Syntheses of 5-Amino-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridin-7-one (1-Deazaguanosine) and Related Nucleosides (1)

*Barry L. Cline, Raymond P. Panzica, and Leroy B. Townsend**

Division of Medicinal Chemistry, Department of Biopharmaceutical Sciences, Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

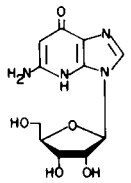
Received January 19, 1978

The synthesis of 5-amino-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridin-7-one (1-deazaguanosine) has been accomplished by three different methods. The 6-thioguanosine analog 5-amino-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridin-7-thione (1-deaza-6-thioguanosine) has been prepared *in situ* by a reduction of the corresponding disulfide. The synthesis of various nucleoside precursors of the above compounds by several condensation procedures are described. The procedures used to unequivocally determine the site of ribosylation and anomeric configuration are also discussed.

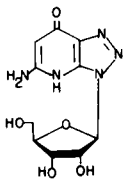
J. Heterocyclic Chem., 15, 839 (1978)

In view of the biological activity demonstrated by guanosine analogs of such divergent structures as 6-thioguanosine (2), 8-azaguanosine (3) and 3-deazaguanosine (4-7), we initiated several routes for the synthesis of 1-deazaguanosine analogs which lack the N1 nitrogen of the puring ring. An important aspect of the Watson-Crick DNA model is the hydrogen bonding requirement for base pairs. Purines, in particular guanines, which lack the N1 nitrogen eliminates one center where hydrogen bonding does occur. Thus, incorporation of 1-deazaguanosines into DNA could disrupt the delicate balance of the double helix and impair the template activity (of DNA) in the synthesis of proteins.

The culmination of our synthetic investigations was the syntheses of 1-deazaguanosine (**1**) (7,8) and 1-deaza-8-azaguanosine (**2**) (9). Our preliminary communication (8) on the synthesis of **1**, described the preparation of this unique analog from **6a**. We now wish to report the synthesis of **1** by yet another route, as well as the syntheses of certain related imidazo[4,5-*b*]pyridine nucleosides and heterocycles.



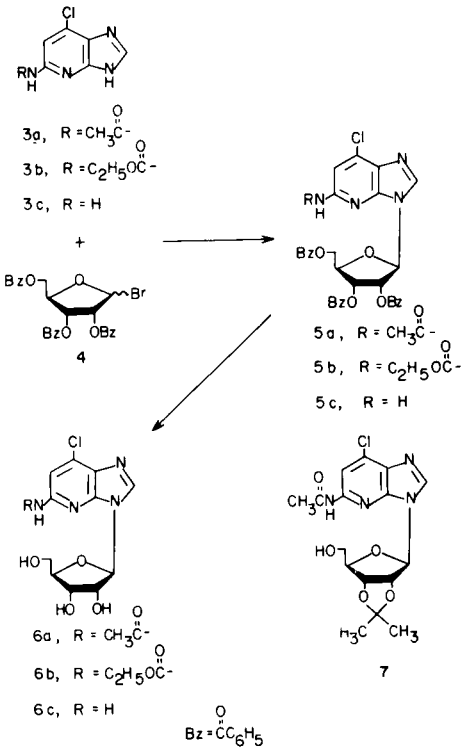
1



2

Our initial route for the synthesis of **1** involved the ribosylation of 5-acetamido-7-chloroimidazo[4,5-*b*]pyridine (**3a**) (10). Condensation of the silyl derivative of **3a** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**4**) was accomplished using a modification (11) of the mercuric cyanide glycosylation procedure (12). A solution of the silyl derivative of **3a** in benzene containing mercuric cyanide was heated to boiling, a benzene solution of **4** was then added and the mixture was heated at reflux for one hour. A work-up of the reaction mixture furnished a 65% yield of crystalline 5-acetamido-7-chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**5a**). Column chromatography of the filtrate afforded an additional quantity of **5a**. This material was combined with the first crop and recrystallization furnished **5a** in an overall 80% yield. The *O*-benzoyl protecting groups of **5a** were quantitatively removed by treatment with sodium methoxide in a mixture of methanol and tetrahydrofuran at room temperature to provide 5-acetamido-7-chloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**6a**). To confirm our assignment of the anomeric configuration as β

REACTION SCHEME I



for these nucleosides, the 2′,3′-*O*-isopropylidene derivative (**7**) of **6a** was synthesized. The doublet for the anomeric proton in the pmr spectrum of **6a** exhibited a coupling constant of 5.7 Hz which decreased to 2.3 Hz in the spec-

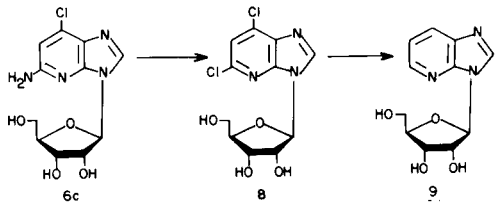
trum of the 2′,3′-*O*-isopropylidene derivative **7**. This spectral feature is generally regarded as reasonable proof for the β configuration (13). Additional evidence for the β configuration was furnished by other pmr spectral data of **7**. The observed difference in the chemical shifts ($\Delta\delta$) of the isopropylidene methyl groups was δ 0.23 which was consistent with the criteria established for β-D-ribofuranosyl nucleosides (14).

The success of the reaction conditions leading to nucleoside **6a** prompted us to apply the same conditions to the ribosylation of ethyl 7-chloroimidazo[4,5-*b*]pyridine-5-carbamate (**3b**) (27). Condensation of the silyl derivative of **3b** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**4**) was accomplished using exactly the same conditions as described above except that the silyl derivative of **3b** was formed using *N,O-bis*-silylacetamide rather than hexamethyldisilizane. The nucleoside product ethyl 7-chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]-pyridine-5-carbamate (**5b**), was obtained as a pure, crystalline solid in 80% yield. As with **5a**, the benzoyl blocking groups of nucleoside **5b** were removed by treatment with sodium methoxide in methanol and tetrahydrofuran to give ethyl 7-chloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]-pyridine-5-carbamate (**6b**, 87%).

The ribosylation of 5-amino-7-chloroimidazo[4,5-*b*]-pyridine (**3c**) *via* the catalyzed fusion procedure had been previously explored (15). The product of this reaction was suggested to be 7-chloro-3-(β-D-ribofuranosyl)-5-ribosylaminoimidazo[4,5-*b*]pyridine, however, neither the structure, site of ribosylation, nor the anomeric configuration were rigorously established. It was of interest to us to see how **3c** would fare under the aforementioned ribosylation conditions. Condensation of the silyl derivative of **3c** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide was accomplished as described for **5a** and **5b** to give a single, major nucleoside product (tlc). Attempts to obtain this nucleoside as a crystalline solid directly from the reaction mixture met with failure. Column chromatography of the reaction mixture gave the major product as a chromatographically pure foam, but again, the compound resisted crystallization. Treatment of the product with 10% methanolic ammonia in a closed reaction vessel for 24 hours afforded pure, crystalline 5-amino-7-chloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**6c**, 75% overall yield). This nucleoside could also be obtained by either treating **6a** or **6b** with a *N* ethanolic potassium hydroxide solution at reflux.

