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Synthesis and anomeric configuration of 2-(erythrofuranosyl)benzimidazole C-nucleoside analogues

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Abstract

Anomeric 2-(α- and β-D-erythrofuranosyl)benzimidazole C-nucleoside analogues **2** and **3**, were prepared from the corresponding epimeric 2-(D-*arabino*, and D-*ribo*-tetritol-1-yl)benzimidazole analogues **1** and **4**, respectively. Similarly, 2-(β-L-erythrofuranosyl)benzimidazole **13** was obtained from the precursor 2-(L-*arabino*-tetritol-1-yl)benzimidazole **12**. The structure and anomeric configuration of the C-nucleoside analogues **2**, **3**, and **13** were determined by acylation, ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry.

Keywords: Benzimidazole, 2-(erythrofuranosyl)-; Benzimidazole C-nucleosides; Acyclic-sugar nucleosides

1. Introduction

Aldobenzimidazoles are compounds of potential value for characterization and identification of carbohydrates. They can be easily prepared and crystallized, and they form certain derivatives that can make them superior to hydrazones and osazones for the characterization of sugars [1]. Benzimidazoles and congeneric compounds also have potential activity as inhibitors of nucleic acid biosynthesis, and as fungicides or insecticides [2]. In addition, the chemistry of benzimidazoles has been of interest since 1950, due to the vital role played by the closely related purines in biological systems [3].

The chemistry of 1-glycosylbenzimidazoles has been of considerable interest since the discovery that 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole (α-ribazole) was an integral part [4–8] of the chemical structure of vitamin B_{12}. The chemistry of benzimidazole N-nucleoside analogues has been reviewed [9]. Our laboratory has explored the synthesis of C-nucleoside analogues by dehydrative cyclization of the polyhydroxyalkyl chain of polyhydroxyalkyl heterocycles [10,11], and used spectroscopic techniques for the determination of the anomeric configuration of the products. The stereocourse of the reaction, the

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ease of dehydration, and the anomeric configuration of the products depend on the type of base moiety and the length of the polyhydroxyalkyl chain. In this work, erythrofuranosyl benzimidazole C-nucleoside analogues are prepared and their structure and anomeric configuration were determined by ^{1}H and ^{13}C NMR spectroscopy. Various criteria for anomeric assignment are applied and the valid ones can be used to define the anomeric configuration of similar benzimidazole C-nucleosides. The structures of these compounds were determined also by mass spectrometry.

2. Results and discussion

2-(D-*arabino*-Tetritol-1-yl)benzimidazole (**1**) was prepared by condensation of potassium D-arabinonate and *o*-phenylenediamine in a strongly acidic medium by the method of Moore and Link [1]. Dehydrative cyclization [12] of **1** or its hydrochloride derivative with concentrated hydrochloric acid at 180 °C in the presence of a catalytic amount of zinc chloride afforded the C-nucleoside analogue, namely, 2-(α-D-erythrofuranosyl)benzimidazole (**2**) (Scheme 1). Its ^{1}H NMR spectrum showed the anomeric proton as a doublet at δ 5.17 having a coupling constant ($J_{1',2'}$ 4.4 Hz). This relatively large coupling constant value does not define [13,14] the anomeric configuration. Likewise, its acetyl derivative **6** showed the anomeric proton H-1′ at δ 5.46 with a coupling constant of $J_{1',2'}$ 5.5 Hz. The ^{1}H NMR spectrum of the *O*-isopropylidene derivative **7** showed the anomeric proton as a doublet at δ 4.89 ($J_{1',2'}$ 3.9 Hz) and a difference Δδ 0.164 (1.475 − 1.311). These coupling constant ($J_{1',2'}$) values for **2** cannot define the anomeric configuration [unless a low enough value (0–1 Hz) is obtained], and the Δδ values are also unsupportable [15–17]. The β-D-anomer **3** was not detected in the reaction mixture of the dehydration of **1**.

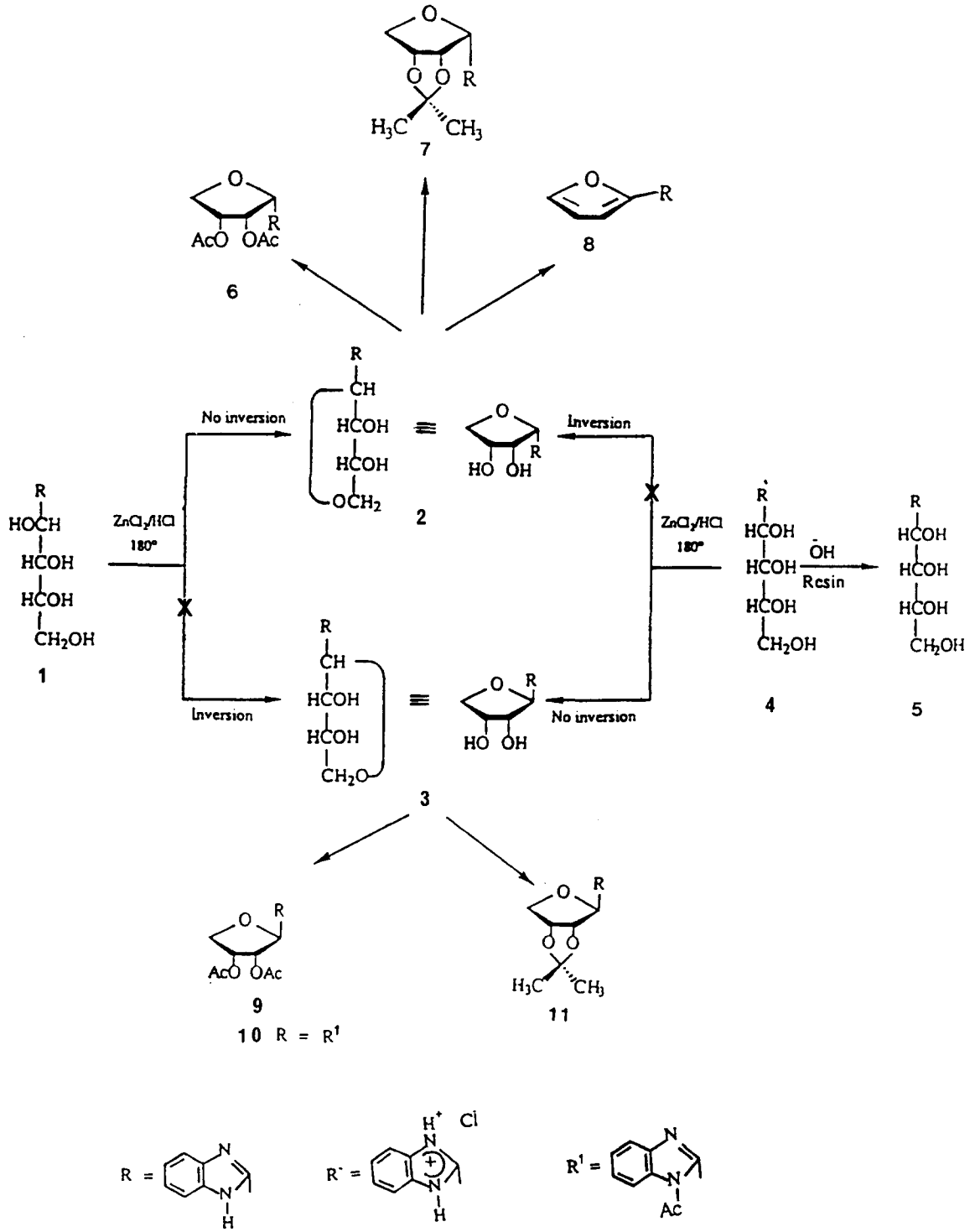
2-(α-Furyl)benzimidazole (**8**) was isolated from the reaction as a byproduct of the acid-catalyzed dehydration of **1** and as a major product from refluxing **2** with acetic anhydride, as a result of the elimination of two molecules of water from the furanosyl ring. Compound **8** was optically inactive. Its ^{1}H NMR spectrum showed the NH signal as a broad singlet downfield at δ 9.98, and the olefinic protons H-2′ and H-3′ were shown at δ 7.22 and 6.58. Its ^{13}C NMR spectrum showed C-2′ and C-3′ overlapped as a singlet downfield at δ 110.6. Its mass spectrum showed molecular ion at *m/z* 184 as the base peak.

