Synthesis of Imidazo[4,5-*d*]pyridazine Nucleosides Related to Inosine

P. Dan Cook (1a), Phoebe Dea (1b), and Roland K. Robins (1c)

Contribution from ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute, Irvine, California 92715

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Several imidazo[4,5-*d*]pyridazine nucleosides which are structurally similar to inosine were synthesized. Anhydrous stannic chloride-catalyzed condensation of persilylated imidazo[4,5-*d*]-pyridazin-4(5*H*)one (**1**) and imidazo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)dione (**16**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**3**) provided (after sodium methoxide deblocking) 6-β-D-ribofuranosylimidazo[4,5-*d*]pyridazin-4(5*H*)one (**5**) and 3,6-di-(β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazin-4-one (**7**); and 1-(β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)dione (**19**) and 1,5 or 6-di-(β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazine-4,7(5*H* or 6*H*)dione (**21**), respecitvely. 4,7-Dichloro-1-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine (**12**) and dimethyl 1-β-D-ribofuranosylimidazole-4,5-dicarboxylate (**26**), both prepared from stannic chloride-catalyzed ribosylations of the corresponding heterocycles, were converted in several steps to 3-β-D-ribofuranosylimidazo[4,5-*d*]pyridazin-4(5*H*)one (**14**) and nucleoside **19**, respectively. Acid-catalyzed isopropylidenation of mesomeric betaine **7** or nucleoside **14** provided 3-(2,3-isopropylidene-β-D-ribofuranosyl)imidazo[4,5-*d*]pyrizin-4(5*H*)one (**31**). 1-β-D-Ribofuranosylimidazo[4,5-*d*]-pyridazine (**29**) was obtained in several steps from nucleoside **12**. The structure of the nucleosides was established by the use of carbon-13 and proton nmr.

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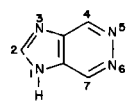
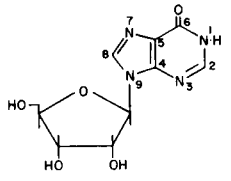
Structural modification of the naturally occurring nucleosides and nucleoside antibiotics has received considerable attention as a source for potential chemotherapeutic agents (2). We have continued this approach to synthesize potential chemotherapeutic agents by selecting



Imidazo[4,5-*d*]pyridazine
A



Inosine
B

the imidazo[4,5-*d*]pyridazine ring system (A) for ribosylation studies. This ring system, isomeric with the naturally occurring purine ring system, has been reviewed recently (3). However, only several imidazo[4,5-*d*]pyridazine nucleosides have been prepared (4). Specifically, in accord with the ongoing program to investigate modified nucleosides as potential antiviral agents (5), we have synthesized several imidazo[4,5-*d*]pyridazine ribosides which possess a tautomeric hydroxyl group (lactam-lactim function) in the 4-position (6-position of purine), thus resembling inosine (B).

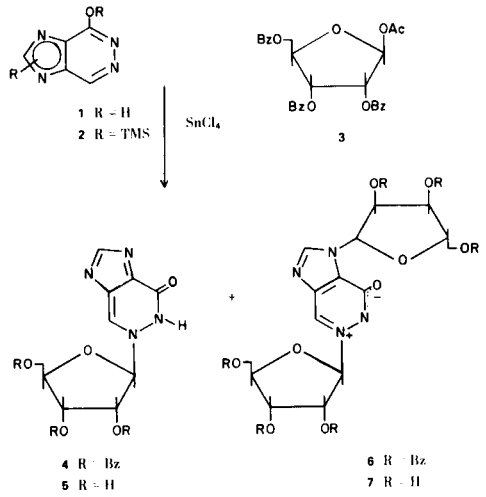
Several other modified nucleosides which resemble inosine and have *in vitro* and *in vivo* antiviral activity are 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (ribavirin) (5a,6), 9-β-D-arabinosylhypoxanthine-5′-phosphate (ara-HxMP) (7), and 6-amino-1-β-D-ribofuranosylimidazo-[4,5-*c*]pyridin-4(5*H*)one (3-deazaguanosine) (8). Biochemical studies reveal that ribavirin and 3-deazaguanosine are potent inhibitors of the biosynthesis of purine nucleotides in Ehrlich ascites tumor cells (9). Specifically, these nucleosides, probably after activation to their 5′-phosphates, are potent inhibitors of inosinate (IMP) dehydrogenase (9). Inhibition of this enzyme, which occupies a key position in purine nucleotide biosynthesis, has been suggested to be a likely mechanism for antiviral activity (9).

We have utilized three approaches to synthesize ribosides of imidazo[4,5-*d*]pyridazinones: a) direct ribosylation of imidazo[4,5-*d*]pyridazinones (Schemes I and III), b) ribosylation of imidazo[4,5-*d*]pyridazines containing an appropriately positioned functionality, which may be converted to imidazo[4,5-*d*]pyridazinone ribosides (Scheme II), and c) cyclization of imidazole nucleosides to desired imidazo[4,5-*d*]pyridazinone ribosides (Scheme IV).

Although each procedure has obvious disadvantages, use of all three can provide a variety of imidazo[4,5-*d*]pyridazinone nucleosides. Common to these procedures is a ribosylation step. The Lewis acid-catalyzed condensation of persilylated heterocycles with peracylated sugars, first described by Niedballa and Vorbrüggen for synthesis of pyrimidine nucleosides (10), has previously been utilized in these Laboratories with excellent results (5b,11). We elected to use this procedure again, mainly because of the prospects of high yields of the β-anomers (usually greater than 90%) (5b,11) and its overall simplicity. Furthermore, the possibility of a complex between the silylated heterocycle and stannic chloride such that a preponderance of one isomer may prevail was intriguing (12).

