Synthesis of Ribonucleosides of 4(5)-Cyano-5(4)-Methylimidazole and Related 4-Substituted-5-Methylimidazole Ribosides

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4-Cyano-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-methylimidazole (**4**) and its corresponding 5-cyano-4-methyl substituted isomer (**5**) have been obtained by ribosylation of 4(5)-cyano-5(4)-methylimidazole (**3**) *via* the mercuric cyanide method or by ribosylation of the trimethylsilyl derivative of **3**. Treatment of **4** with methanolic ammonia, ammonium chloride in liquid ammonia and potassium hydrosulfide provided 4-cyano-1-β-D-ribofuranosyl-5-methylimidazole (**6**), 1-β-D-ribofuranosyl-5-methylimidazole-4-carboxamide (**2**) and 1-β-D-ribofuranosyl-5-methylimidazole-4-thiocarboxamide (**11**) respectively. Reaction of **6** with hydroxylamine afforded the corresponding 4-carboxamidoxime substituted nucleoside (**13**) which on catalytic reduction in the presence of ammonium chloride, was transformed into 1-β-D-ribofuranosyl-5-methylimidazole-4-carboxamidine (**14**) as hydrochloride salt.

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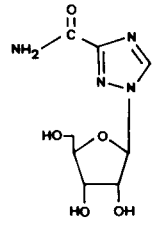
A large number of nucleosides of five-membered heterocycles have been synthesized and tested as antivirals because of the success of the nucleoside 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (Ribavirin, **1**) as a broad spectrum antiviral agent [1,2]. In previous papers, we have described the synthesis and antiviral evaluation of various nucleosides of 2- or 5-methylimidazole-4-carboxamide [3,4], among which the 5-methyl substituted riboside **2** showed a significant *in vitro* antiviral activity against type 1 herpes simplex virus [4]. This result and the fact that substitution of the carboxamide group of Ribavirin by thiocarboxamide or carboxamidine functions gave compounds that, although less active than Ribavirin, proved to possess antiviral activity [5], focused our attention on the glycosylation of 4(5)-cyano-5(4)-methylimidazole (**3**) to obtain 4-cyano-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-methylimidazole (**4**) as a common intermediate for the preparation of the thiocarboxamide and carboxamidine analogs of **2**.



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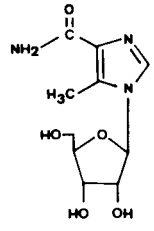

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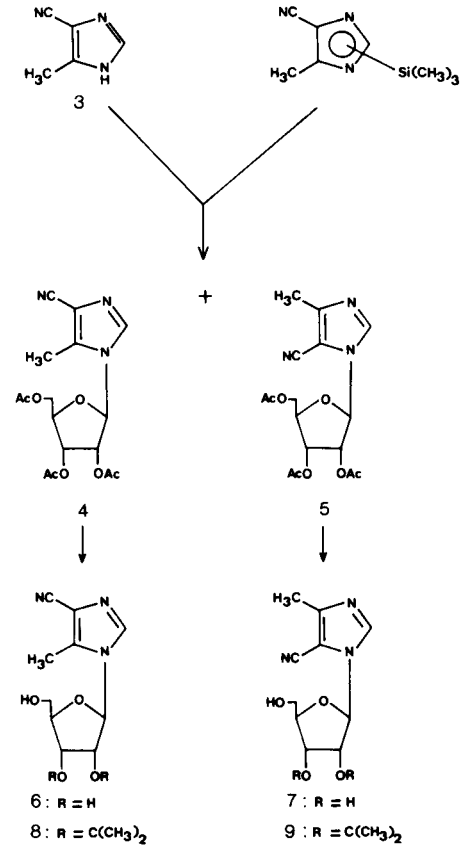
Two different glycosylation procedures were performed in order to obtain the desired 4-cyano-5-methyl substituted nucleoside **4** in the most favourable yield (Scheme I). The first was ribosylation of **3**, obtained by dehydration of 4(5)-methylimidazole-5(4)-carboxamide [6], with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride *via* mercuric cyanide method. This procedure provided compound **4** and its corresponding positional isomer, namely 5-cyano-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-4-methylimidazole (**5**) in 63 and 11% yield respectively. The second approach, which gave **4** and **5** in 16 and 38% yield respectively, was the