Acid-catalyzed dehydrative cyclization of the enantiomeric 2-(L-*arabino*-tetritol-1-yl)benzimidazole (**12**) under the same reaction conditions afforded the enantiomeric 2-(β-L-erythrofuranosyl)benzimidazole C-nucleoside **13** (Scheme 2). Its ^{1}H NMR spectrum showed the NH signal downfield as a broad singlet at δ 12.11, and the spectral pattern was identical to that of its enantiomer **2**. The ^{1}H NMR spectrum of its *O*-isopropylidene derivative **14** showed the anomeric proton as a doublet at δ 4.93 having coupling constant $J_{1',2'}$ 3.5 Hz, and showed Δδ value 0.165 (1.518 − 1.353) in agreement with the value (Δδ 0.164) of its enantiomeric *O*-isopropylidene analogue **7**. The anomeric 2-(α-L-erythrofuranosyl) benzimidazole C-nucleoside **15** was not detected in the reaction mixture.

In order to confirm the anomeric configuration of compounds **2** and **3**, and to investigate the steric course of the *C*-glycosyl formation, 2-(D-*ribo*-tetritol-1-yl)benzimidazole hydrochloride (**4**), was prepared by condensation of D-ribono-γ-lactone with *o*-phenylenediamine dihydrochloride. The hydrochloride derivative **4** was used because of the high solubility of the free base **5**, which can be regenerated from **4** by anion-exchange resin. Similarly, acid-catalyzed dehydrative cyclization of **4** afforded the C-nucleoside analogue, 2-(β-D-erythrofuranosyl)benzimidazole (**3**). Its ^{1}H NMR spectrum showed the anomeric proton (H-1′) as a doublet at δ 4.80 having a coupling constant $J_{1',2'}$ 5.9 Hz. This relatively large coupling constant value does not define the anomeric configuration of **3**. Likewise its di-*O*-acetyl derivative **9** and N^1-acetyl-di-*O*-acetyl derivative **10**, showed the anomeric proton (H-1′) as a doublet at δ 5.30 ($J_{1',2'}$ 5.4 Hz) and δ 5.71 ($J_{1',2'}$ 4.1 Hz), respectively. However, its *O*-isopropylidene derivative **11** showed the anomeric proton H-1′ as a singlet at δ 5.35. This zero coupling constant value is unequivocal proof of the *trans* arrangement of H-1′, H-2′, i.e. the β-D-configuration. The Δδ value 0.184 (1.572–1.388) of the two methyl signals of the 2,2-dimethyldioxolane ring for **11** is in accord [15–17] with the β-D-configuration. Accordingly, its anomer **7** having ($J_{1',2'}$ 3.9 Hz) can be subsequently assigned the α-D- configuration.

Having the two anomers on hand, the assignment of the anomeric configuration of **2** and **3** from their spin–spin coupling constant $J_{1',2'}$ values, was more difficult, since these values are not consistently diagnostic. Similar examples in the literature are reported where the assignment of the anomeric configuration of *C*-glycofuranosyl compounds on the basis of ^{1}H

NMR coupling constants is unreliable [11,18–20]. The anomeric configuration can be ascertained from the chemical shift values for their anomeric proton (H-1′). Compound **3** having the anomeric proton upfield (δ 4.80) can be assigned [11] the *trans* arrangement of H-1′ and H-2′, i.e., the β-D-erythro configuration, and its anomer **2** having the anomeric proton at lower field (δ 5.17) was given the *cis* arrangement of H-1′ and H-2′, i.e., the α-D-erythro configuration. Its enantiomer **13** is subsequently given the β-L-erythro configuration. Analogously, the anomeric proton (H-1′) for the acetyl derivative **9** was shown upfield (δ 5.30) from the anomeric analogue **6** (δ 5.46) in accord with *trans* arrangement of H-1′ and



Scheme 1.