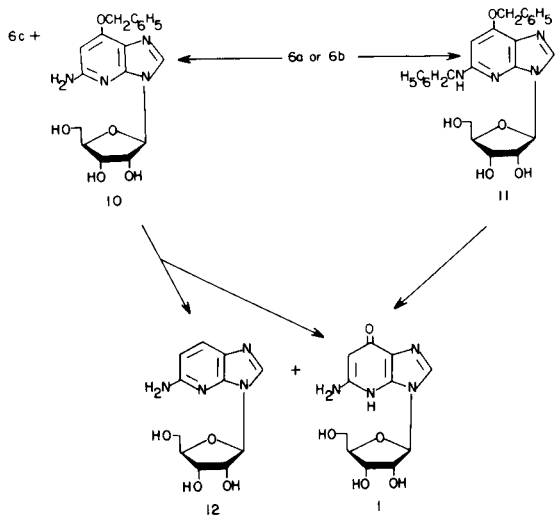
Using **6c**, an unequivocal proof of structure, *i.e.*, site of ribosylation and anomeric configuration, for those nucleosides derived from **5a-c** was accomplished by converting **6c** into 3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**9**), a nucleoside whose structure has been rigorously established (16). The synthetic sequence involved diazotization of **6c** in the presence of cuprous chloride and hydrochloric acid to afford 5,7-dichloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**8**). This nucleoside was then dehalogenated in a hydrogen atmosphere using 5% palladium on charcoal to give **9** whose physicochemical data were identical to that reported (16) for 3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine. Thus, this two-step chemical sequence established the site of ribosylation for **5a-c** as N3 and reaffirmed our earlier assignment of configuration as β.

REACTION SCHEME 2



Having established the site of ribosylation and anomeric configuration of our nucleoside precursors, we focused our attention on the preparation of 1-deazaguanosine [5-amino-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridin-7-one, **1**]. Reaction of either **6a** or **6b** with ten equivalents of sodium benzylate in benzyl alcohol at 110° for 5 hours gave what appeared on tlc to be a single, major nucleoside. A pmr spectrum of this nucleoside, however, indicated that it was a mixture (1/1) of the hydrolysis product 5-amino-7-chloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**6c**) and the desired nucleoside 5-amino-7-benzyloxy-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**10**). The two nucleosides exhibited identical tlc mobility in four different solvent systems, thus preventing an easy separation of the two nucleosides by column chromatography. Instead, this mixture was hydrogenated (palladium/carbon) to afford 1-deazaguanosine (**1**) and 5-amino-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**12**). These two nucleo-

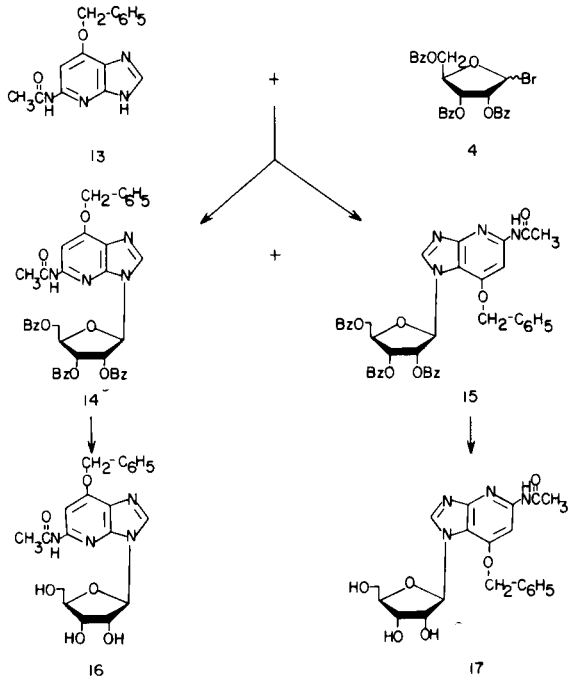
REACTION SCHEME 3



sides were then easily separated by column chromatography to provide 1-deazaguanosine (**1**) in a 30% overall yield. The second nucleoside (**12**) was obtained in low yield and was extremely hygroscopic. Isolation of **12** as a solid could only be accomplished by lyophilization.

In the reactions of **6a** or **6b** with sodium benzylate we found that when either reaction was allowed to run for extended periods, another product appeared in the reaction mixture, as determined by tlc. When the reaction was carried out at 120° for 48 hours, column chromatography of the reaction mixture afforded 5-benzylamino-

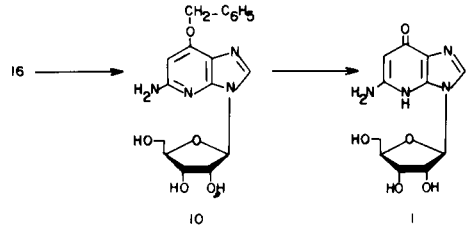
REACTION SCHEME 4



7-benzyloxy-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**11**) in 40% yield. While this product was unexpected, *N*-benzylation under these conditions has been previously observed and, in fact, has been used preparatively for the benzylation of 2-aminopyridines and 2-aminopyrimidines (17). *N*-Benzylation was also observed when 2-amino-6-chloropurine was reacted with sodium benzylate under conditions similar to those described above (18). Hydrogenolysis of nucleoside **11** gave 1-deazaguanosine (**1**) in 83% yield.

While the synthetic route to 1-deazaguanosine described above gave the desired final product and provided an unequivocal proof of its structure, the yields of **1** were too low to provide a sufficient quantity for biological testing. This prompted us to investigate a second synthetic route. The silyl derivative of 5-acetamido-7-benzyloxyimidazo[4,5-*b*]pyridine (10) (**13**) was condensed with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**4**) in refluxing toluene containing mercuric cyanide. This reaction afforded two nucleosides, 5-acetamido-7-benzyloxy-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**14**, 77%) and 5-acetamido-7-benzyloxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**15**, 1.3%; as its hydrobromide salt). Initial exploratory reactions indicated that when benzene was replaced with toluene, as solvent, the formation of the minor nucleoside decreased. Both **14** and **15** were deblocked by treatment with sodium methoxide in a mixture of methanol and tetrahydrofuran to give 5-acetamido-7-benzyloxy-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**16**) and 5-acetamido-7-benzyloxy-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**17**), respectively. The *N*-acetyl group of compound **16** was removed by hydrolysis with 1 *N* potassium hydroxide in ethanol at reflux to afford 5-amino-7-benzyloxy-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**10**, 83%). Hydrogenolysis of the benzyloxy group of **10** furnished 1-deazaguanosine (**1**, 95%) (19) which was identical to **1** synthesized from **6a** or **6b**. The successful conversion of **16** to **1** also indicated that nucleoside **14**, the

REACTION SCHEME 5



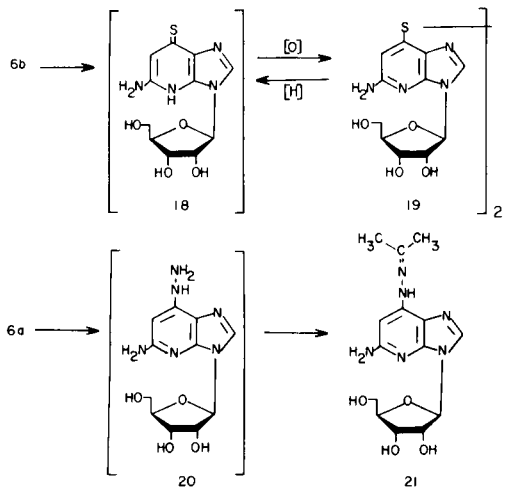
major isomer in this route, was β and N3. Assignment of the minor nucleoside **15** as the N1 isomer was based on a carbon-13 nuclear magnetic resonance spectral analysis (21). The anomeric configuration of **15** was assumed to be β, based on the fact that formation of α-anomers usually do not occur with the method of ribosylation employed.