SCHEME I



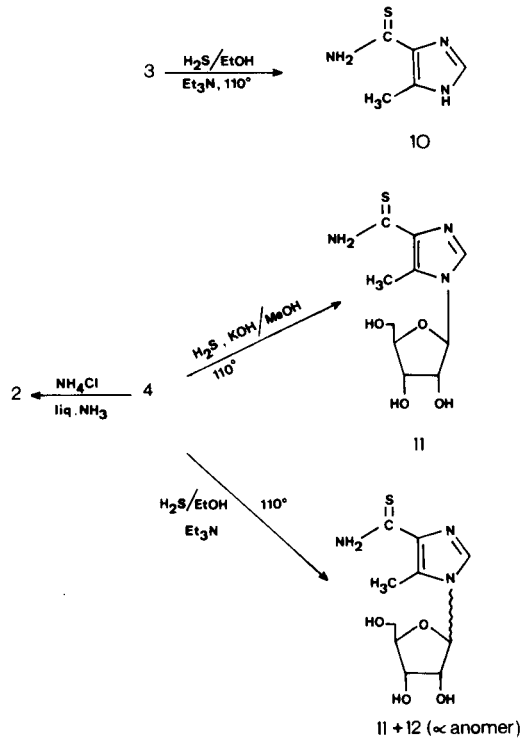
treatment of the trimethylsilyl derivative of **3** with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in 1,2-dichloroethane and in the presence of stannic chloride. The ribosylation site of the positional isomers **4** and **5** was initially established by comparison of their ^{1}H-nmr spectra with each other, on the basis of the signal for the methyl group which, in the case of the 5-methyl substituted derivative **4**, appeared at lower field than that of the 4-methyl derivative **5**, as consequence of the deshielding effect of the adjacent glycosyl moiety [7] (Table 1). The anomeric configuration of these nucleosides could not be unequivocally established by ^{1}H-nmr, since the coupling constant values $J_{1'2'}$ were not less than 1Hz. However, they were temptatively assigned as β on the basis of the mechanism for the glycosylation by the mercuric cyanide procedure [8]. The ribosylation site of **4** and **5** was confirmed by the ^{13}C-nmr data of the resulting deblocked nucleosides, namely 4-cyano-1-β-D-ribofuranosyl-5-methylimidazole (**6**) and 5-cyano-1-β-D-ribofuranosyl-4-methylimidazole (**7**), obtained by deacetylation of **4** and **5** with methanolic ammonia. Table 2 shows the ^{13}C chemical shifts of the anion of the base **3** and of its ribosides **6** and **7**. Assignments of the ^{13}C chemical shifts of the base anion **3** were based on general rules of ^{13}C-nmr [9,10] and on the comparison with related imidazole anions [4]. Assignments of the carbon atoms in ribosides **6** and **7** were based on the theoretical ^{13}C-shieldings reported in parentheses in Table 2 which were calculated using a substitution shift parameter of 7 ppm upfield for the carbons in α position to the substituted nitrogen and a downfield shift of 2 ppm for the carbons in β position [11]. The anomeric configuration of **4** or **6** and **5** or **7** was unequivocally ascertained by conversion to the corresponding 2′, 3′-*O*-isopropylidene derivatives **8** and **9**, whose ^{1}H-nmr spectra showed, in each case, a difference of chemical shift for the isopropylidene methyl groups of 0.24 ppm, only consistent with a β configuration [12].

