Synthesis of Certain Pyrazolo[3,4-*d*]pyrimidin-3-one Nucleosides

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Synthesis of the pyrazolo[3,4-*d*]pyrimidin-3-one congeners of guanosine, adenosine and inosine is described. Glycosylation of 3-methoxy-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**13**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**16**) in the presence of boron trifluoride etherate gave 3-methoxy-6-methylthio-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**17**) which, after successive treatments with 3-chloroperoxybenzoic acid and methanolic ammonia, afforded 6-amino-3-methoxy-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**18**). The guanosine analog, 6-amino-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine-3,4(2*H*,5*H*)-dione (**21**), was made by sodium iodide-chlorotrimethylsilane treatment of 6-amino-3-methoxy-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**19**), followed by sugar deprotection. Treatment of the adenine analog, 4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3(2*H*)-one (**11**), according to the high temperature glycosylation procedure yielded a mixture of N-1 and N-2 ribosyl-attached isomers. Deprotection of the individual isomers afforded 4-amino-3-hydroxy-1-β-D-ribofuranosylpyrazolo-[3,4-*d*]pyrimidine (**26**) and 4-amino-2-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-3(7*H*)-one (**27**). The structures of **26** and **27** were established by single crystal X-ray diffraction analysis. The inosine analog, 1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine-3,4(2*H*,5*H*)-dione (**28**), was synthesized enzymatically by direct ribosylation of 1*H*-pyrazolo[3,4-*d*]pyrimidine-3,4(2*H*,5*H*)-dione (**8**) with ribose-1-phosphate in the presence of purine nucleoside phosphorylase, and also by deamination of **26** with adenosine deaminase.

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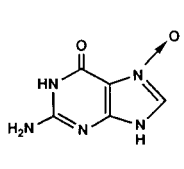
The naturally-occurring antitumor antibiotic PD 113,876 (guanine *N*-7-oxide, **1**) exhibits potent *in vivo* activity against L1210 leukemia [1] and also demonstrates moderate *in vitro* activity against herpes, rhabdo, and infectious pancreatic necrosis virus [2]. Certain N-9 alkyl derivatives of **1** [3] have also shown antitumor activity and the β-D-ribofuranosyl derivative (guanosine *N*-7-oxide, **2**) has exhibited both *in vitro* and *in vivo* antitumor activity against P388 and L1210 leukemias [4]. Compounds **1** and **2** possess an *N*-oxide functionality which is spatially similar to the 3-oxo substituent of the antitumor agent, 2-nitroso-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine-3,4(5*H*)-dione (**3**), reported previously from our laboratory [5]. To explore the importance of the 3-oxo functionality of **3**, we sought to synthesize other compounds in the pyrazolo[3,4-*d*]pyrimidin-3-one ring system and determine their biological activity. We report herein the synthesis and *in vitro* antitumor and antiviral evaluation of the pyrazolo[3,4-*d*]pyrimidin-3-one congeners of guanosine, adenosine and inosine.



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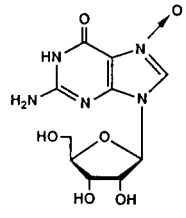

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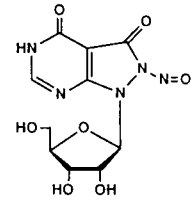
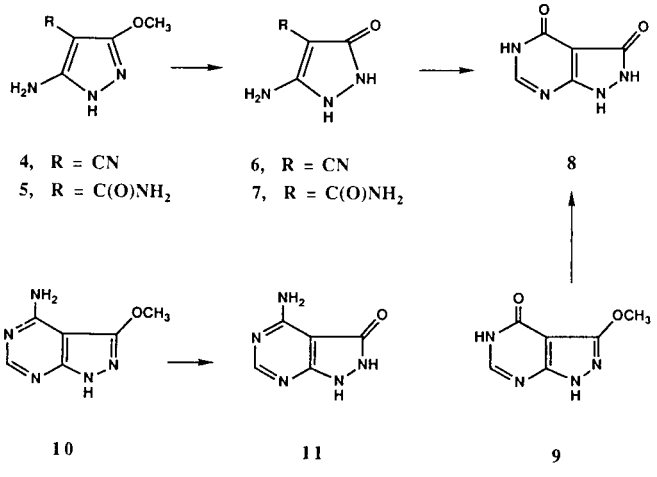


3

Several pyrazolo[3,4-*d*]pyrimidin-3-one derivatives have been previously reported [5,6]. None of these heterocycles, however, were analogous in structure to the naturally-occuring purines (*e.g.*, adenine and guanine). In the reported synthesis of **3**, Cottam *et al.* [5] stated that pyrazolone ring cleavage occurred when attempt was made to reduce the *N*-nitroso group of **3**. We therefore proposed a new synthetic approach for the preparation of the desired pyrazolo[3,4-*d*]pyrimidin-3-ones *via* cleavage of the methyl ether linkage of 3-methoxypyrazolo[3,4-*d*]pyrimidines.

Thus, treatment of 5-amino-3-methoxypyrazole-4-carbonitrile (**4**) [7] with chlorotrimethylsilane and sodium iodide [8] in acetonitrile effected smooth conversion to 5-amino-3(2*H*)-oxopyrazole-4-carbonitrile (**6**) (Scheme I). A similar treatment of the corresponding carboxamide derivative, **5**, gave 5-amino-3(2*H*)-oxopyrazole-4-carboxamide (**7**). Ring closure of **7** in boiling formamide gave 1*H*-pyrazolo[3,4-*d*]-pyrimidine-3,4(2*H*,5*H*)-dione (**8**) which was also prepared by sodium iodide-chlorotrimethylsilane treatment of 3-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**9**) [7]. The adenine analog, 4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3(2*H*)-one (**11**), was prepared by sodium iodide-chlorotrimethylsilane treatment of 4-amino-3-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**10**) [7].

SCHEME I



In an effort to obtain the guanosine analog **21**, 3-methoxy-4,6-bis(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**12**) [7] was initially treated with 3 *N* sodium hydroxide to obtain 3-methoxy-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one, **13** (Scheme II). Successive treatment of **13** with 3-chloroperoxybenzoic acid followed by methanolic ammonia gave 6-amino-3-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**14**). Ether cleavage of **14** using *in situ*-generated iodotrimethylsilane gave the desired 6-amino-1*H*-pyrazolo[3,4-*d*]pyrimidine-3,4(2*H*,5*H*)-dione (**15**). Our attempts to glycosylate **15** using standard methods such as the high temperature, boron trifluoride-catalyzed procedure [5], or by the Vorbrüggen method (using trimethylsilyl trifluoromethane sulfonate [9]) failed to yield the desired guanosine derivative. However, reaction of **13** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**16**) and boron trifluoride etherate in refluxing nitromethane gave a 78% yield of 3-methoxy-6-methylthio-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**17**) which was converted to 3-methoxy-6-amino-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**18**) by treatment with 3-chloroperoxybenzoic acid followed by methanolic ammonia. The overall yield of **18** starting from **12** was 33%. This represented an improvement over the earlier reported synthesis of **18** (6% overall from **12** [7]). To avoid possible iodination of the sugar hydroxyl groups when subjected to iodotrimethylsilane [10], nucleoside **18** was first protected by acetylation using acetic anhydride and 4-dimethylaminopyridine to give 6-amino-3-methoxy-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**19**). Prolonged treatment of **19** with an excess of the ether cleavage reagent gave a product which was difficult to purify. Using ^{1}H nmr and FAB mass spectral data, the product was determined to be 6-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine-3,4(2*H*,5*H*)-dione (**20**). The ^{1}H nmr spectrum of **19** contained a singlet at δ 3.9 ppm which was attributed to the presence of the 3-methoxy substituent. The nmr spectrum of **20** was similar to that of **19**, but lacked the methoxy signal. Deprotection of the sugar moiety of **20** with methanolic ammonia gave the water-soluble guanosine analog, 6-amino-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine-3,4(2*H*,5*H*)-dione (**21**).

