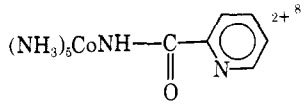
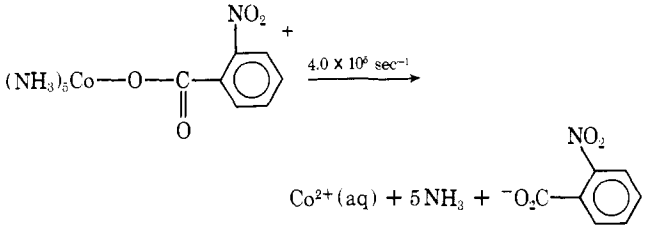
from the reduction of the 2-cyanopyridine complex is identical with the product from the chromium(II) reduction of **6**.[8] It may well be that for the 2-substituted pyridines, the



6

ligand functions solely as a binding group to bring the reductant close enough to the oxidant for resonance transfer to occur rather than radical formation. Cohen and Meyerstein[18] have suggested that the intramolecular electron transfer which occurs in the reaction[19]



may take place by mediation of the electron through one of the adjacent ammine ligands. In the case of 2-cyanopyridine, mixing between the orbitals on the reductant and oxidant may take place as a result of binding to the pyridine nitrogen and direct transfer may be possible or, if a radical is formed, adjacent mediation could also occur.

The reduction of the 3-cyanopyridine complex also proceeds by remote attack with formation of **3**. In this case, only about 55% of the product above was isolated. However, based on the outer-sphere rates of reduction of the pyridine and nicotinamide complexes of 0.004 and 0.014 M^{-1} sec^{-1}, respectively,[5] reduction of the 3-cyanopyridine complex probably occurs predominantly by an inner-sphere process.

Acknowledgment. The author wishes to thank the National Research Council of Canada for financial support of this research.

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Synthesis of 3-Deazaguanine, 3-Deazaguanosine, and 3-Deazaguanylic Acid by a Novel Ring Closure of Imidazole Precursors

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Abstract: 3-Deazaguanine [6-aminoimidazo[4,5-*c*]pyridin-4(5H)-one (**4**)], 3-deazaguanosine [6-amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (**17**)], and 3-deazaguanylic acid [6-amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one 5′-phosphate (**24**)] have been synthesized for the first time by a novel base-catalyzed ring closure of 5(4)-cyanomethylimidazole-4(5)-carboxamide (**3**), 5-cyanomethyl-1-β-D-ribofuranosylimidazole-4-carboxamide (**12**), and 5-cyanomethyl-1-β-D-ribofuranosylimidazole-4-carboxamide 5′-phosphate (**23**), respectively. The imidazole **3** was prepared from the ammonolysis of methyl 5(4)-cyanomethylimidazole-4(5)-carboxylate (**2**). The imidazole nucleoside **12** was obtained from the stannic chloride-catalyzed condensation of methyl 5(4)-cyanomethyl-1-trimethylsilylimidazole-4(5)-carboxylate (**5**) and a fully acylated β-D-ribofuranose (**6** or **7**), followed by ammonolysis of the blocking groups and the ester function. The imidazole nucleotide **23** was obtained from the phosphorylation of **12** with phosphoryl chloride in trimethyl phosphate. The yield and ratio of the ribofuranosyl derivatives of imidazole **2** markedly depends on the ratio of stannic chloride to trimethylsilylimidazole **5** and the fully acylated β-D-ribofuranose. The structures of the nucleosides were established by the use of carbon-13 and proton NMR. 3-Deazaguanine (**4**), 3-deazaguanosine (**17**), and 3-deazaguanylic acid (**24**) have demonstrated a potent broad spectrum activity in vitro against various DNA and RNA viruses, as well as potent in vivo activity against L1210 leukemia and adenocarcinoma 755 in mice.

3-Deazaguanine [6-aminoimidazo[4,5-*c*]pyridin-4(5*H*)-one (**4**)] is the only 3-deaza analogue of the ubiquitous naturally occurring purines whose synthesis has not been realized. 3-Deaza analogues of uric acid,[2] xanthine,[2] hypoxanthine,[3] adenine,[3] and the chemotherapeutically useful 6-thioguanine[4a] and 6-mercaptopurine[4a] have been reported. Furthermore, the nucleoside and nucleotide derivatives of 3-deazaadenine and 3-deazahypoxanthine have been prepared.[5] Poly-3-deazaadenylic acid and poly-1-deazaadenylic acid have been enzymatically prepared from their corre-

sponding nucleoside diphosphates using polynucleotide phosphorylase.[6]

1-Deazaguanine[7] has shown activity against the growth of mouse mammary carcinoma,[8] *L. casei*,[8] and *Tetrahymena pyridormis*.[9] Certain 1- and 3-deazapurines have shown antibacterial,[9,10] anticancer,[11] cytokinin,[12] and antiviral activity.[11c,13] Important biological activity of deaza analogues of guanine and its metabolites is anticipated from our increasing knowledge of guanine nucleotide metabolism in microbial and mammalian systems.[14]

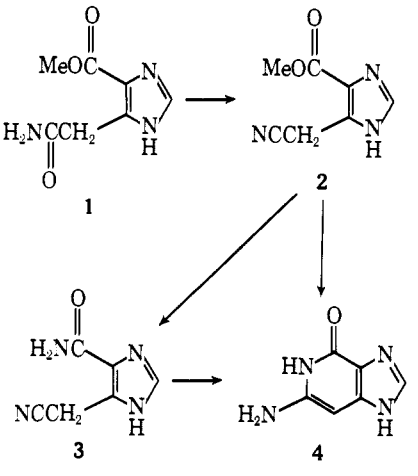
In continuation of our program to discover broad spectrum antiviral agents,[15] we have undertaken the synthesis of various deazapurines and their nucleoside and nucleotide derivatives for biological evaluation. The present study is an account of the synthesis of 3-deazaguanine (**4**), 3-deazaguanosine [6-amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (**17**)], and 3-deazaguanylic acid [6-amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one 5′-phosphate (**24**)].[16] These compounds have demonstrated a potent broad spectrum activity in vitro against various DNA and RNA viruses,[17] as well as potent in vivo activity against L1210 leukemia and adenocarcinoma 755 in mice.[18]

Syntheses of compounds in the imidazo[4,5-*c*]pyridine ring system[2-5,7-11] have generally proceeded from appropriately substituted 3,4-diaminopyridines which were then ring closed by various means to give the requisite imidazo[4,5-*c*]pyridines. In particular, this synthetic sequence has been used to provide the 3-deaza analogues of adenine,[3] hypoxanthine,[3] and 6-mercaptopurine.[4b] Attempts to prepare 3-deazaguanine (**4**) by this approach have failed.[19] An alternative approach to imidazo[4,5-*c*]pyridines (most notably 3-deazaxanthine and 3-deazauric acid) from base-catalyzed ring closure of methyl 4(5)-carbamoylmethylimidazole-5-(4)-carboxylates to form the pyridine portion of the ring system has been described by Robins and coworkers.[2] We found that a modification of this approach led to the synthesis of 3-deazaguanine (**4**), as well as its nucleoside, **17**, and nucleotide, **24**. In fact, it appears that this synthesis is general in that it provides not only the elusive pyridine moiety of **4**, but also the 6-membered ring containing the guanine type Watson–Crick hydrogen bonding sites of other azines which will be reported in later work.