The low yield of the nucleoside intermediate **10** from the chloro-substituted nucleoside **6a** and **6b** using sodium benzylate in benzyl alcohol illustrates the difficulty in effecting nucleophilic displacements on the C7 position in protic solvents. The hydrolysis of the acylamido group occurred at a rate comparable to the displacement reaction even in a relatively nonpolar solvent (benzyl alcohol). This loss of the electron-withdrawing effect of the acylamido group significantly deactivated the ring toward nucleophilic displacement. Understandably, attempts to react **6a** or **6b** with sodium hydrosulfide or sodium azide in such polar, protic solvents as methanol, ethanol or propanol provided only **6c**. A certain degree of success was achieved, however, when **6b** was reacted with anhydrous sodium hydrosulfide in dimethylformamide. Reaction of **6b** with a ten-fold excess of anhydrous sodium hydrosulfide in dimethylformamide at 85° for 48 hours gave a complex mixture (tlc). The three major products

were isolated and identified and shown to be **6c**, the desired 1-deaza-6-thioguanosine (**18**), and the disulfide **19**. Isolation of **18** was difficult because it readily formed the disulfide **19**. When **18** was allowed to stand at room temperature in dimethylsulfoxide (22), it was completely converted to **19**. By treating the crude reaction mixture with dimethylsulfoxide and then using column chromatography, the disulfide could be isolated in 30% yield. Oxidation of **18** to **19** served a unique role. It provided a means of separating 1-deaza-6-thioguanosine from **6c** since these two nucleosides had similar mobilities in the solvent system required for separation, *i.e.*, Rf 0.28 (**18**) and 0.30 (**6c**) in ethyl acetate-ethanol; 9:1, v/v, from **19**. 1-Deaza-6-thioguanosine (**18**) could then be regenerated from **19** by reduction with either an equivalent of dithiothreitol (23), sodium dithionite (24a), or a large excess of 2-mercaptoethanol (24a). Repeated attempts to isolate pure **18** failed as the product was always contaminated with **19**. The susceptibility of aromatic thiols to autooxidation is well documented (24b) and has been observed for some 6-thiopurine compounds and their nucleoside derivatives (24,25). The higher electron density in the pyridine ring of **18** apparently makes this nucleoside even more susceptible to oxidation than the analogous purine compounds.

The strong nucleophilicity of hydrazine overcame the low reactivity of compound **6a** since the reaction of **6a** with 85% hydrazine hydrate at reflux gave 5-amino-7-

REACTION SCHEME 6



hydrazino-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**20**). This product proved to be very hygroscopic and was converted to the crystalline isopropylidinehydrazino derivative **21** by reaction of **20** in acetone at reflux (72% yield).

EXPERIMENTAL

Proton magnetic resonance (pmr) spectra were obtained with Varian A56/60 and Varian XL-100/15 spectrometers (solution in dimethylsulfoxide-d_6 or dimethylformamide-d_7) with chemical shift values reported in δ, parts per million, relative to the internal standard (sodium 2,2-dimethyl-2-silapentane-5-sulfonate or tetramethylsilane). Ultraviolet spectra were recorded on a Beckman Acta CIII spectrophotometer. Infrared spectra were recorded on a Beckman IR8 spectrophotometer. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Garden City, Michigan. The presence of water as indicated by elemental analyses was verified by pmr. Mass spectra were recorded on a LKB 9000S spectrometer; electron impact, ionizing voltage 70 ev, filament current 60 μa; direct insertion probe. The trimethylsilyl derivatives of all mass spectra samples were prepared by the procedure of McCloskey, *et al.*, (26). Thin-layer chromatography was run on glass plates coated (0.25 mm) with silica gel (SilicAR 7GF, Mallinckrodt) unless otherwise stated. Compounds of interest were detected by either ultraviolet lamp (mineralight, 254 nm) or treatment with sulfuric acid followed by heating. Open-bed column chromatography was carried out on SilicAR CC7 (Mallinckrodt) using gravity flow. The columns were dry-packed and pre-equilibrated with the elution solvent. Where noted, low-pressure column chromatography was performed using Altex columns dry-packed with Silica 60 (EM Laboratories) adsorbent. Elution solvent was delivered by a FMC fluid metering pump equipped with low-volume fittings. The sample solution was introduced to the column through a three-way valve in-line between the solvent reservoir and the pump. All solvent proportions are given by volume. Evaporations were performed under reduced pressure (*in vacuo*) at 40° with a rotary evaporator unless otherwise stated. All compounds were dried under reduced pressure over phosphorous pentoxide at room temperature for 12 hours unless otherwise noted.

5-Acetamido-7-chloroimidazo[4,5-*b*]pyridine (**3a**).

A stirred slurry of 5-amino-7-chloroimidazo[4,5-*b*] pyridine (15 g., 80.4 mmoles, prepared by hydrolysis of **3b** (27) as described in reference 28) in acetic anhydride (450 ml.) was heated to boiling and two drops of 85% phosphoric acid were added. The mixture was heated at reflux for 1 hour and then evaporated to dryness *in vacuo* at 70°. The residual solid was triturated with ice water (400 ml.), collected by filtration, washed with water (200 ml.) and then ethyl ether (100 ml.) and air-dried. The solid was dissolved in a mixture of methanol (800 ml.) and concentrated ammonium hydroxide (90 ml.) and the solution stirred at room temperature for 30 minutes. The solution was evaporated to dryness *in vacuo* and the residual solid was recrystallized from methanol/water (1/1) to afford **3a** (16 g., 87%), m.p. 256-257° (monohydrate) [lit. (10) 269-270° (anhydrous)]; uv (λ max in nm, ε x 10^{-3}) (*p*H 1): 298 (15.4), sh 255 (6.3), 248 (8.4), (*p*H 11): 301 (13.8); pmr (DMSO-d_6): δ 10.63 (broad singlet, 1, 5-NH), 8.45 (s, 1, H2), 8.21 (s, 1, H6), 2.21 (s, 3, CH_3) [lit. (10) pmr (DMSO-d_6): δ 10.70 (broad singlet, 5-NH), 8.51 (s, 1, H2), 8.28 (s, 1, H6) 2.21 (s, 3, CH_3)]

Anal. Calcd. for $C_8H_7ClN_4O \cdot H_2O$: C, 42.02; H, 3.97; N, 24.50. Found: C, 42.10; H, 4.11; N, 24.80.

5-Acetamido-7-chloro-3-(2,3,5,-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazo[4,5-*b*]pyridine (**5a**).

A suspension of 5-acetamido-7-chloroimidazo[4,5-*b*]pyridine (**3a**, 10 g., 43.7 mmole) in hexamethyldisilizane (100 ml.) containing a catalytic amount of ammonium sulfate was stirred and heated at reflux for 12 hours. The solution was evaporated *in vacuo* at 80° and the residual foam was dissolved in dry benzene (200 ml.). Mercuric cyanide (22 g., 87.4 mmoles) was added and the mechanically stirred mixture was heated to boiling. A solution

of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**4**, prepared from 25.5 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose) in dry benzene (50 ml.) was added and the mixture was heated at reflux for 1 hour. Methanol (50 ml.) was added and the mixture was evaporated *in vacuo*. The residual syrup was dissolved in chloroform (250 ml.) and the insoluble material was removed by filtration. The chloroform solution was washed with 30% potassium iodide solution (3 x 100 ml.) and the organic phase was dried over anhydrous sodium sulfate. The solution was concentrated *in vacuo* to 100 ml., hexane was added to the cloud point and the mixture was allowed to stand at 5° for 12 hours. The crystalline precipitate was collected by filtration, washed with hexane-ethyl acetate (1/1) and air-dried (18.6 g.). The filtrate was evaporated *in vacuo*, dissolved in hexane-ethyl acetate (50 ml., 1/1) and the sample solution applied to an open-bed silica gel column (2.4 x 95 cm). The column was eluted with hexane/ethyl acetate (2/1) and the combined fractions containing the desired product (tlc: Rf 0.39, hexane/ethyl acetate, 1/1) were evaporated to dryness *in vacuo* to afford an additional 4.5 g. of **5a**. Recrystallization of the combined product from methanol gave 22.9 g. (80%) of 5-acetamido-7-chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**5a**), m.p. 204-205°.