Thus, treatment of one equivalent of silylated imidazo-[4,5-*d*]pyridazin-4(5*H*)one (**2**, Scheme I) with one equivalent of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**3**) in the presence of 1.44 molar equivalents of anhydrous stannic chloride provided a blocked monoribofuranosyl (**4**, 74%) and a blocked diribofuranosyl (**6**, 20%) derivative of heterocycle **1** as determined by elemental and ^{1}H nmr analysis. Treatment of blocked nucleosides **4** and **6** with

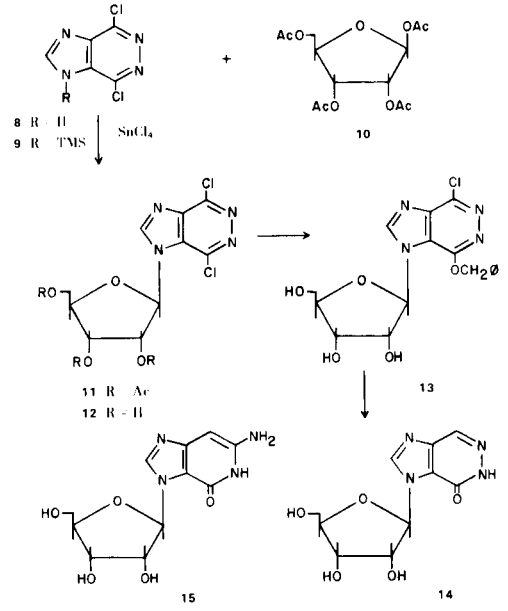
Scheme I



sodium methoxide in methanol provided nucleosides **5** and **7**, respectively. These nucleosides were assigned the structures as shown in Scheme I on the basis of carbon-13 and proton nmr.

An alternative approach to the imidazo[4,5-*d*]pyridazine analog of inosine was obtained by ribosylating (stannic chloride procedure) 4,7-dichloro-1-trimethylsilylimidazo[4,5-*d*]pyridazine (**9**, Scheme II) with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**10**) to afford the versatile intermediate, 4,7-dichloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazine (**11**) in 79% yield. 4,7-Dichloro-1-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine

Scheme II



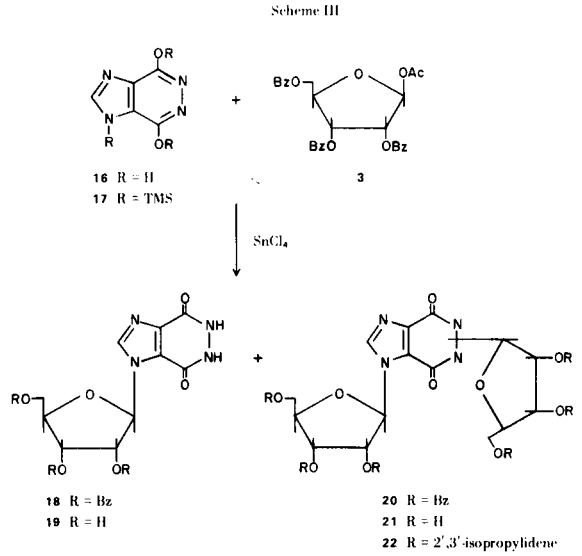
(**12**), obtained from sodium methoxide deblocking of **11**, was treated with sodium benzyloxide to provide 4-benzyloxy-7-chloro-3-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine (**13**) in 74%. Hydrogenolysis of **13** afforded another ribofuranosyl derivative of the imidazo[4,5-*d*]pyridazinone **1**.

The location of the ribofuranosyl group in **11** (and thus **12**) was assumed to be on an imidazole ring nitrogen. The alternative site of ribosylation in the symmetrical imidazo[4,5-*d*]pyridazine base **8** would be on a pyridazine ring nitrogen. This would require ribosylation adjacent to a halogen atom, for which there appears to be no precedent in purine and purine analog nucleoside chemistry.

Displacement of the least sterically hindered chlorine atom in nucleoside **12** was expected due to the report of good yields of only one isomer (chlorine atom in the 4-position was replaced) in nucleophilic displacement reactions of 1-substituted-4,7-dichloroimidazo[4,5-*d*]pyridazines (3). However, in the similar benzyloxy-dechlorination of nucleoside **12**, we obtained displacement of the *more* sterically hindered chlorine atom (chlorine atom in the 7-position) as determined by carbon-13 and proton nmr studies of the hydrogenolyzed product, nucleoside **14** (13). Purine nucleoside analogs which have the β-D-ribofuranosyl moiety located in the position corresponding to the 7-position of the purine ring system rather than the naturally occurring 9-position are of considerable interest due to the recent disclosure of the antibacterial activity of 7-β-D-ribofuranosyl-3-deazaguanine (6-amino-3-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)one, **15**) (14).

Imidazo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)dione (**16**), an xanthine analog, was also directly ribosylated (after silylation) according to this stannic chloride ribosylation procedure (Scheme III). Similarly, a blocked monoribo-

Scheme III

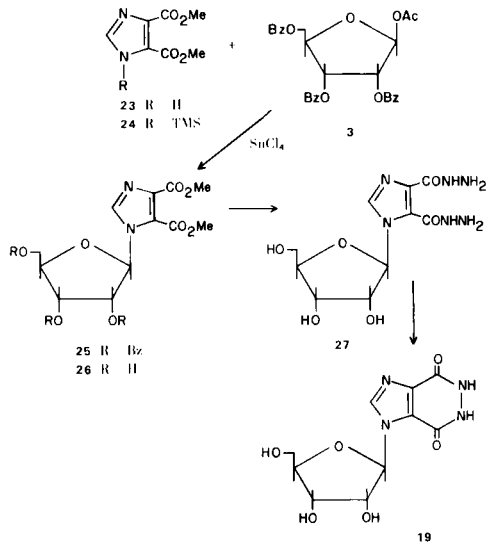


furanosyl (**18**, 38%) and a diribofuranosyl (**20**, 58%) derivative of heterocycle **16** was obtained. Subsequent deblocking of **18** and **20** with sodium methoxide provided 1-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine-4,7-(5*H*,6*H*)dione (**19**) and 1,5 or 6-di-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine-4,7(5*H* or 6*H*)dione (**21**), respec-

tively.