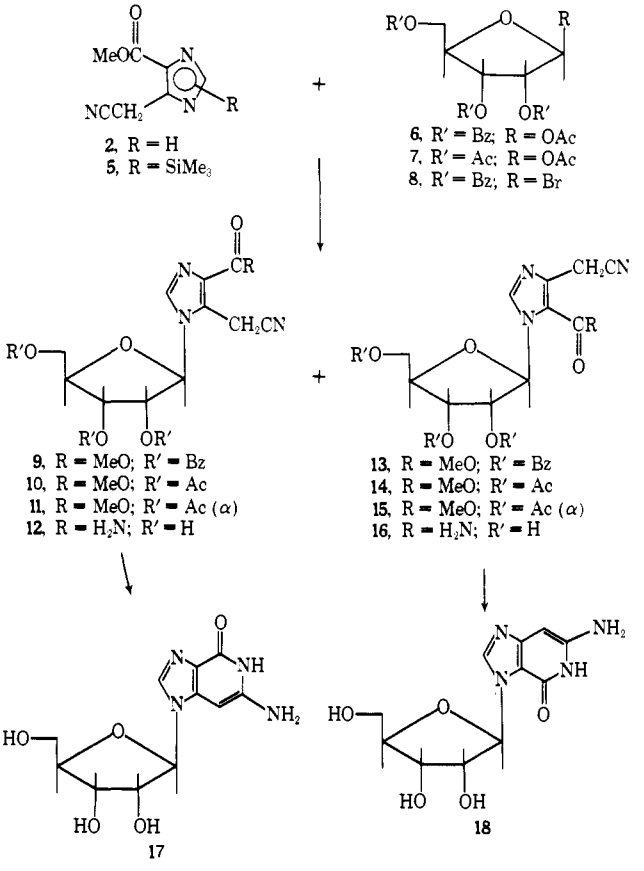
The key intermediate in the synthesis of 3-deazaguanine (**4**) and 3-deazaguanosine (**17**) is methyl 5(4)-cyanomethylimidazole-4(5)-carboxylate (**2**, Scheme I), which was obtained in 80% yield from methyl 5(4)-carbamoylmethylimidazole-4(5)-carboxylate[2] (**1**) and refluxing phosphoryl chloride. Treatment of **2** with liquid ammonia (8 days, 100°) provided 3-deazaguanine (**4**) in 77% yield. The intermediate 5(4)-cyanomethylimidazole-4(5)-carboxamide (**3**) could be obtained in 77% yield by interruption of the reaction of **2** and ammonia after 48 h. Product **3** was smoothly cyclized to 3-deazaguanine (**4**) with aqueous sodium carbonate. The structure of imidazole **2** was confirmed by inspection of its ir spectrum which had a nitrile and ester absorption band at 2260 and 1720 cm^{-1}, respectively. The ir spectrum of imidazole **3** also possessed a nitrile adsorption band at 2260 cm^{-1} as well as an amide carbonyl band at 1660 cm^{-1}, replacing the ester carbonyl band of **2**. Compound **4** was identified as 3-deazaguanine on the basis of an additional aromatic proton resonance at δ 5.56 which was assigned to C_7H, an aromatic amine resonance at δ 5.66, and the lack of a methylene resonance at δ 4.33 which was present in the imidazole **3**. Furthermore, the uv absorption spectrum of **4** exhibits the characteristic bathochromic shifts due to the annellation of the pyridone ring to the imidazole ring.[20]

It was envisaged that the synthesis of 3-deazaguanosine (**17**) might be realized from the cyclization of the appropriate ribofuranosyl derivative of **2** or **3** with ammonia or sodium carbonate, respectively. Ribosylation of **2** was approached by three methods (Scheme II): (A) stannic chloride-catalyzed condensation of trimethylsilylated **2** [methyl 5(4)-cyanomethyl-*N*-trimethylsilylimidazole-4(5)-carboxylate (**5**)] with a fully acylated ribofuranose [1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**6**) or 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**7**)],[21] (B) condensation of **5** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**8**) in acetonitrile,[22] and (C) acid-catalyzed high-temperature fusion of **5** with **7**.[15,23] In general, ribosylations of imidazoles provide a mixture of positional isomers (i.e., a ribose on either the 1- or 3-nitrogen ring atoms).[24] This was the case in methods **B** and **C**; however, it was found that the yield and ratio of positional isomers in method A markedly depends on the ratio of stannic chloride to **5** and the blocked sugars,

Scheme I

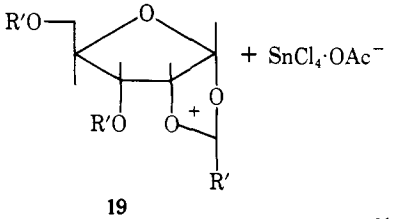


Scheme II



6 or **7**. Thus, treatment of 1 equiv of **5** in 1,2-dichloroethane or acetonitrile with 1 equiv of **6** or **7** and 1.44 molar equiv of stannic chloride afforded a quantitative yield of methyl 5-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl- or acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate, **9** or **10**, respectively. Condensation of 1 equiv of **5** with 1 equiv of **6** and 0.72 molar equiv of stannic chloride affords a 29.5% yield of **6** and a 34.5% yield of methyl 4-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-5-carboxylate (**13**). Further reduction of stannic chloride to 0.36 molar equiv effected a slow and incomplete condensation of **5** with **6** to form **9** and **13** in 10% and 20% yields, respectively. Similar ratios were obtained when the tetraacetyl blocked sugar **7** replaced **6**. The ribosylation of **5** by the bromo sugar **8** in acetonitrile in the absence of stannic chloride (method B) provides a mixture of the positional isomers **9** and **13** in 6% and 48% yields, respectively. Furukawa and Honjo[25] have reported the ribosylation of non-trimethylsilylated *N*-acyl adenines and guanines in good yields with the blocked sugars **6** and **7** and stannic chloride or aluminum chloride in boiling 1,2-dichloroethane or chlorobenzene. In a similar manner, we attempted to ribosylate the imidazole base **2** with **6** and excess stannic chloride in boiling 1,2-dichloroethane; however, no nucleoside material was detected under these reaction conditions.