Anal. Calcd. for $C_{34}H_{27}ClN_4O_8$: C, 62.34; H, 4.16; N, 8.55. Found: C, 62.44; H, 4.38; N, 8.53.

5-Acetamido-7-chloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**6a**).

A solution of sodium methoxide (1.7 g., 30.5 mmoles) in methanol (200 ml.) was added to a solution of **5a** (20 g., 30.5 mmoles) in tetrahydrofuran (100 ml.). The solution was stirred at room temperature for 1 hour and then neutralized (*p*H 6) with Amberlite IRC-50 (H^+) resin (30 g.). The resin was removed by filtration and the filtrate was evaporated to a foam. The residual foam was triturated with ethyl ether (3 x 50 ml.) and the resulting solid was recrystallized from ethanol-water (1/1) to provide **6a** (10.9 g. 99%) (monohydrate), m.p. 240-242°; uv (λ max in nm, ε x 10^{-3}) (*p*H 1): 299 (18.9), sh 257 (10.5), 253 (11.1); (*p*H 11): 297 (17.3), 264 (10.4), 257 (10.7); pmr (DMSO-d_6): δ 10.70 (broad singlet, 1, 5-NH), 8.64 (s, 1, H2), 8.15 (s, 1, H6), 6.07 (d, 1, H1′, $J_{1',2'}$ = 5.7 Hz), 2.20 (s, 3, CH_3).

Anal. Calcd. for $C_{13}H_{15}ClN_4O_5 \cdot H_2O$: C, 43.28; H, 4.75; N, 15.53. Found: C, 43.19; H, 4.95; N, 15.76.

5-Acetamido-7-chloro-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-imidazo[4,5-*b*]pyridine (**7**).

A mixture of dry acetone (20 ml.), acetone dimethyl acetal (0.57 ml.) and 70% perchloric acid (0.76 ml.) was stirred at room temperature for 5 minutes and a solution of **5a** (0.5 g., 1.5 mmoles) in acetone (10 ml.) was then added. The solution was stirred at room temperature for 1.5 hours. A mixture of concentrated ammonium hydroxide (5 ml.) in water (20 ml.) was added to the reaction mixture and the solution was concentrated *in vacuo* to 30 ml. The mixture was allowed to stand at 5° for 12 hours. The crystalline precipitate was collected by filtration, washed with water (20 ml.) and dried to afford **7** (0.31 g., 52%), m.p. 129-131°; pmr (DMSO-d_6): δ 10.62 (broad singlet, 1, 5-NH), 8.67 (s, 1, H2), 8.25 (s, 1, H6), 6.27 (d, 1, H1′, $J_{1',2'}$ = 2.5 Hz), 3.33 (s, 3, H_2O), 2.20 (s, 3, acetyl CH_3), 1.59 and 1.39 (2s, 6, isopropylidene methyls, Δδ = 0.20).

Anal. Calcd. for $C_{16}H_{19}ClN_4O_5 \cdot 1\frac{1}{2}H_2O$: C, 46.89; H, 5.41; N, 13.67. Found: C, 46.67; H, 5.61; N, 13.71.

Ethyl 7-Chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo-[4,5-*b*]pyridine-5-carbamate (**5b**).

A mixture of **3b** (2.0 g., 8 mmoles) and *N,O-bis*-silylacetamide (6 ml.) in methylene chloride (100 ml.) was stirred at room temperature until complete solution occurred (≃ 6 hours). The solution was evaporated *in vacuo* and the residual foam dissolved in dry benzene (100 ml.). Mercuric cyanide (4.0 g.) was added and the mixture was stirred and heated to boiling. A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**4**, prepared from 4.4 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose) in benzene (25 ml.) was added and the mixture was heated at reflux for 1 hour. Methanol (10 ml.) was added and the mixture was evaporated *in vacuo*. The residual syrup was dissolved in chloroform (100 ml.) and the insoluble material was removed by filtration. The filtrate was washed with 30% potassium iodide solution (3 x 50 ml.) and water (3 x 50 ml.) and the organic phase was dried over anhydrous sodium sulfate. Hexane was added to the cloud point and the mixture was allowed to stand at 5° for 12 hours. The white, crystalline precipitate was collected by filtration, washed with hexane-ethyl-acetate (1/1) and air-dried (3.8 g.). The filtrate was evaporated *in vacuo* and the residual syrup was dissolved in hexane (50 ml., 1/1). This solution was applied to an open-bed column (3.5 x 25 cm) and the column was eluted with hexane/ethyl acetate (1/1). The fractions containing the desired product (tlc; Rf 0.29, hexane-ethyl acetate, 2/1) were evaporated *in vacuo* to give an additional 1.1 g. of product. Recrystallization from ethanol afforded 4.4 g. (80%) of pure **5b**, m.p. 169-170°.

Anal. Calcd. for $C_{35}H_{29}ClN_4O_9$: C, 62.83; H, 4.37; N, 8.37. Found: C, 62.91; H, 4.54; N, 8.59.

Ethyl 7-Chloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine-5-carbamate (**6b**).

A solution of sodium methoxide (252 mg., 4.7 mmoles) in methanol (60 ml.) was added to a solution of **5b** (3.2 g., 4.7 mmoles) in tetrahydrofuran (20 ml.). This solution was heated to 40° and then allowed to stir at ambient temperature for 1 hour. The solution was neutralized (*p*H 6) with Amberlite IRC-50 (H^+) resin (5 g.), the resin was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was triturated with ethyl ether (3 x 30 ml.) and the resulting solid was recrystallized from water to furnish **6b** (1.5 g., 97%), m.p. 128-129°; uv (λ max in nm, ε x 10^{-3}) (*p*H 1): 301 (16.8), sh 259 (7.1), 250 (9.9), sh 245 (9.5); (*p*H 11): 299 (15.8), 260 (9.2), 253 (9.9), sh 247 (8.2); pmr (DMSO-d_6): δ 10.37 (s, 1, 5-NH), 8.63 (s, 1, H2), 7.92 (s, 1, H6), 6.02 (d, 1, H1′, $J_{1',2'}$ = 6 Hz), 3.40 (s, 1 1/3, H_2O) 1.33 (t, 3, CH_2CH_3).

Anal. Calcd. for $C_{14}H_{17}ClN_4O_6 \cdot 1\ 1/3\ H_2O$: C, 42.38; H, 4,96; N, 14.12. Found: C, 42.36; H, 5.10; N, 14.18.

5-Amino-7-chloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**6c**).

Method A.

