The Synthesis of 2-Chloro-1-(β-D-ribofuranosyl)benzimidazole and Certain Related Derivatives (1).

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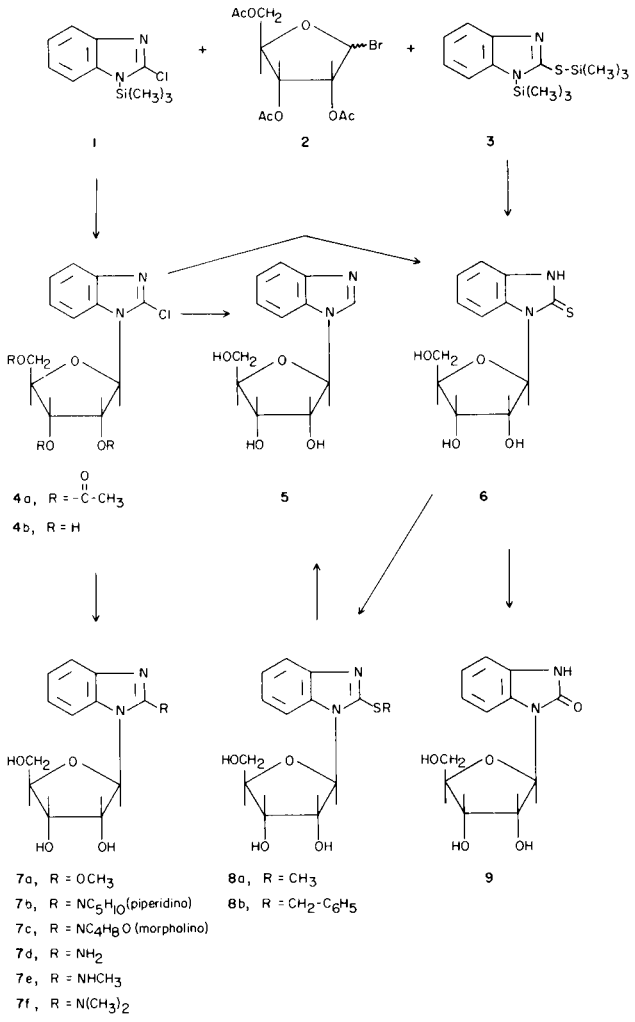
The synthesis of 2-chloro-1-(β-D-ribofuranosyl)benzimidazole (**4b**) has been accomplished by a condensation of 2-chloro-1-trimethylsilylbenzimidazole (**1**) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**2**) followed by subsequent deacetylation. Nucleophilic displacement of the 2-chloro group has furnished several interesting 2-substituted-1-(β-D-ribofuranosyl)benzimidazoles. 1-(β-D-Ribofuranosyl)benzimidazole (**5**) and 1-(β-D-ribofuranosyl)benzimidazole-2-thione (**6**) were prepared from **4b** and **6** was also prepared by condensation of **2** with silylated benzimidazole-2-thione (**3**). Alkylation of **6** furnished certain 2-alkylthio-1-(β-D-ribofuranosyl)benzimidazoles and oxidation of **6** with alkaline hydrogen peroxide produced 1-(β-D-ribofuranosyl)benzimidazole-2-one (**9**). The assignment of anomeric configuration for all nucleosides reported is discussed.

The isolation (2,3) of 1-(α-D-ribofuranosyl)-5,6-dimethylbenzimidazole and the 2′ (or 3′)-phosphate (4) derivative from the mineral acid hydrolysis of vitamin B_{12} has prompted considerable interest in the chemical synthesis of benzimidazole nucleosides. The first methods developed for the synthesis of 1-(D-glycosyl)benzimidazoles included the ring closure of a mono-*N*-glycosyl derivative of *O*-phenylenediamine (2-6) or the condensation of a per-*O*-acetylglycosyl halide with the heavy metal salt of an appropriate benzimidazole (7-11). It is of interest that of all the benzimidazole nucleosides isolated from vitamin B_{12} and the 1-(D-ribofuranosyl)benzimidazoles which have been prepared chemically for potential biological activity none have possessed substituents on the aglycon except in the benzene ring (12). This prompted the present investigation on the preparation of 2-substituted benzimidazole nucleosides. A recent report (13) from this Laboratory has described the synthesis of certain 8-substituted purine nucleosides which have demonstrated significant biological and antitumor activity. It is of considerable interest that the 8-substituent of a purine nucleoside may be considered analogous to the 2-substituent of a benzimidazole nucleoside. The preparation of certain 1-(2′-deoxy-D-ribofuranosyl)benzimidazoles using the acid catalyzed fusion procedure (14) has been reported (12) from this Laboratory, but, the acid catalyzed fusion of several 2-substituted benzimidazoles with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (15), or 1,3,5-tri-*O*-acetyl-2-deoxy-D-ribofuranose (12) using various acidic catalysts and reaction conditions have proved to be unfruitful. We now wish to report the successful preparation of 2-substituted benzimidazole nucleosides using the silylation method.