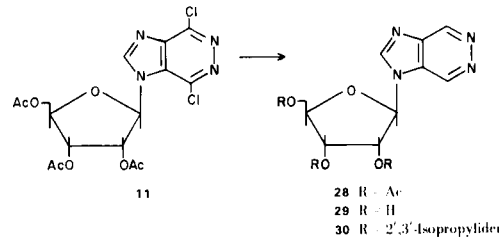
An alternative unequivocal synthesis of nucleoside **19** was obtained from dimethyl imidazole-4,5-dicarboxylate (**23**, Scheme IV). Dimethyl 1-trimethylsilylimidazole-4,5-dicarboxylate (**24**), obtained from the silylation of **23**

Scheme IV



with hexamethyldisilazane, was treated with blocked sugar **3** in the presence of 1.44 molar equivalents of anhydrous stannic chloride to afford dimethyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-4,5-dicarboxylate (**25**) in 90% yield (15). The structure of nucleoside **25** was confirmed by its conversion *via* 1-β-D-ribofuranosylimidazole-4,5-dicarboxamide to xanthosine, according to the procedure of Todd *et al.*, (16). Blocked nucleoside **25** or deblocked nucleoside **26** (deblocked with sodium methoxide) was converted to 1-β-D-ribofuranosylimidazole-4,5-carboxhydrazide (**27**) (17) in 94% yield with refluxing ethanolic hydrazine hydrate. Cyclization of **27** with anhydrous hydrazine provided bicyclic nucleoside **19** (identical to **19** prepared in Scheme III) in 77% yield (17).

The imidazo[4,5-*d*]pyridaizne analog (**29**) of the nucleoside antibiotic nebularine (9-β-D-ribofuranosylpurine) (18) was prepared by removing the chloro groups (palladium/carbon, triethylamine) of **11** and subsequent deblocking (sodium methoxide).



The β-configuration has been assigned to all nucleosides in this paper on the basis of the coupling constants of the H_1' proton (anomeric proton) and the differences between the chemical shift of the methyl groups of the isopropylidene derivatives. Nucleosides **4**, **5**, **6**, **20**, and **27** possessed anomeric protons (H_1') with coupling constants of one Hz or less (Table I), which is indicative of the β-configuration (19). The isopropylidene derivatives of nucleosides **7**, **14**, **21**, and **29**, prepared by the treatment of the appropriate nucleoside with 1,1-dimethoxypropane and perchloric acid in acetone, possessed Δδ methyls of 0.21 to 0.24 ppm (Table I), which is characteristic of the β-configuration (20).

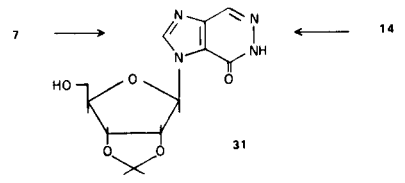
Table I

Proton Magnetic Resonance Data for Imidazo[4,5-*d*]pyridine Nucleosides

Compound	Chemical shift, δ H_1'	$J_{H_1'-H_2'}$	Δδ CH_3 (a)
4	6.71	1	
5	5.82	0.0	
	7.15	4	
6	6.72	0.0	
	6.65	4	
7	5.82	0.0	
14	6.45	5	
19	6.45	5	
20	6.86	0.0	
21	6.40	3	
22	6.51	0.0	0.21 (b)
27	6.62	0.5	
29	6.14	6	
30	6.42	2.5	0.24
31	6.62	2	0.23

(a) Difference in chemical shift of methyls of isopropylidene group. (b) Average value.

The isopropylidenation of nucleosides **7** and **14** provided the same monoisopropylidene blocked nucleoside, **31**. Evidently, the 70% perchloric acid catalyst used for the isopropylidenation cleaved the ribofuranosyl group in the 6-position of the mesomeric betaine nucleoside **7** (21). Mesomeric betaine nucleosides such as 7-methylguanosine are noted for their increased susceptibility to acid cleavage of the glycosyl moiety (22).



Carbon-13 α,β-substitution shifts were used to assign the site of the ribofuranosyl groups in these imidazo[4,5-*d*]pyridazine nucleosides. In heteroacromatic systems, *N*-ribosylation has been observed to produce an upfield shift in the carbon-13 nmr signal of the carbon α to the substituted nitrogen and a downfield shift in the signal

Table II

Carbon-13 Chemical Shifts of Imidazo[4,5-*d*]pyridazine Nucleosides

Compound	Chemical shift, δ, ppm				
	C-2	C-3a	C-4	C-7	C-7a
19	142.8	135.9	151.3	152.5	126.5
anion of **19**	140.2	136.9	154.4 (a)	157.2 (a)	128.4
21	140.9	136.7	156.9 (a)	151.2 (a)	128.2
29	146.4 (a)	141.2	139.1 (a)	145.0 (a)	130.9
anion of **1**	150.7	135.3	159.6	133.4	142.4
14	143.8	125.5	155.2	133.7	142.0
Δδ anion of **1-14**	+6.9	+9.8	+4.4	-0.3	+0.4
5	149.8	134.6	162.4	128.5	139.6
Δδ anion of **1-5**	+0.9	+0.7	-2.8	+4.9	+2.8
7	145.2	128.4	160.1	128.4	140.6
anion of **14**	141.9	124.1	161.5	133.8	141.9
anion of **5**	150.8	136.2	162.6	128.5	139.7
Δδ anion of **14-7**	-3.3	-4.3	+1.4	+5.4	+1.3
Δδ anion of **5-7**	+5.6	+7.8	+2.5	+0.1	-0.9

(a) Assignment tentative.

of the carbon β to that nitrogen when the neutral species is compared with the corresponding anion (23). There are four ring nitrogen atoms (N-1, N-3, N-5, and N-6) available for glycosylation in this ring system (A). The carbon-13 chemical shifts of the base anion and its ribosyl derivatives are summarized in Table II. The chemical shift assignments are accomplished by off-resonance decoupling and by spectral comparisons with the C-3a and C-7a chemical shifts of 1-β-D-ribofuranosylimidazo[4,5-*d*]-pyridazine-4,7(5*H*,6*H*)dione (**19**) and 1-β-D-ribofuranosyl-imidazo[4,5-*d*]pyridazine (**29**). The structures of these compounds, **19** and **29**, are known from the unequivocal synthesis. The carbon-13 chemical shifts of some of the resonances can be assigned from symmetry considerations. In the ionized heterocyclic base of imidazo[4,5-*d*]pyrid-azine and imidazo[4,5-*d*]pyridazine-4,6(5*H*,6*H*)dione, the C-4 and C-7 carbonyl carbons, as well as the bridgehead carbons C-3a and C-7a, are expected to be identical since these anions have C_2 symmetry. Upon ribosylation at N-1, the C-7a (α carbon) is expected to move upfield while the C-7 (β carbon) is shifted downfield from considerations of the α,β substitution parameters. The chemical shifts are included in Table II.