To prepare the adenosine and inosine analogs (Scheme III), 4-amino-3-methoxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**22**) and 3-methoxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]-pyrimidin-4(5*H*)-one (**23**) [7] were individually treated with sodium iodide and chlorotrimethylsilane. Unlike **19**, both nucleosides proved to be resistant to the ether-cleavage at-

SCHEME II

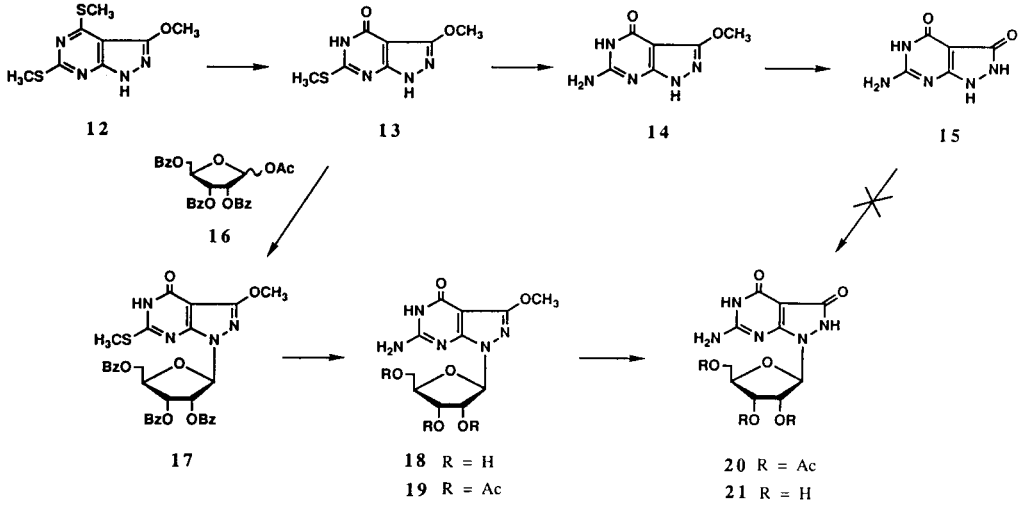


Table 1

Positional and Isotropic Thermal Parameters for Atoms in **26** and **27**

Atom	x/a	y/b	z/c	U[a]	Atom	x/a	y/b	z/c	U[a]
			26						
			Molecule **A**						
N1A	.4753(3)	.32641(11)	.28245(6)	.0282(5)	N2A	.4675(3)	.22412(11)	.27249(6)	.0286(4)
C3A	.5255(3)	.21259(13)	.22293(7)	.0262(5)	C4A	.6494(3)	.34281(14)	.15143(7)	.0270(5)
N5A	.6887(3)	.44223(13)	.14768(6)	.0320(5)	C6A	.6499(3)	.50118(14)	.18955(8)	.0314(5)
N7A	.5763(2)	.47589(12)	.23635(6)	.0284(4)	C8A	.5429(3)	.37608(13)	.23984(6)	.0246(5)
C9A	.5756(3)	.30647(13)	.19984(7)	.0255(5)	O10A	.5337(2)	.12356(10)	.19945(5)	.0339(4)
N11A	.6870(3)	.28609(15)	.10951(7)	.0372(5)	C1'A	.4493(3)	.36405(15)	.33592(7)	.0291(5)
C2'A	.3046(3)	.3043(2)	.36685(7)	.0310(5)	C3'A	.4252(3)	.2350(2)	.40036(7)	.0326(6)
C4'A	.5921(3)	.3002(2)	.41272(7)	.0324(6)	C5'A	.7641(4)	.2413(2)	.42497(10)	.0464(7)
O2'A	.2081(3)	.37498(13)	.39834(6)	.0468(5)	O3'A	.3404(3)	.20204(15)	.44825(6)	.0494(6)
O4'A	.6195(2)	.35725(13)	.36463(5)	.0402(5)	O5'A	.9075(3)	.3003(2)	.44725(7)	.0533(6)
H6A	.676(3)	.575(2)	.1839(8)	.029(6)	H10A	.498(6)	.078(3)	.2209(13)	.085(12)
H11A1	.739(5)	.310(3)	.0782(14)	.073(10)	H11A2	.667(4)	.224(2)	.1109(11)	.047(7)
H1'A	.410(3)	.437(2)	.3312(9)	.032(6)	H2'A	.217(3)	.267(2)	.3411(9)	.030(6)
H3'A	.471(3)	.177(2)	.3778(8)	.024(5)	H4'A	.560(4)	.341(2)	.4438(9)	.041(7)
H5'A1	.734(4)	.187(2)	.4513(10)	.041(7)	H5'A2	.821(4)	.209(2)	.3924(10)	.042(7)
HO2'A	.101(7)	.345(3)	.419(2)	.11(2)	HO3'A	.242(5)	.150(3)	.4371(12)	.069(10)
HO5'A	.891(7)	.286(3)	.485(2)	.103(14)					
			Molecule **B**						
N1B	.3863(3)	.78726(12)	.64426(6)	.0320(5)	N2B	.4583(3)	.84998(12)	.68401(6)	.0324(5)
C3B	.4870(3)	.79088(14)	.72497(7)	.0287(5)	C4B	.4472(3)	.59564(14)	.73962(7)	.0266(5)
N5B	.3851(3)	.51492(12)	.71232(6)	.0305(5)	C6B	.3226(3)	.52846(15)	.66213(8)	.0315(5)
N7B	.3146(2)	.61148(12)	.63339(6)	.0309(5)	C8B	.3765(3)	.69144(14)	.66158(7)	.0275(5)
C9B	.4402(3)	.68932(13)	.71380(7)	.0267(5)	O10B	.5528(3)	.82086(11)	.77205(5)	.0386(5)
N11B	.5139(3)	.58105(15)	.78846(7)	.0368(6)	C1'B	.3588(3)	.81957(14)	.59032(7)	.0307(5)
C2'B	.2564(3)	.91785(14)	.58208(7)	.0295(5)	C3'B	.2957(3)	.9346(2)	.52288(8)	.0338(6)
C4'B	.4898(3)	.8887(2)	.51526(7)	.0343(6)	C5'B	.6380(4)	.9659(2)	.50224(10)	.0488(8)
O2'B	.0652(2)	.91166(14)	.59159(6)	.0439(5)	O3'B	.1714(3)	.87793(15)	.49078(6)	.0423(5)
O4'B	.5325(2)	.83753(14)	.56478(6)	.0462(5)	O5'B	.8008(3)	.9230(2)	.47988(8)	.0626(7)
H6B	.286(4)	.465(2)	.6437(11)	.053(8)	H10B	.570(7)	.900(3)	.7783(14)	.104(13)
H11B1	.510(3)	.519(2)	.8002(8)	.025(5)	H11B2	.556(5)	.632(2)	.8044(10)	.057(8)
H1'B	.297(3)	.767(2)	.5726(9)	.026(5)	H2'B	.315(4)	.969(2)	.6035(10)	.037(6)
H3'B	.289(4)	1.003(2)	.5126(10)	.044(7)	H4'B	.477(4)	.837(2)	.4861(9)	.038(6)
H5'B1	.6725(4)	1.0017(2)	.53585(10)	.077(11)	H5'B2	.5858(4)	1.0150(2)	.47615(10)	.057(8)

Table 1 (continued)