Table 1

^{1}H-NMR Data of Imidazole Nucleosides at 90 MHz with TMS as Internal Standard

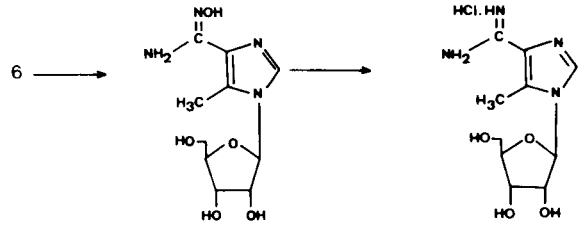
No	Solvent	Chemical Shifts (δ) H-2	H-1′	CH_3	Others	$J_{1',2'}$ (Hz)
4	$CDCl_3$	7.68	5.72	2.42		5.5
5	$CDCl_3$	7.73	5.82	2.36		5.5
6	DMSO	8.05	5.53	2.35		6.0
7	DMSO	8.23	5.60	2.27		6.0
8	$CDCl_3$	7.95	5.65	2.43	1,36 and 1.60 [$C(CH_3)_2$]	3.0
9	$CDCl_3$	7.83	5.75	2.31	1.33 and 1.57 [$C(CH_3)_2$]	3.0
11	DMSO	7.93	5.52	2.72	9.07 ($CSNH_2$)	5.5
12	DMSO	7.75	5.85	2.75	9.07 ($CSNH_2$)	4.0
13	DMSO	7.90	5.50	2.40	9.24 (NOH), 5.45 (NH_2)	6.0
14	DMSO	8.26	5.63	2.50	7.30-9.20 (NH_2-C=NH.HCl)	5.0

SCHEME II



Various reaction conditions were attempted to prepare the thiocarboxamide analogs of compounds **3**, **6** and **7**. In any case, no reaction occurred when the base **3** or the nucleosides **4** and **5** were treated with hydrogen sulfide in ethanol in the presence of triethylamine at room or refluxing temperature. However 4(5)-methylimidazole-5(4)-thiocarboxamide (**10**) was obtained in 56% yield from **3**, when the reaction was achieved in a pressure bottle at 110°. Treatment of the 4-cyano substituted imidazole nucleoside **4** with an excess of hydrogen sulfide and potassium hydroxide in methanol at 110-120° provided 1-β-D-ribofuranosyl-5-methylimidazole-4-thiocarboxamide (**11**) in 75% yield (Scheme II). The structure of **11** was evident from its elemental analysis and its ir (absence of C≡N band), uv and ^{1}H-nmr spectra. The anomeric configuration was initially assigned as β taking account that no anomerization has been described for similar transformations of cyanoimidazole nucleosides into the thiocarboxamide analogs under the same reaction conditions [14]. This assignment was evidenced from comparison of the ^{1}H-nmr spectrum of **11** with that of the mixture of **11** and its corresponding α anomer **12**, since the anomeric proton of **11** appeared at higher field than that of **12** (Table 1) [13]. This anomeric mixture of 4-thiocarboxamide substituted nucleosides was obtained when the cyanoimidazole **4** was treated with hydrogen sulfide in ethanol in the presence of triethylamine in a pressure bottle at 110° (Scheme II).

SCHEME III



13 14

Treatment of the 5-cyano substituted nucleoside **5** under the same conditions to those used for the preparation of **10** or **11** did not provide the corresponding 5-thiocarboxamide substituted analog. A similar difference in the reactivity of isomeric ribofuranosides of methyl 4(5)-cyanomethylimidazole-5(4)-carboxylate or 4(5)-cyano-5(4)-cyanomethylimidazole toward ammonolysis or cyclization has been previously noted [15,16].

Although the most possible anhydrous conditions were tried, all attempts to obtain 1-β-D-ribofuranosyl-5-methylimidazole-4-carboxamidine (**14**) by heating the 4-cyano derivative **4** with an excess of liquid ammonia and 1 molar equivalent of ammonium chloride [5] led exclusively to the 4-carboxamide substituted nucleoside **2**. However, compound **14** was obtained following a similar route to that described for the synthesis of 1-β-D-ribofuranosylimidazole-4-carboxamidine hydrohalide from the corresponding 5-haloimidazole-4-carboxamidoxime ribonucleoside [14]. Thus, reaction of the deblocked cyano derivative **6** with hydroxylamine in boiling ethanol provided 1-β-D-ribofuranosyl-5-methylimidazole-4-carboxamidoxime (**13**), which on hydrogenation under pressure in the presence of Raney nickel catalyst and 1 molar equivalent of ammonium chloride afforded the 4-carboxamidine ribonucleoside **14** as hydrochloride. Structural assignments of compounds **13** and **14** were made on the basis of their analytical and ^{1}H-nmr spectral data (Table 1). The antiviral activity of the 4-thiocarboxamide and 4-carboxamidine substituted nucleosides is under study.

