzimidazole, and their nucleosides and halogenated benzimidazole nucleosides, at concentrations of about 0.2 M in DMSO-d_6 at 22 °C.

Compound	Chemical shifts (ppm)					Coupling constants (Hz)				
	H(2)	H(4)	H(5)	H(6)	H(7)	J(2.4) [a] or J(2.7)	J(4.5) [a] or J(6.7)	J(4.6) [a] or J(5,7)	J(4.7)	J(5.6)
Benzimidazole [b]	8.196	7.588	7.178	7.178	7.588	0.6	8.0	1.2	0.5	6.7
5,6-Dibromobenzimidazole	8.30	7.99	–	–	7.99	c	–	–	c	–
1-β-D-ribofuranosyl-benzimidazole [b]	8.470	7.650	7.213	7.239	7.715	0.5	8.0	1.2	0.5	6.8
1-β-D-ribofuranosyl-5-bromobenzimidazole	8.50	7.85	–	7.38	7.75	c	8.4	1.6	c	–
1-β-D-ribofuranosyl-6-bromobenzimidazole	8.48	7.62	7.35	–	8.07	c	8.5	1.6	c	–
1-β-D-ribofuranosyl-5,6-dibromobenzimidazole	8.55	8.08	–	–	8.34	c	–	–	c	–
1-α-D-arabinofuranosyl-benzimidazole	8.40	7.69	7.28	7.28	7.69	c	8.0	1.2	c	6.7
1-α-D-arabinofuranosyl-5(6)-bromobenzimidazole	8.43	7.87 [d]	7.43 [d]		7.69	c	8.5	1.8	c	–
1-α-D-arabinofuranosyl-5,6-dibromobenzimidazole	8.47	8.08	–	–	8.12	c	–	–	c	–
1-α-D-arabinofuranosyl-5,6-dichlorobenzimidazole	8.50	7.96	–	–	8.00	c	–	–	c	–

[a] For the non-halogenated benzimidazole derivatives, the values of these coupling constants are identical from symmetry considerations. For the 5-bromo and 6-bromo derivatives, the value given corresponds to one of the measured coupling constants, for the appropriate derivative.
[b] The values of the chemical shifts and coupling constants, corresponding to an ABMNX system (for the ribosides), and to an AA'MM'X system (for the free base) were determined accurately with the aid of the non-iterative simulation program LAOCOON III (S. Castellano and A. A. Bothner-By, J. Chem. Phys. **41,** 3863, 1964).
[c] The values for the coupling constants in this case were below the resolution of the instrument.
[d] Assignments are for the 5-bromo derivative; if this were the 6-bromo derivative, then the values of the chemical shifts for H(4) and H(7) should be interchanged.

Assignment of the signals for the individual base protons was provided by the effects of step-wise addition of bromine. The benzimidazole ring system in both the β-riboside and the α-arabinoside possesses symmetry close to that of the free base, which is in the tautomeric equilibrium N(1)-H ⇌ N(3)-H [13]. Introduction of a bromine substituent should lead to similar changes in chemical shifts of protons similarly located relative to the bromine. From Table II it will be noted that, in the fully symmetrical free base, two bromine substituents together result in an identical change in shifts of H(4) and H(7), *i. e.* deshielding by 0.4 ppm. A similar situation prevails for the α-arabinoside, where the deshieldings are 0.40 ppm for H(4) and 0.44 ppm for H(7). There is some departure from symmetry in the case of the β-riboside, where dibromination leads to deshielding of one proton by 0.43 ppm as for the α-arabinoside, and of the other by as much as 0.62 ppm. Since any departures from the symmetrical nature of the influence of the bromine substituents must be due to the presence of the sugar moiety, it is to be expected that this would be reflected by those protons closest to the sugar ring, *i. e.* H(7) and, possibly, H(6). The most deshielded proton in the dibromo derivative is consequently H(7). Analysis of all the different possible assignments of signals in the spectra of the free base, and the monobromo and dibromo derivatives of the nucleosides, demonstrated that the most closely similar effects of bromine substitution on identically located protons in all the compounds corresponded to the assignments given in Table II. Since the consistency of these results did not depend on whether the bromine substituent in the monobromo derivative of the α-arabinoside was at C(5) or C(6), it is not possible to state at this time which of these is the product of monobromination.

The signals of the sugar protons of all the nucleoside products were fully consistent with those expected. A detailed investigation of the conformations

of these nucleosides requires, amongst others, synthesis of appropriate 2-substituted analogues which are constrained to the *syn* conformation. Such an investigation is now under way. Some data on the solution conformation of 1-β-D-ribofuranosylimidazole itself have been reported by Lüdemann *et al.* [14].