A suspension of 5-acetamido-7-chloro-3-(β-D-ribofuranosyl)-imidazo[4,5-*b*]pyridine (**6a**, 1.0 g., 2.8 mmoles) in a 1 *N* solution of potassium hydroxide in ethanol (100 ml.) was stirred and heated at reflux for 1 hour. The cooled solution was neutralized (*p*H 6, paper) with Amberlite IRC-50 (H^+) resin (3 g.) and the resin was removed by filtration. The solution was evaporated *in vacuo* and the solid residue was recrystallized from water to give 0.75 g. (90%) of **6c**, m.p. 175-177°; uv (ε max in nm, x 10^{-9}) (*p*H 1): 319 (11.0), 240 (5.6); (*p*H 11) 311 (11.3), 255 (6.4), 250 (6.5); pmr (DMSO-d_6): δ 8.28 (s, 1, H2), 6.60 (s, 1, H6), 6.21 (broad singlet, 2, NH_2), 5.93 (d, 1, H1′, $J_{1',2'}$ = 6.1 Hz).

Anal. Calcd. for $C_{11}H_{13}ClN_4O_4$: C, 43.93; H, 4.36; N, 18.63. Found: C, 43.99; H, 4.33; N, 18.39.

Method B.

Ethyl 7-Chloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine-5-carbamate (**6b**, 1.0 g., 2.5 mmoles) was treated in a similar fashion to that described in Method A above to give 0.71 g. (94%) of a product with identical melting point, uv, pmr and elemental analysis as that obtained in Method A.

Method C.

A suspension of 5-amino-7-chloroimidazo[4,5-*b*]pyridine (**3c**, 1.4 g., 7.5 mmoles) in hexamethyldisilizane (25 ml.) containing a catalytic amount of ammonium sulfate was stirred and heated at reflux for 12 hours. The solution was evaporated *in vacuo* at 70° and the residual foam was dissolved in dry benzene (100 ml.). Mercuric cyanide (3.8 g., 15 mmoles) was added and the stirred mixture was heated to boiling. A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**4**, prepared from 4.4 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose) in benzene (25 ml.) was added and the mixture was heated at reflux for 1 hour. Methanol (10 ml.) was added and the mixture was evaporated *in vacuo*. The residual syrup was dissolved in chloroform (150 ml.) and the insoluble material was removed by filtration. The filtrate was washed with a 30% potassium iodide solution (3 x 25 ml.) and water (3 x 25 ml.) and the organic phase was dried over anhydrous sodium sulfate. The solution was concentrated *in vacuo* to 30 ml. and applied to an open-bed silica gel column (3 x 60 cm). The column was eluted with hexane-ethyl acetate (3/2) and the fractions containing the desired product (tlc: Rf 0.21, hexane-ethyl acetate, 3/2) were combined and evaporated to dryness *in vacuo*. The residue was dissolved in 10% methanolic ammonia (50 ml.) and stirred at room temperature in a closed reaction vessel for 24 hours. The solution was evaporated *in vacuo* and the residue recrystallized from water to give 1.7 g. (75% overall yield) of a product identical with that obtained in Methods A and B, as shown by tlc, uv, pmr, elemental analysis and melting point.

5,7-Dichloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**8**).

A stirred solution of **6c** (0.46 g., 1.5 mmoles) in concentrated hydrochloric acid (15 ml.) was cooled to -10° and finely ground, solid sodium nitrite (211 mg., 3.1 mmoles) was added in portions over a 5 minute period. The solution was stirred at -10° for 30 minutes, cuprous chloride (145 mg., 1.5 mmoles) was added and the solution was allowed to stir at 0° for 2 hours. Ice (25 g.) was added and the solution was kept at -10° for 5 hours. The precipitate was collected by filtration, washed with cold water (20 ml.) and dried *in vacuo* over potassium hydroxide. The solid was recrystallized from water to provide **8** (0.24 g., 50%), m.p. 155-156°; uv, (λ max in nm, ε x 10^{-3}) (*p*H 1): 287 (9.0), 254 (6.0); (*p*H 11): 289 (8.9), 259 (5.9), sh 254 (5,8); pmr (DMSO-d_6): δ 8.95 (s, 1, H2), 7.76 (s, 1, H6), 6.11 (d, 1, H1′ $J_{1',2'}$ = 5.1 Hz).

Anal. Calcd. for $C_{11}H_{11}Cl_2N_3O_4$: C, 41.27; H, 3.46; N, 13.13. Found: C, 41.18; H, 3.65; N, 13.10.

3-(β-D-Ribofuranosyl)imidazo[4,5-*b*]pyridine (**9**).

To a solution of **8** (150 mg., 0.47 mmole) in ethanol-water (40 ml., 2/1) was added 10% palladium/charcoal (50 mg.). The mixture was shaken on a Parr apparatus in a hydrogen atmosphere (42 psi) for 2 hours. The mixture was filtered through a Celite bed, the bed was washed with hot ethanol (25 ml.), and the filtrate was evaporated to dryness *in vacuo*. Recrystallization of the solid from water afforded 110 mg. (93%) of **9**, m.p. 222-224° [lit. (16) 220-222°]; uv (λ max in nm, ε x 10^{-3}) (*p*H 1): 283 (8.5), 277 (9.9), 237 (5.3); (*p*H 11): 288 (6.6), 282 (8.3), 279 (8.0), 244 (5.6).

Anal. Calcd. for $C_{11}H_{13}N_3O_4$: C, 52.60; H, 5.22; N, 16.73. Found: C, 52.53; H, 5.43; N, 16.98.

5-Benzylamino-7-benzyloxy-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]-pyridine (**11**).

A suspension of **6a** (0.5 g., 1.4 mmoles) in dry benzyl alcohol (150 ml.) containing sodium benzylate (1.8 g., 14 mmoles) prepared by the reaction of sodium with benzyl alcohol) was heated in a 120° oil bath for 48 hours. The solvent was evaporated *in vacuo* at 80° and the residual syrup was dissolved in ethanol (200 ml.). The solution was neutralized (*p*H 6) with Amberlite IRC-50 (H^+) resin (10 g.) and the resin was removed by filtration. The solution was evaporated to dryness *in vacuo* and the solid residue was dissolved in ethyl acetate-ethanol (100 ml., 1/1). The sample solution was applied to an open-bed silica gel column (3 x 90 cm) and the column was eluted with ethyl acetate-ethanol (9/1). The fractions containing the desired product (tlc; Rf 0.65, ethyl acetate-ethanol, 9/1) were combined and evaporated to dryness *in vacuo*. Recrystallization from water afforded 260 mg. (40%) of **11**, m.p. 146-149° (hemihydrate); uv (λ max in nm, ε x 10^{-3}) (*p*H 1): 309 (14.1), sh 250 (11.2); (*p*H 11) 300 (12.8), 260 (11.5), 255 (11.6); pmr (DMSO-d_6): δ 8.21 (s, 1, H2), 7.60 (broad singlet, 5, 7-$CH_2C_6H_5$), 7.50 (broad singlet, 5, 5-$CH_2C_6H_5$), 6.28 (s, 1, H_6), 6.03 (d, 1, H1′ $J_{1',2'}$ = 2.5 Hz), 5.50 (s, 2, 7-$CH_2C_6H_5$), 4.63 (s, 2, 5-$CH_2C_6H_5$).

Anal. Calcd. for $C_{25}H_{26}N_4O_5 \cdot \frac{1}{2}H_2O$: C, 63.68; H, 5.77; N, 11.88. Found: C, 63.31; H, 5.98; N, 11.69.

5-Acetamido-7-benzyloxy-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazo[4,5-*b*]pyridine (**14**) and 5-Acetamido-7-benzyloxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**15**).