The intermediacy of a stannic chloride–heterocycle **5** complex, which provides a regiospecific ribosylation of **5**, may be a plausible explanation to these results. However, although it is generally assumed that Lewis acids, such as stannic chloride, promote the formation of acyloxonium ions of fully acylated ribofuranoses, such as **19**, as noted by



19

usually exclusive formation of β-nucleosides,[21,26] no account of the interaction of silylated heterocycles with stannic chloride or other Lewis acids has been reported.

Fusion of imidazole **2** with **7** at 155° in the presence of bis(*p*-nitrophenyl) phosphate (method C) provided, after silica gel chromatography, **10** (19%), methyl 5-cyanomethyl-1-(2,3,5-tri-*O*-acetyl-α-D-ribofuranosyl)imidazole-4-carboxylate (**11**, 4.7%), methyl 4-cyanomethyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-5-carboxylate (**14**, 47%), and methyl 4-cyanomethyl-1-(2,3,5-tri-*O*-acetyl-α-D-ribofuranosyl)imidazole-5-carboxylate (**15**, 11.8%). Studies to directly ribosylate 3-deazaguanine (**4**) by methods A or B provided complex reaction mixtures from which 3-deazaguanosine (**17**) was isolated in relatively low yields.

3-Deazaguanosine (**17**) could be obtained directly from the blocked imidazole nucleosides **9** or **10** and liquid ammonia (22 h, 110°) in 20–30% yield. Although TLC of the reaction mixture indicated a fairly clean conversion of **9** or **10** to **17**, it was difficult to isolate and purify **17**. An alternative route to **17** was developed which provided the analytically pure nucleoside in 69% yield (from **9**). Thus, treatment of **9** with liquid ammonia (3 h, 100°) followed by silica gel chromatography of the reaction residue provided the versatile intermediate, 5-cyanomethyl-1-β-D-ribofuranosylimidazole-4-carboxamide (**12**), in 81% yield. When **12** was refluxed in aqueous sodium carbonate–ethanol, 3-deazaguanosine (**17**) was formed and crystallized from the reaction in 85% yield.

Table I. ^{13}C Chemical Shifts of 4- and 5-Substituted Imidazole Anions and Their Nucleosides[a]

Compound	Chemical shift, ppm		
	C-2	C-4	C-5
Anion of **20**	145.7	130.1	133.7
Anion of **2**	143.5	124.8	136.4
Anion of **3**	144.3	129.5	133.9
10	136.8	128.0	130.7
	(136.5)	(126.8)	(129.4)
12	136.1	133.3	124.3
	(137.3)	(131.5)	(126.9)
14	139.9	138.4	118.4
	(136.5)	(138.4)	(117.8)
16	(137.3)	(135.9)	(122.5)

[a] Values in parentheses are predicted chemical shifts using α- and β-substitution shifts of +7 and −2 ppm, respectively.

On the other hand, the corresponding positional isomer to **12**, 4-cyanomethyl-1-β-D-ribofuranosylimidazole-5-carboxamide (**16**), could not be isolated (using the same or milder reaction conditions) and was directly converted to 7-β-D-ribofuranosyl-3-deazaguanine [6-amino-3-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one, (**18**)] in 80% yield.

The ribosylation site of the imidazole nucleosides **9–15**, and therefore of 3-deazaguanosine (**17**) and 7-β-D-ribofuranosyl-3-deazaguanine (**18**), was established by using proton and carbon-13 NMR spectroscopy. The use of proton and carbon-13 chemical shifts for structural assignment of the alkylation or glycosylation site has recently been demonstrated in both 5-membered and 6-membered heterocyclic ring systems,[27] as well as complex-fused heterocyclic systems.[28] The assignments were made on the basis of the α- and β-substitution shifts observed when the neutral species were compared with the anion of the parent base.[29]

Table I summarizes the pertinent carbon-13 chemical shifts of the anions of methyl 5-cyanomethylimidazole-4-carboxylate (**2**) and 5-cyanomethylimidazole-4-carboxamide (**3**), as well as their ribosylated derivatives. The spectral shifts of the anion of ethyl imidazole-4-carboxylate (**20**, not shown) are included for chemical shift comparison. The C-2 carbon atom is assigned to be the most downfield carbon since it is bonded to two nitrogen atoms which appreciably deshield it.[30] The C-4 and C-5 carbon atoms of **21** can be readily assigned from the proton-coupled spectrum where the C-5 carbon atom exhibits a large coupling constant from the proton directly attached. For structures **2** and **3**, where the H_5 proton is replaced by a cyanomethyl group, the same relative ordering of the C-4 and C-5 carbon atoms are assumed in view of the fact that methyl substitutions have been reported to shift the α-carbon atoms downfield in various heterocyclic systems,[31] and the cyanomethyl group is expected to affect the π-electron charge distribution in a similar manner. The C-4 and C-5 carbon atoms in nucleosides **10**, **12**, **14**, and **16** are assigned based on chemical shift comparison with related compounds,[29c] as well as the theoretical carbon-13 shieldings reported in parentheses in Table I. These predicted values of theoretical shifts for the various nucleosides are computed from the chemical shift of the base anions using a substitution shift parameter of +7 ppm upfield for the α carbon and a downfield shift of −2 ppm for the β carbon. These αβ shifts correspond to the chemical shift difference between *N*-methylimidazole and the imidazole anion.[29c] Reasonable agreement between the predicted and the experimental values could be obtained only if the indicated structures in Scheme II are used.