Experimental

1-O-acetyl-2,3,5-tri-O-benzoylribofuranose was obtained from Pharma Waldhof (Düsseldorf, GFR) and 1-O-methyl-2,3,5-tri-O-benzoylarabinofuranose was prepared by the method of Fletcher [15].

Melting points (uncorr.) were measured on a Boetius microscope hot stage. UV spectra were run on a Zeiss (Jena, GDR) VSU-2 spectrophotometer. Elementary microanalyses were performed on a Perkin-Elmer Model 240 instrument by Miss I. Celler of the Institute of Organic Chemistry.

^{1}H NMR spectra were recorded on a JEOL JNM-4H-100 instrument, at concentrations of about 0.2 M in DMSO-d_6. Chemical shifts, *vs* internal TMS, are accurate to ± 0.01 ppm and, in the case of simulated spectra, to ± 0.002 ppm. Coupling constants were determined to an accuracy of ± 0.2 Hz. For accurate determinations of the NMR parameters of more complex systems of the type AA'MM'X (benzimidazole base) and ABMNX (benzimidazole riboside), simulation of spectra was carried out for different initial values of the parameters with the aid of the non-iterative program LAOCOON III. Initial approximate values of the parameters were based on a first-order analysis of the system AA'MM'X for the benzimidazole protons. The locations of the signals in the simulated spectra did not differ from those in the recorded spectra by more than 0.002 ppm.

1-α-D-arabinofuranosylbenzimidazole: To 4.4 gm (23 mmol) of 1-trimethylsilylbenzimidazole in 50 ml of 1,2-dichloroethane was added 10.5 gm (~22 mmol) 1-O-methyl-2,3,5-tribenzoyl-α-D-arabinofuranose in 20 ml of 1,2-dichloroethane, followed by about 2.5 ml (~22 mmol) of freshly distilled $SnCl_4$. The mixture was heated under reflux, with maintenance of anhydrous conditions, for 30 min, then cooled and diluted with 60 ml 1,2-dichloroethane. The mixture was vigorously shaken with a saturated solution of $NaHCO_3$ and passed through a Celite pad. The organic phase was dried with anhydrous Na_2SO_4 and brought to dryness under reduced pressure. The resulting syrupy residue was dissolved in 20 ml methanol containing 1.25 g sodium methoxylate. After 4 h, the solution was brought to neutrality with HCl and deposited on a 35 × 4 cm column of Al_2O_3 previously equilibrated with EtOH. The column was eluted with ethanol (500 ml) and then with 2 litres of EtOH-H_2O (1 : 1, v/v), with collection of 25-ml fractions. The fractions containing the nucleoside (15 to 45) were combined, brought to dryness under reduced pressure and the residue crystallized from aqueous ethanol to yield 1.01 g (18%) of microscopic needles, m.p. 228.5–229.5 °C. Elem. anal.: C, 57.29%; H, 11.20%; N, 5.56%. Calcd. for $C_{12}H_{14}O_4N_2$: C, 57.60%; H, 11.20%; N, 5.60%.

1-α-D-arabinofuranosyl-5,6-dichlorobenzimidazole: To 6.5 g (25 mmol) of 1-trimethylsilyl-5,6-dichlorobenzimidazole in 50 ml of 1,2-dichloroethane was added 12.9 g (~ 27 mmol) 1-O-methyl-2,3,5-tribenzoyl-α-D-arabinofuranose in 50 ml 1,2-dichloroethane, followed by 2.5 ml $SnCl_4$. After 6 h at room temperature, only about 5% of the starting substance had reacted. A total of 6 ml $SnCl_4$ was then added portionwise at intervals of 2 h. After 26 h the mixture was heated under reflux for 15 min, then cooled and further worked up as for 1-α-D-arabinofuranosylbenzimidazole, above. The resulting syrupy product was applied to a 40 × 5 cm column of silica gel and eluted with benzene (300 ml), benzene-acetone (99 : 1, v/v, 500 ml), benzene-acetone (98 : 2, 500 ml), benzene-acetone (97 : 3, 500 ml) and benzene-acetone (96 : 4, 500 ml). The nucleoside was eluted from the column with 400 ml of 5% acetone in benzene. Following removal of solvent, the syrupy residue was dissolved in 60 ml ethanol containing 656 mg sodium ethoxylate, heated for 2 h at 60 °C, cooled and brought to neutrality with HCl. The solution was brought to dryness, taken up in water and again brought to dryness. This was repeated several times. The residue was then crystallized from aqueous ethanol (2.5 g), and recrystallized from water in the form of needles (2.2 g, 24%), m. p. 215–217 °C. Elem. anal.: C, 45.10%; H, 3.74%; N, 8.69%. Calcd. for $C_{12}H_{12}O_4N_2Cl_2$: C, 45.14%; H, 3.76%; N, 8.78%.