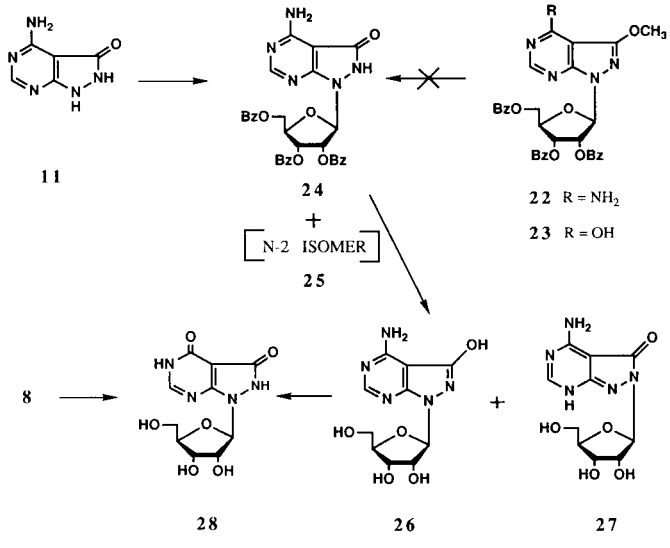
Atom	x/a	y/b	z/c	U[a]	Atom	x/a	y/b	z/c	U[a]
HO2'B	.045(6)	.911(3)	.627(2)	.100(13)	HO3'B	.068(5)	.889(3)	.5003(12)	.067(10)
HO5'B	.771(7)	.908(3)	.4437(6)	.13(2)					
OW	.9054(3)	.56462(13)	.07984(7)	.0451(5)	HOW1	.849(10)	.511(3)	.098(2)	.22(2)
HOW2	.914(11)	.542(4)	.0448(8)	.22(2)					
			27						
N1	.2698(3)	.6	.78648(9)	.0343(4)	N2	.4104(2)	.4501(2)	.80097(8)	.0307(3)
C3	.6081(3)	.4607(2)	.86205(8)	.0265(4)	C4	.7514(3)	.7273(2)	.94189(8)	.0279(4)
N5	.6874(3)	.8937(2)	.94986(8)	.0346(4)	C6	.4863(3)	.9524(3)	.90405(10)	.0347(4)
N7	.3319(3)	.8683(2)	.84944(8)	.0339(4)	C8	.3880(3)	.7015(2)	.83855(9)	.0288(4)
C9	.5974(3)	.6291(2)	.88740(8)	.0267(4)	O10	.7560(2)	.3412(2)	.88683(6)	.0331(3)
N11	.9593(3)	.6735(2)	.98692(9)	.0353(4)	C1'	.3619(3)	.3110(2)	.74792(8)	.0282(4)
C2'	.0747(3)	.2546(2)	.73668(8)	.0272(4)	C3'	.0620(3)	.1687(3)	.65609(9)	.0336(4)
C4'	.2478(3)	.2777(3)	.61260(9)	.0344(4)	C5'	.1042(4)	.4107(3)	.56137(12)	.0519(6)
O2'	.0113(2)	.1441(2)	.79639(7)	.0348(3)	O3'	.1654(3)	.0049(2)	.66423(8)	.0463(4)
O4'	.4290(2)	.3570(2)	.67170(7)	.0396(4)	O5'	.2794(4)	.5051(3)	.51904(9)	.0591(5)
OW1	.1652(3)	.2819(3)	.27977(13)	.0554(6)	OW2	.5223(3)	.3004(3)	.41650(10)	.0562(5)
OW1D	.111(5)	.237(3)	.324(2)	.056[b]	H6	.442(4)	1.068(3)	.9088(12)	.039(5)
H7	.224(5)	.916(3)	.8189(14)	.049(6)	H11A	1.040(4)	.746(3)	1.0200(13)	.042(6)
H11B	1.008(5)	.581(4)	.982(2)	.059(8)	H1'	.478(4)	.220(3)	.7704(12)	.035(5)
H2'	-.041(4)	.353(3)	.7325(13)	.046(6)	H3'	-.127(5)	.165(3)	.630(2)	.051(6)
H4'	.346(5)	.210(3)	.5789(15)	.055(7)	H5'A	-.002(6)	.490(4)	.599(2)	.071(8)
H5'B	-.024(6)	.333(4)	.522(2)	.080(9)	HO2'	-.074(5)	.200(4)	.8316(15)	.057(7)
HO3'	.042(8)	-.056(5)	.690(2)	.114(13)	HO5'	.339(11)	.621(8)	.544(3)	.171(15)
HW1A	.067(6)	.194(5)	.270(2)	.069(8)	HW1B	.287(9)	.244(6)	.327(3)	.115(14)
HW2A	.651(7)	.371(5)	.391(2)	.089(10)	HW2B	.459(11)	.380(7)	.460(3)	.168(15)

[a] For nonhydrogen atoms (except OW1D on **27**), U is $U_{eq} = 1/3\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* A_{ij}$, where A_{ij} is the dot product of the i^{th} and j^{th} direct-space unit-cell vectors. [b] U for OW1D was fixed at the approximate average of the U_{eq} values of OW1 and OW2.

tempt and remained essentially unchanged even after several days of heating at reflux temperature. Direct glycosylation of **11** using **16** and boron trifluoride etherate gave two nucleoside products. The major product was identified as 4-amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyrazolo[3,4-*d*]pyrimidin-3(2*H*)-one (**24**) and the minor product identified as the corresponding N-2 ribosyl-attached isomer (**25**). Treatment of **24** with sodium methoxide in methanol effected debenzoylation of the glycosyl moiety to give 4-amino-3-hydroxy-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (**26**) and similar deprotection of **25** gave 4-amino-2-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-3(7*H*)-one (**27**). The structures of **26** and **27** were confirmed by single crystal X-ray diffraction analysis. It is interesting to note the differences in structure of the 3-substituent of **26** in the solid and solution states. The solid state structure shows that the 3-substituent exists in the hydroxy form (see X-ray section). When nucleoside **26** is in solu-

tion, however, the *keto* tautomer predominates. The ^{1}H nmr spectrum of **26** (in DMSO-d_6) shows a broad singlet at δ 11.4 ppm which indicates that the tautomeric proton resides on a ring nitrogen. The ^{1}H nmr spectrum of **27** shows a downfield N-H proton (at δ 12.2 ppm) which indicates that the *keto* tautomer for this isomer also predominates in solution. The solid state structure of **27** is also in the *keto* form, but the tautomeric proton resides at N-7 instead of the pyrazolone N-1 nitrogen.

SCHEME III



Attempted glycosylation of **8** by the high temperature, boron-trifluoride-catalyzed procedure gave less than 5% yield of nucleoside product. Moreover, treatment of **8** according to the Vorbrüggen glycosylation procedure gave an intractable mixture of nucleoside products. Earlier workers [11] have also reported obtaining similar mixtures upon glycosylation attempts with allopurinol, a derivative of **8**. Attempts to deaminate **26** by treatment with sodium nitrite also gave a complex mixture of products. The inosine analog, 1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-3,4(2*H*,5*H*)-dione (**28**) was successfully prepared by deamination of **26** using adenosine deaminase. Utilizing a variation of an earlier-reported procedure [28], nucleoside **28** was made by enzyme-catalyzed glycosylation of **8** with purine nucleoside phosphorylase in the presence of ribose-1-phosphate.

Single Crystal X-Ray Diffraction Analysis of Nucleosides **26** and **27**.

Atomic coordinates for **26** and **27** are listed in Table 1. Bond lengths and bond angles are given in Tables 2 and 3, respectively. The N-1 isomer **26** crystallizes in two distinct conformations (designated **A** and **B**) which are illustrated in Figures 1 and 2. The N-2 isomer **27** is illustrated in Figure 3.

Table 2

Bond Lengths (Å) in **26** and **27** [a]

1	2	1 - 2	1 - 2	1 - 2
		26-A	**26-B**	**27**
N2	N1	1.390(2)	1.402(2)	1.406(2)
C8	N1	1.350(2)	1.353(2)	1.306(2)
C1'	N1(N2)	1.444(2)	1.434(2)	1.440(2)
C3	N2	1.321(2)	1.312(2)	1.379(2)
C9	C3	1.428(2)	1.426(3)	1.418(3)
O10	C3	1.328(2)	1.334(2)	1.264(2)
N5	C4	1.361(3)	1.354(2)	1.380(3)
C9	C4	1.412(3)	1.410(3)	1.397(2)
N11	C4	1.324(3)	1.331(2)	1.318(2)
C6	N5	1.342(3)	1.350(3)	1.312(2)
N7	C6	1.332(3)	1.324(3)	1.340(2)
C8	N7	1.357(2)	1.357(2)	1.381(3)
C9	C8	1.388(2)	1.389(3)	1.411(2)
C2'	C1'	1.528(3)	1.521(3)	1.524(2)
O4'	C1'	1.429(3)	1.430(3)	1.424(2)
C3'	C2'	1.525(3)	1.528(3)	1.532(2)
O2'	C2'	1.415(3)	1.406(3)	1.409(2)
C4'	C3'	1.520(3)	1.543(3)	1.530(3)
O3'	C3'	1.419(2)	1.424(3)	1.414(3)
C5'	C4'	1.503(3)	1.523(3)	1.518(3)
O4'	C4'	1.441(2)	1.451(3)	1.444(2)
O5'	C5'	1.417(3)	1.424(3)	1.418(3)
ave C-H		1.01(2)	0.98(3)	1.01(5)
ave N-H		0.88(6)	0.86(2)	0.83(5)
ave O-H		0.97(8)	0.93(12)	0.96(8)
ave O-H (water)		0.93		0.97(7)

[a] Atoms in parentheses pertain to compound 27.