The silylation of 2-chlorobenzimidazole with hexamethyldisilazane using a catalytic amount of ammonium sulfate under anhydrous conditions furnished 2-chloro-1-trimethylsilylbenzimidazole (**1**) in an 88% yield. Since **1** is extremely susceptible toward hydrolysis (cleavage of the Si-N bond), it was always prepared immediately before utilization in the condensation reaction. The condensation of **1** with 1-bromo-2,3,5-tri-*O*-acetyl-D-ribofuranose (**2**) in the presence of a catalytic amount of sodium iodide at 110° afforded a 69% yield of crystalline 2-chloro-1-(2′, 3′, 5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzimidazole (**4a**). Removal of the blocking groups from the carbohydrate moiety of **4a** was accomplished with methanolic ammonia at room temperature. That complete deacetylation had occurred was evident by the absence of any absorption peaks at δ 2.1 in the pmr spectrum of **4b**. An assignment of anomeric configuration for ribofuranosides, excluding conformational changes, can be made by utilization of pmr spectroscopy (coupling constants) only for the β-anomer which possesses neighboring *trans*-hydrogens and then only if the coupling constant is less than 3.5 cps (16-18). The pmr spectra of **4a** and **4b** in dmso-d_6 revealed a $J_{1,2}$ of 6.0 cps and 7.0 cps, respectively. The coupling constants ($J_{1,2}$) observed for **4a** and **4b** definitely precluded the use of the above method for the assignment of anomeric configuration and suggested that an alternate method should be investigated.

Removal of the 2-chloro group from 2-chloro-1-(β-D-ribofuranosyl)benzimidazole (**4b**) was effected catalytically to afford a 74% yield of 1-(β-D-ribofuranosyl)-benzimidazole (**5**). The preparation of **5** has been previously described (7) using a condensation of chloromercuribenzimidazole and 1-chloro-2,3,5-tri-*O*-acetyl-D-

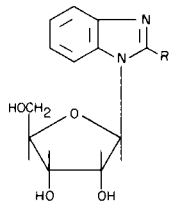


ribofuranose. The nucleoside material (**5**) prepared from **4b** possessed a $[\alpha]_D^{25}$ + 16° which is very similar to the specific rotation observed ($[\alpha]_D^{29}$ + 13°) for this nucleoside prepared by other methods (7,19) and therefore established the β-configuration for all nucleosides reported herein. Displacement of the 2-chloro group of **4b** was accomplished with thiourea in ethanol to furnish a 78% yield of 1-(β-D-ribofuranosyl)benzimidazole-2-thione (**6**). There was observed an absorption band in the infrared spectrum (potassium bromide) at 1605 cm^{-1} which was assigned as C=S stretching and part of a -N-C=S system (20) which indicated that 6 exists in the thione rather than the thiol form. There was an absence of a band at 2550-2600 cm^{-1} usually attributable (21) to -SH stretching and there was observed an absorption peak in the pmr spectrum at δ 12.8 (1 proton) which was assigned to N-3 of **6** and provided additional support for the thione form. The preparation of **6** was also accomplished *via* an alternate route. Treatment of benzimidazole-2-thione with hexamethyldisilazane and a catalytic amount of ammonium sulfate furnished a syrup which was assumed to be the disilylated derivative and this was condensed with 1-bromo-2,3,5-tri-*O*-acetyl-D-ribofuranose to furnish the tri-*O*-acetyl derivative of **6** as a syrup. Deacetylation with methanolic ammonia afforded a nucleoside which was found to be identical in all respects with **6** prepared from **4b** with thiourea. It is of interest that a 1-substituted-benzimidazole-2-thione (1-(β-4-pyridethyl)benzimidazole-2-thione) has recently demonstrated the ability to act as a reversible inhibitor of nucleic acid synthesis (22) presumably prior to the formation of inosinic acid in the *de novo* pathway of purine biosynthesis. It was also proposed that it could be acting as an antagonist in the synthesis of vitamin B_{12}. Treatment of **6** in an aqueous ammoniacal solution with methyl iodide furnished an 85% yield of 2-methylthio-1-(β-D-ribofuranosyl)benzimidazole (**8a**). The site of methylation was initially assigned on the basis of ultraviolet absorption (hypsochromic shift) and pmr spectroscopy (based on the chemical shift between a methyl group on an exocyclic mercapto group and a ring nitrogen, value observed being δ 2.8). This assignment of methylation was corroborated when desulfurization of **8a** with Raney nickel furnished 1-(β-D-ribofuranosyl)benzimidazole (**5**) identical in all respects with **5** prepared from **4b**. Alkylation of **6** with benzyl chloride in an aqueous ammoniacal solution produced 2-benzylthio-1-(β-D-ribofuranosyl)benzimidazole (**8b**). A facile conversion of sulfur to oxygen has been recently described (23) and was accomplished with alkaline hydrogen peroxide. Treatment of **6** with alkaline hydrogen peroxide gave 1-(β-D-ribofuranosyl)benzimidazole-2-one (**9**). The ultraviolet absorption spectral data observed for **9** (Table I) was very similar to the data reported (24) for 1-ethylbenzimidazole-2-one and the infrared spectrum (potassium bromide) of **9** revealed an absorption band at 1710 cm^{-1} which is similar to the C=O absorption band observed for a 5-membered cyclic ureide.