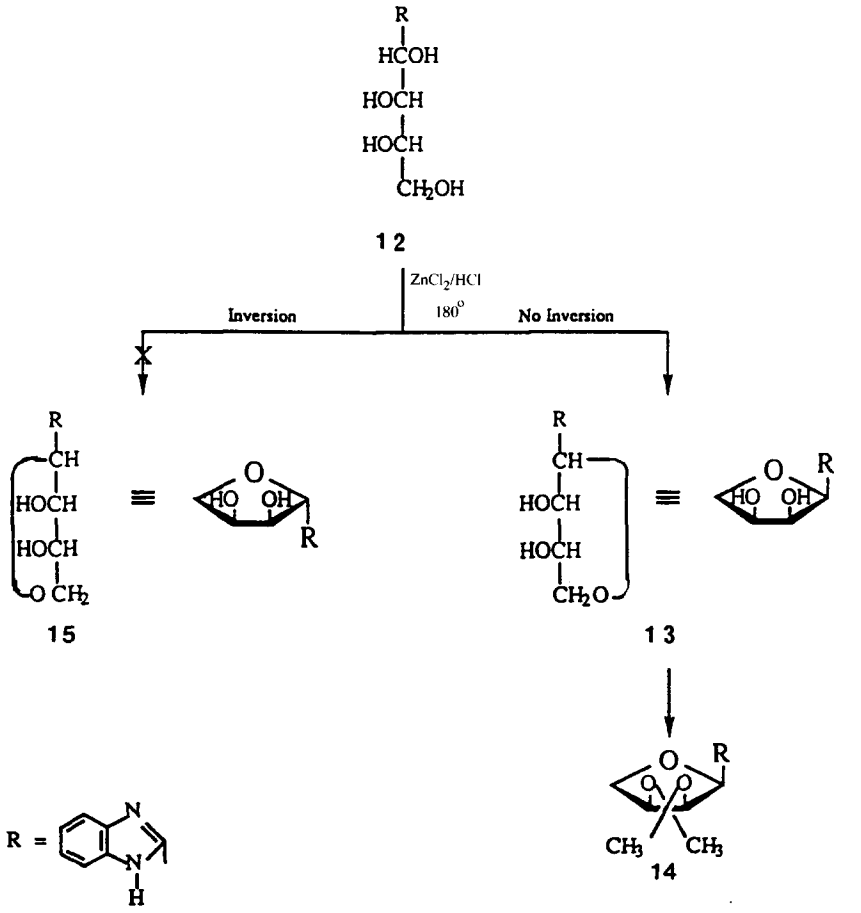
H-2′ (β-D- configuration) for **9** and *cis* arrangement of H-1′ and H-2′ (α-D- configuration) for **6**. However, the *O*-isopropylidene derivatives **7** and **11** showed the opposite correlation; compound **11** having the *trans* arrangement of H-1′ and H-2′ showed the anomeric proton at lower field (δ 5.35) than compound **7** (δ 4.89) having the *cis* arrangement.

The anomeric configuration of **2** and **3** can be confirmed from the multiplicity of the geminal protons H-4′ and H-4″, which were shown as multiplets for **3** and triplets for **2**, in agreement [21,22] with the β-D- configuration for **3** and the α-D- configuration for **2**.

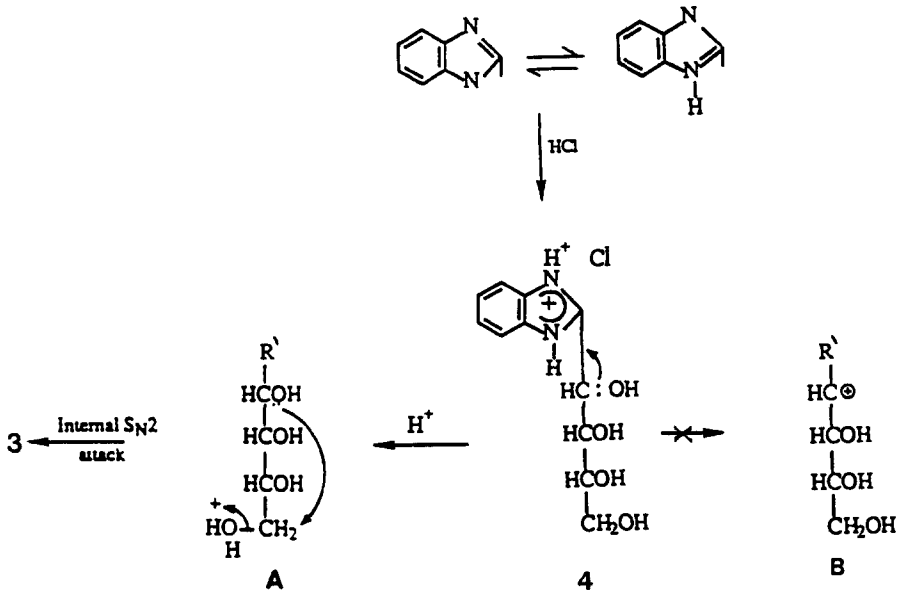
Additional evidence for the anomeric configuration of **2** and **3** was obtained from their optical properties. The C-nucleoside **3** showed larger negative specific rotation ($[\alpha]_D^{22}$ in N HCl: **3**, −81.8°; **2**, −4.9°) in accord with the Hudson isorotation rule [23].

In conclusion, the anomeric configuration of these benzimidazole C-nucleosides cannot be determined from the coupling constant values of the anomeric proton ($J_{1',2'}$), or the $\Delta\delta$ values for their *O*-isopropylidene derivatives even if the two anomers are available. The anomeric configuration is determined from the chemical shift values of the anomeric proton (H-1′) of the C-nucleoside anomeric pair or their acetyl derivatives, but not from their *O*-isopropylidene derivatives. The Hudson isorotation rule, and the multiplicity of the geminal protons, are also applicable.

The anomeric configuration of compounds **2**, **13**, and **3** is important for the investigation of the steric course of the *C*-glycosyl formation from the precursor acyclic benzimidazoles **1**, **12**, and **4**, respectively. The α-D- configuration of **2**, β-L- configuration of **13**, and the β-D- configuration of **3** suggest that these C-nucleosides are formed from their precursor acyclic analogues without inversion in the configuration of C-1′ as the favored steric course of the cyclization process. The 1′,4′-dehydrative cyclization process takes place by the initial protonation of the 4′-primary hydroxyl group forming the 4′-primary oxonium ion 'A' as a kinetic product. The latter undergoes spontaneous intramolecular S_N2 displacement by the favor-



Scheme 2.



Scheme 3.

ably disposed 1′-hydroxyl group giving the thermodynamically controlled C-nucleoside analogue **3**, without inversion at C-1′ (Scheme 3). Similar explanation can be given for the formation of the C-nucleoside analogues **2** and **13**, without inversion in the configuration of C-1′ at **1** and **12**, respectively. The formation of inversion products requires racemization at C-1′ of the precursor acyclic benzimidazolium cation **4** by abstraction of the 1′-OH^- anion to give the carbocation 'B' [24] or an olefinic intermediate [25]. Such a reaction is difficult to achieve due to the positively charged benzimidazolium moiety that retards the removal of 1′-OH^- anion.