Additional evidence for the assignment of structure of the imidazole nucleosides **9–15** and the imidazopyridine nu-

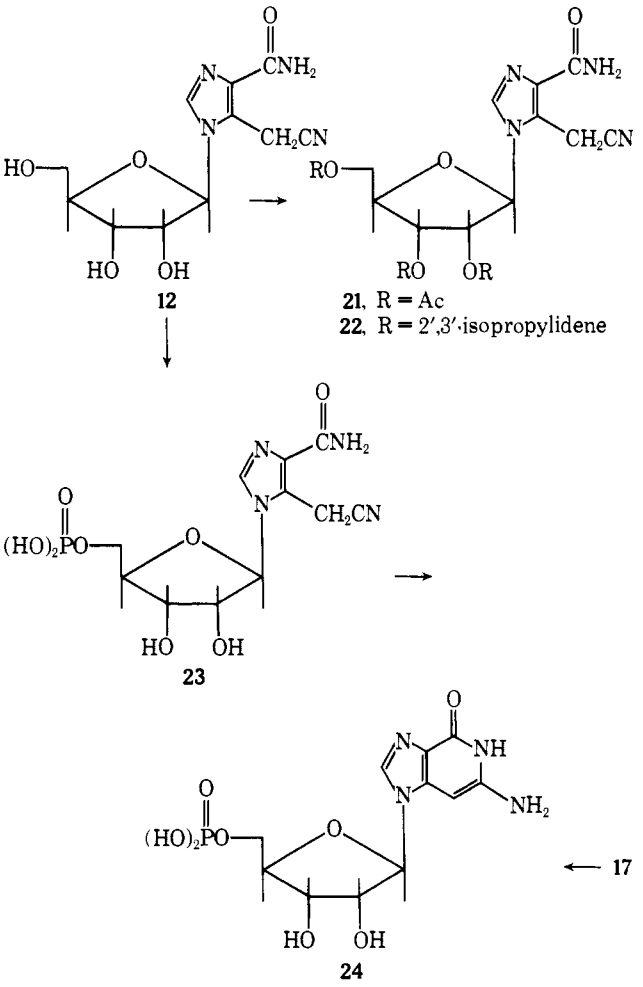
cleosides **17** and **18** was obtained by consideration of the anisotropic effect of a carbonyl group (ester or amide) in the base on the chemical shift of the anomeric proton ($H_{1'}$) of the ribose moiety. This method has recently been successfully used to determine the site of ribosylation in 1,2,4-triazoles,[27a,32] pyrimidines,[33] benzimidazoles,[34] and various nitrogen bridgehead purine analogues.[28] The ^1H NMR spectra indicated that when the ribose moiety was attached to the nitrogen atom adjacent to the carbonyl function (as shown in **13, 14,** and **15**), a downfield shift of the anomeric proton ($H_{1'}$) (0.29–0.32 ppm) was observed as compared with the $H_{1'}$ of their respective positional isomers (i.e., **9, 10,** and **11**). This shift, as also noted with previous nucleosides,[28a,28,32-34] is attributed to the close proximity of the anisotropic carbonyl group on the anomeric proton ($H_{1'}$). This assignment of structure is supported by the examination of space-filling molecular models which indicate that only the anti conformation can be formed.[35] The same anisotropic effect of a carbony group (lactam in this case) was also apparent in the imidazopyridine nucleosides, **17** and **18,** since $H_{1'}$ of **18** is shifted 0.73 ppm downfield from $H_{1'}$ of **17**. Furthermore, an anisotropic effect of a lactam group is evident in the comparison of 7-ribofuranosylguanine with guanosine (Δ0.46 ppm) and 7-ribofuranosylhypoxanthine with inosine (Δ0.49 ppm).[36]

The β configuration of the imidazole nucleosides **9, 10, 13,** and **14,** and hence the imidazopyridine nucleosides **17** and **18,** was established on the bases of several empirical rules obtained from ^1H NMR observations. First, Montgomery has observed that the 2′-acetoxyl signal of a number of acetylated α-D-ribofuranosylpurines occurs upfield (0.11–0.34 ppm) from the highest signal of the corresponding β-D-ribofuranosylpurines.[37] The blocked nucleosides **10, 11, 14,** and **15,** obtained from the fusion of imidazole **2** and **7** (method C), were determined to be two pairs of anomers from examination of their uv and ^1H NMR spectra. The 2′-acetoxyl signal of **11** and **15** was upfield (0.13 and 0.12 ppm, respectively) from the corresponding signals of **10** and **14,** thus establishing **11** and **15** as α anomers and **10** and **14** as β anomers. Montgomery has also observed that the acetoxyl-group signals of a number of β-D-ribofuranosylpurines occur downfield from 2.05 ppm.[37] This is the case in **10** and **14,** as well as 5-cyanomethyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**21**). Second, Imbach[38] has found that the anomeric configuration of a variety of ribofuranosyl nucleosides can be determined by the difference in proton chemical shifts between the methyl groups of their isopropylidene derivatives. The difference in the chemical shift of the methyl groups of the isopropylidene derivative of the key imidazole nucleoside **12,** 5-cyanomethyl-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (**22**), is 0.19 ppm which is characteristic of the β configuration. Finally, the chemical shift of a β anomer has without exception been found to appear upfield from the corresponding α anomer.[37] Examination of the ^1H NMR spectra of the two pair of anomers, **10** and **11** and **14** and **15** indicates $H_{1'}$ of **10** and **14** to be upfield (0.33 and 0.30 ppm, respectively) from **11** and **15,** thus establishing **10** and **14** as the β anomers.

The β configuration of the imidazole nucleosides **9, 10, 13,** and **14** prepared by method A was expected due to the participation of the 2-acyloxy group of **6** and **7** and, subsequently, the formation of the acyloxonium ion, **19.** Stereospecific ribosylations of this nature have been generally accepted in the chemical literature.[26] Furthermore, although the stannic chloride-catalyzed condensation of silylated heterocycles with fully acylated glycoses containing a *trans*-2-acyloxy group is a relatively new procedure, all chemical literature reports,[21] to our knowledge, have only described high yields of the β nucleosides with no isolation of any α nucleosides. Thus, it appears that stannic chloride, like the mercuric halides in the heavy-metal procedure,[26d] is extremely efficient in promoting the formation of acyloxonium ions, such as **19,** as noted by the quantitative yields of **9** and **10,** and high yields of other β nucleosides.[21]

3-Deazaguanylic acid [6-amino-1-β-D-ribofuranosyl[4,5-*c*]pyridin-4(5*H*)-one 5′-phosphate (**24**), Scheme III] was

Scheme III



synthesized directly from the corresponding imidazopyridine nucleoside **17** or from the cyclization of the corresponding imidazole nucleotide [5-cyanomethyl-1-β-D-ribofuranosylimidazole-4-carboxamide 5′-phosphate (**23**)]. It was found that, just as in the synthesis of 3-deazaguanine (**4**) and 3-deazaguanosine (**17**), the bicyclic nucleotide **24** was best obtained by cyclization of the imidazolecarboxamide nucleotide. Thus, the imidazole nucleoside **12** was phosphorylated at 0° with phosphoryl chloride in the presence of trimethyl phosphate[39] to provide **23** (80%) as the free acid, after ion-exchange chromatography. Treatment of **23** with aqueous sodium carbonate (pH 10, 100°, 40 min) provided the bicyclic nucleotide **24** (75%) as the free acid after ion-exchange chromatography. Direct phosphorylation of **17,** in the manner just described, provided a mixture of products from which **24** was isolated in 30% yield.