Considering first the monoribosylated compounds, the structure of 3-β-D-ribofuranosylimidazo[4,5-*d*]pyridazin-4(5*H*)one (**14**) can be assigned from the upfield shift of 6.9 ppm and 9.8 ppm of the α-carbons, C-2 and C-3a, respectively, when compared with the anion of the parent heterocycle **1**. These large upfield shifts indicate that N-5 is probably not the ribosylation site, although a smaller upfield shift was observed at C-4. The change in chemical shift of C-7a (+0.4 ppm) represents an average of δ and α positional effects and is difficult to predict; but the lack of a large upfield shift in this carbon when compared to that of the heterocycle anion **1** eliminates the possibility of N-1 being the site of ribosylation. The C-7 carbon which was shifted downfield by 0.3 ppm can be used to eliminate N-6 as a possible ribosylation site in **14**.

The other ribofuranosyl isomer was assigned the structure of 6-β-D-ribofuranosylimidazo[4,5-*d*]pyridazin-4(5*H*)-one (**5**) based on the upfield α-shift of 4.9 ppm for C-7 and downfield β-shift of 2.8 ppm for C-4. Since C-4 is α to N-5, this downfield shift indicates that the ribofuranosyl moiety is not attached at N-5. The small shift change (+0.9 ppm) observed in C-2 when compared to that of the heterocycle anion **1** can be used to eliminate N-1 and N-3 as ribosylation sites.

The structure of the diribofuranosyl derivative has been assigned as 3,6-di-β-D-ribofuranosylimidazo[4,5-*d*]pyrid-azin-4-one (**7**). As shown in Table II, the chemical shift of **7** is quite similar to the average chemical shift of the monoribofuranosyl derivatives **5** and **14**, indicating that the same ribosylation sites (N-3 and N-6) are involved. When the chemical shifts of **7** are compared with those of the anions of **5** and **14**, all of the α-substitution shifts are consistent with the structure as shown, being +5.6 and +7.8 ppm in the first case and +5.4 and +5.4 ppm in the second case. Small deviations in some of the β-shifts are observed in these systems, namely +1.4 ppm and +2.5 ppm for C-4, respectively, when **7** was compared with the anions of **14** and **5**, respectively. Deviations in α,β substitution parameters have been reported in the diprotonated pyrazole and imidazole cations (24). These deviations are expected to arise from the competitive and buttressing effects which violate the requirements for additive results.

The structure of a diribofuranosyl nucleoside **21** could

not be determined unequivocally because the C-4 and C-5 resonances of the parent anion (anion of **19**) could not be readily assigned. However, we can conclude that diribofuranosyl nucleoside **21** is not the 1,3-diribofuranosyl or 5,6-diribofuranosyl derivative of heterocycle **16** from symmetry considerations, since all of the carbon resonances are well resolved, indicating the absence of C_2 symmetry in the diribofuranosyl nucleoside.

The proton chemical shifts of the anomeric protons (H_1') of the ribofuranosyl moieties in these nucleosides are consistent with their assigned structures. The chemical shifts of the anomeric protons are summarized in Table I for comparison. The anomeric proton of the ribofuranosyl bonyl function occurred considerably downfield (0.7-0.8 ppm) compared to its positional isomers. This downfield shift, as also was noted with other nucleosides (5b), is attributed to the close proximity of the anisotropic carbonyl group to the anomeric proton. Finally, the large deshielding of C_2H in the mesomeric betaine **7** relative to C_2H in nucleoside **5** (Δ 0.45 ppm) is expected due to the delocalization of the positive charge in **7** and furnishes additional evidence for the mesomeric betaine structure (25).

The biological activity of these compounds will be reported elsewhere.

EXPERIMENTAL

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 (pmr) spectra were obtained on a Varian A-60 spectrometer and a Perkin-Elmer R-20A spectromer in DMSO-d_6 using DSS as an internal reference. Carbon-13 magnetic resonance (cmr) spectra of 20% DMSO-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°. A Fabri-Tek 1074 signal averager with 4096 word memory was used for data acquisition and a Digital PDP-8/e computer for data processing. Chemical shifts are measured from DMSO-d_6, converted to TMS scale using the relationship δ TMS = δ DMSO-d_6 + 39.5 ppm. The anions of various heterocycles were formed by neutralization with lithium hydroxide in DMSO-d_6. Ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer and infrared spectra on a Perkin-Elmer 257 spectrophotometer (potassium bromide 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, Life Sciences Group, Woelm F254) was by ultraviolet light and with anisaldehyde, methanol, sulfuric acid (1:100:10) spray followed by heating. ICN, Life Sciences Group, Woelm silica gel (0.063-0.2 mm) was used for column chromatography.

6-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)one (**4**) and 3,6-Di-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazo[4,5-*d*]pyridazin-4-one (**6**). Method A.