The mass spectra of compounds **2**, **3**, and **13** showed molecular ion at *m/z* 220. The fragment BCHOH (B + 30), which is characteristic for C-nucleosides [10], was shown at *m/z* 147 as the base peak for compounds **2**, **3**, and **13**. The *O*-isopropylidene derivatives **7** and **11** showed molecular ion at *m/z* 260, and the base peak was also the fragment BCHOH at *m/z* 147. Fragments formed by fragmentation of the base moiety and sequential loss of two molecules of HCN were shown at *m/z* 90 and 63 (see Experimental).

3. Experimental

General procedures.—Melting points were determined with a Fisher–Johns melting point apparatus and are uncorrected. Evaporations were performed under diminished pressure below 60 °C. Thin-layer chromatography (TLC) was conducted on silica gel (Kieselgel G, E. Merck) with solvent A, 10:3 $CHCl_3$–EtOH, solvent B, 10:2 $CHCl_3$–EtOH, and solvent C, 1:1 EtOAc–hexane, solvent D, 2:3 EtOAc–hexane, and solvent E, 3:1 EtOAc–hexane, and spots were detected under ultraviolet light at 254 nm. Infrared absorption spectra were recorded with a Perkin–Elmer 1430 instrument. Optical rotations were obtained at 20 ± 2 °C with a Perkin–Elmer 241 polarimeter (10 cm, 1 mL microcell). ^1H NMR spectra were recorded with Bruker 200 MHz, 360 MHz, or 500 MHz instruments, or with a Jeol EX 400 MHz, spectrometers using tetramethylsilane as the internal standard. ^{13}C NMR spectra were recorded with a Bruker 200 instrument at 50 MHz, with a Bruker 360 instrument at 90 MHz, with a Bruker 500 at 125.8 MHz or with a Jeol EX 400 instrument at 100.4 MHz. Mass spectra were recorded with Shimadzu GC–MS-QP 1000 EX and AEI MS 902 spectrometers. High-resolution mass spectra (EI) were measured with a VG 70-250S spectrometer. Combustion analyses were performed in the Department of Chemistry, Cairo University, Cairo, Egypt.

*Preparation of 2-(*D*-aldo-pentitol-1-yl)benzimidazoles.*—2-(D-*arabino*-Tetritol-1-yl)benzimidazole (**1**) and 2-(L-*arabino*-tetritol-1-yl)benzimidazole (**12**) were prepared from potassium D- and L-*arabinonate* and *o*-phenylenediamine by the method of Moore and Link [1]. The products were recrystallized from water as colorless needles.

2-(D-arabino-Tetritol-1-yl)benzimidazole (**1**).—mp 239–240 °C (Lit [26] mp 240–241 °C), R_f 0.22 (solvent B); ν_{max}^{KBr}: 3387 (OH), and 1625 cm^{-1} (C=N); for ^1H NMR data, see Table 1; MS data (selected ions): *m/z* 239 (2, M + 1), 238 (17, M), 221 (6, M − OH), 220 (1, M − H_2O), 208 (4, M − CHOH), 207 (31, M − CH_2OH), 179 (2, $BH_2CHOHCHOH$, where B = benzimidazol-2-yl- moiety), 178 (18, BHCHOHCHOH), 177 (72, BCHOHCHOH), 162 (6, $BH_2CHCHOH$), 161 (54, BHCHCHOH), 160 (6, BCHCHOH), 159 (11, BCHCHO), 149 (30, $BHCH_2OH$), 148 (100, BCH_2OH), 147 (100, BCHOH), 146 (24, BCHO), 145 (4, BCO), 132 (10, BCH_3), 131 (13, BCH_2), 119 (68, BH_2), 118 (35, BH), 117 (4, B), 104 (3, PhCNH), 103 (4, PhCN), 92 (38, BH_2 − HCN), 91 (21, BH − HCN), 90 (9, B − HCN), 77 (9, Ph), 65 (41, BH_2 − HCN − HCN), 64 (14, BH − HCN − HCN), 63 (13, B − HCN − HCN).

2-(α-D-Erythrofuranosyl)benzimidazole (**2**).—2-(D-*arabino*-Tetritol-1-yl)-benzimidazole hydrochloride [1] (0.859 g, 3.6 mmol), was treated with 5 M zinc chloride (0.63 mL, 3.12 mmol) and concentrated hydrochloric acid (0.53 mL, 6 mmol). The mixture was heated for 1.5 h on an oil bath kept at 180 °C. The amber-colored syrup resulting was dissolved in about 15 mL of water, treated with charcoal, filtered, and the filtrate made alkaline by adding ammonium hydroxide (1.2 mL). Acetic acid was then added almost enough to dissolve the precipitate that formed. The mixture was filtered hot after treatment with hydrogen sulfide, concentrated ammonium hydroxide (1.2 mL) was added, and the solution was left to cool at room temperature, giving colorless needles; yield 0.22 g; mp 214–216 °C (Lit [12] mp 206–208 °C), $[\alpha]_D^{20}$ −4.9° (*c* 1.1, N HCl); Lit [12] $[\alpha]_D^{20}$ +2.7° (*c* 2.5% aq citric acid); R_f 0.42 (solvent A). The mother liquor was concentrated to a syrup which was then applied to a column (1.7 × 40 cm) of Dowex 50 W-X2 (H^+) (200–400 mesh), and eluted successively with water, 0.5, 1.5, and 2 N hydrochloric acid. The TLC-positive 2 N hydrochloric acid fractions were collected and evaporated to dryness, and traces of hydrochloric acid were removed by spin coevaporation with toluene. The remaining precipitate was recrystallized from dilute ethanol, giving an additional crop of **2**; 0.17 g, total yield 0.39 g (49%).

Similar treatment of the free base **1** (4.76 g, 20 mmol), with 5 M zinc chloride (4.0 mL, 20 mmol) and concentrated hydrochloric acid (3.4 mL, 38 mmol) afforded compound **2**; total yield 2.43 g (55%); mp and mixed mp 214–216 °C; ν_{max}^{KBr}: 3449, 3373 (OH), and 1612 cm^{-1} (C=N); for ^1H NMR data, see Table 1; MS data (selected ions): *m/z* 221 (2, M + 1) 220 (16, M), 162 (11, $BH_2CHCHOH$), 161 (60, BH_2CHCHO), 160 (3, BCHCHOH), 159 (8, BCHCHO), 148 (13, BCH_2OH), 147 (100, BCHOH), 146 (5, BCHO), 145 (5, BCO), 132 (11, BCH_3), 131 (10, BCH_2), 119 (27, BH_2), 118 (10, BH), 117 (1,B), 104 (3, PhCNH), 103 (2, PhCN), 92 (12, BH_2 − HCN), 91 (7, BH − HCN), 90 (5, B − HCN), 77 (6, Ph), 65 (13, BH_2 − HCN − HCN), 64 (8, BH − HCN − HCN), and 63 (8, B − HCN − HCN). HRMS: Calcd for $C_{11}H_{12}N_2O_3$, 220.0848. Found: 220.0845. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.98; H, 5.49; N, 12.73. Found: C, 59.63; H, 5.71; N, 12.57.