Table 2

^{13}C Chemical Shifts (ppm) of the Base Anion **3** and its Nucleosides **6** and **7** at 300 MHz in DMSO with TMS as Internal Reference

No	C-2	C-4	C-5	CN	CH_3
3	142.65	107.41	145.95	119.32	12.22
6	136.99	111.04	138.36	115.42	9.17
	(135.65)	(109.41)	(138.95)		
7	139.62	100.21	150.70	111.67	13.32
	(135.65)	(100.41)	(147.95)		

Values in parentheses are theoretical chemical shifts using α-and β-substitution of +7 and −2 ppm respectively.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ^{1}H-nmr spectra were recorded at 90 MHz on a Varian EM-390 spectrometer using TMS as internal standard. The ^{13}C-nmr spectra were recorded at 300 MHz on a Varian XL-300 spectrometer using TMS as internal reference. The anion of the imidazole **3** was formed by neutralization with lithium hydroxide in DMSO-d_6. The uv and ir spectra were taken with a Perkin-Elmer 402 and 257 spectrophotometers respectively. Analytical tlc was performed on aluminium sheets coated with a 0.2 mm layer of silica gel $60F_{254}$ (Merck) and preparative tlc on 20 x 20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} (Merck). Silica gel PF_{254} (Merck) was also used for column chromatography. The compounds were detected with uv light of 254 nm or by spraying with sulfuric acid in ethanol 30%.

4(5)-Cyano-5(4)-methylimidazole (**3**).

A mixture of 10 g (80 mmoles) of 4(5)-methylimidazole-5(4)-carboxamide [6] and 175 ml of phosphoryl chloride was refluxed with stirring for 3 hours. After this time the solvent was removed under reduced pressure to leave a residue which was triturated with hot methylene chloride (5 x 100 ml). The resultant solid residue was dissolved in 100 ml of water, and then was neutralized to *p*H 7 with concentrated ammonium hydroxide, maintaining the temperature at 0°. The mixture was kept at 4-5° for 18 hours, the precipitate was collected by filtration, dissolved in methanol and then placed on a silica gel column. Elution with methanol and removal of the solvent left a solid which was recrystallized from isopropyl alcohol, to yield 7.80 g (91%) of **3**, mp 144-145°; ir (nujol): 2250 cm^{-1} (C≡N); ^{1}H-nmr (deuteriodimethylsulphoxide): δ 7.62 (s, 1, H-2), 2.32 (s, 3, CH_3).

Anal. Calcd. for $C_5H_5N_3$: C, 56.07; H, 4.67; N, 39.25. Found: C, 55.84; H, 4.92; N, 38.97.

4-Cyano-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-methylimidazole (**4**) and 5-cyano-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-4-methylimidazole (**5**).

To a mixture of 4.41 g (15 mmoles) of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride, 2.5 g (10 mmoles) of mercuric cyanide and molecular sieve in 150 ml of dry nitromethane, was added 1.07 g (10 mmoles) of **3**. The mixture was refluxed for 4 hours. After this, it was filtered while still hot and washed with more hot nitromethane. The filtrate was evaporated to dryness *in vacuo* and the residue was dissolved in chloroform and washed with 30% of aqueous potassium iodide, water, and then dried over sodium sulfate. The residue obtained after removing the solvent was chromatographed on a silica gel column with ethyl acetate-chloroform-hexane (2:1:1). The fractions containing the first isomer off the column were collected and evaporated to leave a form which was crystallized from ethyl acetate-hexane to give 2.3 g (63%) of a white solid which was identified as **4**, mp 104-105°; ir (nujol): 2250 cm^{-1} (C≡N); uv (ethanol): λ max 223 nm (ε 6600).

Anal. Calcd. for $C_{16}H_{19}N_3O_7$: C, 52.60; H, 5.20; N, 11.51. Found: C, 52.65; H, 5.45; N, 11.27.

Further elution of the column with ethyl acetate-chloroform-hexane (2:1:1) provided 0.41 g (11%) of **5** as a foam which could not be crystallized, ir (nujol): 2250 cm^{-1} (C≡N); uv (ethanol): λ max 230 nm (ε 4500).