The mechanism of these ring closures may be visualized simply as occurring by base abstraction of an amide proton from the imidazole precursors, followed by attack of the generated anion on the nitrile carbon. It may be noted, however, that aqueous sodium carbonate appears to be a superior reagent for such ring closures. For example, liquid am-

monia was inferior to aqueous sodium carbonate in converting **3** and **9** to 3-deazaguanine (**4**) and 3-deazaguanosine (**17**), respectively. The conversion of **23** to 3-deazaguanylic acid (**24**) with sodium hydroxide produced additional reaction products.

The biological activity of these compounds will be reported elsewhere.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Proton magnetic resonance (^{1}H NMR) spectra were obtained on a Varian A-60 spectrometer and a Perkin-Elmer R-20A spectromer in Me_2SO-d_6 using DSS as an internal reference. Carbon-13 magnetic resonance (^{13}C NMR) spectra of 20% Me_2SO-d_6 solutions were obtained on a Bruker HX-90 NMR spectrometer operating at 22.62 MHz in the Fourier transform mode at a probe temperature of 35°C. Chemical shifts are measured from Me_2SO-d_6, converted to Me_4Si scale using the relationship δ Me_4Si = δ Me_2SO-d_6 + 39.5 ppm. The anions of various heterocycles were formed by neutralization with LiOH in Me_2SO-d_6. Ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer and infrared spectra on a Perkin-Elmer 257 spectrophotometer (KBr pellets). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Evaporations were carried out under reduced pressure with bath temperature below 40°. Detection of components on silica gel (ICN, Woelm F254) was by ultraviolet light and with 10% sulfuric acid in methanol spray followed by heating.

Methyl 5(4)-Cyanomethylimidazole-4(5)-carboxylate (2). A mixture of methyl 5(4)-carbamoylmethylimidazole-4(5)carboxylate[2] (**1**) (20.0 g, 109.5 mmol) and phosphoryl chloride (100 ml) was refluxed with stirring for 1 h. The cooled solution was triturated with petroleum ether (30–60°, 400 ml) followed by ether (2 × 150 ml). With occasional cooling in a dry ice–acetone bath, ice (150 g) was added to the residue, followed by concentrated NH_4OH, maintaining the temperature <10°. When the pH had stabilized at ca. 6.0, the solution was evaporated to dryness in vacuo. The product was extracted from the residue by trituration with several portions of hot ethyl acetate (until no further uv absorbing material was extracted), and the extracts were dried ($MgSO_4$) and taken to dryness. Recrystallization from H_2O provided **2** (14.3 g, 80%) as straw-colored needles: mp 170–171°; ir cm^{-1} (KBr) 2260 (m) (C≡N), 1720 (s) (C=O); λ_{max} (pH 1) 222 nm (ϵ 10 700); λ_{max} (pH 11) 251 (10 600); ^{1}H NMR (Me_2SO-d_6) δ 3.89 (s, 3, CH_3), 4.20 (s, 2, CH_2), 7.90 (s, 1, C_2H), 13.3 (br, s, 1, NH).

Anal. ($C_7H_7N_3O_2$) C, H, N.

5(4)-Cyanomethylimidazole-4(5)-carboxamide (3). A mixture of **2** (16.5 g, 100 mmol) and liquid ammonia (150 ml) was heated (100°) in a steel bomb (300 ml) for 48 h. The ammonia was allowed to evaporate, and a vacuum was applied to the residue overnight to remove last traces of solvent. Recrystallization from water (charcoal) provided **3** as colorless needles (11.6 g, 77%): mp 232–234° dec (after drying at 100° in vacuo for 12 h); ir cm^{-1} (KBr) 2260 (m) (C≡N), 1660 (s) (C=O); λ_{max} (pH 1) 210 nm (ϵ 14 000); λ_{max} (pH 7) 242 (10 800); λ_{max} (pH 11) 257 (11 600); ^{1}H NMR (Me_2SO-d_6) δ 4.33 (s, 2, CH_2), 7.42 (s, 2, NH_2), 7.79 (s, 1, C_2H).

Anal. ($C_6H_6N_4O$) C, H, N.

6-Aminoimidazo[-4,5-*c*]pyridin-4(5*H*)-one (3-Deazaguanine 4). Method A. A mixture of **2** (16.5 g, 100 mmol) and liquid ammonia (150 ml) was heated (100°) for 8 days. The ammonia was allowed to evaporate, and a vacuum was applied to the residue to remove the last traces of solvent. Recrystallization from water (charcoal) provided **4** (11.2 g, 77%) as light sensitive, light yellow needles: mp >350° (after drying at 100° for 12 h); ir cm^{-1} (KBr) 1670 (s) (C=O); λ_{max} (pH 1) 273 nm (ϵ 11 320), 311 (6380); λ_{max} (pH 7) 262 (10 250), 298 (8070); λ_{max} (pH 11) 262 (9630), 298 (7780); ^{1}H NMR (Me_2SO-d_6) δ 5.56 (s, 1, C_7H), 5.66 (s, 2, NH_2), 7.82 (s, 1, C_2H), 10.75 (s, 1, NH), 12.38 (br, s, 1, NH).

Anal. ($C_6H_6N_4O$) C, H. N.

Method B. A mixture of **3** (1.5 g, 10 mmol) and 10% sodium carbonate (15 ml) was refluxed 4 h, neutralized to pH 6 with concentrated hydrochloric acid, and allowed to stand at 4° for 16 h. The precipitate was collected, washed well with ice-water, and dried at 100° in vacuo to yield 750 mg (50%) of **4**. This material was identical with 3-deazaguanine prepared in method A.