2-(2,3-Di-O-acetyl-α-D-erythrofuranosyl)benzimidazole (**6**).—Compound **2** (100 mg, 0.45 mmol) was treated with 1:1 acetic anhydride–pyridine (5 mL) for 31 h at room temperature, evaporated to dryness and traces of pyridine were removed by spin coevaporation with toluene (3 × 10 mL). The dry residue was purified by chromatography on a column of silica gel (10 × 1 cm), and eluted with solvent C, giving a colorless syrup which was recrystallized from ether as colorless needles; yield 65 mg (47%): mp 145–146 °C; R_f 0.33 (solvent C); for ^1H NMR data, see Table 1; MS data (selected ions) *m/z* 305 (7, M + 1), 304 (28, M), 245 (12, M − AcO), 203 (33, M − AcO − CH_2O), 185 (75, M − AcOH − AcO), 184 (11, M − 2 AcOH), 173 (12), 161 (26, BCH_2CHOH), 160 (5, BCH_2CHO), 159 (5, BCHCHO), 157 (18), 148 (14, BCH_2OH), 147 (100, BCHOH), 132 (6), 131 (5), 119 (11, BH_2), 118 (9, BH), 117 (1, B), 115 (12, B − 2 H), 65 (2, BH_2 − HCN), and 43 (52, CH_3CO); HRMS: Calcd for $C_{15}H_{16}N_2O_5$, 304.1059. Found: 304.1057. Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.42; H, 5.67; N, 9.44.

2-(2,3-O-Isopropylidene-α-D-erythrofuranosyl)-benzimidazole (**7**).—Compound **2** (0.5 g, 2.27 mmol) was suspended in dry acetone (100 mL), treated with *p*-toluenesulfonic acid (1.2 g, 7.0 mmol) and stirred at room temperature. The reaction was monitored by TLC (solvent B). The starting material disappeared after 6 h, and a more mobile spot (R_f 0.61) was obtained. The mixture was poured onto a satd solution of sodium bicarbonate, extracted with chloroform, and the organic layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the chloroform solution gave a precipitate that was recrystallized from dilute methanol as colorless needles; yield 0.52 g (88.0%): mp 194–195 °C (Lit. [12] mp 195–196 °C); ν_{max}^{KBr}: 1657 (C=N) and 1379 cm^{-1} (CMe_2); for ^1H NMR data, see Table 1; for

^{13}C NMR data, see Table 2; MS data (selected ions): *m/z* 261 (5, M + 1), 260 (34, M), 245 (13, M − CH_3), 231 (3, M − CHO), 217 (5, M − CH_3CO), 203 (8, MH − CH_3COCH_3), 202 (2, M − CH_3COCH_3), 201 (8, M − CH_3COO), 187 (24, MH − CH_3 − CH_3COO), 186 (3, M − CH_3 − CH_3COO), 185 (10, M − CH_3COOH − CH_3), 174 (3, M − CH_3COCH_3 − CO), 173 (18, M − CH_3COCH_3 − CHO), 161 (11, BCH_2CHOH), 160 (5, BCHCHOH), 159 (6, BCHCHO), 157 (12), 148 (13, BCH_2OH), 147 (100, BCHOH), 146 (31, BCHO), 145 (23, BCO), 144 (8), 143 (8), 132 (17, BCH_3), 131 (6, BCH_2), 119 (13, BH_2), 118 (37, BH), 117 (4, B), 104 (2, PhCNH), 103 (2, PhCN), 92 (8, BH_2 − HCN), 91 (14, BH − HCN), 90 (9, B − HCN), 77 (5, Ph), 65 (6, BH_2 − HCN − HCN), 64 (9, BH − HCN − HCN), and 63 (8, B − HCN − HCN). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.15; N, 10.76. Found: C, 64.92; H, 6.30; N, 10.62.

2-(α-Furyl)benzimidazole (**8**).—Compound **2** (50 mg, 0.23 mmol) was heated to reflux in Ac_2O (5 mL) for 1.5 h. The mixture was treated with charcoal, filtered, and evaporated to dryness giving a precipitate. Recrystallization of the precipitate from EtOH gave colorless needles; yield 37.9 g (90.6%), mp 283–284 °C (Lit [12] mp 285–286 °C). R_f 0.69 (solvent A). The isolated product was also identified by TLC in the mother liquor of the dehydration of **1** having the same R_f value. ν_{max}^{KBr}: 1624 cm^{-1} (C=N); for ^{1}H NMR data, see Table 1; for ^{13}C NMR data, see Table 2; MS data (selected ions): *m/z* 185 (12, M + 1), 184 (100, M), 183 (18, M − H), 157 (4, MH − CO), 156 (33, M − CO), 155 (26, M − CHO), 130 (3, M − CO − C_2H_2), 104 (3, PhCNH), 103 (8, PhCN), 92 (11, BH_2 − HCN), 91 (4, BH − HCN), 90 (10, B − HCN), 77 (6, Ph), 65 (7, BH_2 − HCN − HCN), 64 (14, BH − HCN − HCN), and 63 (16, B − HCN − HCN). Anal. Calcd For $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.22. Found: C, 71.51; H, 4.23; N, 15.20.