5-Acetamido-7-benzyloxyimidazo[4,5-*b*]pyridine (10) (**13**, 3.0 g., 10.6 mmoles) and *N,O-bis*-silylacetamide (10 ml.) in dry toluene (300 ml.) was stirred at room temperature until complete solution had occurred (1 hour). Mercuric cyanide (5.4 g.) was added and the mechanically stirred mixture was heated to boiling. A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**4**, prepared from 5.9 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose) in toluene (50 ml.) was added and the mixture was heated at reflux for 30 minutes. Methanol (50 ml.) was added and the mixture was evaporated *in vacuo*. The residual syrup was dissolved in chloroform (250 ml.) and the insoluble material was removed by filtration. The filtrate was washed with 30% potassium iodide solution (3 x 100 ml.) and water (3 x 100 ml.) and the organic phase was dried over anhydrous sodium sulfate. The solution was evaporated *in vacuo*. The residual syrup was dissolved in boiling ethanol (400 ml.) and allowed to stand at room temperature for 12 hours. The white, crystalline precipitate was collected by filtration, washed with ethanol (50 ml.) and dried to give 3.5 g. of the 3-isomer (**14**). The filtrate was evaporated *in vacuo* and the residue was dissolved in a mixture of hexane-ethyl acetate (100 ml., 1/1). This solution was applied to an open-bed silica gel column (3.5 x 25 cm) and the column was eluted with hexane-ethyl acetate (1/1). The fractions containing the major nucleoside product **14** (tlc; Rf 0.49, hexane-ethyl acetate, 1/1; Rf 0.92, ethyl acetate) were combined and evaporated *in vacuo*. The combined product was recrystallized from ethanol to give a total yield of 5.9 g. (77%) of 5-acetamido-7-benzyloxy-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**14**), m.p. 177-178°.

Anal. Calcd. for $C_{41}H_{34}N_4O_9$: C, 67.76; H, 4.72; N, 7.71. Found: C, 67.71; H, 4.72; N, 7.70.

The column was then eluted with ethyl acetate and the fractions containing a second nucleoside product (tlc; Rf 0.03, hexane-ethyl acetate, 1/1; Rf 0.40, ethyl acetate) were combined and evaporated to dryness *in vacuo*. Recrystallization from ethanol

afforded 100 mg. (1.2%) of 5-acetamido-7-benzyloxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**15**, hydrobromide salt), m.p. 205-207°.

Anal. Calcd. for $C_{41}H_{34}N_4O_9 \cdot HBr$: C, 61.04; H, 4.50; N, 6.95. Found: C, 60.95; H, 4.77; N, 7.22.

5-Acetamido-7-benzyloxy-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]-pyridine (**16**).

A solution of sodium methoxide (372 mg., 6.9 mmoles) in methanol (200 ml.) was added to a solution of **14** (5.0 g., 6.9 mmoles) in tetrahydrofuran (50 ml.). The solution was stirred at room temperature for 1 hour and then neutralized (*p*H 6) with Amberlite IRC-50(H^+) resin (7 g.). The resin was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The resulting foam was dissolved in hot water (150 ml.) and the aqueous solution was extracted with ethyl acetate (15 x 100 ml.). The combined ethyl acetate extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to 50 ml. The solution was allowed to stand at 5° for 12 hours. The precipitate was collected by filtration, washed with ethyl acetate (20 ml.) and dried to furnish **16** (2.6 g., 90%), m.p. 155-157°; uv: (λ max in nm, ε x 10^{-3}) (*p*H 1): 284 (17.2), 263 (13.8); (*p*H 11): 282 (15.5), 265 (15.5); pmr; (DMSO-d_6): δ 10.50 (broad singlet, 1, 5-NH), 8.50 (s, 1, H2), 7.87 (s, 1, H6), 7.48 (multiplet, 5, C_6H_5), 6.08 (d, 1, H1' $J_{1',2'}$ = 5.5 Hz), 5.52 (s, 2, CH_2), 2.15 (s, 3, CH_3).

Anal. Calcd. for $C_{20}H_{22}N_4O_6$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.77; H, 5.41; N, 13.51.

5-Acetamido-7-benzyloxy-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]-pyridine (**17**).

A solution of sodium methoxide (10 mg.) in methanol (25 ml.) was added to a solution of **15** (100 mg., 0.14 mmole) in tetrahydrofuran (5 ml.). The solution was stirred at room temperature for 1 hour. The solution was neutralized (*p*H 6) with Amberlite IRC-50(H^+) resin (10 mg.), the resin was removed by filtration and the filtrate was evaporated *in vacuo*. The residual foam was triturated with ethyl ether (3 x 20 ml.) and the resulting solid was recrystallized from ethyl acetate-ethanol (4/1) to afford 50 mg. (88%) of **17**, m.p. 214-216°; uv: (λ max in nm, ε x 10^{-3}) (*p*H 1): sh 301 (5.3), 289 (7.6), 263 (5.5); (*p*H 11), 284 (6.1), 253 (5.8).

Anal. Calcd. for $C_{20}H_{22}N_4O_6$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.88; H, 5.30; N, 13.44.

5-Amino-7-benzyloxy-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**10**).

A suspension of **16** (2.0 g., 4.8 mmoles) in ethanolic potassium hydroxide (1 *N*, 200 ml.) was stirred and heated at reflux for 3 hours. The cooled solution was neutralized (*p*H 6) with Amberlite IRC-50(H^+) resin (10 g.), the resin was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The solid residue was recrystallized from water-ethanol (9/1) to furnish 1.6 g. of **10** (monohydrate), m.p. 120-125° (with loss of water). The product was dried in an Abderhalden apparatus over toluene at reflux *in vacuo* for 6 hours to give 1.5 g. (83%) of anhydrous **10**, m.p. 194-195° [lit. (20) 203°]; uv (λ max in nm, ε x 10^{-3}), (*p*H 1): 298 (12.5), 246 (9.3); (*p*H 11): 288 (10.3), 250 (9.0); pmr (DMSO-d_6): δ 8.09 (s, 1, Hz), 7.51 (multiplet, 5, C_6H_5), 5.89 (s, 2, NH_2), 6.17 (s, 1, H6), 5.90 (d, 1, H1', $J_{1',2'}$ = 3.0 Hz), 5.40 (s, 2, CH_2).

Anal. Calcd. for $C_{18}H_{20}N_4O_5$: C, 58.06; H, 5.41; N, 15.05. Found: C, 58.09; H, 5.44; N, 15.09.

5-Amino-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridin-7-one (1-Deazaguanosine, **1**).

Method A.

A solution of 5-benzylamino-7-benzyloxy-3-(β-D-ribofuranosyl)-imidazo[4,5-*b*]pyridine (**11**, 200 mg., 0.42 mmole) in ethanol-water (50 ml., 1/1) containing 10% palladium/charcoal (200 mg.) and a drop of concentrated hydrochloric acid was stirred at room temperature in a hydrogen atmosphere (atmospheric pressure) for 4 days. The mixture was filtered through a Celite bed. The filtrate was concentrated *in vacuo* to 10 ml. and allowed to stand at 5° for 12 hours. The precipitate was collected by filtration washed with water (10 ml.) and dried to give 114 mg. (85%) of **1** as a dihydrate, m.p. 137-138°.

Anal. Calcd. for $C_{11}H_{14}N_4O_5 \cdot 2H_2O$: C, 41.51; H, 5.70; N, 17.60. Found: C, 41.37; H, 5.67; N, 17.46.

