27 mg (50%) of **33**, mp 132–133°. A mixture melting point of the two samples of **33** was unchanged.

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**Registry No.**—**1**, 56783-59-6; **2**, 40773-64-6; **3**, 50272-14-5; **4**, 50272-15-6; **5**, 50272-16-7; **6**, 50272-17-8; **7**, 50272-18-9; **8**, 50272-19-0; **9**, 50421-06-2; **10a**, 50272-20-3; **10** isomer A, 56783-60-9; **12**, 50272-21-4; **13**, 50272-22-5; **14**, 50272-23-6; **15**, 56783-61-0; **16**, 20196-81-0; **17**, 56783-62-1; **18**, 56783-63-2; **19**, 56783-64-3; **20**, 56783-65-4; **21**, 56783-66-5; **22**, 56783-67-6; **23**, 56783-68-7; **24**, 56783-69-8; **25**, 56783-70-1; **26**, 56783-71-2; **28**, 56783-72-3; **29**, 56816-60-5; **30**, 22395-75-1; **31**, 56783-73-4; **32**, 50272-24-7; **33**, 50272-13-4; benzyl chloride, 100-44-7; methanesulfonyl chloride, 124-63-0; *p*-toluenesulfonyl chloride, 98-59-9; acetone, 67-64-1.

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# Imidazo[1,2-*c*]pyrimidine Nucleosides. Synthesis of N-Bridgehead Inosine Monophosphate and Guanosine Monophosphate Analogues Related to 3-Deazapurines[1]

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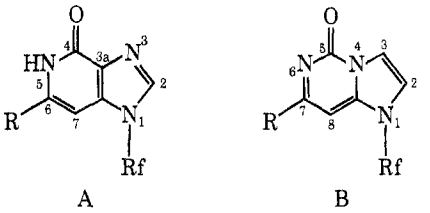
The first chemical syntheses of imidazo[1,2-*c*]pyrimidine nucleosides are described. Cyclization of 4-amino-6-chloro-2-pyrimidinol (**2**) with bromoacetaldehyde diethyl acetal gave 7-chloroimidazo[1,2-*c*]pyrimidin-5-one (**3**). Direct glycosylation of the trimethylsilyl derivative of **3** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile gave an anomeric mixture of 7-chloro-1-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (**12**) which on deacetylation and separation of anomers furnished 7-chloro-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**10**) and its α anomer (**11**). However, the glycosylation of $Me_3Si$-**3** with tetra-*O*-acetyl-β-D-ribofuranose in dichloroethane containing stannic chloride, followed by aminolysis, gave only the β anomer **10**. Catalytic dehalogenation of **10** and **11** furnished the 3-deazainosine analogue, 1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**15**), and its α anomer (**17**), respectively. Amination of **10** gave 7-amino-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**13**), an analogue of 3-deazaguanosine possessing a bridgehead nitrogen atom. Phosphorylation of **15**, **17**, and **13** gave 1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one 5′-monophosphate (**16**), the IMP analogue, its α anomer (**18**), and 7-amino-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one 5′-monophosphate (**14**), the GMP analogue, respectively. The assignment of site of ribosylation has been determined unequivocally by using $^{13}C$ NMR spectroscopy and the anomeric configurations have been established by using $^1H$ NMR of the 2′,3′-*O*-isopropylidene derivatives of **10** and **11**.

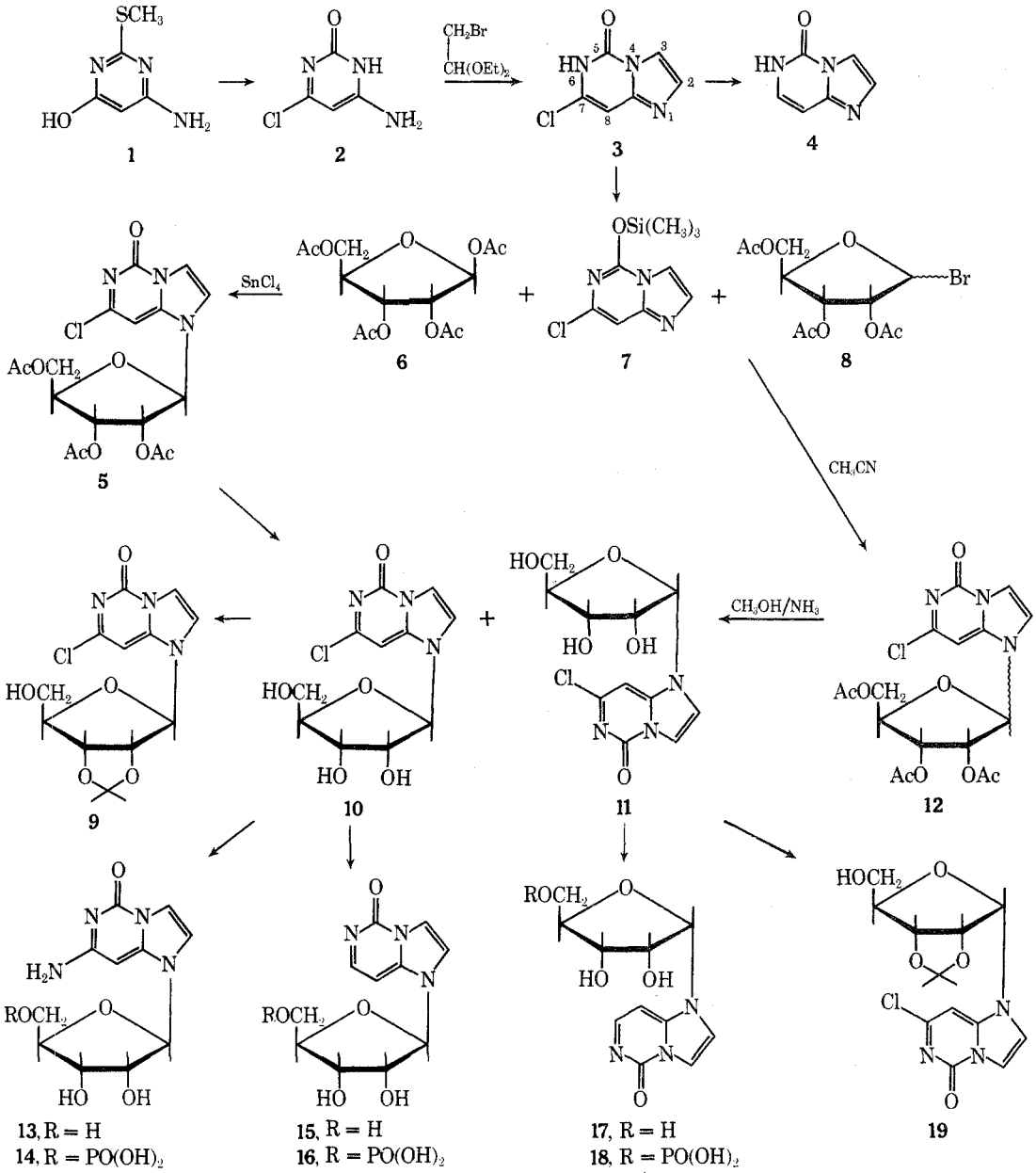
It is well established that alterations of either the furanose or the base moiety of naturally occurring purine nucleosides may produce analogues that exert interesting biological effects.[2] The role of the various nitrogen atoms of purine nucleosides as binding sites for important enzymes in biological systems has become the subject of considerable interest.[3] The isolation of a number of antibiotics of the deazapurine series (e.g., viomycin,[4] tubercidin,[5] toyocamycin[6]) which are isomeric or isosteric with purine are of particular interest because of their structural uniqueness and their biological properties.[6b,7] Since the majority of purine-type ribosides exist in the anti conformation (some exist in the syn conformation in the solid state[8]), 3-deazapurine nucleosides deserve special attention because $N_3$ of purine nucleosides is presumed to be involved in stabilizing the syn conformation through intramolecular hydrogen bonding [5′-OH···$N_3$H].[9] The syntheses of several 3-deazapurine nucleosides[10] and nucleotides[10f,g,11] (A) have been