The most interesting feature of the N-1 isomer is the unusual tautomeric form that is observed in the solid state. Both conformers exist in the 3-hydroxy form with the proton in the plane of the heterocycle and directed

Table 3

Bond Angle(°) in **26** and **27** [a]

1	2	3	1 - 2 - 3 **26-A**	1 - 2 - 3 **26-B**	1 - 2 - 3 **27**
N2	N1	C8	110.81(14)	110.86(15)	102.57(13)
C8(C3)	N1(N2)	C1'	127.7(2)	125.5(2)	126.2(2)
C1'	N1(N2)	N2(N1)	120.24(14)	122.9(2)	119.70(12)
C3	N2	N1	105.72(14)	104.8(2)	113.70(15)
C9	C3	O10	126.5(2)	123.0(2)	131.01(13)
C9	C3	N2	111.1(2)	112.4(2)	104.00(14)
O10	C3	N2	122.4(2)	124.7(2)	125.0(2)
N5	C4	C9	118.3(2)	117.5(2)	118.98(14)
C9	C4	N11	124.3(2)	124.5(2)	124.8(2)
N11	C4	N5	117.4(2)	118.0(2)	116.2(2)
C6	N5	C4	118.3(2)	118.4(2)	117.7(2)
N7	C6	N5	128.6(2)	129.4(2)	127.2(2)
C8	N7	C6	112.1(2)	111.2(2)	117.63(14)
C9	C8	N1	107.8(2)	107.7(2)	114.7(2)
C9	C8	N7	125.5(2)	125.8(2)	118.11(14)
N1	C8	N7	126.7(2)	126.5(2)	127.18(13)
C3	C9	C4	138.3(2)	138.2(2)	134.51(15)
C3	C9	C8	104.6(2)	104.2(2)	105.01(13)
C4	C9	C8	117.1(2)	117.6(2)	120.3(2)
C2'	C1'	O4'	107.51(15)	102.8(2)	105.91(11)
C2'	C1'	N1(N2)	112.3(2)	117.1(2)	114.30(13)
O4'	C1'	N1(N2)	109.5(2)	110.6(2)	109.4(2)
C3'	C2'	O2'	112.3(2)	110.9(2)	111.9(2)
C3'	C2'	C1'	101.8(2)	99.7(2)	101.66(12)
O2'	C2'	C1'	105.8(2)	113.9(2)	112.28(12)
C4'	C3'	O3'	110.4(2)	107.0(2)	109.50(14)
C4'	C3'	C2'	102.7(2)	103.4(2)	101.81(14)
O3'	C3'	C2'	114.0(2)	110.7(2)	110.15(13)
C5'	C4'	O4'	109.5(2)	110.7(2)	109.5(2)
C5'	C4'	C3'	113.5(2)	113.5(2)	113.09(15)
O4'	C4'	C3'	104.0(2)	105.9(2)	107.16(12)
O5'	C5'	C4'	113.3(2)	113.2(2)	112.0(2)
C1'	O4'	C4'	109.7(2)	106.0(2)	109.23(13)

[a] Atoms in parentheses pertain to compound **27**.

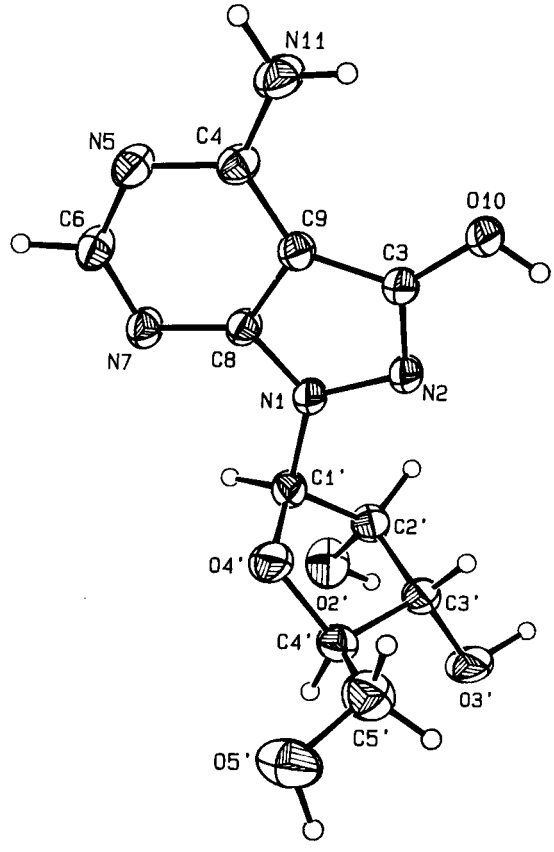


Figure 1. Perspective drawing of molecule **A** of compound **26** showing atom labeling and molecular conformation. The sugar conformation is $C_{3'}$-endo. Thermal ellipsoids are drawn at the 50% probability level.

away from the amino group. In contrast, the N-2 isomer exists in the 3-oxo form with the tautomeric proton residing on N-7 rather than on the expected nitrogen, N-1. In a review dealing with the possible tautomeric structures of pyrazolones, Elguero [12] concluded that 1-substituted-3-pyrazolones and 1-substituted-3-indazolones (which correspond to N-1 substitution in the pyrazolo-[3,4-*d*]pyrimidin-3-one system) exist in the *enol* form while 1-substituted-5-pyrazolones and 2-substituted-3-indazolones (which correspond to N-2 substitution in the pyrazolo[3,4-*d*]pyrimidin-3-one system) exist in the *keto* form. A search of the Cambridge Structural Database [13] to find crystallographic support of Elguero's generalizations produced evidence for the structure of the pyrazolones, but not for the indazolones. The solid-state structures of **26** and **27**, however, now provide support for the fused pyrazolones.

The nucleoside **26** is the 3-hydroxy derivative of 4-amino-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (4APPR), the structure of which was reported by Sprang and coworkers [14] (therein referred to as "8-azatubercidin").

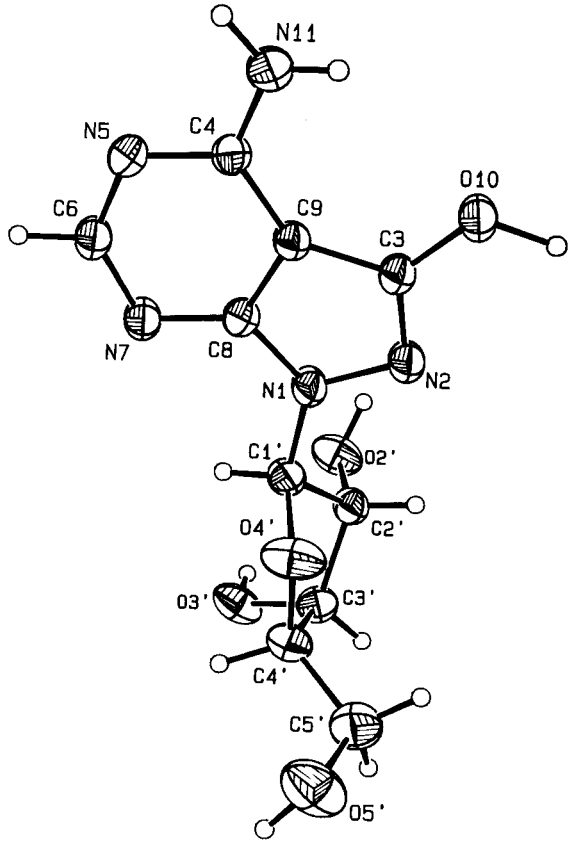


Figure 2. Perspective drawing of molecule **B** of compound **26** showing atom labeling and molecular conformation. The sugar conformation is $C_{1'}$-exo. Thermal ellipsoids are drawn at the 50% probability level.

The two unique conformers of **26** differ mainly in the sugar puckering. The root-mean-square deviation (rmsd) in the bond lengths in the pyrazolopyrimidine bases of **A** and **B** is 0.006 Å, and 0.009 Å for all bond lengths. There is no significant difference in the corresponding bond lengths of 4APPR and the two unique molecules of **26** within experimental error. There are some very significant differences in the bond angles between conformers **A** and **B** of **26**. These differences, which range from 1.1-8.1° in magnitude, involve C1′ of the ribose moiety and the 3-hydroxy function. The distinct sugar conformations of the two conformers may account for the difference in bond angles at C1′.

In compound **27**, the shortest bonds in the heterocycle are N1–C8, N5–C6 and C4–C9, consistent with the N7-protonated tautomer depicted in Scheme III. This is in contrast to **26** in which the C4–N5, N5–C6, C6–N7 and N7–C8 bond lengths have a maximum difference of 0.031 Å in each conformer. The conjugation with the heterocycle of the oxygen atoms attached at C3 is seen in the short C–O bonds in **26** and the long C=O bond in **27**. In all three structures, the C4–N11 bond has considerable double bond character consistent with other adenosine analogs [14,15], and the C4–NH_2 four-atom fragments are essentially planar.