The dihydrate was dried in an Abderhalden apparatus *in vacuo* over refluxing toluene for 24 hours to give 198 mg. of anhydrous **1**, m.p. 148-150° (hygroscopic) [lit. (20) 152°]; uv (λ max in nm, ε x 10^{-3}) (*p*H 1): 297 (13.5), 250 (7.1), 244 (7.4); (*p*H 11): sh 272 (13.8), 264 (16.4); pmr (DMSO-d_6): δ 8.02 (s, 1, H2), 5.86 (s, 1, H6), 5.80 (d, 1, H1' $J_{1',2'}$ = 3.5 Hz), 5.86 (broad singlet, 2, NH_2).

Method B.

Ethyl 7-chloro-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine-5-carbamate (**6**), 1.0 g., 2.5 mmoles) was added to a solution of sodium benzylate in benzyl alcohol [prepared by the reaction of sodium metal (0.6 g., 26 mmoles) with freshly distilled benzyl alcohol (50 ml.) in a nitrogen atmosphere]. The stirred reaction mixture was heated in a 110° oil bath for 5 hours in a nitrogen atmosphere. The solvent was removed *in vacuo* at 80° and the residual syrup was dissolved in ethanol (100 ml.). The insoluble salts were removed by filtration and the filtrate was neutralized (*p*H 6) with Amberlite IRC-50(H^+) resin (2 g.). The resin was removed by filtration and the filtrate was evaporated *in vacuo*. The residual syrup was dissolved in ethyl acetate (50 ml.) and the solution was applied to an open-bed silica gel column (4 x 20 cm). The column was eluted with ethyl acetate (300 ml.) and then a mixture of ethyl acetate-ethanol (9/1). The fractions containing the desired material (tlc: Rf 0.30, ethyl acetate-ethanol, 9/1) were combined and evaporated to dryness *in vacuo* to afford 0.60 g. of a 1/1 mixture of 5-amino-7-chloro-3-(β-D-ribofuranosyl)imidazo-[4,5-*b*]pyridine (**6c**) and 5-amino-7-benzyloxy-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**10**), as determined by pmr. The mixture was dissolved in ethanol (150 ml.) and 5% palladium/charcoal (0.5 g.) was added. The mixture was shaken on a Parr apparatus in a hydrogen atmosphere (42 psi) for 3 hours. The mixture was filtered through a Celite bed and the bed was washed with a boiling mixture of ethanol and water (50 ml., 1/1). The filtrate was evaporated to dryness *in vacuo*. The solid residue was dissolved in ethyl acetate-ethanol (50 ml., 1/1) and the solution was introduced onto a low-pressure column apparatus (2.5 x 95 cm column). The column was eluted with ethyl acetate-ethanol (9/1) at a flow rate of 10 ml./min. The fractions containing 1-deazaguanosine (**1**) (tlc; Rf 0.46, ethyl acetate-ethanol, 4/1) were combined and evaporated to dryness. Recrystallization of the residual solid from water afforded 1-deazaguanosine (**1**, dihydrate) in 30% overall yield (based on **6c**). The melting point, pmr, uv and elemental analysis of this product were identical to that of the product of Method A.

The fractions containing the second product, 5-amino-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**12**), (tlc; Rf 0.29, ethyl acetate-ethanol, 4/1) were combined and evaporated to dryness to furnish a hygroscopic solid. The semisolid was dissolved in water and lyophilized to give 60 mg. of **12**, m.p. loss of water above 90°, melts 130-135° (hygroscopic); uv (λ max in nm)

(*p*H 1): 317, 240; (*p*H 11): 309, 247; pmr (DMSO-d_6): δ 8.23 (s, 1, H2), 7.72 (d, 1, H7, $J_{6,7}$ = 7.3 Hz), 6.54 (d, 1, H6, $J_{6,7}$ = 7.3 Hz), 5.94 (d, 1, H1′, $J_{1',2'}$ = 3.5 Hz); ms: m/e 555 (M^+ + H, $C_{11}H_{11}N_4O_4 \cdot 4((CH_3)_3Si)$.

Method C.

5-Amino-7-benzyloxy-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (**10**, 1.25 g., 3.4 mmoles) was dissolved in a mixture of ethanol and water (200 ml., 1/1) and 5% palladium/charcoal (0.5 g.) was added. The mixture was shaken on a Parr apparatus in a hydrogen atmosphere (42 psi) for 3 hours. The mixture was filtered through a Celite bed and the bed was washed with hot ethanol-water (300 ml., 1/1). The filtrate was concentrated *in vacuo* to 50 ml. and the solution was allowed to stand at 5° for 12 hours. The precipitate was collected by filtration, washed with water (50 ml.) and dried to provide **1** (1.0 g., 95%) as a dihydrate. The melting point, pmr, uv and elemental analysis of this product were identical to the data obtained for **1** from Methods A and B.

Bis(5-amino-3-β-D-ribofuranosylimidazo[4,5-*b*]pyrid-7-yl)disulfide (**19**).

A solution of **6b** (0.5 g., 1.3 mmoles) and anhydrous sodium hydrosulfide (0.7 g., 13 mmoles) [prepared by saturating a solution of sodium ethoxide in ethanol at -10° with hydrogen sulfide, evaporating the solution to dryness *in vacuo*, and then the solid was dried *in vacuo* at 80° over potassium hydroxide in dry dimethylformamide (100 ml.)] was heated at 95° (oil bath) for 48 hours under anhydrous conditions. The solvent was removed *in vacuo* over a steam bath and the residue was dissolved in ethanol (200 ml.). The insoluble salts were removed by filtration and the filtrate was neutralized (*p*H 6) with Amberlite IRC-50(H^+) resin (10 g.). The resin was removed by filtration and the filtrate was evaporated to dryness *in vauco*. The residue was dissolved in dimethylsulfoxide (4 ml.) and the solution was allowed to stand at room temperature for 12 hours. Ethyl acetate (20 ml.) was added to the solution and the solution was applied to an open-bed silica gel column (3 x 30 cm). The column was eluted first with ethyl acetate (500 ml., 9/1). The column was then eluted with ethanol and the fractions containing the desired product (tlc; Rf 0.55, ethanol) were combined and evaporated to dryness. The solid was recrystallized from a minimal amount of ethanol-water (1/9) to give 130 mg. (30%) of the disulfide **19** (hydrate), m.p. 205-207°; uv (λ max in nm, ε x 10^{-3}) (*p*H 1): 324 (15.9), 270 (14.4); (*p*H 11) 308 (19.5), 267 (15.4); (ethanol): 319 (17.8), 267 (17.5); pmr (DMSO-d_6): δ 8.29 (s, 1, H2), 6.56 (s, 1, H6), 6.18 (broad singlet, 2, NH_2), 5.91 (d, 1, H1′, $J_{1',2'}$ = 6.0 Hz); ms: m/e 823 ($C_{17}H_{13}N_8O_4S_2 \cdot 5((CH_3)_3Si)$), 586 ($C_{11}H_{10}N_4O_4S \cdot 5((CH_3)_3Si)$).

Anal. Calcd. for $C_{22}H_{26}N_8O_8S_2 \cdot 1\frac{1}{2}H_2O$: C, 44.81; H, 4.96; N, 19.00; S, 10.88. Found: C, 44.44; H, 4.92; N, 18.94; S, 10.78.

5-Amino-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine-7-thione (**20**).

This nucleoside was prepared *in situ* by heating a solution of the disulfide derivative (**19**, 10 mg., 0.016 mmole) and dithiothreitol (3.7 mg., 0.024 mmole) in ethanol (5 ml.) at reflux for 15 minutes (tlc; Rf 0.28, ethyl acetate-ethanol). The following ultraviolet data was obtained on this compound: (λ max in nm, ε x 10^{-3}) (*p*H 1): sh 326 (9.4), 314 (9.9), 275 (6.6), 240 (9.4); (*p*H 11): 299 (16.0), 245 (11.6); (ethanol): 311 (11.2), 269 (6.4), sh 258 (7.3), sh 250 (8.9), 239 (12.4).