Imidazo[4,5-*d*]pyridazin-4(5*H*)one (**1**) (1.36 g., 10 mmoles) was refluxed and stirred under anhydrous conditions for 12 hours with hexamethyldisilazane (HMDS) (50 ml.) and ammonium sulfate (20 mg.). The excess HMDS was removed by distillation under reduced pressure, providing the trimethylsilyl derivative as an off-white solid. The solid was dissolved in dry 1,2-dichloroethane (100 ml.). 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**3**) (5.04 g., 10 mmoles) was added to the solution followed by direct addition of anhydrous stannic chloride (1.68 ml., 14.4 mmoles) in one portion. Tlc (silica gel, chloroform-methanol, 10:1) of an ethanolized aliquot indicated almost complete conversion of **1** and **3** to two major products after 15 minutes of stirring at ambient temperature. The light yellow solution was stirred at ambient temperature for 12 hours and then poured slowly into a vigorously sitrred 5% sodium hydrogen carbonate solution (100 ml.). Chloroform (200 ml.) was added, and after 10 minutes of stirring the organic layer was removed. In some experiments an emulsion forms. This is filtered through celite before separating the layers. The aqueous layer was extracted with chloroform, and the combined, dried (magnesium sulfate) extracts are concentrated *in vacuo* to a hard white foam (5.4 g.). The foam was dissolved in chloroform and placed on a column of silica gel (200 g. packed in chloroform). Elution with chloroform and then chloroform-methanol (20:1) provided first 1.0 g. (20%) of blocked nucleoside **6**, white foam; ^{1}H nmr (DMSO-d_6): δ 6.72 (s, 1, H_1'), 7.15 (d, 1, J = 4 Hz, H_1'), 9.0 (s, 1, C_2H), 9.6 (s, 1, C_7H).

Anal. Calcd. for $C_{57}H_{44}N_4O_{15}$ (1025.02): C, 66.79; H, 4.32; N, 5.46. Found: C, 66.68; H, 4.58; N, 5.39.

Next, nucleoside **4** (3.9 g., 74%) was removed from the column, white foam; ^{1}H nmr (DMSO-d_6): δ 6.71 (s, 1, H_1'), 8.61 (s, 1, C_2H), 9.57 (s, 1, C_7H).

Anal. Calcd. for $C_{31}H_{24}N_4O_7$ (564.53): C, 65.95; H, 4.29; N, 9.93. Found: C, 65.85; H, 4.28; N, 9.87.

Method B.

The use of 1.5 equivalent of blocked sugar **3**, one equivalent of heterocycle **1** and 1.5 molar equivalent of stannic chloride in the procedure described in Method A provided a 40% yield of **6** (based on **3**) and a 40% yield of **4** (based on **1**).

Method C.

Reaction of 2.0 equivalent of **3**, one equivalent of **1**, and 2.88 molar equivalent of stannic chloride provided a 50% yield of **6** (based on **3**) and a 44% yield of **4** (based on **1**).

6-β-D-Ribofuranosylimidazo[4,5-*d*]pyridazin-4(5*H*)one (**5**).

Blocked nucleoside **4** (3.8 g., 7.15 mmoles) was refluxed in a sodium methoxide solution (100 ml. of dry methanol containing 5 mg. of dissolved sodium) for 0.75 hours and then treated with Amberlite IRC-50 resin. The resin was removed by filtration and the filtrate evaporated to dryness *in vacuo*. Recrystallization of the residue from methanol furnished nucleoside **5** (1.4 g., 71%) as small white rosettes, m.p. > 300°; $[\alpha]_D^{25}$ -8.11 (*c* 1, water); uv λ max (*p*H 1) 280 nm (ϵ, 4730), λ max (*p*H 7) 302 (5550), λ max (*p*H 11) 312 (8630); ^{1}H nmr (DMSO-d_6): δ 5.82 (s, 1, H_1'), 8.55 (s, 1, C_2H), 9.62 (s, 1, C_7H).

Anal. Calcd. for $C_{10}H_{12}N_4O_5$ (268.2): C, 44.78; H, 4.51; N, 20.89. Found: C, 44.52; H, 4.62; N, 20.72.

3,6-Di-β-D-ribofuranosylimidazo[4,5-*d*]pyridazin-4-one (**7**).

Blocked nucleoside **6** was deblocked in the manner described to provide nucleoside **7** as white crystals (87%), m.p. 182-184° dec.; $[\alpha]_D^{25°}$ + 57.1 (*c* 1, water); λ max (*p*H 1): 283 nm (ϵ, 4440), 295 (sh) (4070); λ max (*p*H 7): 303 (ϵ, 5190), λ max (*p*H 11) 303 (5560); ^{1}H nmr (DMSO-d_6): δ 5.82 (s, 1, H_1'), 6.65 (d, 1, J = 4 Hz, H_1'), 8.90 (s, 1, C_2H), 9.63 (s, 1, C_7H).

Anal. Calcd. for $C_{15}H_{20}N_4O_9$ (400.34): C, 45.00; H, 5.04; N, 14.00. Found: C, 45.21; H, 5.22; N, 13.99.

4,7-Dichloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazine (**11**).

A mixture of dry, powdered 4,7-dichloroimidazo[4,5-*d*]pyridazine (**8**, 7.05 g., 37.3 mmoles), HMDS (200 ml.), and ammonium sulfate (0.60 mg.) was stirred and refluxed 12 hours. The excess HMDS was removed by distillation under reduced pressure, and the white crystalline residue was dissolved in dry 1,2-dichloroethane (200 ml.). 1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose (11.9 g., 37.3 mmoles) was added to the solution followed by direct addition of anhydrous stannic chloride (6.3 ml., 53.7 mmoles). The yellow solution was allowed to stand at ambient temperature for 12 hours, extracted with 5% sodium hydrogen carbonate (750 ml.), and filtered through celite. The dried (magnesium sulfate) organic layer and washings were evaporated *in vacuo* to a light yellow foam (15.4 g.). The foam was dissolved in chloroform and placed on a column of silica gel (400 g., packed in chloroform). Elution with chloroform-acetone (40:1) provided blocked nucleoside **11** as a white foam (13.2 g., 79%); λ max (*p*H 1,7,11) 249 nm (ε, 5560); ^{1}H nmr (DMSO-d_6): δ 2.14 (s, 9, CH_3), 6.75 (d, 1, J = 4 Hz, H_1'), 9.13 (s, 1, C_2H).