The pyrazolo[3,4-*d*]pyrimidine moiety of conformer **A** is less planar than that of conformer **B**. Maximum deviation of the mean plane for **A** is 0.035(2) Å [N2] (rmsd = 0.023

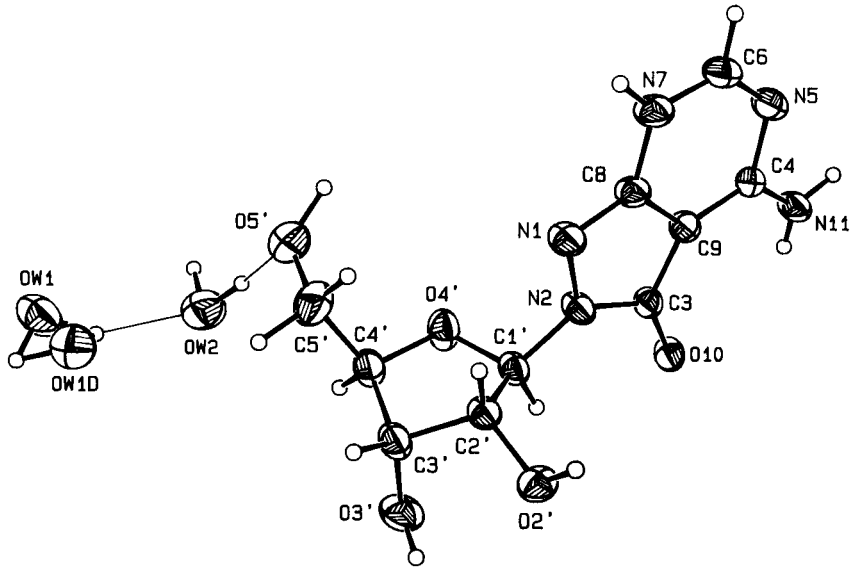


Figure 3. Perspective drawing of compound **27** showing atom labeling and molecular conformation. The waters of solvation are included. Thin lines indicate hydrogen bonds. Water OW1 is ~8% disordered. Thermal ellipsoids are drawn at the 50% probability level.

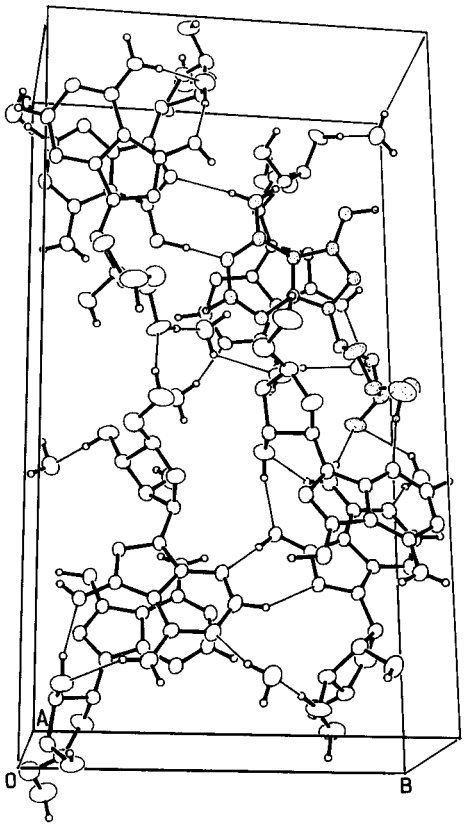


Figure 4. Perspective drawing of the unit cell of compound **26** viewed perpendicular to the base plane of the shaded molecule (molecule **B**). The high degree of overlap of the bases of the shaded molecule **B** with molecule **A** behind **B** is noted. Hydrogen bonding is indicated by thin lines. Base-to-base hydrogen bonding does not occur between different conformers.

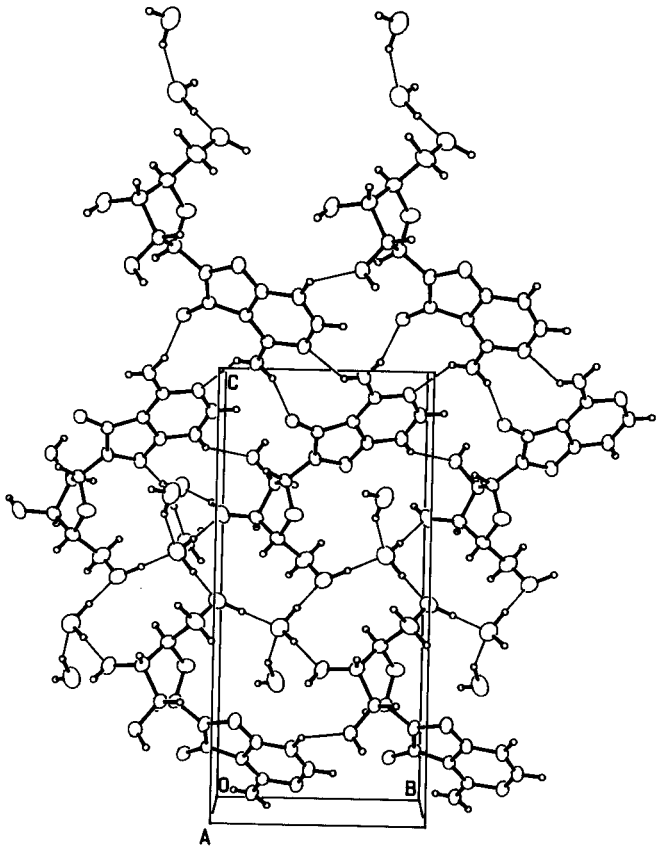


Figure 5. Perspective drawing of the unit cell of compound **27** viewed perpendicular to the *bc* plane. Hydrogen bonding is indicated by thin lines.

Å for plane-determining atoms) whereas for **B** the maximum is 0.016(2) Å [C3 and C4] (rmsd = 0.011 Å). In both conformers the O10 and N11 atoms are on opposite sides of their respective planes [−0.022(2) and 0.036(2) Å in **A**; −0.043(2) and 0.077(2) Å in **B**]. Atoms C1′ in the two conformers are substantially out of the plane [−0.214(2) Å in **A**; 0.212(2) Å in **B**], the former on the same side as O10 and the latter on the opposite side from O10. The heterocycle of **27** is nearly planar with all atoms within 0.038 Å of the mean plane (rmsd = 0.023 Å) similar to **26-A**. Respectively, atoms O10, N11 and C1′ of **27** are −0.0467(12), 0.075(2) and 0.2507(15) Å from the mean plane of the heterocycle, similar in this respect to **26-B**. The dihedral angles between the pyrazole and pyrimidine rings are 2.76(8)°, 1.01(7)° and 2.86(7)° for **26-A**, **26-B** and **27**, respectively.

In the ^{1}H nmr spectra of **26** and **27**, the two NH_2 protons are nonequivalent ($\Delta\delta$ = 0.9 and 0.45 ppm, respectively). These phenomena suggest that there is intramolecular hydrogen bonding between the NH_2 and O10 groups. The H112···O10 distances are 2.77(3), 2.64(3) and 2.75(3) Å for **26-A**, **26-B** and **27**, respectively. With N-H bond lengths normalized to 1.0 Å, the average H···O distance is 2.62 Å, which is slightly less than the sum of the hydrogen and oxygen van der Waals radii (2.70 Å) [16]. This would imply that intramolecular hydrogen bonding may be present albeit very weak. Other work in our laboratories [17] on systems containing an amino and an oxo group on adjacent fused six-membered rings, α to the bridgehead carbon, shows nonequivalency of the NH_2 protons with $\Delta\delta$ values in the range 1.2-2.0 ppm, suggesting a stronger hydrogen bonding interaction in these fused six-membered ring structures. Correspondingly, H···O distances are in the range 1.91-2.05 Å. Comparison of these data with those of **26** and **27** suggest that the hydrogen bonding in **26** and **27** is very weak.

The conformational parameters of the ribofuranose moieties are given in Table 4. Conformer **A** exists in the $C_{3'}$-endo conformation whereas conformer **B** has a $C_{1'}$-exo conformation. The latter conformation is nearly identical to the $C_{1'}$-exo/$C_{2'}$-endo conformation of 4APPR and the ribose bond angles reflect this similarity [14]. Atom C3′ is

Table 4

Sugar Conformational Parameters in **26** and **27** [a]

Parameter		**26-A**	**26-B**	**27**
		Sugar conformation		
τ_0(°)	C4'–O4'–C1'–C2'	-2.0(2)	-42.8(2)	-21.0(2)
τ_1(°)	O4'–C1'–C2'–C3'	-21.0(2)	46.6(2)	35.7(2)
τ_2(°)	C1'–C2'–C3'–C4'	34.8(2)	-32.7(2)	-35.6(2)
τ_3(°)	C2'–C3'–C4'–O4'	-36.9(2)	8.8(2)	24.5(2)
τ_4(°)	C3'–C4'–O4'–C1'	24.4(2)	21.0(2)	-2.5(2)
τ_m(°)	amplitude of pucker	37.4	46.5	36.9
P(°)	pseudorotation angle	21.6	134.7	164.8
	conformation	$C_{3'}$-endo	$C_{1'}$-exo	$C_{2'}$-endo
		^3E	$_1T^2$	^2E
		Glycosidic linkage		
χ_{CN}(°)	O4'-C1'-N1(N2)-C8(C3)	-83.4(2)	-100.9(2)	-109.6(2)
χ'_{CN}(°)	O4'-C1'-N1(N2)-N2(N1)	82.6(2)	67.7(2)	62.2(2)
		Side chain conformation		
ϕ_{OO}(°)	O4'-C4'-C5'-O5'	76.9(2)	78.8(2)	63.2(2)
ϕ_{CO}(°)	C3'-C4'-C5'-O5'	-167.4(2)	-162.3(2)	-177.4(2)

[a] Atom labels in parentheses pertain to compound 27.