Rf = -β-D-ribofuranosyl

reported. Some of these 3-deazapurine derivatives have demonstrated significant antibacterial,[12] anticancer,[10b,e] and antiviral[10g] activity. The imidazo[1,2-*c*]pyrimidine ring system (B), which has not been explored appreciably, may be regarded as 3-deazapurine with a bridgehead nitrogen atom in which $N_3$ and $C_{3a}$ are interchanged. The nucleoside analogues of imidazo[1,2-*c*]pyrimidine have the potential, therefore, either to emulate or to antagonize the functions of the naturally occurring nucleosides and nucleotides.

Scheme I



These nucleoside analogues are also of particular interest since they lack an N(H) function at position 1 of purine; hydrogen bonding of the Watson–Crick type, therefore, would not be possible.

For these reasons we pursued the synthesis of 3-deaza analogues with a bridgehead nitrogen atom of some naturally occurring nucleotides, inosine monophosphate and guanosine monophosphate. The complete synthetic route consists of three parts: synthesis of an appropriate imidazo[1,2-c]pyrimidine; conversion of the starting imidazo[1,2-c]pyrimidine to the required nucleoside; and finally, the phosphorylation of the nucleoside to the corresponding 5′-monophosphate.

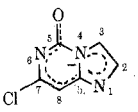
The most frequently encountered procedure for the synthesis of imidazo[1,2-c]pyrimidines involves the cyclization of 4(6)-aminopyrimidine derivatives with an α-halocarbonyl compound.[13] The possibility of utilizing this approach was investigated for the synthesis of 7-chloroimidazo[1,2-c]pyrimidin-5(6*H*)-one (**3**). Compound **3** was particularly elected as the starting material, since the halogen group is known to deactivate its neighboring nitrogen in a glycosylation reaction[14] thereby producing the requisite $N_1$ glycosyl derivative. The logical key intermediate, 4-amino-6-chloro-2-pyrimidinol[15] (**2**), was prepared in 83% yield in one step from 2-methylthio-4-amino-6-pyrimidinol[16] (**1**) (Scheme I). Compound **1** was chlorinated with phosphorus oxychloride and without isolation of the intermediate, 2-methylthio-4-amino-6-chloropyrimidine, the acidic aqueous solution was heated on a steam bath to obtain crystalline **2**. Ring closure of **2** with bromoacetaldehyde diethyl acetal in aqueous media at reflux gave exclusively 7-chloroimidazo[1,2-c]pyrimidin-5-one (**3**) in 86% yield. The assignment of this structure is based on the fact that the $^1H$ NMR ($Me_2SO$-$d_6$–NaOD) spectrum of **3** revealed a singlet at δ 6.46 ($C_8H$) in addition to two doublets at δ 7.54 ($J$ = 2 Hz, $C_2H$) and 7.24 ($J$ = 2 Hz, $C_3H$). Catalytic dehalogenation of **3** with 10% palladium on carbon in a hydrogen atmosphere readily gave imidazo[1,2-c]pyrimidin-5-one (**4**). The identity of this compound was confirmed by rigorous comparison of the physicochemical data reported[13e] for **4**, thereby confirming the structure of **3**. It is of particular interest to note that earlier attempts[17] to remove the chloro groups of 5-substituted 2,7-dichloroimidazo[1,2-c]pyrimidines by hydrogenation were unsuccessful.

The glycosylation of **3** was next considered. Treatment of 7-chloroimidazo[1,2-*c*]pyrimidin-5(6*H*)-one with hexamethyldisilazane in the presence of ammonium sulfate, according to the general procedure described by Wittenburg,[18] gave the trimethylsilyl derivative (**7**) which without further purification was treated with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**8**) in acetonitrile at room temperature as described previously.[14,19] Under these conditions a 93% yield of an anomeric mixture of 7-chloro-1-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (**12**) was obtained, which resisted our efforts to separate the pure anomers by silicic acid column chromatography. Deacetylation of the anomeric mixture **12** with methanolic ammonia at ambient temperature gave 7-chloro-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**10**) and its α anomer (**11**). The anomeric nucleosides were separated by fractional crystallization using methanol as the solvent; the less soluble α anomer **11** crystallizes first, the anomeric ratio being almost 1:1. The purity of these nucleosides was assured by elemental analysis and by $^1$H NMR spectroscopy. The formation of **11** is not surprising, since a number of exceptions to the Baker "trans" rule have been reported.[20] The formation of **10** established the retainment of the 7-chloro group, and confirmed the directive effect of the halogen group to give exclusively the $N_1$ glycosyl derivative.