Anal. Calcd. for $C_{16}H_{19}N_3O_7$: C, 52.60; H, 5.20; N, 11.51. Found: C, 52.93; H, 5.45; N, 11.23.

Method B.

A mixture of 1.07 g (10 mmoles) of compound **3**, 50 ml of hexamethyldisilazane and 1 ml of trimethylchlorosilane was refluxed under anhydrous conditions for 2 hours. The excess hexamethyldisilazane was removed under reduced pressure providing the trimethylsilyl derivative as a brown solid which was dissolved in 50 ml of 1,2-dichloroethane. To this solution were added 3.20 g (10 mmoles) of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose and 1.54 ml (13.2 mmoles) of stannic chloride. The reaction mixture was stirred at room temperature for 16-20 hours and then poured slowly into 150 ml of a 5% sodium hydrogen carbonate solution.

The mixture was filtered through Celite, extracted with chloroform (3 x 100 ml), and the combined organic extracts were dried over sodium sulfate and evaporated to dryness to leave a syrup. Column chromatography as described above provided **4** and **5** in 16 and 38% yield respectively.

4-Cyano-1-β-D-ribofuranosyl-5-methylimidazole (**6**).

A solution of 1.1 g (3 mmoles) of **4** in 100 ml of saturated methanolic ammonia was allowed to stand at room temperature overnight. The solution was evaporated to dryness to leave a residue, which was chromatographed on a silica gel column eluting with chloroform-methanol (9:1) and then rechromatographed by preparative tlc using chloroform-methanol (5:1). Elution of the major band afforded 0.71 g (99%) of **6** as a syrup; ir (nujol) 2250 cm^{-1} (C≡N).

Anal. Calcd. for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.44; N, 17.57. Found: C, 50.02; H, 5.57; N, 17.36.

5-Cyano-1-β-D-ribofuranosyl-4-methylimidazole (**7**).

A solution of 1.1 g (3 mmoles) of **5** in 100 ml of saturated methanolic ammonia was allowed to stand at room temperature overnight. The solution was evaporated to dryness to leave a residue which was chromatographed on a silica gel column with chloroform-methanol (9:1) to give 0.70 g (98%) of **7** as a syrup; ir (nujol): 2250 cm^{-1} (C≡N).

Anal. Calcd. for $C_{10}H_{13}N_3O_4 \cdot H_2O$: C, 46.69; H, 5.84; N, 16.34. Found: C, 46.70; H, 6.05; N, 16.39.

4-Cyano-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-methylimidazole (**8**).

To a stirred suspension of 0.22 g (0.9 mmole) of **6** and 0.10 g (0.6 mmole) of *p*-toluenesulfonic acid in 25 ml of dry acetone was added 0.6 ml (3.8 mmoles) of triethyl orthoformate. The reaction mixture was stirred at room temperature for 4 hours, and then the solution was adjusted to *p*H 7 with concentrated ammonium hydroxide. The solvent was removed under reduced pressure to leave a residue which was chromatographed by preparative tlc using chloroform-methanol (9:1). Elution of the major band afforded 0.19 g (76%) of **8** as a white solid with mp 107-108° (from carbon tetrachloride).

Anal. Calcd. for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.09; N, 15.05. Found: C, 55.62; H, 5.98; N, 15.03.

5-Cyano-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4-methylimidazole (**9**).

To a stirred suspension of 0.24 g (1 mmole) of **7** and 0.11 g (0.7 mmole) of *p*-toluenesulfonic acid in 25 ml of dry acetone was added 0.63 ml (4 mmoles) of triethyl orthoformate. The reaction mixture was stirred at room temperature for 6 hours, and then neutralized with concentrated ammonium hydroxide. Removal of the solvent left a residue which was chromatographed by preparative tlc using chloroform-methanol (9:1). Elution of the major band afforded 0.18 g (65%) of **9** as a solid which was recrystallized from ethyl acetate-hexane, mp 124°.

Anal. Calcd. for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.09; N, 15.05. Found: C, 55.64; H, 6.12; N, 15.20.

4(5)-Methylimidazole-5(4)-thiocarboxamide (**10**).