0.571(2) Å above the plane of the other four furanose ring atoms in **26-A**; atom C1' is 0.657(2) Å below the plane of the other ring atoms in **26-B**. The ribose ring of **27** has the C2' envelope conformation (^2E, $C_{2'}$-endo) with C2' 0.576(2) Å above the plane of the other four atoms. The C5'-O5' orientation is *trans* to the C3'-C4' bond in all molecules as was observed in 4APPR [14].

The glycosyl bond lengths are about the same in the three molecules studied here, although somewhat shorter than observed in 4APPR [14]. The glycosidic torsion angles χ'_{CN} is such that N1 of **27** is similarly oriented with respect to the ribose moiety as N2 is in the conformers of **26**. The glycosidic torsion angles [χ'_{CN} = 82.6(2)° and 67.7(2)° for **A** and **B**; 62.2(2)° for **27**] are in the "mid-*anti*" region. As pointed out by Sprang, *et al.* [14], N8-unprotonated 8-aza nucleosides (purine numbering) often exhibit "high-*anti*" glycosyl conformations which tend to bring N8 close to H2'. While **26** and **27** are not in the "high-*anti*" region, the unprotonated ring nitrogen (N2 or N1) tends to be close to H2' in these compounds as well.

Packing.

The crystal packing of **26** is illustrated in Figure 4. Pairwise stacking of molecules **A** and **B** produces the greatest degree of overlap. The overlap pattern is similar to that observed in 4APPR [14]. In each pair, the base planes have a dihedral angle of 1.58(4)° and an interplanar separation of 3.37 Å (rmsd). The pairs translated along the *a*-axis are 3.33 Å (rmsd) apart but have very little base overlap. Hydrogen bonding is detailed in Table 5. All hydroxyl groups are hydrogen bond donors. The hydrogen bonds formed by the 3-hydroxyl groups of both conformers are particularly strong. The base planes are approximately parallel to the 101 and 10$\bar{1}$ diffraction planes. The water molecule interacts strongly as a donor and acceptor with only molecule **A** although there is a weak interaction with molecule **B** in which water is the donor.

The crystal packing of **27** is shown in Figure 5. The hydrogen bonding is given in Table 5. There is no base stacking in this structure. Again, all hydroxyl and amino hydrogen atoms participate in some hydrogen bonding. The 3-oxo group is acceptor in two intermolecular hydrogen bonds in contrast to a single intermolecular hydrogen bond involving the 3-hydroxyl groups as acceptors in the crystal structure of **26**. The principle directions for hydrogen bonding are in the *bc*-plane. A single O2'-HO2'···O10 hydrogen bond propagates the structure along the *a*-axis.

Table 5

Hydrogen Bonding and Close Intermolecular Contacts in **26** and **27**

D - H ••• A	Symmetry of A relative to D	d(D•••A) (Å)	d(H•••A) (Å)	∠(D-H••A) (°)
26				
C6A H6A N2A	1.0-x, 0.5+y, 0.5-z	3.239(2)	2.50(2)	130.(2)
O10A H10A N7A	1.0-x,y-0.5, 0.5-z	2.668(2)	1.81(4)	177.(3)
N11A H11A1 O3'B	1.0-x,y-0.5, 0.5-z	2.980(2)	2.06(3)	173.(3)
N11A H11A2 O10A	x,y,z	3.321(2)	2.77(3)	125.(3)
N11A H11A2 O2'B	0.5-x, 1.0-y, z-0.5	3.241(3)	2.52(3)	145.(3)
O2'A HO2'A O5'A	x-1.0,y,z	2.688(3)	1.68(5)	173.(4)
O3'A HO3'A OW	1.0-x,y-0.5, 0.5-z	2.651(3)	1.62(3)	177.(3)
O5'A HO5'A O3'A	0.5+x, 0.5-y, 1.0-z	2.666(2)	1.72(4)	163.(3)
O10B H10B N5B	1.0-x, 0.5+y, 1.5-z	2.660(2)	1.58(4)	175.(4)
N11B H11B1 N2B	1.0-x, y-0.5, 1.5-z	3.244(2)	2.31(2)	168.(2)
N11B H11B2 O10B	x,y,z	3.241(2)	2.64(3)	128.(2)
C5'B H5'B1 O2'A	0.5+x, 1.5-y, 1.0-z	3.315(3)	2.347(3)	162.8(3)
O2'B HO2'B O10A	0.5-x, 1.0-y, 0.5+z	2.838(2)	1.97(4)	165.(4)
O3'B HO3'B O5'B	x-1.0,y,z	2.761(3)	2.05(4)	148.(3)
O3'B HO3'B O2'B	x,y,z	2.681(2)	2.31(3)	109.(3)
O5'B HO5'B N7B	0.5+x, 1.5-y, 1.0-z	2.880(2)	1.98(2)	157.(4)
OW HOW1 N5A	x,y,z	2.833(2)	1.94(5)	159.(4)
OW HOW2 O3'B	1.0-x,y-0.5,-z	3.109(2)	2.44(4)	128.(3)
27				
N7 H7 O2'	x,y+1.0,z	2.840(2)	2.14(3)	144.(2)
N11 N11A O10	2.0-x, 0.5+y, 2.0-z	2.815(2)	1.96(2)	161.(2)
N11 N11B N5	2.0-x,y-0.5, 2.0-z	3.006(2)	2.38(3)	138.(3)
N11 N11B O10	x,y,z	3.272(2)	2.75(3)	126.(2)
O2' HO2' O10	x-1.0,y,z	2.635(2)	1.75(3)	169.(3)
O3' HO3' O2'	x,y,z	2.697(2)	2.44(4)	96.(3)
O3' HO3' OW1	-x,y-0.5, 1.0-z	2.691(3)	1.78(4)	164.(4)
O3' HO3' OW1D	-x,y-0.5, 1.0-z	2.59(2)	1.84(5)	135.(4)
O5' HO5' OW2	1.0-x, 0.5+y, 1.0-z	2.755(3)	1.71(6)	173.(5)
OW1 HW1A N1	-x,y-0.5, 1.0-z	2.795(2)	2.03(3)	146.(3)
OW1 HW1B OW2	x,y,z	2.817(3)	1.89(4)	149.(4)
OW1D HW1A N1	-x,y-0.5, 1.0-z	2.79(2)	2.03(3)	133.(3)
OW1D HW1B OW2	x,y,z	2.55(2)	1.89(4)	129.(4)
OW2 HW2A O3'	1.0-x, 0.5+y, 1.0-z	2.743(2)	1.75(4)	171.(3)
OW2 HW2B O5'	x,y,z	2.755(3)	1.74(5)	166.(5)

Table 6

Crystal and Experimental Data [a, b] for Compounds **26** and **27**

	26	**27**
Empirical formula	$C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$	$C_{10}H_{13}N_5O_5 \cdot 2H_2O$
Formula weight	292.25	319.27
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1$
a(Å)	7.2318(10)	5.0900(6)
b(Å)	13.354(3)	7.9987(12)
c(Å)	25.080(6)	17.046(3)
β (°)	90.	95.575(11)
V (Å^3)	2422.0(9)	690.7(2)
Z	8	2
ρ_{calcd} (g cm^{-3})	1.603	1.535
F(000) (electrons)	1224	334
Radiation, λ (Å)	CuKα, 1.54178	CuKα, 1.54178
Crystal dimensions (mm)	0.30x0.30x0.07	0.46x0.165x0.03
Crystal volume (mm^3)	0.00630	0.00229
μ (cm^{-1})	10.877	10.814
Max 2θ (°)	152	152
Total refls, measd, unique	5632, 5020	3199, 2859
R_{int}	0.0155	0.0157
Observed refls ($F \geq 4\sigma_F$)	4425	2596
No. of variables	476	271
S (goodness of fit)	1.520	1.232
R, wR [c]	0.0354, 0.0481	0.0279, 0.0378
Extinction parameter	6.0(6) x 10^{-7}	6.2(3) x 10^{-6}
Max Δ/σ	0.008	0.014
Max, min in Δρ map (e/Å^3)	0.45, -0.37	0.37, -0.25

[a] Unit-cell parameters were obtained by least-squares refinement of the setting angles of 25 reflections in the ranges: 50.0<2θ<57.5° for **26**; 50.8<2θ<59.5° for **27**. [b] Intensity measurements were made on an Enraf-Nonius CAD4 automatic diffractometer equipped with a graphite monochromator using an ω-2θ scan procedure and variable scan speeds. Data reduction was accomplished with the SDP-Plus program package and included Lorentz, polarization, decay [correction on I: 1.000-1.001 for **26**; 0.994-1.000 for **27**] and absorption corrections [27]. Absorption corrections were based on crystal size and shape measurements; the transmission factors were 0.680-0.926 for **26** and 0.730-0.977 for **27**. [c] Function minimized was $\Sigma w(|F_o| - |F_c|)^2$, where $w = (\sigma_F^2 + 0.0004F^2)^{-1}$ for both structures. R and wR have conventional definitions. $\sigma_F = F\sigma_I/2I$ and $\sigma_I = (N_{pk} + N_{bg1} + N_{bg2})^{1/2}$

Biological Evaluation.