In an effort to improve the yield of the β anomer **10** we have examined the use of Friedel–Crafts catalyzed glycosylation procedure.[21] Thus, treatment of 1 equiv of the trimethylsilyl derivative of **3** (**7**) in 1,2-dichloroethane with 1 equiv of fully acylated ribofuranose (**6**) and 1.44 molar equiv of stannic chloride afforded, after silicic acid column chromatography, a 64% yield of 7-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (**5**) as light yellow foam. Nucleoside **5** was the only nucleoside product which could be detected by TLC or column chromatography procedures. Aminolysis of **5** with methanolic ammonia at ambient temperature gave an 81% yield of **10**.

Although the anomeric configuration of **10** and **11** could tentatively be assigned as β and α, respectively, on the basis of several empirical rules,[22] and by a large negative specific rotation for **10** ($[\alpha]^{25}$D −39.5°) and positive specific rotation for **11** ($[\alpha]^{25}$D +34.07°), this could not be used for the unequivocal assignment of anomeric configuration, since there are no imidazo[1,2-*c*]pyrimidine $N_1$ ribosides available for comparison. Therefore, a more rigorous proof was in order for this unusual heterocyclic nucleoside series. The $^1$H NMR spectra of **10** and **11** in $Me_2SO$-$d_6$ revealed a doublet (for $C_1$'H) centered at δ 5.85 and 6.23, respectively, with a $J_{1,2}$ of approximately 4.5 Hz, which contemplated the preparation of the 2′,3′-*O*-isopropylidene derivative in order to reduce the magnitude of the coupling constant to within the acceptable limits.[23] Isopropylidenation of **10** and **11** with 70% perchloric acid and 2,2-dimethoxypropane in acetone furnished 7-chloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (**9**) and the α anomer (**19**) in good yield. The $^1$H NMR spectrum of **9** in $Me_2SO$-$d_6$ revealed a doublet centered at δ 6.13 with a $J_{1,2}$ of 3.5 Hz indicating the β configuration. The spectrum also revealed the difference between the chemical shift of the two methyl signals of isopropylidene group to be 0.23 ppm, a difference characteristic of the β configuration.[24] Similarly, the $^1$H NMR spectrum of **19** in $Me_2SO$-$d_6$ revealed the difference in proton chemical shifts between the isopropylidene methyl groups to be almost 0.0 ppm, indicating the α configuration.[24] Based on this data, the anomeric configuration for **9** and **19**, and hence for **10** and **11**, were unequivocally assigned as β and α, respectively.

Table I
Comparison of $^{13}$C Chemical Shifts for the Anion of 7-Chloroimidazo[1,2-*c*]pyrimidin-5-one (C) and its Nucleosides (10 and 11)

| Compd | Chemical shift, δ, ppm[a] | | | | | |
|---|---|---|---|---|---|---|
| | $C_2$ | $C_3$ | $C_5$ | $C_7$[b] | $C_8$ | $C_b$[b] |
|  C | 129.4 | 109.4 | 150.9 | 147.2 | 92.2 | 148.4 |
| **10** | 118.9 | 111.0 | 155.3 | 148.0 | 89.6 | 144.6 |
| **11** | 121.3 | 109.9 | 154.7 | 148.2 | 86.2 | 144.6 |
| Δδ C-**10** | 10.5 | −1.6 | −4.4 | −0.8 | 2.6 | 3.8 |
| Δδ C-**11** | 8.1 | −0.5 | −3.8 | −1.0 | 6.0 | 3.8 |

[a] Chemical shifts are measured from $Me_2SO$-$d_6$, converted to $Me_4Si$ scale using the relationship $\delta_{Me_4Si} = \delta_{Me_2SO\text{-}d_6} + 39.5$ ppm. [b] Assignments tentative.

The site of ribosylation was established by using $^{13}$C NMR spectroscopy. The use of $^{13}$C chemical shifts for the determination of glycosylation site in nucleosides of fused nitrogen heterocycles has recently been documented.[25] The assignments were made on the basis of the α and β substitution shifts observed when the ribofuranosyl derivatives were compared with the corresponding ionized base.[26] The pertinent $^{13}$C chemical shifts of the anion of **3** and its ribosylated derivatives are summarized in Table I. The assignment of various carbons was obtained through examination of the multiplicity patterns in the proton-coupled spectra as well as comparisons of the $^{13}$C chemical shifts with related compounds.[25] By comparing the $^{13}$C chemical shifts of the anion of **3** (C), **10**, and **11**, we note that upfield shifts of 10.5 and 3.8 ppm were observed for $C_2$ and $C_b$ (α carbons to $N_1$) and a downfield shift of 1.6 ppm was observed for $C_3$ (β carbon to $N_1$) for the nucleoside **10**; similar substitution shifts were observed for the nucleoside **11**. These changes in chemical shifts are consistent with the large upfield α shifts and small downfield β shifts predicted for the nucleosides, which leads to the conclusion that $N_1$ is the ribosylation site. The downfield shifts observed for the $C_5$ and $C_7$ (α carbons to $N_6$) in **10** and **11** also indicate that ribosylation has not occurred at the $N_6$ position. Additional support for the site of ribosylation was also obtained by the direct comparison of the reported ultraviolet absorption spectra of 6-methylimidazo[1,2-*c*]pyrimidin-5-one[27] or the fluorescent 6-ribosylimidazo[1,2-*c*]pyrimidin-5-one[28] [$\lambda_{max}$ (0.05 *N* HCl) 248 s, 288, 302 nm s (ε 4.4, 12.3, 7.0 × $10^3$); $\lambda_{max}$ (pH 7) 272, 281 s, 292 nm s (ε 11.7, 11.1, 6.7 × $10^3$); $\lambda_{max}$ (0.05 *N* NaOH) 272, 281 s, 292 nm s (ε 12.0, 10.9, 5.3 × $10^3$)] with the ultraviolet absorption spectra observed for **15** and **17** (see Experimental Section), which conclusively established that the ribosylation has not taken place at $N_6$.