It has been previously reported (25) that the ease of nucleophilic displacement of the 2-chloro group from 2-chlorobenzimidazoles is greatly facilitated by a substituent at N-1. Nucleophilic substitution has now been observed to proceed readily utilizing **4b** as starting material to produce several 2-substituted-1-(β-D-ribofuranosyl)benzimidazoles. Treatment of **4b** with piperidine and morpholine in ethanol at reflux temperature has produced 2-(*N*-piperidino)-1-(β-D-ribofuranosyl)benzimidazole (**7b**) and 2-(*N*-morpholino)-1-(β-D-ribofuranosyl)benzimidazole (**7c**), respectively. 2-Methylamino-1-(β-D-ribofuranosyl)benzimidazole (**7e**) was prepared from **4b** and aqueous methylamine (40%) at reflux temperature. 2-Amino-1-(β-D-ribofuranosyl)benzimidazole (**7d**) and 2-dimethylamino-1-(β-D-ribofuranosyl)benzimidazole (**7f**) were also prepared *via* a nucleophilic displacement of the 2-chloro group from **4b**.

TABLE I

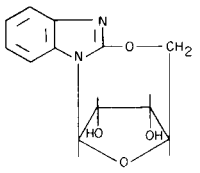
Ultraviolet Absorption Spectra of Certain
2-Substituted-1-(β-D-ribofuranosyl)benzimidazoles (a)



		pH 1		MeOH		pH 11	
Compound	R	λ max nm	ε	λ max nm	ε	λ max nm	ε
4b	Cl	247	6460	242	7630	243	7335
		272	7335	273	5870	273	5580
		280	6750	281	5870	281	5580
6	SH	247	10430	248	9870	258 (b)	9305
		294 (b)	21140			265 (b)	9020
		303	25370	305	26800	300	18320
5	H	254 (b)	4750	251	6250	251	5000
		262 (b)	5500	265 (b)	3750	264.5 (b)	3000
		269	6500	272	4250	272	3750
		275	5500	280	4000	279.5	3500
8a	SCH_3	238	10650	252 (b)	8880	252 (b)	7995
		282	15700	282	11250	282	11250
		291	16300	290	11550	290	11550
8b	$S\text{-}CH_2C_6H_5$		-	253 (b)	10050	253 (b)	7810
		285 (b)	14150	284	13750	284	12650
		292	14900	290	14500	290	13000
9	OH	276	5320	279	5320	279	4790
7a	OCH_3	267	4200	238 (b)	4200	237 (b)	4200
		273.5	4200	273.5	4760	273	3080
				280	4480	279	3080
7b	NC_5H_{10}	234 (b)	13650	250	9990	250	10300
		280	15000	284	9325	284	9990
		287	15650				
7c	NC_4H_8O	232	12400	250	8375	249	7370
		278	12050	280	7370	280	7035
7d	NH_2	274	4505	275	3710	275 (b)	3975
		280	4505	280.5	3975	280	4505
7f	$N(CH_3)_2$			248	9965	247	9965
		280	9670	280.5	7035	280.5	7325
7e	$NHCH_3$			245	7130	245	8020
		275	7725	282.5	6535	282.5	6685
10		266	5210	272	3720	271	3720
		272.5	5210	279	3720	278	3720

(a) Ultraviolet absorption spectra were obtained with a Beckman DK-2 Ultraviolet Spectrophotometer. (b) Shoulder.