*2-(*L-arabino-*Tetritol-1-yl)benzimidazole* (**12**).—Physicochemical and spectral data: mp 234–235 °C (Lit [1] mp 235 °C dec.), R_f 0.21 (solvent A); ν_{max}^{KBr}: 3385 (OH), and 1619 cm^{-1} (C=N); for ^{1}H NMR data, see Table 1; for ^{13}C NMR, see Table 2; MS data (selected ions): *m/z* 240 (86, M + 2), 239 (100, M + 1), 222 (4, MH − OH), 221 (5, M − OH), 208 (11, M − CHOH), 207 (12, M − CH_2OH), 179 (1, $BH_2CHOHCHOH$), 178 (23, BHCHOHCHOH), 177 (27, BCHOHCHOH), 162 (3, $BH_2CHCHOH$), 161 (26, BHCHCHOH), 160 (7, BCHCHOH), 159 (8, BCHCHO), 149 (11, $BHCH_2OH$), 148 (96, BCH_2OH), 147 (87, BCHOH), 146 (7, BCHO), 145 (2, BCO), 132 (6, BCH_3), 131 (9, BCH_2), 119 (38, BH_2), 118 (15, BH), 117 (2, B), 104 (2, PhCNH), 103 (2, PhCN), 92 (21, BH_2 − HCN), 91 (11, BH − HCN), 90 (4, B − HCN), 77 (4, Ph), 65 (22, BH_2 − HCN − HCN), 64 (8, BH − HCN − HCN), 63 (8, B − HCN − HCN). Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.44; H, 5.93; N, 11.76. Found: C, 55.63; H, 5.79; N, 11.91.

*2-(β-*L*-Erythrofuranosyl)benzimidazole* (**13**).—Compound **12** (1.25 g, 5.30 mmol), was treated in a boiling tube with 5 M zinc chloride (1.0 mL, 5.1 mmol) and concentrated hydrochloric acid (0.8 mL, 6 mmol), heated for 1.5 h, and treated as for the preparation of **2** giving colorless needles; yield 290 mg; mp 215–217 °C, R_f 0.42 (solvent A). Another batch (338 mg) was obtained by column chromatography of the mother liquor on Dowex WX2 (H^+) ion-exchange resin. The column was first washed with water then eluted with 2 N ammonium hydroxide solution giving another batch (388 mg), total yield 628 mg (54.4%): ν_{max}^{KBr}: 3447, 3398 (OH), and 1612 cm^{-1} (C=N); for ^{1}H NMR data, see Table 1; MS data (selected ions): *m/z* 221 (10, M + 1) 220 (12, M), 162 (9, $BH_2CHCHOH$), 161 (57, BHCHCHOH), 160 (3, BCHCHOH), 159 (7, BCHCHO), 148 (13, BHCHOH), 147 (100, BCHOH), 146 (4, BCHO), 145 (4, BCO), 132 (9, BCH_3), 131 (11, BCH_2), 119 (28, BH_2), 118 (10, BH), 117 (1, B), 104 (3, PhCNH), 103 (3, PhCN), 92 (14, BH_2 − HCN), 91 (9, BH − HCN), 90 (4, B − HCN), 77 (7, PH), 65 (16, BH_2 − HCN − HCN), 64 (9, BH − HCN − HCN), and 63 (9, B − HCN − HCN). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.98; H, 5.49; N, 12.73. Found: C, 59.73; H, 5.77; N, 12.45.

*2-(2,3-*O*-Isopropylidene-β-*L*-erythrofuranosyl)-benzimidazole* (**14**).—A suspension of **13** (0.5 g, 2.27 mmol) in dry acetone (100 mL), was treated with *p*-toluenesulfonic acid (1.2 g, 6.3 mmol), and the mixture was stirred at room temperature for 6 h. The mixture was worked up as for **7** and recrystallized from dilute methanol giving colorless needles; yield 540 mg (91.4%): mp 194–195 °C, not depressed when admixed with **7**; $[\alpha]_D^{20}$ +137.7 °C (*c* 1.05, $CHCl_3$); ν_{max}^{KBr}: 1615 cm^{-1} (C=N), and 1429 cm^{-1} (CMe_2); for ^{1}H NMR data, see Table 1; for ^{13}C NMR data, see Table 2. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.15; N, 10.76. Found: C, 64.39; H, 6.28; N, 10.55.

*2-(*D*-ribo-Tetritol-1-yl)benzimidazole hydrochloride* (**4**).—Potassium-D-ribonate [26] (5.0 g, 24 mmol) was dissolved in water (20 mL) and demineralized by

Table 1
^{1}H NMR data: chemical shifts (δ) [a] and first-order coupling constants (J Hz) [a] for compounds **1–3** and **5–14**

Compound	Glycosyl moiety								Benzimidazol-2-yl moiety [b]				
	H-1′	H-2′	H-3′	H-4′	H-4″	OH	OAc (NAc)	CMe_2	H-5	H-6	H-4	H-7	NH
1 [c]	5.10d $J_{1',2'}$ 1.9	3.78d $J_{2',3'}$ 5.9	— 3.64m —		3.49dd $J_{3',4''}$ 5.0 $J_{4',4''}$ 9.8	4.43m 4.65d 4.73m 5.50d			— 7.13m —		— 7.50m —		12.21bs
2 [c]	5.17d $J_{1',2'}$ 4.4	— 4.33m —		4.00t $J_{3',4'}$ 6.4	3.85t $J_{3',4''}$ 8.0 $J_{4',4''}$ 14.4	5.13d 5.34bs			—7.16m —		—7.55m —		12.21bs
3 [c]	4.80d $J_{1',2'}$ 5.9	4.32m	—4.14m —		3.74m	5.06d 5.29d			— 7.15m —		— 7.51m —		12.45bs
5 [c]	5.02d $J_{1',2'}$ 4.5	3.86dd $J_{2',3'}$ 6.3	— 3.52m —			3.53m 4.49bs 5.02m 5.86d			— 7.15m —		— 7.53m —		12.01bs
6 [d]	5.46d $J'_{,2'}$ 5.5	5.83t $J_{2',3'}$ 5.3	5.60m	4.27dd $J_{3',4'}$ 5.8	4.14dd $J_{3',4''}$ 4.8 $J_{4',4''}$ 9.9		1.81s 2.04s		— 7.26m —		— 7.58m —		9.52bs
7 [e]	4.89d $J_{1',2'}$ 3.9	4.94dd $J_{2',3'}$ 3.4	5.03dd	4.21d	3.73dd $J_{3',4''}$ 3.9 $J_{4',4''}$ 10.7			1.475s 1.311s $\Delta\delta$ 0.164	— 7.26m —		— 7.30m —		9.64bs
8 [e]		7.22d	6.58m $J_{2',3'}$ 3.9 $J_{3',4'}$ 2.0		7.28m				— 7.28m —		— 7.54m —		9.98bs