Catalytic dehalogenation of **10** and **11** with 10% palladium on carbon in a hydrogen atmosphere at room temperature gave the 3-deazainosine analogue 1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**15**) in 65% yield, and the corresponding α anomer (**17**) in 68% yield, respectively. Treatment of **10** with anhydrous methanol containing liquid ammonia at elevated temperature and pressure furnished a 64% yield of 7-amino-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**13**), the 3-deazaguanosine analogue possessing a bridgehead nitrogen atom in which $N_3$ and $C_{3a}$ are interchanged. Typical of most of the compounds in the present work, **13**, **15**, and **17** were obtained as well-defined crystalline products. Phosphorylation[29] of unprotected **15** with phosphorus oxychloride using trimethyl

phosphate as solvent at ambient temperature provided a rather low yield of N-bridgehead IMP analogue, 1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one 5′-monophosphate (16), which was isolated in the free acid form. Similarly, the nucleoside 17 was phosphorylated to 1-α-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one 5′-monophosphate (18). Direct phosphorylation of 13 in the manner as described above provided the GMP analogue with a bridgehead nitrogen atom, 7-amino-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one 5′-monophosphate, isolated as the free acid after ion-exchange chromatography. The structure of these IMP and GMP analogues was confirmed by $^1$H NMR spectra and elemental analyses. The purity was assured by the homogeneity in several thin layer systems and on paper electrophoresis.

## Experimental Section

Melting points were taken on 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. Nuclear magnetic resonance ($^1$H NMR) spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer R-20A spectrometer in $Me_2SO$-$d_6$ or $D_2O$ using DSS as an internal standard. A Bruker HX-90 NMR spectrometer operating at 22.62 MHz in the Fourier transform mode was used to obtain the $^{13}$C NMR spectra (20% solutions in $Me_2SO$-$d_6$). A Fabri-Tek 1074 signal averager with 4096 word memory was used for data accumulation and a Digital PDP-8/e computer for data processing. Ultraviolet spectra (uv, $\epsilon \times 10^3$, s = shoulder) were recorded on a Cary Model 15 spectrometer and infrared spectra (ir) on a Perkin-Elmer 257 spectrophotometer (KBr pellets). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Chromatography solvent mixtures were by volume and the systems used were: D, ethyl acetate–water–1-propanol (4:2:1, upper phase); E, ethyl acetate–ethanol–water (4:2:1); F, 2-propanol–concentrated ammonium hydroxide–water (7:1:2). Evaporations were carried out under reduced pressure with bath temperature below 30°.

**4-Amino-6-chloro-2-pyrimidinol (2).** To a suspension of dry 2-methylthio-4-amino-6-pyrimidinol[16] (1, 20.0 g, 127 mmol) in phosphorus oxychloride (100 ml) was added with agitation *N,N*-diethylaniline (10 ml) and the mixture was gently refluxed for 6 hr. The excess phosphorus oxychloride (about 65 ml) was removed in vacuo, and the residual syrup poured over crushed ice (200 g) with stirring. The cold mixture was slowly brought to room temperature with continuous stirring, during which time nearly all insoluble material went into solution. The clear solution was decanted from a small amount of insoluble gum and was heated on a steam bath overnight. After refrigeration the solid that crystallized out was collected to give 19.9 g of the HCl salt. The salt was dissolved in hot water (1 l.), treated with charcoal, and filtered, and the hot filtrate was adjusted to pH 6–7 with 40% aqueous sodium hydroxide solution. After cooling the crystalline solid was collected and dried to yield 15.4 g (83%) of 2, mp >300° (lit.[15] mp >300°).

**7-Chloroimidazo[1,2-c]pyrimidin-5-one (3).** To a suspension of 4-amino-6-chloro-2-pyrimidinol (2, 19.0 g, 130 mmol) in water (400 ml) was added bromoacetaldehyde diethyl acetal (26.0 g, 132 mmol). The mixture was refluxed with stirring for 1.5 hr and then an additional 26.0 g of bromoacetaldehyde diethyl acetal was added. Refluxing was continued until solution was complete (2–3 hr). The heating mantle was replaced with an ice bath, and the brown solution was immediately neutralized with solid sodium bicarbonate. The cooled mixture was filtered, and the solid was washed with cold water, then acetone, and finally with ether. The tan-colored solid, weighing 19.1 g (86%), was used directly without further purification. A small sample was crystallized from water to afford an analytical sample: mp >300°; $^1$H NMR ($Me_2SO$-$d_6$–NaOD) δ 6.46 (s, $C_8H$), 7.24 (d, $J$ = 2.0 Hz, $C_3H$), 7.54 (d, $J$ = 2.0 Hz, $C_2H$); uv $\lambda_{max}$ (pH 1) 260 nm s (ε 5.5), 292 (12.8), 304 s (7.3); $\lambda_{max}$ (pH 7) 265 nm s (ε 6.2), 292 (13.5); $\lambda_{max}$ (pH 11) 283 nm (ε 12.4), 301 s (7.2); ir 1680 (C=O), 3110 cm$^{-1}$ (NH).

Anal. Calcd for $C_6H_4ClN_3O$ (169.57): C, 42.50; H, 2.38; N, 24.78. Found: C, 42.25; H, 2.26; N, 24.59.