A small amount of nucleoside material (m.p. 236°) of unknown structure was isolated from the deacetylation of **4a** and was found to possess an empirical formula of $C_{12}H_{12}N_2O_4$. The pmr spectrum in dmso-d_6 revealed the absence of an aromatic proton at C-2 and also the absence of one proton usually attributable to the carbohydrate moiety. This indicated that a 2,5′-anhydronucleoside had probably been formed, since the starting material (**4a**) possessed a β-configuration and a visual



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examination using Stuart models revealed that the C-5′-hydroxyl group is the only group in a suitable juxtaposition for anhydro formation. Treatment of **4b** with sodium methoxide in methanol at reflux temperature produced a good yield of 2-methoxy-1-(β-D-ribofuranosyl)-benzimidazole (**7a**) which possessed ultraviolet absorption data very similar to the data observed for the anhydronucleoside. Treatment of **7a** and the anhydronucleoside with 20% hydrochloric acid at 100° for 30 minutes apparently effected a cleavage of the glycosidic bond (N-C bond) to furnish the corresponding 2-alkoxybenzimidazole derivatives since the ultraviolet absorption spectral data (λ max) observed for these two hydrolysis reaction mixtures were identical (*p*H 1, *p*H 11 and methanol) to the ultraviolet absorption spectra of 2-methoxybenzimidazole. On the basis of the above data we have assigned the anhydronucleoside the structure **10**.

The synthesis of other benzimidazole nucleosides utilizing the silylation procedure is under active investigation in this Laboratory.

EXPERIMENTAL (26)

2-Chloro-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzimidazole (**4a**).

A mixture of dry 2-chlorobenzimidazole (27) (5 g.), freshly distilled hexamethyldisilazane (6 g.) and a few crystals of ammonium sulfate (approximately 50 mg.) were heated at reflux temperature with stirring under anhydrous conditions for 15 hours. The clear reaction mixture was fractionated by distillation to obtain 6.5 g. (88%) of 2-chloro-1-trimethylsilylbenzimidazole (**1**) as a colorless liquid (b.p. 120-122° at 0.2 mm). Since this material was extremely susceptible to moisture, it was used in the following condensation reaction immediately after distillation. 2-Chloro-1-trimethylsilylbenzimidazole (**1**) (4.5 g.) was thoroughly mixed with 1-bromo-2,3,5-tri-*O*-acetyl-D-ribofuranose (28) (**2**) (7.5 g.) and a catalytic amount of sodium iodide (0.025 g.). This mixture was heated at 110° (oil bath temperature) for 30 minutes *in vacuo* with efficient stirring and within 6 minutes the reaction mixture became clear and after 10 minutes a solid began to separate from solution. The reaction mixture was cooled to room temperature and dissolved in chloroform (200 ml.). A small amount of insoluble material (0.4 g.) was removed by filtration and the filtrate washed with cold saturated aqueous sodium bicarbonate solution (4 x 100 ml. portions) and with cold water (4 x 100 ml. portions). The chloroform phase was dried over anhydrous sodium sulfate and then evaporated *in vacuo* to a syrup. The residual syrup was dissolved in anhydrous methanol (100 ml.), charcoal added and the charcoal then removed by filtration. The filtrate was concentrated to 10 ml. and an excess of ligroin (40-60°) was added to a cloud point. The solution was then allowed to stand at 5° for 18 hours and the crystalline colorless needles which had separated from solution were collected by filtration and dried at 80° over phosphorus pentoxide to yield 5.8 g. (69%). A small sample was recrystallized from a mixture of methanol-ligroin (40-60°) to obtain an analytically pure sample of 2-chloro-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzimidazole (**4a**), m.p. 117-118°, $[\alpha]_D^{25}$ -54.4° (C=1, ethanol).