9 [d]	5.30d $J_{1',2'}$	5.70dd $J_{2',3'}$ 5.4	5.47m	4.40dd $J_{3',4'}$ 5.4	4.06dd $J_{3',4'}$ 4.3 $J_{4',4''}$ 10.2		2.12s 2.14s		— 7.35m —	7.73m	7.53m	9.56bs
10 [d]	5.71d $J_{1',2'}$ 4.1	6.11dd $J_{2',3'}$ 4.4	5.65m	4.38dd $J_{3',4'}$ 5.7	4.03dd $J_{3',4''}$ 4.5 $J_{4',4''}$ 9.8		2.11s 2.13s (2.86s)		— 7.39m —	— 7.79m —		
11 [e]	5.35s	5.66d	4.88dd $J_{2',3'}$ 6.4	4.14d	3.67dd $J_{3',4''}$ 3.9 $J_{4',4''}$ 10.7			1.572s 1.388s $\Delta\delta$ 0.184	— 7.28m —	— 7.62m —		9.72bs
12 [f]	5.11d $J_{1',2'}$ 2.0	3.79d $J_{2',3'}$ 8.3	3.66m	3.62dd $J_{3',4'}$ 2.4	3.46dd $J_{3',4''}$ 5.9 $J_{4',4''}$ 10.8	4.43t 4.65d 4.73d 5.50d			— 7.12m —	— 7.49m —		12.11bs
13 [c]	5.12m	— 4.30m —		3.98dd $J_{3',4'}$ 6.3	3.83dd $J_{3',4'}$ 6.7 $J_{4',4''}$ 14.4	5.12m 5.30s			— 7.14m —	— 7.51m —		12.14bs
14 [d]	4.93d $J_{1',2'}$ 3.5	5.07dd $J_{2',3'}$ 3.5	4.98dd	4.25d	3.76dd $J_{3',4''}$ 4.0 $J_{4',4''}$ 11.0			1.518s 1.353s $\Delta\delta$ 0.165	— 7.30dd —	7.75bs	7.56bs	9.74bs

[a] J and δ values are measured after exchanging with CD_3CO_2D for the sugar protons.
[b] The aromatic protons H-4 and H-7 are observed together as a multiplet downfield from the multiplet of H-5 and H-6.
[c] In Me_2SO-d_6 + CD_3CO_2D at 200 MHz.
[d] In $CDCl_3$ at 500 MHz.
[e] In $CDCl_3$ at 400 MHz.
[f] In Me_2SO-d_6 + CD_3CO_2D at 400 MHz.

Table 2
^{13}C NMR data: chemical shifts (δ) for compounds **7**, **8**, **10**, **11**, **12**, and **14**

Compound	Glycosyl moiety							Benzimidazol-2-yl moiety			
	C-1′	C-2′	C-3′	C-4′	OAc (NAc)		CMe_2 (acetonide C)	C-5, C-6	C-4, C-7	C-8, C-9	C-2
					CO	CH_3					
7 [a]	78.7	81.8	80.9	73.2			25.9 24.2 (112.6)	123.1	115.1	136.7	149.5
8 [a]	143.8 *	—	110.6 —	123.1 *				123.1	112.5	143.7	145.4
10 [b]	78.0	74.6	71.8	70.8	169.7, 170.0 (169.0)	20.6, 20.7 (26.5)		124.8, 125.7	114.1, 121.3	133.0, 142.2	151.7
11 [e]	80.6	80.8	83.7	73.3			26.2 24.6 (112.8)	123.2	115.3	137.7	150.6
12 [c]	73.8	70.9	67.4	63.4				120.7, 121.1	111.2, 118.1	133.9, 143.0	157.3
14 [d]	79.3	81.7	80.9	73.3			26.1 24.2 (112.6)	122.5	112.6	111.0 *, 119.9 *	149.3

[a] In $CDCl_3$ at 100.4 MHz.
[b] In $CDCl_3$ at 125.8 MHz.
[c] In Me_2SO-d_6 at 100.4 MHz.
[d] In $CDCl_3$ at 90 MHz.
[e] In $CDCl_3 + CD_3CO_2D$ at 100.4 MHz.
* Assignments may be reversed.

passing several times through a column of Amberlite IR 120 (H^+). The column was washed with water, and the solution and washings were combined and evaporated to a thick syrup, which was lactonized by further heating under vacuum for 4 h. The remaining thick syrup (4.01 g) was dissolved in a mixture of EtOH (2.5 mL) and butanol (12.5 mL), and the mixture was treated with *o*-phenylenediamine dihydrochloride (4.6 g, 25 mmol) and *o*-phenylenediamine (2.4 g, 22 mmol). The mixture was refluxed for 8 h. Upon cooling compound **4** crystallized, was filtered off, washed with acetone, and dried; yield 5.26 g. Recrystallization from absolute EtOH gave colorless needles: mp 196–198 °C (Lit [26] mp 196–198 °C); ν_{max}^{KBr}: 3425–3363 (OH), 3159 ($\rangle N^+HCl$), and 1625 cm^{-1} (C=N). Anal. Calcd for $C_{11}H_{14}N_2O_4 \cdot HCl$: C, 48.08; H, 5.50. Found: C, 48.25; H, 5.63.

*2-(*D-ribo-*Tetritol-1-yl)benzimidazole* (**5**).—Compound **4** (5.0 g, 19 mmol) was dissolved in water (100 mL), and desalted by passing several times though a column (1.7 × 40 cm) of Amberlite IR 400 (OH^-) ion-exchange resin. The column was washed with water, and the combined eluant and washings were evaporated to dryness. The resulting precipitate was recrystallized from absolute EtOH; yield 3.9 g (87%): mp 189–191 °C dec (Lit [26] mp 190 °C), R_f 0.24 (solvent B); ν_{max}^{KBr}: 3444, 3335 (OH), 3220 (NH), and 1615 cm^{-1} (C=N); for ^1H NMR data, see Table 1. Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.93; N, 11.76. Found: C, 55.38; H, 5.74; N, 11.86.