**Imidazo[1,2-c]pyrimidin-5-one (4).** 7-Chloroimidazo[1,2-c]pyrimidin-5-one (3, 2.0 g, 11.8 mmol) was dissolved in 50% aqueous ethanol (200 ml) containing concentrated ammonium hydroxide (5 ml), and to this solution was added 10% palladium on carbon (0.20 g). The mixture was shaken under hydrogen (45 psi) at room temperature for 1.5 hr. The mixture was filtered through a Celite pad and the filtrate concentrated to 20 ml. After cooling, the crystalline solid was collected by filtration and dried to give 1.46 g (93%). A small sample was recrystallized from water to give pure 4: mp 278° dec (lit.[13e] mp 272–274°); $^1$H NMR ($Me_2SO$-$d_6$) δ 6.63 (d, $J$ = 8.0 Hz, $C_8H$), 7.32 (d, $J$ = 8.0 Hz, $C_7H$), 7.45 (d, $J$ = 2.0 Hz, $C_3H$), 7.82 (d, $J$ = 2.0 Hz, $C_2H$), 11.90 (broad, NH); uv $\lambda_{max}$ (pH 1) 248 nm s (ε 5.4), 282 (10.4), 297 s (5.8); $\lambda_{max}$ (pH 7) 267 nm (ε 11.3), 275 s (10.0), 287 s (5.0); $\lambda_{max}$ (pH 11) 276 nm (λ 11.1), 294 s (5.7); ir 1720 cm$^{-1}$ (C=O).

Anal. Calcd for $C_6H_5N_3O$ (135.12): C, 53.33; H, 3.73; N, 31.09. Found: C, 53.14; H, 3.66; N, 30.96.

**7-Chloro-1-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one (12).** Methylene chloride (30 ml) saturated with anhydrous hydrogen bromide at −20° was added to a solution of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (5.7 g, 17.5 mmol) in dry methylene chloride (30 ml) at −20°. The solution was protected from moisture and allowed to warm to 0°. The excess HBr and solvents were removed on a rotary evaporator, and the residual syrup was coevaporated with dry toluene (3 × 50 ml). This syrupy 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (8) was dissolved in "nanograde" acetonitrile[30] (85 ml) and added to the trimethylsilyl compound (7) obtained by refluxing 3 (2.77 g, 16.3 mmol) in hexamethyldisilazane (HMDS, 10 ml) in the presence of a catalytic amount of ammonium sulfate for 14 hr, under anhydrous conditions, and distilling off the excess HMDS in vacuo. The flask was stoppered and stirred at room temperature for 3.5 days. The reaction mixture was filtered to remove 0.15 g of unreacted 3. The dark filtrate was evaporated to dryness, and the residue was dissolved in chloroform (150 ml), washed with saturated aqueous sodium bicarbonate solution (2 × 50 ml) followed by water (2 × 50 ml), and then dried over anhydrous sodium sulfate. The chloroform was evaporated to dryness and the residual foam was chromatographed on silica gel (400 g) prepacked in ethyl acetate and eluted with solvent D. The band carrying the products was collected and evaporated to dryness, leaving 6.15 g (93%, based on the recovery of unreacted 3) of a yellow foam: uv $\lambda_{max}$ (pH 1) 250 nm (ε 4.3), 292 s (11.7), 302 (14.5), 313 s (10.6); $\lambda_{max}$ (pH 7) 253 nm (ε 4.5), 304 (16.1), 313 s (14.1); $\lambda_{max}$ (pH 11) 253 nm (ε 4.5), 304 (16.1), 313 s (14.1); ir 1670 (C=O of heterocycle), 1750 cm$^{-1}$ (OAc of sugar moiety).

**7-Chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one (5).** To a solution of 7 [prepared from 3.5 g (20.6 mmol) of 3] in anhydrous 1,2-dichloroethane (125 ml) was added 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (6, 5.6 g 20.6 mmol) followed by stannic chloride (7.9 g, 29.8 mmol). The reaction mixture was protected from moisture and stirred for 24 hr at ambient temperature. The reaction solution was then poured into 120 ml of saturated aqueous sodium bicarbonate solution with stirring. The resulting emulsion was filtered through Celite, and the organic layer was washed with water (50 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated to a light brown foam which was chromatographed on silica gel (600 g) prepacked in ethyl acetate and eluted with solvent D–ethyl acetate (1:1). The band containing the requisite product was evaporated to leave 5.6 g (64%) of light yellow foam: uv $\lambda_{max}$ (pH 1) 250 nm (ε 4.3), 292 s (11.8), 302 (14.6), 313 s (10.6); $\lambda_{max}$ (pH 7) 253 nm (ε 4.6), 304 (16.2), 313 s (14.1); $\lambda_{max}$ (pH 11) 253 nm (ε 4.6), 304 (16.2), 313 s (14.1); ir 1670 (C=O of heterocycle), 1750 cm$^{-1}$ (OAc).

**7-Chloro-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (10) and 7-Chloro-1-α-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (11).** The anomeric mixture of 7-chloro-1-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one (12, 6.7 g, 15.3 mmol) was dissolved in methanolic ammonia (150 ml, saturated at 0°) and the solution was allowed to stand at room temperature overnight. The volume of the reaction solution was reduced to about 75 ml and the solution was kept at room temperature for 4 hr. The tan-colored solid that crystallized was collected by filtration (G) and dried to give a chromatographically homogenous sample of the α anomer (11), 1.96 g (42%), mp 206–208°. Recrystallization from aqueous methanol afforded an analytically pure sample: mp 209°; $[\alpha]^{25}$D +34.07° (*c* 1.0, $Me_2SO$); $^1$H NMR ($Me_2SO$-$d_6$) δ 6.23 (d, $J$ = 4.5 Hz, $C_1'H$), 6.86 (s, $C_8H$), 7.77 (d, $J$ = 1.5 Hz, 2 H, $C_2H$ and $C_3H$); uv $\lambda_{max}$ (pH 1) 250 nm s (ε 4.2), 289 s (13.3), 299 (14.9), 312 s (9.8); $\lambda_{max}$ (pH 7) 253 nm (ε 4.2), 302 (16.4), 311 s (14.7); $\lambda_{max}$ (pH 11) 253 nm (ε 4.2), 302 (16.4), 311 s (14.7); ir 1645 cm$^{-1}$ (C=O of heterocycle).