Anal. Calcd. for $C_{18}H_{19}ClN_2O_7 \cdot \frac{1}{2}H_2O$: C, 51.50; H, 4.76; N, 6.67; Cl, 8.46. Found: C, 51.75; H, 4.63; N, 6.64; Cl, 8.40.

Reaction of 2-Chloro-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-benzimidazole (**4a**) with Methanolic Ammonis (**4b** and **10**).

2-Chloro-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzimidazole (**4a**) (5 g.) was dissolved in methanolic ammonia (methanol saturated with ammonia at 0°, 250 ml.) and the solution allowed to stand at room temperature for 24 hours. The solution was then evaporated *in vacuo* on a steam bath to a syrup. The syrup was triturated with cold water (30 ml.) and a solid material separated from solution. The solid was removed by filtration and crystallized from aqueous ethanol. The first crop of needles which had separated within 4 hours were collected by filtration. The crystalline solid was recrystallized again from aqueous ethanol as colorless bright needles and dried at 120° (*ca.* 0.2 mm) for 6 hours over phosphorus pentoxide (0.60 g., 20.3%), m.p. 236°. This material was established as a 2,5′-cyclonucleoside (**10**).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.07; H, 4.83; N, 11.30. Found: C, 58.11; H, 4.78; N, 11.31.

The mother liquor (aqueous ethanol) from the above cyclonucleoside (**10**) was concentrated on a hot plate (20 ml.) and then allowed to stand at 5-10° for 12 hours. The crystalline needles that formed were collected by filtration and recrystallized twice from water containing a few drops of ethanol to afford 2-chloro-1-(β-D-ribofuranosyl)benzimidazole (**4b**) as colorless needles (2.30 g., 65.7%). The crystalline material was dried at 120° (*ca.* 0.2 mm) over phosphorus pentoxide for 6 hours for analysis, m.p. 173°, $[\alpha]_D^{25}$ -94.6° (C=1, ethanol).

Anal. Calcd. for $C_{12}H_{13}ClN_2O_4 \cdot \frac{1}{2}H_2O$: C, 49.07; H, 4.76. N, 9.54; Cl, 12.10. Found: C, 49.36; H, 4.43; N, 9.46; Cl, 12.01.

1-(β-D-Ribofuranosyl)benzimidazole-2-thione (**6**).

Method A.

To a solution of 2-chloro-1-(β-D-ribofuranosyl)benzimidazole (**4b**, 1.0 g.) in anhydrous ethanol (25 ml.) was added 0.25 g. of thiourea. The mixture was heated at reflux temperature under anhydrous conditions for 1 hour and then allowed to stand at room temperature for 12 hours. A small amount of solid was removed by filtration, discarded and the filtrate evaporated *in vacuo* over a hot water bath to an oil. The oil was triturated with cold water (10 ml.) for one hour and the solid material which

had separated was collected by filtration and washed with cold water (2 x 5 ml.). The solid was recrystallized from aqueous ethanol as colorless needles (0.75 g., 78%). A small sample was recrystallized from aqueous ethanol for analysis, m.p. 120°; $[\alpha]_D^{25}$ -35.1° (C=1, ethanol).

Anal. Calcd. for $C_{12}H_{14}N_2SO_4$: C, 51.07; H, 4.96; N, 9.93; S, 11.34. Found: C, 51.04; H, 5.05; N, 9.93; S, 11.27.

Method B.

A mixture of dry benzimidazole-2-thione (3 g.), freshly distilled hexamethyldisilazane (4 g.) and a few crystals of ammonium sulfate was heated at reflux temperature with stirring and with the exclusion of moisture for 15 hours. The clear reaction mixture was fractionated by distillation to remove unreacted hexamethyldisilazane and to afford a glassy gum of disilylated benzimidazole-2-thione (**3**). The silylatedbenzimidazole-2-thione (**3**) (2.5 g.) was thoroughly mixed with 1-bromo-2,3,5-tri-*O*-acetyl-D-ribofuranose (**2**) (3.75 g.) and sodium iodide (0.050 g.). The mixture was then fused at 110° (oil bath temperature) with stirring for 45 minutes *in vacuo*. The reaction mixture which had been cooled to room temperature was dissolved in chloroform (200 ml.) and a small amount of insoluble material (0.2 g.) was removed by filtration and discarded. The chloroform solution was washed with cold saturated aqueous sodium bicarbonate solution (4 x 100 ml.) and cold water (4 x 100 ml.). The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo* to yield a syrup [1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzimidazole-2-thione (2.8 g.)]. The syrup was dissolved in methanolic ammonia (methanol saturated with ammonia at 0°, 125 ml.) and allowed to stand at room temperature for 24 hours. After the methanolic ammonia had been removed *in vacuo* at room temperature, a syrup remained which was triturated with cold water (50 ml.). The solid material which separated was collected by filtration and crystallized from aqueous ethanol to furnish **6** as needles (1.8 g., overall yield, 34%), m.p. 120°; $[\alpha]_D^{25}$ -35.4° (C = 1, ethanol).