5-Amino-7-isopropylidenehydrazino-3-(β-D-ribofuranosyl)imidazo-[4,5-*b*]pyridine (**21**).

A suspension of 5-acetamido-7-chloro-3-(β-D-ribofuranosyl)-imidazo[4,5-*b*]pyridine (**6a**, 3.0 g., 8.3 mmoles) in 85% hydrazine hydrate (100 ml.) was heated at reflux in a nitrogen atmosphere for 2 hours. The solution was evaporated *in vacuo* and the residual syrup was coevaporated with ethanol (2 x 50 ml.). The residue was dissolved in acetone (100 ml.) and the solution was heated at reflux for 12 hours. The solution was evaporated *in vacuo* and the solid residue was recrystallized from ethanol to give 2.0 g. (72%) of **21**, m.p. 197-199°; uv (λ max in nm, ε x 10^{-3}) (*p*H 1): 298 (13.2), 259 (12.0); (*p*H 11): 287 (23.8), 248 (14.4); pmr (DMSO-d_6): δ 8.60 (s, 1, H2), 7.98 (s, 1, 7-NH), 6.28 (s, 1, H6), 5.85 (d, 1, H1′, $J_{1',2'}$ = 3.5 Hz), 5.57 (broad singlet, 2, 5-NH_2), 1.02 (s, 6, CH_3).

Anal. Calcd. for $C_{14}H_{20}N_6O_4$: C, 49.99; H, 6.00; N, 24.98. Found: C, 49.81; H, 6.31; N, 24.83.

Acknowledgements.

The authors wish to thank Ms. Suzanne Mason for technical assistance, Mr. Steven J. Manning for large scale preparations of pertinent starting materials, and Professor James A. McCloskey and co-workers for the mass spectra.

REFERENCES AND NOTES

(1) This research was supported by Research Contract N01-CM-77142 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

(2) A. R. P. Patterson and D. M. Tidd in "Handbook of Experimental Pharmacology", Vol. XXXVIII/2, A. C. Sartorelli and D. G. Johns, Eds., Springer-Verlag, New York, N. Y., 1974, p. 384.

(3) R. E. Parks, Jr., and K. C. Agarwal in "Handbook of Experimental Pharmacology", Vol. XXXVIII/2, A. C. Sartorelli and D. G. Johns, Eds., Springer-Verlag, New York, N. Y., 1974, p. 458.

(4a) P. D. Cook, R. J. Rousseau, A. M. Mian, P. Dea, R. B. Meyer, J. T. Witkowski and R. K. Robins, *J. Am. Chem. Soc.*, **98**, 1492 (1976); (b) L. B. Allen, J. H. Huffman, R. B. Meyer, P. D. Cook, J. T. Witkowski, L. N. Simon, R. K. Robins and R. W. Sidwell, *Fifteenth Interscience Conf. Antimicrob. Agents Chemother. (Abst. No. 245)*, Washington, D. C., Sept. 1975.

(5a) T. A. Khwaja, L. Kigwana, R. B. Meyer, and R. K. Robins, *Proc. Am. Assoc. Cancer Res.*, **16**, 162 (1975); (b) D. G. Streeter and H. H. P. Koyama, *Biochem. Pharmacol.*, **25**, 1 (1975).

(6) J. A. May and L. B. Townsend, *J. Carbohydr. Nucleosides Nucleotides*, **2**, 371 (1975).

(7) B. L. Cline, R. P. Panzica and L. B. Townsend, *Proc. Utah Acad. Sci. Arts Letters*, **52**, (part 1), 79 (1975).

(8) B. L. Cline, R. P. Panzica and L. B. Townsend, *J. Heterocyclic Chem.*, **12**, 603 (1975).

(9a) B. L. Cline, R. P. Panzica and L. B. Townsend, *ibid.*, **13**, 1365 (1976); (b) B. L. Cline, R. P. Panzica and L. B. Townsend, *J. Org. Chem.*, submitted for publication.

(10) J. E. Schelling and C. A. Salemink, *Rec. Trav. Chim.*, **93**, 160 (1974).

(11) W. W. Lee, A. P. Martinez, L. Goodman and D. W. Henry, *J. Org. Chem.*, **37**, 2923 (1972).

(12) N. Yamaoka, K. Aso and K. Matsuda, *ibid.*, **30**, 149 (1965).

(13) L. B. Townsend in "Synthetic Procedures in Nucleic Acid Acid Chemistry", Vol. 2, Eds., W. W. Zorbach and R. S. Tipson, Wiley-Interscience, New York, N. Y., 1973, p. 267.

(14a) J.-L. Imbach, J.-L. Barascut, B. L. Kam, B. Rayner, C. Tamby and C. Tapiero, *J. Heterocyclic Chem.*, **10**, 1069 (1973); (b) J.-L. Imbach, *Ann. N. Y. Acad. Sci.*, **255**, 177 (1975).

(15) P. C. Jain and N. Anand, *Indian J. Chem.*, **6**, 616 (1968).

(16) Y. Mizuno, M. Ikehara, T. Itoh and K. Saito, *J. Org. Chem.*, **28**, 1837 (1963); *Chem. Pharm. Bull. (Tokyo)*, **11**, 265 (1963).

(17) I. Hirao and M. Hoyoski, *Yakugaku Zasski*, **74**, 853 (1954).

(18) C. R. Frihart and N. J. Leonard, *J. Am. Chem. Soc.*, **95**, 7174 (1973).

(19) Shortly after our preliminary communication describing the synthesis of 1-deazaguanosine (**1**) (8), Schelling and Salemink reported their preparative route toward **1** (20). Their synthetic procedure involved the condensation of 5-acetamido-7-benzyloxyimidazo[4,5-*b*]pyridine (**13**) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in refluxing nitromethane containing potassium cyanide. The desired nucleoside intermediate **14** was only obtained in a 21% yield.

(20) J. E. Schelling and C. A. Salemink, *Rec. Trav. Chim.*, **94**, 153 (1975).

(21) B. L. Cline, P. E. Fagerness, R. P. Panzica and L. B. Townsen, Abstracts, *172nd National Meeting of the American Chemical Society*, San Francisco, Calif., Sept. 1976, ORG 255; submitted for publication.

(22) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons, New York, N. Y., 1967, p. 307.

(23) W. W. Cleland, *Biochemistry*, **3**, 480 (1964).

(24a) "The Chemistry of the Thiol Group", S. Patai, Ed., John Wiley and Sons, Bristol, GB, 1974, p. 220; (b) *ibid.*, p. 785.

(25) J. J. Fox, I. Wempen, A. Hampton and I. L. Doerr, *J. Am. Chem. Soc.*, **80**, 1669 (1958).

(26) J. A. McCloskey, A. M. Lawson, K. Tsuboyama, P. M. Krueger and R. N. Stilwell, *ibid.*, **90**, 4182 (1968).

(27) B. L. Cline, R. P. Panzica and L. B. Townsend, "Nucleic Acid Chemistry, New or Imporved Synthetic Procedures, Methods, and Techniques", Vol. 1, L. B. Townsend and R. S. Tipson, Eds., John Wiley, New York, N. Y., 1978, p. 129.

(28) C. Temple, Jr., B. H. Smith and J. A. Montgomery, *J. Org. Chem.*, **38**, 613 (1973).