Anal. Calcd for $C_{11}H_{12}ClN_3O_5$ (301.69): C, 43.79; H, 4.01, N, 13.92. Found: C, 43.40; H, 3.85; N, 13.78.

The filtrate from above (G) was allowed to stand in an open beaker until crystals began to form; then the container was covered and refrigerated. The crystalline solid was collected and dried to give 2.25 g (48%) of the β anomer (**10**), mp 190–191°. An analytical sample was obtained by recrystallization from aqueous ethanol: mp 192°; $[\alpha]^{25}D$ −39.6° (*c* 1.0, $Me_2SO$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 5.85 (d, *J* = 4.5 Hz, $C_{1'}H$), 6.95 (s, $C_8H$), 7.83 (d, *J* = 3.0 Hz, $C_3H$), 7.98 (d, *J* = 3.0 Hz, $C_2H$); uv $\lambda_{max}$ (pH 1) 250 nm (ε 4.4), 293 s (14.2), 301 (15.4), 312 s (11.5); $\lambda_{max}$ (pH 7) 253 nm (ε 5.5), 303 (17.1), 312 s (15.7); $\lambda_{max}$ (pH 11) 253 nm (ε 5.5), 303 (17.1), 312 s (15.7); ir 1650 $cm^{-1}$ (C=O of heterocycle).

Anal. Calcd for $C_{11}H_{12}ClN_3O_5$ (301.69): C, 43.79; H, 4.01, N, 13.92. Found: C, 43.52; H, 3.76; N, 13.78.

**7-Chloro-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (10).** A solution of 7-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (**5**, 3.5 g, 8.15 mmol) in methanolic ammonia (80 ml, saturated at 0°) was allowed to stand at room temperature overnight. The volume was reduced to about 35 ml, and the solution was decolorized with carbon and chilled. The colorless crystals that separated were collected and dried to afford 1.98 g (81%): mp 192°; $[\alpha]^{25}D$ −40.06° (*c* 1.0, $Me_2SO$); uv, ir, and $^1H$ NMR identical with those of **10** prepared as above.

**7-Chloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (9).** 2,2-Dimethoxypropane (0.5 ml) and 70% perchloric acid (0.5 ml) were added to dry acetone (120 ml). The mixture was protected from moisture and stirred at room temperature for 5 min before 7-chloro-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**10**, 0.40 g, 1.33 mmol) was added in one portion. The mixture was stirred for 3 hr and pyridine (0.5 ml) was added. The volume was reduced to about 15 ml, 10% aqueous potassium carbonate solution (15 ml) was added, and the remaining acetone was removed. Cold water (15 ml) was added to the aqueous solution, which was then left at 5° overnight. The crystals that deposited were collected and recrystallized from aqueous ethanol to yield 0.34 g (73%) of **9**: mp 191–192°; $[\alpha]^{25}D$ −29.5° (*c* 1.0, $Me_2SO$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.36 (s, $CH_3$), 1.59 (s, $CH_3$), 6.13 (d, *J* = 3.5 Hz, $C_{1'}H$), 6.88 (s, $C_8H$), 7.82 (d, *J* = 2.5 Hz, $C_3H$), 7.93 (d, *J* = 2.5 Hz, $C_2H$); uv $\lambda_{max}$ (pH 1) 249 nm (ε 2.7), 292 s (7.9), 302 (8.9), 314 s (6.2); $\lambda_{max}$ (pH 7) 253 nm (ε 4.1), 304 (11.4), 313 s (10.0); $\lambda_{max}$ (pH 11) 253 nm (ε 3.4), 304 (9.8), 313 s (9.3).

Anal. Calcd for $C_{14}H_{16}ClN_3O_5 \cdot 0.5H_2O$ (350.75): C, 47.93; H, 4.88; N, 11.98. Found: C, 48.14; H, 4.52; N, 11.96.

**7-Chloro-1-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (19).** Isopropylidenation of 7-chloro-1-α-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**11**, 0.40 g, 1.33 mmol) according to the procedure as described for **9** furnished 0.28 g (60%) of **19** after recrystallization from aqueous ethanol as needles: mp 202°; $[\alpha]^{25}D$ −45.8° (*c* 1.0, $Me_2SO$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.28 (s, 6 H of 2 $CH_3$, *J* = 0.0 Hz), 6.34 (d, *J* = 5.1 Hz, $C_{1'}H$), 6.87 (s, $C_8H$), 7.72 (d, *J* = 2.3 Hz, $C_3H$), 7.78 (d, *J* = 2.3 Hz, $C_2H$); uv $\lambda_{max}$ (pH 1) 249 nm (ε 4.4), 292 s (13.5), 301 (15.5), 313 s (10.7); $\lambda_{max}$ (pH 7) 252 nm (ε 6.3), 303 (17.4), 312 s (15.7); $\lambda_{max}$ (pH 11) 252 nm (ε 5.3), 303 (16.8), 312 s (15.3).

Anal. Calcd for $C_{14}H_{16}ClN_3O_5 \cdot 0.5H_2O$ (350.75): C, 47.93; H, 4.88; N, 11.98. Found: C, 48.17; H, 4.45; N, 11.99.

**1-β-D-Ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (15).** 7-Chloro-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**10**, 1.6 g, 5.32 mmol) was dissolved in 50% aqueous ethanol (120 ml) containing a few drops of concentrated ammonium hydroxide. To this solution was added 10% palladium on carbon (0.40 g) and the mixture was hydrogenated at 40 psi at room temperature for 1 hr. The mixture was filtered through a Celite pad and washed with hot water (2 × 10 ml). The combined filtrate and washings were concentrated to about 20 ml in vacuo. The white crystalline solid that separated was collected and dried to yield 0.92 g (65%) of **15**. It was recrystallized from ethanol as colorless needles: mp 196–197°; $[\alpha]^{25}D$ −52.4° (*c* 1.0, $Me_2SO$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 5.86 (d, *J* = 5.2 Hz, $C_{1'}H$), 6.73 (d, *J* = 6.1 Hz, $C_8H$), 7.84 (d, *J* = 3.0 Hz, $C_3H$), 7.98 (d, *J* = 3.0 Hz, $C_2H$), 8.05 (d, *J* = 6.1 Hz, $C_7H$); uv $\lambda_{max}$ (pH 1) 244 nm (ε 5.0), 285 s (12.1), 292 (12.3), 305 s (7.9); $\lambda_{max}$ (pH 7) 251 nm (ε 6.4), 302 (14.9), 309 s (12.8); $\lambda_{max}$ (pH 11) 251 nm (ε 6.3), 302 (15.5), 309 s (14.1); ir 1645 $cm^{-1}$ (C=O of heterocycle).