Anal. Calcd. for $C_{12}H_{14}N_2SO_4$: C, 51.07; H, 4.96; N, 9.93; S, 11.34. Found: C, 51.12; H, 5.07; N, 9.84; S, 11.29.

2-Methylthio-1-(β-D-ribofuranosyl)benzimidazole (**8a**).

1-(β-D-Ribofuranosyl)benzimidazole-2-thione (**6**) (1.0 g.) was suspended in cold water (20 ml.) and concentrated ammonium hydroxide (4 ml.) was then added with stirring to effect a clear solution. To this solution was added methyl iodide (0.5 ml.) and the stirring continued at room temperature for two hours. The reaction mixture was allowed to stand at 5° for 8 hours and the crystalline material which had separated was collected by filtration and washed with cold water. The residue was dissolved in water, decolorized with charcoal and crystallized as needles, 0.9 g. (85.7%). A small sample was recrystallized from water for analysis, m.p. 99-100°, $[\alpha]_D^{25}$ -36.6° (C=1, ethanol).

Anal. Calcd. for $C_{13}H_{16}N_2SO_4$: C, 52.70; H, 5.40; N, 9.46; S, 10.81. Found: C, 52.57; H, 5.41; N, 9.52; S, 10.64.

1-(β-D-Ribofuranosyl)benzimidazole (**5**).

Method A.

2-Chloro-1-(β-D-ribofuranosyl)benzimidazole (**4b**)(0.8 g.) was dissolved in a solution of water (40 ml.) and concentrated ammonium hydroxide (2 ml.) containing a few drops of ethanol. To this solution was added 0.2 g. of palladium on carbon (10%) and the mixture hydrogenated at 40 psi at room temperature for 5 hours after which the catalyst was removed by a celite pad. The catalyst was then washed with hot water (5 x 2 ml.). The combined filtrate and washings were evaporated to dryness *in vacuo* over a hot water bath and the residual material crystallized from aqueous ethanol as needles, (0.5 g., 73.4%). A small sample was recrystallized from aqueous ethanol for analysis, m.p. 168°, $[\alpha]_D^{25}$ +16° (C=1, 0.1 *N* hydrochloric acid). [Lit. $[\alpha]_D^{29}$ +13° (0.1 *N* hydrochloric acid)].

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.60; H, 5.60; N, 11.20. Found: C, 57.60; H, 5.71; N, 11.07.

Method B.

2-Methylthio-1-(β-D-ribofuranosyl)benzimidazole (**8a**)(0.5 g.) was dissolved in absolute methanol (10 ml.). Raney nickel (1 g.) was added and the reaction mixture heated at reflux temperature for 1 hour with the exclusion of moisture. The Raney nickel was then removed by filtration and washed with boiling methanol (2 x 10 ml.). The combined filtrate and washings were evaporated to dryness *in vacuo* to afford a solid. The solid (0.25 g.) was found to possess an ultraviolet absorption spectra identical with that observed for **5** prepared by Method A, m.p. 168°. Mixed m.p. with **5** (method A) was 166-168°.

2-Benzylthio-1-(β-D-ribofuranosyl)benzimidazole (**8b**).

1-(β-D-Ribofuranosyl)benzimidazole-2-thione (**6**) (1.0 g.) was dissolved in cold water (10 ml.) containing concentrated ammonium hydroxide (2.5 ml.). To this solution was added benzyl chloride (1 ml.) with stirring and the stirring continued at room temperature for 5 hours. The white solid which had separated from solution was collected by filtration, washed thoroughly with cold water and dried *in vacuo* over phosphorus pentoxide. The dry residue was extracted with ethyl acetate (100 ml.) and the ethyl acetate washed with cold water (3 x 30 ml.). The ethyl acetate phase was dried over anhydrous magnesium sulfate and then evaporated *in vacuo* to a syrup which solidified after trituration with ligroin (60-90°). The residual solid was collected by filtration and recrystallized from an ethyl acetate-ligroin (60-90°) mixture as colorless needles, (0.9 g., 68.2%). A small sample was recrystallized from the same solvent mixture for analysis, m.p. 132°; $[\alpha]_D^{25}$ -102.9° (C=1, ethanol).