1-α-D-arabinofuranosyl-5(6)-bromobenzimidazole: To 200 mg (0.8 mmol) of 1-α-D-arabinofuranosylbenzimidazole and 250 mg K_2HPO_4, dissolved by heating in 30 ml water, was added 13 ml bromine water over a period of 30 min. Stirring was continued for 30 min, and the mixture applied to a

35 × 2 cm column of Amberlite XAD-4. Elution was carried out with a gradient of water and 50% isopropanol (2 litres). The main peak (40 – 45% isopropanol) was brought to dryness and crystallized from aqueous ethanol to yield 150 mg (57%) in the form of needles, m. p. 193 – 195 °C. Elem. anal.: C, 43.89%; H, 4.04%; N, 8.29%. Calcd. for $C_{12}H_{13}O_4N_2Br$: C, 43.93%; H, 3.96%; H, 8.53%.

1-α-D-arabinofuranosyl-5,6-dibromobenzimidazole: To 200 mg (0.8 mmol) 1-α-D-arabinofuranosylbenzimidazole in 25 ml water was added, over a period of 1 h, 30 ml bromine water. Stirring was continued for 4 h at room temperature. The mixture was treated with charcoal, filtered and the filtrate brought to pH 8, and applied to a 35 × 2 cm column of Amberlite XAD-4. Elution was with a gradient of water and 50% isopropanol (2 litres). The dibromonucleoside eluted in the range 45 – 50% isopropanol. The main peak was brought to dryness and the residue crystallized from aqueous ethanol to yield 205 mg (63%) in the form of platelets, m. p. 186 to 189 °C. Elem. anal.: C, 35.35%; H, 2.86%; N, 6.80%. Calcd. for $C_{12}H_{12}N_2O_4Br_2$: C, 35.33%; H, 2.94%; N, 6.86%.

1-β-D-ribofuranosyl-5(6)-bromobenzimidazole: To 260 mg (1.04 mmol) of 1-β-D-ribofuranosylbenzimidazole and 350 mg KH_2PO_4 in 25 ml water was added 15 ml bromine water over a period of 30 min. The mixture was stirred for an additional 30 min and then applied to a 35 × 2 cm column of Amberlite XAD-4. Elution was carried out with a linear gradient of water and 50% isopropanol (2 litres). The major peak (eluted in the range 40 – 45% isopropanol) was brought to dryness and crystallized from 50% aqueous methanol to yield 230 mg (68%) of tiny needles, m. p. 182 – 184 °C. Elem. anal.: C, 42.70%; H, 4.05%; N, 8.29%. Calcd. for $C_{12}H_{13}O_4N_2Br \cdot 0.5\ H_2O$: C, 42.72%; H, 4.15%; N, 8.31%.

1-β-D-ribofuranosyl-5,6-dibromobenzimidazole: To 260 mg (1.04 mmol) 1-β-D-ribofuranosylbenzimidazole in 20 ml H_2O was added, during the course of 1 h, 35 ml bromine water and the mixture stirred for an additional 3 h. It was then treated with activated charcoal, filtered, and the filtrate brought to pH 8 with NH_4OH, applied to a 35 × 2 cm column of Amberlite XAD-4, and elution carried out with a linear gradient of water and 50% isopropanol (2 litres). The major peak (45 – 50% isopropanol) was brought to dryness and crystallized from 50% aqueous ethanol to yield 245 mg (59%) in the form of parallelopipeds, m. p. 186 °C. Elem. anal.: C, 34.47%; H, 3.09% N, 6.76%. Calcd. for $C_{12}H_{12}N_2O_4Br \cdot 0.5\ H_2O$: C, 34.53%; H, 3.12%; N, 6.71%.

Acid hydrolysis: A solution of 10 mg of the foregoing product in 3 ml 6 N HCl was heated on a water bath for 10 h, then brought to dryness and the residue taken up in a small volume of 50% methanol. This was brought to pH 8 with NH_4OH and subjected to thin-layer chromatography on silica gel HF_{254} with the solvent system chloroform-methanol (9:1). The chromatogram showed only one spot identical chromatographically ($R_F = 0.70$) and spectrally with 5,6-dibromobenzimidazole as reported by Weygand *et al.* [8].

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