Methyl 5-Cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-4-carboxylate (9). Compound **2** (25.0 g, 0.151 mol) was refluxed under anhydrous conditions for 12 h with hexamethyldisilazane (300 ml) and ammonium sulfate (0.5 g). The excess hexamethyldisilazane was removed by distillation under reduced pressure providing the trimethylsilyl derivative as a yellowish brown oil. The oil was dissolved in dry 1,2-dichloroethane[40] (800 ml). 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**6**) (76.5 g, 0.151 mol) was added to the solution followed by addition of stannic chloride (25.4 ml, 0.218 mol) in one portion. Some brown precipitate forms after ca. 0.5 h of stirring at ambient temperature TLC (silica gel, benzene–ethyl acetate, 1:1) of an ethanolyzed aliquot indicated almost complete conversion of the sugar and base to the title compound after 15 min of stirring. The reaction mixture was stirred further for 4–24 h and then poured into a 5% sodium hydrogen carbonate solution (3 l.). The mixture was filtered through Celite and extracted with chloroform (3 × 800 ml), and the combined dried ($MgSO_4$) extracts were evaporated under reduced pressure (50°) to a light-beige foam (92 g, 100%). This material is of high purity and was used for further reactions. An analytical sample was obtained by passing 1 g of the foam dissolved in benzene–ethyl acetate (1:1) through a column of silica gel (10 g) packed in benzene–ethyl acetate (1:1) white foam; ^{1}H NMR (Me_2SO-d_6) δ 3.85 (s, 3, CH_3), 4.52 (s, 2, CH_2), 6.6 (d, 1, J = 5 Hz, $H_{1'}$), 8.38 (s, 1, C_2H).

Anal. ($C_{33}H_{27}N_3O_9$) C, H, N.

Methyl 4-Cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-5-carboxylate (13) and Methyl 5-Cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-4-carboxylate (9). Method A. The procedure described above for the preparation of methyl 5-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-4-carboxylate (**9**) was followed except that 0.72 molar equiv of stannic chloride was used instead of 1.44 molar equiv, and the reaction was allowed to proceed for 24 h. TLC [silica gel, benzene–ethyl acetate (1:1)] indicated that the reaction had ceased after ca. 9 h. Column chromatography [30 g of silica gel packed in benzene–ethyl acetate (1:1) to 1 g of the dried reaction mixture syrup and eluted with benzene–ethyl acetate (1:1)] provided, as the first isomer off the column, methyl 4-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-5-carboxylate (**13**) in 34.5% yield, white foam: ^{1}H NMR (Me_2SO-d_6) δ 3.78 (s, 3, CH_3), 4.20 (s, 2, CH_2), 6.8 (d, 1, J = 2 Hz, $H_{1'}$), 8.43 (s, 1, C_2H).

Anal. ($C_{33}H_{27}N_3O_9$) C, H, N.

Further elution of the column with benzene–ethyl acetate (1:1) provided **9** in a 29.5% yield. This material was identical with the isomer previously prepared.

Again, utilizing the same conditions, except that the amount of stannic chloride was decreased to 0.36 molar equiv and the reaction was allowed to proceed for 48 h, provided **9** and **13** in 10% and 20% yields, respectively.

Method B. Silylated methyl 5(4)-cyanomethylimidazole-4(5)-carboxylate (**5**, 10 mmol), as obtained previously, was dissolved in acetonitrile (100 ml) and 2,3,5-tri-*O*-benzoylribofuranosyl bromide (**8**, 10 mmol) in acetonitrile (25 ml) was added. The reaction solution was stirred at room temperature in a tightly stoppered flask for 3 days. Methanol (10 ml) was added and the reaction mixture was evaporated in vacuo to a syrup. Column chromatography, as described above, provided **13** and **9** in 48% and 6% yields, respectively.

Methyl 5-Cyanomethyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole-4-carboxylate (10). Methyl 5-cyanomethyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate (**10**) was obtained as a syrup in 95% yield from **5** and 1,2,3,5-tetra-*O*-acetylribofuranose (**7**) according to the preparation of **9**; λ_{max} (pH 1) 227 nm (ϵ 8400); λ_{max} (pH 7) 235 (8820); λ_{max} (pH 11) 237 (8400); ^{1}H NMR (Me_2SO-d_6) δ 2.06, 2.10, 2.16 (s, 9, $COCH_3$), 3.86 (s, 3, CO_2CH_3), 4.39 (s, 2, CH_2), 6.16 (d, 1, J = 5 Hz, $H_{1'}$), 8.20 (s, 1, C_2H).

Anal. ($C_{18}H_{21}N_3O_9$) C, H, N.

Fusion of Methyl 5(4)-Cyanomethylimidazole-4(5)-carboxylate (2) with 1,2,3,5-Tetra-*O*-acetylribofuranose (7). Methyl 5(4)-cyanomethylimidazole-4(5)-carboxylate (**2**) (1.65 g, 10 mmol) was

thoroughly mixed with 1,2,3,5-tetra-*O*-acetylribofuranose (**7**) (3.18 g, 10 mmol) and heated with stirring at 170° until a clear melt was obtained (ca. 1 min). Bis(*p*-nitrophenyl) phosphate (20 mg) was added and heating at 170–175° under vacuum was continued for 25 min. The reddish-brown residue was dissolved in chloroform, extracted with 5% $NaHCO_3$, dried ($MgSO_4$), and placed on a column of silica gel (120 g packed in chloroform). Elution with ethyl acetate provided the following four pure nucleosides in the order listed: methyl 4-cyanomethyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-5-carboxylate (**14**) as white needles (2.0 g, 47%): mp 92–93° (EtOH); λ_{max} (pH 1) 235 nm (ε 9810); λ_{max} (pH 7 and 11) 242 nm (11 600); ^1H NMR (Me_2SO-d_6) δ 2.13 (s, 9, $COCH_3$), 3.87 (s, 3, CO_2CH_3), 4.19 (s, 2, CH_2), 6.48 (d, J = 3 Hz, $H_{1'}$), 8.33 (s, 1, C_2H).

Anal. ($C_{18}H_{21}N_3O_9$) C, H, N.

Methyl 4-cyanomethyl-1-(2,3,5-tri-*O*-acetyl-α-D-ribofuranosyl)imidazole-5-carboxylate (**15**) as a syrup (0.5 g, 11.8%): λ_{max} (pH 1) 238 nm (ε 9800); λ_{max} (pH 7 and 11) 247 (11 550); ^1H NMR (Me_2SO-d_6) δ 1.82, 1.99, 2.01 (s, 9, $COCH_3$'s), 3.86 (s, 3, CO_2CH_3), 4.19 (s, 2, CH_2), 6.78 (d, 1, J = 5 Hz, $H_{1'}$), 8.18 (s, 1, C_2H).

Anal. ($C_{18}H_{21}N_3O_9$) C, H, N.