Anal. Calcd. for $C_{16}H_{16}Cl_2N_4O_7$ (447.3): C, 42.96; H, 3.61; N, 12.52. Found: C, 42.80; H, 3.47; N, 12.30.

4,7-Dichloro-1-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine (**12**).

A solution of blocked nucleoside **11** (8.94 g., 20 mmoles), dry methanol (100 ml.), and sodium methoxide solution (~ 5 mg. of sodium dissolved in 5 ml. of methanol) was allowed to stand at room temperature for 3 hours and then treated with IRC-50 resin until neutral. The resin was removed and the foam, obtained after evaporating the filtrate, was recrystallized from ethanol to afford nucleoside **12** as white needles (5.1 g., 79%); m.p. dec. > 150° (after drying at 80° for 12 hours); $[\alpha]_D^{25°}$ + 23.0° (*c* 1, water); λ max (*p*H 1,7,11) 250 nm (ε, 6020); ^{1}H nmr (DMSO-d_6): δ 6.48 (d, 1, J = 2 Hz, H_1'), 9.33 (s, 1, C_2H).

Anal. Calcd. for $C_{10}H_{10}Cl_2N_4O_4$ (321.1): C, 37.45; H, 3.14; N, 17.45. Found: C, 37.48; H, 3.15; N, 17.30.

An analytically pure sample of nucleoside **11**, stored in a dessicator at room temperature, completely decomposed within 6 months.

4-Benzyloxy-7-chloro-3-β-D-ribofuranoxylimidazo[4,5-*d*]pyridazine (**13**).

A mixture of **12** (3.21 g., 10 mmoles), benzyl alcohol (10 ml.) and sodium benzyloride solution (253 mg., 6.32 mmoles), dissolved in 10 ml. of benzyl alcohol) was stirred and heated (85°) for 4.5 hours. Tlc (silica gel, chloroform-methanol, 4:1) indicated a clean conversion of **12** to one product. The solution was evaporated *in vacuo* to a syrup which was treated with dry ether (200 ml.). The precipitated residue was recrystallized from ethanol-water to furnish **13** (2.1 g., 74%) as white crystals, m.p. 184-185° dec. (after drying at 80° for 4 hours); $[\alpha]_D^{25°}$ + 12.9° (*c* 1, DMF); λ max (*p*H 1,7,11): 248 nm (ε, 6610); ^{1}H nmr (DMSO-d_6): δ 5.78 (s, 2, CH_2), 6.35 (d, 1, J = 4 Hz, H_1'), 7.5 (m, 5, C_6H_5), 9.08 (s, 1, C_2H).

Anal. Calcd. for $C_{17}H_{17}ClN_4O_5$ (392.8): C, 51.98; H, 4.36; N, 14.26. Found: C, 51.94; H, 4.43; N, 14.20.

3-β-D-Ribofuranosylimidazo[4,5-*d*]pyridazin-4(5*H*)one (**14**).

A mixture of **13** (786 mg., 2 mmoles), 10% palladium on charcoal (1 g.), sodium acetate (164 mg., 2 mmoles), and 50% aqueous ethanol (150 ml.) was stirred under 45 psi of hydrogen for 4.5 hours and then filtered through celite. The filtrate was evaporated *in vacuo* to dryness and the residue coevaporated with toluene (2x) and then with ethanol. The residue was absorbed on silica gel (6 g., with aid of methanol) and placed on a column of silica gel (25 g., packed in chloroform). Elution with chloroform-methanol (4:1) provided **14**, which was recrystallized from ethanol to afford 450 mg. (84%), m.p. dec. > 120° (after drying at 60° for 12 hours); $[\alpha]_D^{25°}$ + 24.2 (*c* 1, DMF); λ max (*p*H 1,7,11): 258 nm (ε, 5500); ^{1}H nmr (DMSO-d_6): δ 6.45 (d, 1, J = 5 Hz, H_1'), 8.49 (s, 1, C_2H), 8.83 (s, 1, C_7H), 13.05 (brs, 1, N*H*).

Anal. Calcd. for $C_{10}H_{12}N_4O_5$ (268.23): C, 44.78; H, 4.51; N, 20.8. Found: C, 44.62; H, 4.60; N, 20.67.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazine-4,7(5*H*,7*H*)dione (**18**) and 1,5 or 7-Di-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazine-4,7-(5*H* or 7*H*)dione (**20**).

One equivalent of silylated imidazo[4,5-*d*]pyridazine-4,7(5*H*, 6*H*)dione (**17**) was ribosylated with one equivalent of blocked sugar **3** in the presence of 1.44 molar equivalents of anhydrous stannic chloride as described for the preparation of blocked nucleosides **4** and **6**. Column chromatography (silica gel in benzene-ethyl acetate, 1:1; elution with benzene-ethyl acetate, 1:1; then ethyl acetate-methanol, 10:1) provides a 58% yield of **20** and a 38% yield of **18**, both as white foams; ^{1}H nmr of **20** (DMSO-d_6): δ 6.86 (s, 1, H_1'), 8.78 (s, 1, C_2H), 12.9 (s, 1, N*H*).

Anal. Calcd. for $C_{57}H_{44}N_4O_{16}$ (1040.7): C, 65.78; H, 4.26; N, 5.38. Found: C, 65.71; H, 4.26; N, 5.29.

Compound **18** had ^{1}H nmr (DMSO-d_6): δ 6.99 (d, 1, J = 5 Hz, H_1'), 8.81 (s, 1, C_2H).

Anal. Calcd. for $C_{31}H_{24}N_4O_9$ (596.53): C, 62.41; H, 4.06; N, 9.39. Found: C, 62.19; H, 4.35; N, 9.25.

1-β-D-Ribofuranosylimidazo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)dione (**19**). Method A.