Anal. Calcd for $C_{11}H_{13}N_3O_5$ (267.23): C, 49.43; H, 4.90; N, 15.73. Found: C, 49.20; H, 4.78; N, 15.49.

**1-α-D-Ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (17).** 7-Chloro-1-α-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**11**, 1.8 g, 6.0 mmol) was catalytically dehalogenated according to the procedure described for **15** to afford 1.08 g (68%) of (**17**). An analytical sample was obtained by recrystallization from aqueous ethanol: mp 208° dec; $[\alpha]^{25}D$ +63.7° (*c* 1.0 $Me_2SO$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 6.26 (d, *J* = 6.5 Hz, $C_{1'}H$), 6.67 (d, *J* = 7.1 Hz, $C_8H$), 7.74 (d, *J* = 2.5 Hz, $C_3H$), 7.85 (d, *J* = 2.5 Hz, $C_2H$), 8.01 (d, *J* = 7.1 Hz, $C_7H$); uv $\lambda_{max}$ (pH 1) 246 nm (ε 4.4), 283 s (10.9), 292 (11.6), 304 s (7.0); $\lambda_{max}$ (pH 7) 251 nm (ε 5.5), 300 (13.2); $\lambda_{max}$ (pH 11) 251 nm (ε 5.9), 301 (14.5); ir 1647 $cm^{-1}$ (C=O of heterocycle).

Anal. Calcd for $C_{11}H_{13}N_3O_5$ (267.23): C, 49.43; H, 4.90; N, 15.73. Found: C, 49.26; H, 5.14; N, 15.65.

**7-Amino-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (13).** A suspension of 7-chloro-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**10**, 1.5 g, 49.9 mmol) in anhydrous methanol–liquid ammonia (3:1, 70 ml) was heated in a sealed steel reaction vessel at 100–105° for 45 hr. The resulting dark solution was evaporated to dryness and the residue was chromatographed on silica gel (250 g) prepacked in ethyl acetate and eluted with solvent E. The band containing the requisite product was collected and evaporated to dryness and the residue was triturated with hot ethanol (30 ml) and refrigerated. The solid was collected and dried to yield 0.89 g (64%) of **13**. A small sample was crystallized from water: mp >300° dec (sinters at 215°); $[\alpha]^{25}D$ −20.4° (*c* 1.0, $Me_2SO$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 5.53 (d, *J* = 5.5 Hz, $C_1H$), 5.62 (s, $C_8H$), 6.73 (broad, s, $NH_2$), 7.46 (d, *J* = 2.0 Hz, $C_3H$), 7.56 (d, *J* = 2.0 Hz, $C_2H$); uv $\lambda_{max}$ (pH 1) 265 nm (ε 9.2), 301 (22.1); $\lambda_{max}$ (pH 7) 293 nm (ε 22.6); $\lambda_{max}$ (pH 11) 292 nm (ε 22.9): ir 1635 (C=O of heterocycle), 3349 $cm^{-1}$ ($NH_2$).

Anal. Calcd for $C_{11}H_{14}N_4O_5$ (282.25): C, 46.80; H, 4.99; N, 19.85. Found: C, 46.56; H, 4.82; N, 19.60.

**1-β-D-Ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one 5′-Monophosphate (16).** Freshly distilled phosphorus oxychloride (0.80 g) and trimethyl phosphate (8 ml) were cooled to <5° in an ice-bath. Dry 1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**15**, 0.80 g, 3 mmol) was added all at once. The mixture was stirred at 0–10° until solution was complete (35 min), and then refrigerated at 3° for 4.5 hr. The reaction mixture was poured into ice–water (20 ml) containing sodium bicarbonate (1.0 g), with stirring. The cold solution was kept in an ice bath for 1 hr with occasional stirring, adding solid sodium bicarbonate periodically to keep the pH 5–6. The pH-stabilized solution was extracted with ether (2 × 15 ml) and the aqueous phase concentrated in vacuo until salts began to crystallize. Enough water was added to complete solution, the pH was checked at 6–7, and the solution was applied to a Barneby Cheney[31] charcoal column (80 g). The charcoal was washed with water (4 l.) to remove inorganic salts, and the product was eluted with water–methanol–concentrated ammonium hydroxide (45:45:10). The solution containing the product was concentrated in vacuo, acidified with Dowex 50 ($H^+$) resin (10 ml), and filtered. The filtrate was frozen and lyophilized to afford 0.105 g (10.0%) of light, fluffy powder: mp >148° dec; $[\alpha]^{25}D$ −30.2° (*c* 1.0, $H_2O$); $^1H$ NMR ($D_2O$) δ 6.17 (d, *J* = 5.2 Hz, $C_{1'}H$), 7.24 (d, *J* = 8.0 Hz, $C_8H$), 8.00 (d, *J* = 8.0 Hz, $C_7H$), 8.13 (d, *J* = 1.8 Hz, $C_3H$), 8.21 (d, *J* = 1.8 Hz, $C_2H$); uv $\lambda_{max}$ (pH 1) 244 nm (ε 2.9), 292 (7.8), 305 s (4.8); $\lambda_{max}$ (pH 7) 249 nm (ε 4.2), 300 (8.7); $\lambda_{max}$ (pH 11) 249 nm (ε 3.6), 300 (9.9), 309 s (8.7).

Anal. Calcd for $C_{11}H_{14}N_3O_8P$ (347.22): C, 38.04; H, 4.07; N, 12.10. Found: C, 37.74; H, 4.11; N, 11.90.