Methyl 5-cyanomethyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate (**10**) as a syrup (0.8 g, 19%); this material was identical to the single isomer prepared by the stannic chloride procedure.

Methyl 5-cyanomethyl-1-(2,3,5-tri-*O*-acetyl-α-D-ribofuranosyl)imidazole-4-carboxylate (**11**) as a syrup (0.2 g, 4.7%); λ_{max} (pH 1) 226 nm (ε 10 100); λ_{max} (pH 7) 236 (10 500); λ_{max} (pH 11) 238 (10 900); ^1H NMR (Me_2SO-d_6) δ 1.93, 2.04 and 2.13 (s, 3, $COCH_3$), 3.84 (s, 3, CO_2CH_3), 4.35 (s, 2, CH_2), 6.49 (d, 1, J = 6 Hz, $H_{1'}$), 8.03 (s, 1, C_2H).

Anal. ($C_{18}H_{21}N_3O_9$) C, H, N.

5-Cyanomethyl-1-β-D-ribofuranosylimidazole-4-carboxamide (12). Compound **9** or **10** (0.046 mol) and liquid ammonia (150 ml) were placed in a steel bomb (300 ml). The bomb was three-quarters submerged in a steam bath and heated for 3 h. At this point, TLC [silica gel, chloroform–methanol (4:1)] indicated a trace of the intermediate, methyl 5-cyanomethyl-1-β-D-ribofuranosylimidazole-4-carboxylate, remaining and that a small amount of 3-deazaguanosine had formed. The ammonia was allowed to evaporate at room temperature, and the residue was subjected to a vacuum overnight to remove the last traces of ammonia. The brown residue was dissolved in methanol, absorbed on silica gel (25 g), and placed on a column of silica gel (500 g) packed in chloroform. Elution was with chloroform–methanol (4:1). The uv-absorbing fractions containing the major product were pooled, and the volume was reduced by evaporation under reduced pressure until crystallization began. Crystallization was allowed to proceed overnight at 0° to provide 10.5 g (81%) of **12** as colorless needles: mp 90–91° (after drying at 65° for 4 h); $[\alpha]^{25}D$ −46.9° (*c* 1.04, water); ir cm^{-1} (KBr) 2250 (w) (C≡N), 1666 (s) (C=O); λ_{max} (pH 1) 217 nm (ε 8750), 231 (sh) (8190); λ_{max} (pH 7) 219 (sh) (8190), 232 (8760); λ_{max} (pH 11) 234 (8750); ^1H NMR (Me_2SO-d_6) δ 4.52 (s, 2, CH_2), 3.71 (d, 1, J = 6 Hz, $H_{1'}$), 7.33 and 7.52 (s, 1, NH), 8.12 (s, 1, C_2H).

Anal. ($C_{11}H_{14}N_4O_5$) C, H, N.

6-Amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (3-Deazaguanosine, 17). Method A. A mixture of **12** (4.64 g, 20 mmol), 5% sodium carbonate solution (50 ml), and ethanol (25 ml) was refluxed with stirring for 0.5 h. Complete dissolution was obtained as reflux started. The colorless solution was filtered while hot. Crystallization begins ca. 0.5 h after filtration and was allowed to proceed overnight at room temperature. The crystals were filtered, washed thoroughly with water and ethanol, and dried at 100° for 8 h to provide 4.0 g of small white needles. An additional 0.8 g of product of the same purity was obtained from a second crop of crystals; total yield was 4.8 g (85%): mp 255–257° dec; $[\alpha]^{25}D$ −59.3 (*c* 0.97, 0.1 N NaOH); uv λ_{max} (pH 1) 284 nm (ε 13 650), 309 (sh) (6570); λ_{max} (pH 7) 270 (10 120), 298 (8140); λ_{max} (pH 11) 272 (10 120), 295 (sh) (8140); ^1H NMR (Me_2SO-d_6) δ 5.51 (d, 1, J = 6 Hz, $H_{1'}$), 5.52 (s, 1, C_7H), 5.68 (s, 2, NH_2), 7.95 (s, 1, C_2H), 10.5 (s, 1, NH).

Anal. ($C_{11}H_{14}N_4O_5$) C, H, N.

Method B. Compound **9** or **10** (30 mmol) and liquid ammonia (60 ml) were heated in a steel bomb (120 ml) for 22 h at 110°. The ammonia was allowed to evaporate at room temperature, and the brown residue was triturated with ethanol (500 ml in 4 portions). The light-brown residue was recrystallized three times from ethanol–water and provided 1.7 g (20%) of 3-deazaguanosine as light beige needles. This material was identical with 3-deazaguanosine prepared in method A.

6-Amino-3-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one (18). A mixture of **13** or **14** (9.53 mmol) and liquid ammonia (20 ml) was placed in a steel bomb (40 ml). The bomb was three-quarters submerged in a steam bath and heated for 2 h. The ammonia was allowed to evaporate at room temperature, and the residue was subjected to a vacuum overnight. The residue was triturated with methanol (300 ml) and then recrystallized from water (charcoal) to provide **18** as white needles (2.15g, 80%): mp 210° dec after drying at 100° for 5 h; $[\alpha]^{25}D$ +21.4 (*c* 0.96, 0.1 N NaOH); λ_{max} (pH 1) 277 nm (ε 11 400), 317 (5940); λ_{max} (pH 7) 258 (6400), 317 (7400); λ_{max} (pH 11) 258 (6210), 316 (7000); ^1H NMR (Me_2SO-d_6) δ 5.42 (s, 2, NH_2), 5.61 (s, 1, C_7H), 6.24 (d, 1, J = 5 Hz, $H_{1'}$), 8.34 (s, 1, C_2H), 10.73 (s, 1, NH).

Anal. ($C_{11}H_{14}N_4O_5$) C, H, N.

5-Cyanomethyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (21). A suspension of 5-cyanomethyl-1-β-D-ribofuranosylimidazole-4-carboxamide (1.41 g, 5 mmol), acetic anhydride (15 ml), and *p*-dimethylaminopyridine (20 mg) was stirred at room temperature for 8 h. TLC [silica gel, $CHCl_3$–MeOH (4:1)] indicated three products. Additional *p*-dimethylaminopyridine (20 mg) and acetic anhydride (5 ml) was added and stirring continued at room temperature for 36 h. The solution was evaporated in vacuo to a syrup which was dissolved in chloroform and placed on a column of silica gel (60 g). Elution with chloroform–methanol (20:1) provided the triacetate (2.0 g, 95%) as a white foam; ^1H NMR (Me_2SO-d_6) δ 2.08, 2.10, 2.16 (s, 3, $COCH_3$), 4.40 (s, 2, CH_2), 6.13 (d, 1, J = 5 Hz $H_{1'}$), 7.39 and 7.58 (s, 2, NH), 8.19 (s, 1, C_2H).