A solution of 2.14 g (20 mmoles) of **3** and 2.75 ml (20 mmoles) of triethylamine in 50 ml of ethanol was saturated at 0° with hydrogen sulfide gas. The solution was stored in a stainless steel reaction vessel at 110-120° for 24 hours. On cooling, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure to leave a solid residue which was recrystallized from water to give 1.55 g (56%) of **10**, mp 154-155°; ^{1}H-nmr (deuteriodimethylsulphoxide): δ 7.55 (s, 1, H-2), 2.62 (s, 3, CH_3).

Anal. Calcd. for $C_5H_7N_3S \cdot \frac{1}{2} H_2O$: C, 40.00; H, 5.33; N, 28.00; S, 21.33. Found: C, 40.01; H, 5.45; N, 27.72; S, 21.26.

1-β-D-Ribofuranosyl-5-methylimidazole-4-thiocarboxamide (**11**).

A solution of 0.51 g (1.4 mmoles) of **4** and 0.2 g of potassium hydroxide in 25 ml of methanol was saturated at 0° with hydrogen sulfide. The reaction mixture was heated at 110° in a stainless steel bomb for 6 hours. On cooling, the solvent was removed under reduced pressure to leave a yellow foam which was dissolved in 4 ml of water. The solution was adjusted to *p*H 6 by adding dropwise an 1 *N* solution of hydrochloric acid, maintaining the mixture at 0° with an ice bath. The precipitate which was formed after ½ hour was collected by filtration and recrystallized from methanol to yield 0.29 g (75%) of **11** with mp 172-173°; uv (water): λ max 266 nm (ε 1900), 303 (2050).

Anal. Calcd. for $C_{10}H_{15}N_3O_4S$: C, 43.96; H, 5.49; N, 15.38; S, 11.72. Found: C, 44.10; H, 5.37; N, 15.69; S, 12.02.

When compound **4** was treated with hydrogen sulfide under identical conditions to that described for the synthesis of **10**, a mixture of **11** and its corresponding α anomer **12** was obtained in 32% yield (1:1 ratio). This mixture, which was not separated, was identified by ^{1}H-nmr.

1-β-D-Ribofuranosyl-5-methylimidazole-4-carboxamide (**2**).

A mixture of 1.1 g (3 mmoles) of **4**, 0.16 g (3 mmoles) of ammonium chloride and 15 ml of liquid ammonia was heated in a stainless steel bomb at 110-120° for 24 hours. After removal of the ammonia, the residue was crystallized from methanol to provide 0.75 g (97%) of compound **2**, identical in all respects to that previously described [4].

1-β-D-Ribofuranosyl-5-methylimidazole-4-carboxamidoxime (**13**).

A mixture of 0.4 g (1.67 mmoles) of **6**, 15 ml of absolute ethanol, 0.25 g (3.6 mmoles) of hydroxylamine hydrochloride and 0.5 ml (3.6 mmoles) of triethylamine was refluxed for 3 hours. The solution was concentrated and the crystalline product which appeared was filtered off and washed with cold ethanol. The solid was chromatographed on a silica gel column with chloroform-methanol (2:1). Evaporation of the solvent left a white solid which was recrystallized from methanol to provide 0.32 g (70%) of **13**, mp 174-175° dec; uv (water): λ max 227 nm (ε 4200).

Anal. Calcd. for $C_{10}H_{16}N_4O_5$: C, 44.12; H, 5.88; N, 20.59. Found: C, 44.36; H, 5.91; N, 20.31.

1-β-D-Ribofuranosyl-5-methylimidazole-4-carboxamidine Hydrochloride (**14**).

A solution of 0.25 g (0.92 mmole) of **13** and 0.05 g (0.93 mmole) of ammonium chloride in 15 ml of water was hydrogenated on a Parr apparatus in the presence of 0.3 g of wet Raney nickel at room temperature and 45 psi for 2 hours. The insoluble material was discarded by filtration. Solvent from the filtrate was evaporated and the residue was crystallized from absolute ethanol to provide 0.19 g (70%) of **14**, mp 173-175° dec; uv (water): λ max 250 nm (ε 2900).

Anal. Calcd. for $C_{10}H_{16}N_4O_4 \cdot HCl$: C, 41.02; H, 5.81; N, 19.14; Cl, 12.13. Found: C, 40.85; H, 6.07; N, 18.93; Cl, 12.01.

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