The 3-oxo-substituted pyrazolo[3,4-*d*]pyrimidines **8** and **11**, as well as the ribonucleosides **18**, **21** and **26** were tested *in vitro* for antiviral activity against several virus strains (including rhinovirus, influenza and adenovirus) according to previously reported procedures [18]. No antiviral activity was exhibited. The compounds were also measured for their cytotoxicity against L1210, LoVo, Wi-L2 and MX-1 cancer cell lines. Compound **26**, which is a derivative of the cytotoxic agent, 4-amino-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (APPR) [19], was the most active, showing a modest ID_{50} of 23 μ*M* against L1210. No *in vivo* antitumor effect was noted when **26** was tested in mice which were injected with lethal doses (10^6 cells) of L1210 leukemia [20].

EXPERIMENTAL

Melting points (uncorrected) were determined in a Haake-Buchler capillary melting point apparatus. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ. Thin-layer chromatography (tlc) was conducted on plates of silica gel (60F-254, EM Reagents). Silica gel (E. Merck; 230-400 mesh) was used for flash column chromatography. All solvents used were reagent grade. The enzymes, purine nucleoside phosphorylase (from calf spleen) and adenosine deaminase (type VIII, from calf intestinal mucosa), were purchased from Sigma Chemical Co. Ribose-1-phosphate (dicyclohexylammonium salt form) was obtained from Calbiochem-Behring. A semi-preparative C-18 column (2.5 x 30 cm, 5μ particle size; Rainin Instrument Co. Inc.) was used for reversed-phase hplc purifications (Delta Prep 3000, Waters Millipore). To perform the ether cleavage reactions, the heterocycle, sodium iodide, and solvent were combined in a dry flask, the atmosphere inside the flask was then replaced with dry argon (by use of a firestone value - Aldrich), and the chlorotrimethylsilane was subsequently added. Nucleoside components were detected on tlc by uv light, and with 7% sulfuric acid in methanol spray followed by heating. Evaporations were carried out under reduced pressure using a Büchi rotovapor with the water bath temperature below 30°. Infrared (ir) and ultraviolet (uv) spectra were recorded with Perkin-Elmer 1420 and Beckman DU-50 spectrometers, respectively. The 3-oxo substituted nucleosides were analyzed at the University of California, Riverside, by fast atom bombardment (FAB) using a VG ZAB2FHF. Electron impact (at 70eV using a VG7070EHF) was utilized to record mass spectral data for the heterocyclic bases. Nuclear magnetic resonance (^{1}H nmr) spectra were recorded at 300 MHz with an IBM NR/300 spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to dimethylsulfoxide (DMSO) as an internal standard. The presence of water as indicated by elemental analysis was verified by ^{1}H nmr spectroscopy.

5-Amino-3(2*H*)-oxo-1*H*-pyrazole-4-carbonitrile (**6**).

To a stirring suspension of dry 5-amino-3-methoxypyrazole-4-carbonitrile [7] (**4**, 1.12 g, 8.1 mmoles) and sodium iodide (1.45 g, 9.7 mmoles) in dry acetonitrile (80 ml) was added chlorotrimethylsilane (1.14 ml, 8.9 mmoles) at ambient temperature. The mixture was heated under an atmosphere of dry argon at 50° for 18 hours. The reaction mixture was then cooled in an ice-bath and filtered. The filtered solid was washed successively with cold satu-

rated solutions of sodium thiosulfate (50 ml) and brine (50 ml). Evaporation of the acetonitrile filtrate gave more solid product, which was also washed with the two solutions described above. The combined solid residue was suspended in boiling water, brought into solution by adding *N,N*-dimethylformamide, and allowed to cool to yield 0.68 g (68%) of **6**, mp >350°; ir: ν max 3150-3400 (NH_2), 2200 (CN), 1620 (C=O) cm^{-1}; uv (*p*H 1): λ max 227 nm (ε 10,200); (*p*H 7): 220 nm (sh) (ε 8,100); (*p*H 11): 222 nm (sh) (ε 8,800); ^1H nmr (DMSO-d_6): δ 7.05 (s, 2H, N*H*$_2$), 9.4-10.2 (br s, 2H, ring N*H*'s); ms: m/e 124 (M^+).

Anal. Calcd. for $C_4H_4N_4O$: C, 38.71; H, 3.25; N, 45.15. Found: C, 38.45; H, 3.47; N, 45.26.

5-Amino-3(2*H*)-oxo-1*H*-pyrazole-4-carboxamide (**7**).

5-Amino-3-methoxy-1*H*-pyrazole-4-carboxamide [7] (**5**, 7.75 g, 49.7 mmoles) was added, with stirring, to a solution of sodium iodide (8.2 g, 54.7 mmoles) in dry acetonitrile (300 ml) in an inert atmosphere as described for the synthesis of **6**. Chlorotrimethylsilane (6.95 ml, 54.7 mmoles) was added *via* syringe and the reaction heated to 80°. The reaction mixture was stirred for 40 hours, cooled, and filtered. Additional solid product was recovered after evaporation of the the acetonitrile filtrate. The combined solids were washed successively with cold saturated solutions of sodium thiosulfate (100 ml) and brine (100 ml). The product was then suspended in boiling water, brought into solution by adding *N,N*-dimethylformamide, and allowed to cool. A white solid formed, which was filtered and dried to yield 5.98 g (85%), mp >350°; ir: ν max 3200-3450 (NH_2), 1650 and 1690 (C=O) cm^{-1}; uv (*p*H 1): λ max 238 nm (ε 7,300); (*p*H 7): 240 nm (ε 6,400); (*p*H 11): 245 nm (ε 7,200); ^1H nmr (DMSO-d_6): δ 6.60 and 7.30 (2 br s, 2H, CON*H*$_2$), 6.78 (s, 2H, N*H*$_2$), 9.1-10.0 (br s, 2H, N$_1$*H* and N$_2$*H*); mass spec. m/e 142 (M^+).

Anal. Calcd. for $C_4H_6N_4O_2$: C, 33.81; H, 4.26; N, 39.42. Found: C, 33.55; H, 4.10; N, 39.23.

1*H*-Pyrazolo[3,4-*d*]pyrimidine-3,4(2*H*,5*H*)-dione (**8**).

Method A.

Compound **7** (0.20 g, 1.4 mmoles) was heated in formamide (15 ml) at 185° for 25 minutes and allowed to cool to room temperature. The resulting solid was suspended in water (50 ml), brought to *p*H 8 by the addition of 2 *N* aqueous sodium hydroxide, and quickly filtered. The filtrate was neutralized with glacial acetic acid and cooled in an ice bath. A yellow precipitate formed, which was collected by filtration, and treated with decolorizing carbon (Norit). The product was crystallized from *N,N*-dimethylformamide/water, as described above, to yield yellow microneedles, 77 mg (36%), mp >360°; ir: ν max 1680 and 1720 (C=O) cm^{-1}; uv (*p*H 1): λ max 218 nm (ε 10,900); (*p*H 7 and 11): 223 nm (ε 12,900), 265 (2,300); ^1H nmr (DMSO-d_6): δ 7.85 (s, 1H, C$_6$*H*), 10.8-11.1 (br s, 2H, N$_1$*H* and N$_2$*H*), 11.64 (br s, 1H, N$_5$*H*); mass spec. m/e 152 (M^+).