Anal. ($C_{17}H_{20}N_4O_8$) C, H, N.

5-Cyanomethyl-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (22). A solution of **12** (1.41 g, 5 mmol), dry acetone (20 ml), and 2,2-dimethoxypropane (10 ml) was cooled in an ice bath and stirred as perchloric acid (70%, 280 mg) was added. The ice bath was removed, and the reaction was allowed to stir at room temperature for 3 h. The reddish-orange solution was adjusted to ca. pH 7 with 10% aqueous potassium hydroxide and evaporated in vacuo to a syrup which was dissolved in chloroform, filtered, and placed on a column of silica gel (45 g). Elution with chloroform–methanol (20:1) provided the isopropylidene derivative (1.35 g, 84%) as a white foam: λ_{max} (pH 1) 217 nm (ε 9850); λ_{max} (pH 7) 233 (9690); λ_{max} (pH 11) 239 (9690); ^1H NMR (Me_2SO-d_6) δ 1.39 and 1.58 (s, 3, CH_3), 4.48 (s, 2, CH_2), 6.00 (d, 1, J = 2 Hz, $H_{1'}$), 7.35 and 7.53 (s, 1, NH), 8.14 (s, 1, C_2H).

Anal. ($C_{14}H_{18}N_4O_5$) C, H, N.

5-Cyanomethyl-1-β-D-ribofuranosylimidazole-4-carboxamide 5′-Phosphate (23). To a solution of phosphoryl chloride (4.9 g, 32 mmol) and trimethyl phosphate (40 ml) (cooled to 0° with an ice bath) was added, with stirring, powdered **12** (2.26 g, 8 mmol). The suspension was stirred at 0° (protected from moisture) for 4 h. Complete dissolution was obtained within 0.5 h. TLC [aliquot hydrolyzed with water, silica gel, acetonirile–0.2 M ammonium chloride (3:1)] indicated a complete and clean conversion of the nucleoside to the nucleotide. The light-beige solution was added dropwise to a vigorously stirred flask of anhydrous ether (500 ml). The ether was decanted, and additional ether (250 ml) was added to the residual syrup. After stirring for 10 min, the ether was decanted. This process was repeated once more with additional ether (250 ml). The residual syrup was dissolved in crushed ice (ca. 50 g) and the solution then extracted with chloroform (2 × 50 ml). The aqueous solution was allowed to stand overnight at room temperature, then adjusted to pH 8 with 1 N sodium hydroxide solution and placed on a column of Bio-Rad AG-1 × 8 (formate form, 50–100 mesh, 50 ml). The column was first washed with water (250 ml) and then with a gradient of 0.2 M to 0.5 M formic acid (1 l. each). The product appeared after ca. 1 l. of gradient had passed through the column. The product containing fractions were pooled and evaporated under reduced pressure to a small volume. Addition of ethanol (100 ml) provided the desired phosphate as a white powder (1.61 g, 80%) after washing successively with ethanol and ether and drying at 100° for 5 h; mp >160°; $[\alpha]^{25}D$ −27.5 (*c* 1.06,

0.1 N NaOH); λ_{max} (pH 1) 213 nm (ϵ 10 100); λ_{max} (pH 7) 235 (8750); λ_{max} (pH 11) 238 (7410); ^{1}H NMR (Me_2SO-d_6) δ 5.72 (d, 1, J = 4 Hz, $H_{1'}$), 8.08 (s, 1, C_2H).

Anal. ($C_{11}H_{15}N_4O_8P \cdot H_2O$) C, H, N.

6-Amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)-one 5′-phosphate [3-Deaza-5′-guanylic Acid (24)], Method A. A solution of **23** (1.09 g, 3 mmol) and water (50 ml) was adjusted to pH 10.0 with 10% sodium carbonate and refluxed 40 min. The light-yellow solution was adjusted to pH 6.5 with Dowex 50(H^+) and placed on a column of Bio-Rad Ag-1 × 8 (formate form, 50–100 mesh, 40 ml). The column was first washed with water (250 ml) and then with a 0.2 M to 0.5 M formic acid gradient (1 l. each). The product appeared after ca. 1 l. of gradient had passed through the column. The fractions containing the product were pooled and evaporated to a small volume. Addition of ethanol (150 ml) precipitated a light-beige powder which was filtered and washed successively with ethanol and ether to provide 0.82 g (75%) of **24**, mp >180° dec after drying at 100° for 12 h: $[\alpha]^{25}D$ −11.4 (*c* 1.06, water); λ_{max} (pH 1) 287 nm (ϵ 8400), 306 (sh) (4930); λ_{max} (pH 7) 272 (8400), 303 (6380); λ_{max} (pH 11) 272 (8130), 303 (6090); ^{1}H NMR (D_2O) δ 5.89 (d, 1, J = 4 Hz, $H_{1'}$), 9.00 (1, s, C_2H).

Anal. ($C_{11}H_{15}N_4O_8P$) C, H, N.

Method B. To a solution of phosphoryl chloride (2.82 g, 18.44 mmol) and trimethyl phosphate (11.5 ml) (cooled to 0° with an ice bath) was added powdered **17** (1.3 g, 4.61 mmol). The suspension was stirred at 0° (protected from moisture) for 10 h. The amber solution was added dropwise to a vigorously stirred flask of anhydrous ether (250 ml). The ether was decanted and additional ether (150 ml) was added to the beige precipitate. After stirring for 0.5 h, the ether was decanted, and this procedure was repeated once more with additional ether (150 ml). The precipitate was filtered, washed with ether, and then dissolved in ice-water (ca. 30 g). The aqueous solution was allowed to stand at room temperature overnight, adjusted to pH 8 with 1 N NaOH, and placed on a column of Bio-Rad Ag-1 × 8 (formate form, 50–100 mesh, 15 ml). After washing with water (150 ml), the column was eluted with a gradient of 0.2 to 0.5 M formic acid (500 ml each, 15-ml fractions were collected). Fractions 20–75 were pooled and reduced to a small volume in vacuo. Addition of ethanol (150 ml) precipitated **23** which was filtered, washed with ethanol and ether, and dried under high vacuum at 100° for 12 h (0.5 g, 30%). The material was identical with **24** prepared in method A.

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