**1-α-D-Ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one 5′-Monophosphate (18).** 1-α-D-Ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**17**, 0.79, 2.95 mmol) was phosphorylated with phosphorus oxychloride (0.9 g) using trimethyl phosphate (9.5 ml) as the solvent. It was treated as described in **16** to yield 0.125 g (12.2%) of **18**: mp >183° dec; $[\alpha]^{25}D$ +17.2° (*c* 1.0, $H_2O$); $^1H$ NMR ($D_2O$) δ 6.51 (d, *J* = 6.0 Hz, $C_{1'}H$), 7.10 (d, *J* = 8.0 Hz, $C_8H$), 7.92 (d, *J* = 8.0 Hz, $C_7H$), 8.01 (d, *J* = 2.5 Hz, $C_3H$), 8.09 (d, *J* = 2.5 Hz, $C_2H$); uv $\lambda_{max}$ (pH 1) 244 nm (ε 3.2 ), 291 (7.8), 305 s (4.5); $\lambda_{max}$ (pH 7) 250 nm (ε 3.9), 297 (8.9); $\lambda_{max}$ (pH 11) 250 nm (ε 3.9), 298 (9.7), 310 s (8.9).

Anal. Calcd for $C_{11}H_{14}N_3O_8P \cdot H_2O$ (365.23): C, 36.17; H, 4.41; N, 11.50. Found: C, 35.80; H, 4.30; N, 11.12.

**7-Amino-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one 5′-Monophosphate (14).** Redistilled phosphorus oxychloride (0.80 g) and trimethyl phosphate (8 ml) were cooled to <0° in an ice bath. Dry 7-amino-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (**13**, 0.70 g, 2.48 mmol) was added and the mixture was stirred at 0–5° for 1 hr until solution was almost complete. The mixture was then stored at 3° for 3 hr with occasional agitation. The light brown solution (a small amount of solid remained undissolved) was poured into ice–water (30 ml) containing sodium carbonate (1.1 g) with stirring and external cooling. The mixture was occasionally stirred in an ice bath for 1 hr, and the pH was monitored at 5–6 by adding solid sodium carbonate when needed. The pH-stabilized solution was extracted with ether (2 × 15 ml) and

the aqueous phase was concentrated in vacuo until salts began to crystallize. Enough water was added to complete solution, the pH was adjusted to 6–7, and then the solution was applied to a column containing Dowex 1 × 2 (100–200 mesh, formate form, 40 ml). The resin was washed with water (2 l.) to remove unreacted **13** and the inorganic salts. The compound was obtained by gradient elution (0.1 *M* formic acid to $H_2O$). The eluent containing the compound was pooled, frozen, and lyophilized to yield 0.24 g (23.5%) of **14**, mp >169° dec. This was slightly impure, so 0.17 g of this product was passed through a column containing the same resin as above (15 ml), to give 0.11 g of pure (**14**) after work-up as above: mp >172° dec; $[\alpha]^{25}D$ −62.9° (*c* 1.0, $H_2O$); $^1H$ NMR ($D_2O$) δ 5.71 (d, *J* = 5.5 Hz, $C_{1'}H$), 7.50 (s, 2 H, $C_2H$ and $C_3H$); uv $\lambda_{max}$ (pH 1) 265 nm (ε 8.4), 302 (19.4); $\lambda_{max}$ (pH 7) 293 nm (ε 19.9); $\lambda_{max}$ (pH 11) 292 nm (ε 20.3).

Anal. Calcd for $C_{11}H_{15}N_4O_8P \cdot 1.5H_2O$ (389.25): C, 33.94; H, 4.66; N, 14.39. Found: C, 34.14; H, 4.38; N, 14.54.

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**Registry No.**—**1**, 1074-41-5; **2**, 3289-35-8; **3**, 56817-09-5; **4**, 55662-66-3; **5**, 56817-10-8; **6**, 13035-61-5; **7**, 56817-11-9; **9**, 56817-12-0; **10**, 56817-13-1; **11**, 56817-14-2; **β-12**, 56817-10-8; **α-12**, 56817-15-3; **13**, 56817-16-4; **14**, 56817-17-5; **15**, 56817-18-6; **16**, 56817-19-7; **17**, 56817-20-0; **18**, 56817-21-1; **19**, 56817-22-2; 2,2-dimethoxypropane, 77-76-9; phosphorus oxychloride, 10025-87-3; 7-chloroimidazo[1,2-*c*]pyrimidin-5-one anion, 56817-23-3.

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# Pyrimido[4,5-*b*][1,4]oxazines, 8-Oxadihydropteridines[1]

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The synthesis and characterization of several 2-amino-4-hydroxy-6- and/or -7-(substituted)pyrimido[4,5-*b*]-[1,4]oxazines (8-oxadihydropteridines) have been accomplished. These compounds are homeosteric analogues of the 7,8-dihydropteridine moiety and were produced by the condensation of 2,5-diamino-4,6-pyrimidinediol and an α-halo ketone. Hydrogenation of the $N_5$–$C_6$ double bond in formic acid produced a mixture of cis and trans isomers when both the 6 and 7 positions were substituted. An analysis of their NMR spectra indicated a preference for cis isomer formation.

Homeosteric[2] replacement of the $N_8$ nitrogen in the pteridine nucleus by oxygen has not been widely studied. However, synthesis of the pyrimido[4,5-*b*][1,4]oxazine (8-oxadihydropteridine) ring system has been accomplished by cyclization of 5-(chloroacetamido)-4-methyl-2,6-pyrimidinediol to give 2,6-dihydroxy-4-methyl-8-oxadihydropteridine.[3,4] More recently, another route has been reported by the reaction of an α-halo ketone and 2,4,5-triamino-6-pyrimidinol to yield 2,4-diamino-8-oxadihydropteridine derivative.[5] Unfortunately, this method often yielded a pteridine as the major product in preference to a 8-oxadihydropteridine derivative. A synthesis of the 8-oxadihydropteridine ring system was then attempted by the condensation of an α-halo ketone and 2,5-diamino-4,6-pyrimidinediol.[1] In con-