*2-(β-*D*-Erythrofuranosyl)benzimidazole* (**3**).—Compound **4** (3.25 g, 13.6 mmol), was mixed with 5 M zinc chloride (2.37 mL, 11.9 mmol) and concentrated hydrochloric acid (2.0 mL, 23.72 mmol), and the mixture was treated as described for the preparation of **2**. The filtrate, after neutralization with ammonium hydroxide (4.5 mL), gave a syrup that was dissolved in water (5.0 mL) and applied to a column (3 × 60 cm) of Dowex 50 WX2 (H^+), (200–400 mesh), and eluted successively with water, 0.5, 1.5, and 2 N hydrochloric acid. The TLC-positive 2 N hydrochloric acid fractions, were collected and evaporated to a syrup that was recrystallized from dilute ethanol to give compound **3** as colorless needles; yield 1.348 g. (45%): R_f 0.38 (solvent B); mp 167–168 °C (Lit [27] mp 82–83 °C, dihydrate); $[\alpha]_D^{20}$ −81.8° (*c* 0.77, N HCl); Lit [12] $[\alpha]_D^{20}$ −84.5° (*c* 2, EtOH); ν_{max}^{KBr}: 3446 (OH), and 1616 cm^{-1} (C=N); for ^1H NMR data, see Table 1; MS data (selected ions): *m/z* 221 (3, M + 1) 220 (17, M), 191 (3, M − CHO), 190 (2, M − CHOH), 162 (6, $BH_2CHCHOH$), 161 (41, BHCHCHOH), 160 (3, BCHCHOH), 159 (10, BCHCHO), 149 (1, $BHCH_2OH$), 148 (15, BCH_2OH), 147 (100, BCHOH), 146 (2, BCHO), 145 (4, BC=O), 132 (13, BCH_3), 131 (16, BCH_2), 119 (30, BH_2), 118 (15, BH), 117 (3, B), 104 (4, PhCNH), 103 (4, PhCN), 92 (13, BH_2 − HCN), 91 (11, BH − HCN), 90 (5, B − HCN), 77 (7, Ph), 65 (2, BH_2 − HCN − HCN), 64 (12, BH − HCN − HCN), and 63 (9, B − HCN − HCN); HRMS: Calcd for $C_{11}H_{12}N_2O_3$, 220.0848. Found: 220.0857. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.73; H, 5.56; N, 12.48.

*2-(2,3-Di-*O*-acetyl-β-*D*-erythrofuranosyl)benzimidazole* (**9**).—Compound **3** (10 mg, 0.05 mmol) was treated with a 1:1 pyridine–Ac_2O mixture (5 mL) for 24 h at room temperature and worked up as described for **6**. It gave a syrup showing two spots on TLC: R_f 0.26 and 0.09 in the ratio of 1:1, which were separated on a short column of silica gel (10 × 1 cm), and eluted with solvent D, giving the less-mobile spot **9**, as a colorless syrup (yield 8.5 mg), which was recrystallized from EtOAc–hexane as colorless needles mp 184–186 °C, R_f 0.42 (solvent E); for ^1H NMR data, see Table 1; MS data (selected ions): *m/z* 305 (1, M + 1) 304 (0.5, M), 245 (4, M − AcO), 244 (19, M − AcOH), 186 (13, M − 2 AcO), 185 (100, M − AcOH − AcO), 184 (9, M − 2 AcOH) 160 (5, BCH_2CHO), 159 (6, BCHCHO), 148 (4, BCH_2OH), 147 (30, BCHOH), 119 (9, BH_2) 118 (2, BH), 117 (1, B), 115 (4, B − 2 H), 91 (4, BH − HCN), 77 (2, Ph), 65 (3, BH_2 − HCN − HCN), 64 (1, BH − HCN − HCN), 63 (1, B − HCN − HCN), and 43 (40, CH_3CO); HRMS: Calcd. for $C_{15}H_{16}N_2O_5$, 304.1059. Found: 304.1037.

N^1*-acetyl-2-(2,3-di-*O*-acetyl-β-*D*-erythrofuranosyl)benzimidazole* (**10**).—This compound was isolated from the column chromatography of **9** as a syrup (yield 9 mg) and was more mobile than **9**: R_f 0.75 (solvent E); for ^1H NMR data, see Table 1; for ^{13}C NMR data, see Table 2; MS data (selected ions) *m/z* 347 (3, M + 1), 346 (0.3, M), 305 (7, MH − CH_2CO), 286 (19, M − AcOH), 245 (8, MH − AcOH − CH_2CO), 244 (19, M − AcOH − CH_2CO), 227 (28, M − AcOH − AcO), 203 (6), 201 (10), 186 (16, M − 2 AcO − CH_2CO), 185 (M − 2 AcO − Ac), 184 (19, M − AcOH − AcO − Ac), 173 (6), 161 (13, BCH_2CHOH), 160 (11, BCH_2OH), 159 (10, BCH_2CO), 157 (15), 148 (3, BCH_2OH), 147 (45, BCHOH), 132 (8), 131 (8), 119 (BH_2), 118 (11, BH), 115 (8), 92 (6, BH_2 − HCN), 91 (4, BH − HCN), 77 (3), 65 (1, BH_2 − HCN − HCN), 63 (2, B − HCN − HCN), and 43 (96, CH_3CO); HRMS: Calcd for $C_{17}H_{18}N_2O_6$, 346.1165. Found: 346.1173.

2-(2,3-O-Isopropylidene-β-D-erythrofuranosyl)-benzimidazole (**11**).—Compound **3** (300 mg, 1.36 mmol) was suspended in dry acetone (50 mL), treated with *p*-toluenesulfonic acid (1.2 g, 6.97 mmol) as described for **7**. The resulting precipitate was recrystallized from dilute MeOH as colorless needles; yield 319 mg (90%): mp 172–173 °C; ν_{max}^{KBr}: 1617 (C=N) and 1413 cm^{-1} (CMe_2); for ^1H NMR data, see Table 1; for ^{13}C NMR data, see Table 2; MS data (selected ions): *m/z* 261 (5, M + 1), 260 (22, M), 245 (17, M − CH_3), 231 (4, M − CHO), 217 (4, M − CH_3CO), 203 (12, MH − CH_3 − $COCH_3$), 202 (7, M − CH_3COCH_3), 201 (7, M − CH_3COO), 187 (17, MH − CH_3 − CH_3COO), 186 (2, M − CH_3 − CH_3COO), 185 (8, M − CH_3COOH − CH_3), 174 (6, M − CH_3COCH_3 − CO), 173 (26, M − CH_3COCH_3 − CHO), 161 (10, BCH_2CHOH), 160 (4, BCHCHOH), 159 (7, BCHCHO), 157 (15), 156 (6), 148 (13, BCH_2OH), 147 (100, BCHOH), 146 (29, BCHO), 145 (24, BCO), 144 (11), 143 (12), 132 (18, BCH_3), 131 (8, BCH_2), 119 (16, BH_2), 118 (44, BH), 117 (5, B), 104 (3, PhCNH), 103 (3, PhCN), 92 (11, BH_2 − HCN), 91 (17, BH − HCN), 90 (10, B − HCN), 77 (7, Ph), 65 (13, BH_2 − HCN − HCN), 64 (12, BH − HCN − HCN), and 63 (12, B − HCN − HCN). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.84; H, 6.45; N, 10.49.

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