Anal. Calcd. for $C_{19}H_{20}N_2SO_4$: C, 61.30; H, 5.37; N, 7.52; S, 8.60. Found: C, 61.45; H, 5.46; H, 7.45; S, 8.42.

1-(β-D-Ribofuranosyl)benzimidazole-2-one (**9**).

1-(β-D-Ribofuranosyl)benzimidazole-2-thione (**6**) (1.0 g.) was dissolved in cold water (10 ml.) containing concentrated ammonium hydroxide (2.5 ml.). To this solution was added 30% aqueous hydrogen peroxide slowly (1.5 ml.) with stirring while maintaining the reaction temperature below 25° with an ice bath. The stirring was continued for 5 hours at room temperature and then evaporated to dryness *in vacuo*. The resulting residue was dissolved in absolute ethanol (50 ml.) and again evaporated to dryness *in vacuo*. The dry residue was slurried with absolute methanol (50 ml.) for one hour and the solid removed by filtration. The insoluble material (0.1 g.) was discarded and the filtrate evaporated to dryness *in vacuo* to a syrup. The syrup was dissolved in methanol, decolorized with charcoal and concentrated to 5 ml. Acetone (excess) was added and the solution allowed to stand at 5° for 12 hours. The needles which had separated were collected by filtration and dried *in vacuo* over phosphorus pentoxide, (0.4 g., 42.4%), m.p. 120° (foaming).

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.14; H, 5.26; N, 10.53. Found: C, 53.96; H, 5.52; N, 10.68.

2-Methoxy-1-(β-D-ribofuranosyl)benzimidazole (**7a**).

2-Chloro-1-(β-D-ribofuranosyl)benzimidazole (**4b**) (0.60 g.) was

dissolved in 0.5 *M* methanolic sodium methoxide (10 ml.) and the solution heated at reflux temperature for 2 hours under anhydrous conditions. The reaction mixture was allowed to stand at room temperature for 8 hours and the solid which had separated was collected by filtration. The *p*H of the filtrate was adjusted to 7 with 6 *N* hydrochloric acid and then evaporated to dryness *in vacuo* over a hot water bath. The resulting residue was extracted with acetone (30°, 50 ml.) and the acetone extract then evaporated to dryness *in vacuo*. The residual material was crystallized from acetone containing a few drops of water to afford needles (0.4 g., 71%). A small sample was recrystallized from the same solvent pair for analysis, m.p. 200°, $[\alpha]_D^{32}$ -56.8° (C=1, ethanol).

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.71; N, 10.00. Found: C, 55.56; H, 5.83; N, 9.94.

2-(*N*-Piperidino)-1-(β-D-ribofuranosyl)benzimidazole (**7b**).

2-Chloro-1-(β-D-ribofuranosyl)benzimidazole (**4b**) (0.6 g.) was dissolved in anhydrous ethanol (12 ml.) containing 0.35 g. of piperidine. The solution was heated at reflux temperature for 5 hours under anhydrous conditions and then allowed to stand for 12 hours at room temperature. The reaction mixture was evaporated to dryness *in vacuo* over a hot water bath to yield a semi-solid residue which was then dissolved in absolute ethanol (20 ml.) and again evaporated to dryness *in vacuo*. This procedure was repeated until the last traces of piperidine had been removed. The dry residue was triturated with acetone (75 ml.) and the suspended solid removed by filtration. The acetone filtrate was evaporated to dryness *in vacuo* and the residual material crystallized from aqueous ethanol as needles (0.35 g., 52.6%). A small sample was recrystallized from aqueous ethanol for analysis, m.p. 226°, $[\alpha]_D^{31}$ -26.1° (C=1, ethanol).

Anal. Calcd. for $C_{17}H_{23}N_3O_4$: C, 61.27; H, 6.90; N, 12.61. Found: C, 61.15; H, 6.96; N, 12.64.

2-(*N*-Morpholino)-1-(β-D-ribofuranosyl)benzimidazole (**7c**).