Blocked nucleoside **18** was deblocked with sodium methoxide as described for the preparation of nucleosides **5** and **7**. Recrystallization from ethanol provided white micro-crystals (81%), m.p. gradual dec. > 170°; $[\alpha]_D^{25°}$ + 18.3° (*c* 1, water); λ max (*p*H 1): 255 nm (ε, 3640), 233 (8180), 225 (sh) (15,150); λ max (*p*H 7): 279 (4240), 234 (sh) (12,120), 228 (16,360); λ max (*p*H 11): 279 (4240), 234 (sh) (11,210), 228 (14,540); ^{1}H nmr (DMSO-d_6): δ 6.45 (d, 1, J = 5 Hz, H_1'), 8.76 (s, 1, C_2H).

Anal. Calcd. for $C_{10}H_{12}N_4O_6$ (284.23): C, 42.25; H, 4.26; N, 19.71. Found: C, 42.01; H, 4.24; N, 19.81.

Method B.

A solution of 1-β-D-ribofuranosylimidazole-4,5-dicarboxhydrazide (**27**) (3.34 g., 10 mmoles) and 97% hydrazine was refluxed 1 hour. The excess hydrazine was removed by distillation *in vacuo* and the gummy residue coevaporated several times with water. The crystalline residue was dissolved in water (50 ml.) and the *p*H was adjusted to *ca.* 3 with 20% hydrochloric acid. The precipitate was filtered and washed with cold water. Recrystallization from 80° water (~ 45 ml.) provided small white micro-crystals (2.2 g., 77%), m.p. gradual dec. > 170°.

Anal. Calcd. for $C_{10}H_{12}N_4O_6$ (284.23): C, 42.25; H, 4.26; N, 19.71. Found: C, 42.20; H, 4.14; N, 9.54.

This material was identical to **19** prepared in Method A.

1,5 or 6-Di-β-D-ribofuranosylimidazo[4,5-*d*]pyridazine-4,7(5*H* or 6*H*)dione (**21**).

Blocked nucleoside **20** was treated with sodium methoxide as described for the preparation of nucleosides **5** and **7** to provide a 93% yield of nucleoside **21** as white micro-crystals, m.p. > 200°; $[\alpha]_D^{25°}$ - 37.5° (*c* 1, water); λ max (*p*H 1): 275 nm (ε, 5000), 230 (sh) (12,080); λ max (*p*H 7): 290 (5000), 238 (10,830), 232 (15,000); λ max (*p*H 11): 290 (5000), 238 (10,830), 233 (14,170); ^{1}H nmr (DMSO-d_6): δ 6.40 (d, 2, J = 3 Hz, H_1'), 8.45 (s, 1, C_2H).

Anal. Calcd. for $C_{15}H_{20}N_4O_{10}$ (416.34): C, 43.27; H, 4.84; N, 13.46. Found: C, 43.18; H, 4.97; N, 13.39.

Dimethyl 1-(2,3,4-Tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-4,5-dicarboxylate (**25**).

Dimethyl imidazole-4,5-dicarboxylate (**23**, 11.04 g., 60 mmoles) was refluxed with stirring under anhydrous conditions for 8 hours with hexamethyldisilazane (HMDS) (150 ml.) and ammonium sulfate (160 mg.). The excess HMDS was removed by distillation under reduced pressure providing the silylated heterocycle **24** as a colorless oil which was dissolved in dry 1,2-dichloroethane (150 ml.). 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**3**, 30.24 g., 60 mmoles) was added to the solution followed by direct addition of anhydrous stannic chloride (10.08 ml., 86.4 mmoles). Tlc (silica gel, chloroform-methanol, 10:1) of a methanolyzed aliquot indicated almost complete conversion of the sugar and heterocycle to the product after 15 minutes at ambient temperature. The reaction solution, which gradually darkens, was stirred at ambient temperature for 6-12 hours, diluted with chloroform (150 ml.), poured with vigorous overhead stirring into a 5% sodium hydrogen carbonate solution (1.2 l.), and filtered through a bed of celite. The organic layer was separated, washed with water (50 ml.), dried (magnesium sulfate), and evaporated *in vacuo* to a beige foam (37.0 g.). Recrystallization of the foam ethanol provided the blocked nucleoside **25** as white micro-crystals (33.9 g., 90%); m.p. 121-122° (after drying at 80° for 3 hours); $[\alpha]_D^{25°}$ - 11.0 (*c* 1, methanol); ^{1}H nmr (DMSO-d_6): δ 3.76 (s, 3, C*H*$_3$), 3.82 (s, 3, C*H*$_3$), 6.63 (d, 1, J = 6 Hz, H_1'), 8.41 (s, 1, C$_2$*H*).

Anal. Calcd. for $C_{33}H_{28}N_2O_{11}$ (628.57): C, 63.06; H, 4.49; N, 4.46. Found: C, 63.00; H, 4.44; N, 4.29.

Dimethyl 1-β-D-ribofuranosylimidazole-4,5-dicarboxylate (**20**).

A solution of **25** (5.0 g., 7.96 mmoles), sodium (20 mg., dissolved in 10 ml. of dry methanol), and dry methanol (150 ml.) was refluxed 45 minutes, cooled to room temperature, and treated with Amberlite IRC-50 ion-exchange resin (10 ml.). After stirring 30 minutes, the resin was removed by filtration and the filtrate evaporated *in vacuo* to a semi-solid residue. The residue was triturated with anhydrous ether (25 ml. in 2 portions) and recrystallized from methanol to provide **26** as small white needles, m.p. 134-135° (after drying at 100° for 2 hours); $[\alpha]_D^{25°}$ - 4.41 (*c* 1, water); λ max (*p*H 1): 242 nm (ε, 6750); λ max (*p*H 7): 252 (7360), λ max (*p*H 11) 250 (7670); ^{1}H nmr (DMSO-d_6): δ 3.84 (s, 3, C*H*$_3$), 3.90 (s, 3, C*H*$_3$), 5.92 (d, 1, J = 4 Hz, H_1'), 8.41 (s, 1, C$_2$*H*).

Anal. Calcd. for $C_{12}H_{16}N_2O_8$ (316.26): C, 45.57; H, 5.10; N, 8.86. Found: C, 45.61; H, 5.23; N, 8.88.

1-β-D-Ribofuranosylimidazole-4,5-dicarboxhydrazide (**27**).