2-Chloro-1-(β-D-ribofuranosyl)benzimidazole (**4b**) (0.60 g.) was dissolved in absolute ethanol (12 ml.) containing 0.35 g. of morpholine. The solution was heated at reflux temperature for 16 hours under anhydrous conditions and then allowed to stand at room temperature for 18 hours. The reaction mixture was then evaporated to dryness *in vacuo* and the residual syrup dissolved in dry ethanol (25 ml.) and the evaporation procedure repeated until the last traces of morpholine had been removed. The dry syrup was triturated with acetone (10 ml.) and the solid which had separated was collected by filtration. The solid was dissolved in aqueous ethanol, decolorized with charcoal and crystallized as needles, (0.4 g., 59.7%). A small sample was recrystallized from aqueous ethanol for analysis, m.p. 230°, $[\alpha]_D^{29}$ -8.1° (C=1, ethanol).

Anal. Calcd. for $C_{16}H_{21}N_3O_5$: C, 57.32; H, 6.26; N, 12.54. Found: C, 57.24; H, 6.36; N, 12.50.

2-Amino-1-(β-D-ribofuranosyl)benzimidazole (**7d**).

2-Chloro-1-(β-D-ribofuranosyl)benzimidazole (**4b**) (2.0 g.) was dissolved in methanolic ammonia (200 ml., methanol saturated with ammonia at 0°) and the solution then heated in a steel reaction vessel at 165° for 10 hours. A small amount of insoluble material was removed by filtration and the filtrate evaporated *in vacuo* to a syrup. The residual syrup was dissolved in methanol (50 ml.), decolorized with charcoal and evaporated *in vacuo* to yield a foam. This foam was dissolved in water (10 ml.) and cooled to 5-10° for 24 hours. The light orange crystals which separated were collected by filtration and dried *in vacuo* over phosphorus pentoxide (1.0 g., 55.5%), m.p. decomposes above 120°.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.35; H, 5.65; N, 15.85. Found: C, 54.82; H, 5.91; N, 15.94.

2-Dimethylamino-1-(β-D-ribofuranosyl)benzimidazole (**7f**).

2-Chloro-1-(β-D-ribofuranosyl)benzimidazole (**4b**) (1.0 g.) was dissolved in absolute ethanol (20 ml.) containing 20 ml. of anhydrous dimethylamine. The mixture was heated in a steel reaction vessel at 100° for 5 hours. A small amount of insoluble material was then removed by filtration and the filtrate evaporated *in vacuo* to a syrup which was dissolved in absolute ethanol (25 ml.) and again evaporated *in vacuo*. This procedure was repeated until the syrup solidified and all the traces of dimethylamine had been removed. The crude product was dissolved in dry methanol (30 ml.), decolorized with charcoal, and concentrated to 5 ml. Acetone was added and the solution allowed to stand at 5° for 12 hours. The needles which had separated were collected by filtration, (0.60 g., 60%). A small sample was recrystallized from a mixture of methanol-acetone for analysis, m.p. 130° (dec.), $[\alpha]_D^{29}$ -44.1 (C=1 methanol).

Anal. Calcd. for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.48; N, 14.33. Found: C, 57.68; H, 6.83; N, 14.57.

2-Methylamino-1-(β-D-ribofuranosyl)benzimidazole (**7e**).

2-Chloro-1-(β-D-ribofuranosyl)benzimidazole (**4b**) (1.0 g.) was dissolved in 40% aqueous methylamine solution (30 ml.) and heated at reflux temperature for 3 hours. The solution was evaporated *in vacuo* on a steam bath to a syrup. The syrup was dissolved in absolute ethanol (25 ml.) and again evaporated to dryness *in vacuo*. This process was repeated three times to remove the last traces of methylamine. The resulting residue was dissolved in dry methanol (50 ml.), decolorized with charcoal and again evaporated *in vacuo* to yield a foam. The dry foam was then triturated with 25 ml. of ligroin (60-90°) for 2 hours, the solid removed by filtration and washed thoroughly with ligroin. The product was then dried at 80° over phosphorus pentoxide for 10 hours, (0.5 g., 49.5%), m.p. 130-132°.

Anal. Calcd. for $C_{13}H_{17}N_3O_4 \cdot H_2O$: C, 52.52; H, 6.40; N, 14.14. Found: C, 53.00; H, 6.69; N, 13.94.

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