A solution of **25** (5 g., 7.96 mmoles), ethanol (80 ml.), and hydrazine hydrate (99%, 6 ml.) was refluxed 6 hours. After cooling, the precipitate was filtered, washed with ethanol, and recrystallized from aqueous ethanol to provide 2.5 g. (94%) of white rosettes, m.p. 135-140° partial melt, 193-196° dec.; λ max (*p*H 1): 262 nm (ε, 9660), λ max (*p*H 7): 241 (10,340), λ max (*p*H 11): 236 (sh) (10,340); ^{1}H nmr (DMSO-d_6): δ 4.67 (bs, 4, N*H*$_2$), 6.6 (d, 1, J = 0.5, H_1'), 8.53 (s, 1, C$_2$*H*), 9.85 (bs, 1, N*H*), 12.25 (bs, 1, N*H*).

Anal. Calcd. for $C_{10}H_{16}N_6O_6 \cdot \frac{1}{2}H_2O$ (325.28): C, 36.92; H, 5.23; N, 25.84. Found: C, 36.98; H, 5.44; N, 25.57.

1-β-D-Ribofuranosylimidazo[4,5-*d*]pyridazine (**29**).

A mixture of **11** (4.47 g., 10 mmoles), 10% palladium on charcoal (1 g.), sodium acetate (1.64 g., 2 mmoles), and 50% aqueous ethanol (100 ml.) was stirred under 45 psi of hydrogen until uptake had ceased. The mixture was filtered and the filtrate evaporated to dryness *in vacuo*. Water was added and the mixture extracted with chloroform. The dried (magnesium sulfate) extracts were evaporated to dryness *in vacuo*, the residue was dissolved in dry methanol (100 ml.), and sodium methoxide solution (5 mg. dissolved in 10 ml. of methanol) was added. After refluxing 0.75 hour, the solution was treated with IRC-50 resin, filtered, and evaporated to dryness *in vacuo*. Recrystallization from ethanol provided **29** (2.01 g., 80%) as white crystals, m.p. 185-187° dec. (after drying at 80° for 12 hours); $[\alpha]_D^{25°}$ - 42.5 (*c* 1, water): λ max (*p*H 1): 252 nm (ε, 4880), λ max (*p*H 7): 242 (4520); λ max (*p*H 11): 243 (4880); ^{1}H nmr (DMSO-d_6): δ 6.14 (d, 1, J = 6 Hz, H_1'), 8.92 (s, 1, C$_2$*H*), 9.72 (d, 1, J = 1 Hz, C$_4$*H* or C$_7$*H*), 9.98 (d, 1, J = 1 Hz, C$_7$*H* or C$_4$*H*).

Anal. Calcd. for $C_{10}H_{12}N_4O_4$ (252.23): C, 47.62; H, 4.80; N, 22.22. Found: C, 47.48; H, 4.88; N, 22.42.

3-(2,3-Isopropylidene-β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)one (**31**). Method A.

A mixture of **7** (600 mg., 1.5 mmoles), dry acetone (5 ml.), and 2,2-dimethoxypropane (5 ml.) was cooled to 0° and, with stirring, 70% perchloric acid (214 mg., 1.5 mmoles) was added dropwise. The ice-bath was removed and the reaction allowed to proceed at ambient temperature for 2.5 hours. Sodium carbonate (10%, 7 ml.) was added and the suspension was chilled before filtering. The filtrate was absorbed on silica gel (2 g. with aid of methanol) and placed on a column of silica gel (30 g., packed in chloroform). Elution with chloroform-methanol (4:1) provided **31**, which was recrystallized from ethanol to provide white microcrystals (400 mg., 87%), m.p. 206-208° dec. (after drying at 100° for 2 hours); λ max (*p*H 1,7): 258 nm (ε, 5080), λ max (*p*H 11): 260 (5700); ^{1}H nmr (DMSO-d_6): δ 1.37 (s, 3, C*H*$_3$), 1.60 (s, 3, C*H*$_3$), 6.62 (d, 1, J = 2 Hz, H_1'), 8.50 (s, 1, C$_2$*H*), 8.81 (s, 1, C$_7$*H*).

Anal. Calcd. for $C_{13}H_{16}N_4O_5$ (308.29): C, 50.64; H, 5.23; N, 18.18. Found: C, 50.63; H, 5.21; N, 18.16.

Method B.

Isopropylidenation of **14** in the manner described provided **31** in 91% yield.

1,5 or 6-Di(2,3-isopropylidene-β-D-ribofuransoyl)imidazo[4,5-*d*]-pyridazine-4,7(5*H* or 6*H*)dione (**22**).

Isopropylidenation of **21** in the manner described provided an 81% yield of **22**, m.p. 162-166° dec.; ^{1}H nmr (DMSO-d_6): δ 1.31 (s, 3, C*H*$_3$), 1.35 (s, 3, C*H*$_3$), 1.52 (s, 3, C*H*$_3$), 1.56 (s, 3, C*H*$_3$), 6.51 (s, 1, H_1'), 8.63 (s, 1, C$_2$*H*).

Anal. Calcd. for $C_{21}H_{28}N_4O_{10}$ (496.47): C, 50.80; H, 5.68; N, 11.29. Found: C, 51.02; H, 5.57; N, 11.19.

1-(2,3-Isopropylidene-β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazine (**30**).

Isopropylidenation of **29** provided **30** in 66%, colorless foam; ^{1}H nmr (DMSO-d_6): δ 1.40 (s, 3, C*H*$_3$), 1.64 (s, 3, C*H*$_3$), 6.42 (d, 1, J = 2.5, H_1), 8.90 (s, 1, C$_2$*H*), 9.66 (s, 1), 9.81 (s, 1).

Anal. Calcd. for $C_{13}H_{16}N_4O_4$ (292.29): C, 53.42; H, 5.52; N, 19.17. Found: C, 53.38; H, 5.46; N, 19.02.

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(1a) Author to whom correspondence should be addressed; present address: Warner-Lambert/Parke-Davis Research Labora-

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