Anal. Calcd. for $C_5H_4N_4O_2 \cdot \frac{1}{4}H_2O$: C, 38.35; H, 2.90; N, 35.77. Found: C, 38.48; H, 2.95; N, 35.96.

Method B.

To a suspension of 3-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one [7] (**9**, 0.5 g, 3 mmoles) and sodium iodide (2.3 g, 15 mmoles) in dry acetonitrile (150 ml), was added chlorotrimethylsilane (1.9 ml, 15 mmoles) and the reaction mixture stirred in an atmosphere of dry argon at 80° for 48 hours. The reaction mixture was cooled, filtered, and the solid was washed with sodium thiosulfate and brine solutions following the procedure for compound **6**. The residual solid was then crystallized from water containing a little *N,N*-dimethylformamide to give 0.2 g (44%) of material which possessed the same physicochemical characteristics as the product obtained from method A.

4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3(2*H*)-one (**11**).

4-Amino-3-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine [7] (**10**, 3.7 g, 22.4 mmoles) and sodium iodide (5.0 g, 33.3 mmoles) were added to dry acetonitrile (300 ml) and the mixture stirred in an inert atmosphere as described for **6**. Chlorotrimethylsilane (4.27 ml, 33.6 mmoles) was added and the mixture was refluxed for 24 hours. The reaction was monitored by tlc (0.1 *M* ammonium chloride/-acetonitrile, 3:7, v/v, as developing solvent). Additional sodium iodide (10.0 g, 66 mmoles) and chlorotrimethylsilane (8.5 ml, 67 mmoles) were added to the cooled reaction mixture and refluxing was continued for an additional 3 days. The reaction mixture was then worked up following the procedure for compound **6**, and crystallized from the same solvent to yield light green needles, 1.97 g (58%), mp >350°; ir: ν max 3100-3400 (NH_2), 1660 and 1680 (C=O) cm^{-1}; uv (*p*H 1): λ max 231 nm (ε 14,000); (*p*H 7): 235 nm (ε 12,100); (*p*H 11): 220 nm (ε 8,300), 233 (9,000), 310 (1,300); ^1H nmr (DMSO-d_6): δ 7.23-7.48 (br s, 2H, N*H*$_2$), 7.98 (s, 1H, C$_6$*H*), 10.8-11.2 (br s, 2H, ring N*H*'s); mass spec. m/e 151 (M^+).

Anal. Calcd. for $C_5H_5N_5O \cdot \frac{3}{4}H_2O$: C, 36.48; H, 3.98; N, 42.54. Found: C, 36.81; H, 4.07; N, 42.25.

3-Methoxy-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**13**).

3-Methoxy-4,6-bis(methylthio)pyrazolo[3,4-*d*]pyrimidine [7] (**12**), 10 g, 41 mmoles) was combined with 3*N* sodium hydroxide (400 ml) and the mixture was refluxed for 6 hours. The solution was then neutralized with glacial acetic acid and filtered while still hot. Reprecipitation from hot (70°) 1 *N* sodium hydroxide solution using glacial acetic acid gave 6.2 g (71%) of **13** as a microcrystalline product, mp 291-292° (effervesces); uv (*p*H 1): λ max 218 nm (ε 30,800), 232 (32,100), 268 (22,300); (*p*H 7): 217 nm (ε 32,300), 233 (32,300), 263 (22,000); (*p*H 11): 236 nm (ε 40,500), 260 (26,100); ^1H nmr (DMSO-d_6): δ 2.49 (s, 3H, SC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 12.15 and 12.64 (2s, 2H, N$_1$*H* and N$_5$*H*).

Anal. Calcd. for $C_7H_8N_4O_2S$: C, 39.62; H, 3.80; N, 26.40; S, 15.11. Found: C, 39.67; H, 3.93; N, 26.16; S, 14.79.

6-Amino-3-methoxy-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**14**).

Compound **13** (5.78 g, 27 mmoles) was added to dry *N,N*-dimethylformamide (100 ml) and heated (100°) to dissolve. The resulting solution was cooled to 0° and 3-chloroperoxybenzoic acid (5.7 g, 33 mmoles) was added. The solution was stirred at 0° for 30 minutes and more 3-chloroperoxybenzoic acid (5.7 g, 33 mmoles) was added. After cooling the reaction to −10° (alcohol-ice bath), a precipitate formed (6.7 g) which was filtered and combined with methanolic ammonia (150 ml) in a sealed steel reaction vessel and heated for 18 hours at 120°. The bomb contents were then cooled and filtered and the resulting white precipitate was dissolved in 1 *N* sodium hydroxide solution and reprecipitated by addition of glacial acetic acid to give 3.1 g (63%) of **14**. The sodium salt of **14** was obtained by dissolving a crude sample in 1 *N* sodium hydroxide at 70° and allowing the resulting solu-

tion to cool. An analytically pure sample of the free base was obtined by reprecipitation of the sodium salt from aqueous sodium hydroxide (80°) using glacial acetic acid, mp >340°; ir: ν max 1680 (C=O) cm^{-1}; uv (*p*H 1): λ max 219 nm (ε 38,700), 242 (sh) (13,900); (*p*H 7): 222 nm (ε 47,100), 250 (13,800); (*p*H 11): 252 nm (ε 15,300); ^1H nmr (DMSO-d_6): δ 3.89 (s, 3H, OCH_3), 6.52 (br s, 2H, NH_2), 10.4 and 11.8 (2 br s, 2H, N_1H and N_5H); ^{13}C nmr (NaOD in D_2O) δ 89.1 (C_{3a}), 57.1 (OCH_3); mass spec. m/e 181 (M^+).

Anal. Calcd. for $C_6H_7N_5O_2$: C, 39.78; H, 3.90; N, 38.66. Found: C, 39.50; H, 3.80; N, 38.40.

6-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidine-3,4(2*H*,5*H*)-dione (**15**).

Compound **14** (1.48 g, 8.2 mmoles) was combined with sodium iodide (4 g, 26 mmoles) and chlorotrimethylsilane (3.2 ml, 25 mmoles) in acetonitrile (100 ml) and refluxed under anhydrous conditions for 18 hours. After addition of dry *N,N*-dimethylformamide (150 ml) and more chlorotrimethylsilane (1 ml), the suspension was heated at reflux temperature for an additional four hours, cooled, and filtered. The solid residue was washed with ethanol, suspended in hot water and filtered to give 0.82 g (60%) of crude product. Reprecipitation of the compound from aqueous sodium hydroxide using glacial acetic acid gave analytically pure **15**; mp >400°; ir: ν max 1680, 1700 (C=O) cm^{-1}; uv (*p*H 1): λ max 227 nm (ε 28,300), 250 (sh) (10,600); (*p*H 7 and 11): 229 nm (ε 32,700); ^1H nmr (DMSO-d_6): δ 6.53 (s, 2H, NH_2), 10.1 (s, 1H, N_5H); 10.9 (br s, 2H, N_1H and N_2H); ^{13}C nmr (sodium deuteroxide in deuterium oxide): δ 88.5 (C_{3a}).

Anal. Calcd. for $C_5H_5N_5O_2 \cdot \frac{1}{4}H_2O$: C, 34.99; H, 3.23; N, 40.81. Found: C, 35.27; H, 3.26; N, 40.43.

3-Methoxy-6-methylthio-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**17**).

Compound **13** (3.69 g, 17.4 mmoles) was combined with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (11.7 g, 23 mmoles) and dry nitromethane (100 ml). After heating the suspension to reflux temperature, boron trifluoride ethyl etherate (2.9 ml, 23 mmoles) was added and the resulting solution heated at reflux temperature for 40 minutes. The reaction mixture was then evaporated to dryness, and the residue was dissolved in ethyl acetate (300 ml) and washed with a saturated aqueous solution of sodium bicarbonate (200 ml) followed by water (200 ml). The organic layer was dried over anhydrous sodium sulfate, combined with silica gel (30 g), and evaporated to dryness. The resulting solid was placed atop a silica gel column and eluted with dichloromethane followed by 7% acetone in dichloromethane to yield 8.9 g (78%) of syrupy **17**. Crystallization with ethanol gave a colorless, microcrystalline product, mp 232-234°; ir: ν max 1730 (ester C=O) cm^{-1}; uv (*p*H 1 and 7): λ max 237 nm (ε 19,700), 276 (12,200); (*p*H 11): 226 nm (ε 40,800), 260 (sh) (15,400); ^1H nmr (DMSO-d_6): δ 2.55 (s, 3H, SCH_3), 3.83 (s, 3H, OCH_3), 6.54 (d, J = 2.1 Hz, 1H, $C_1{\cdot}H$), 7.4-7.9 (m, 15H, benzoyl aromatics), 12.5 (s, 1H, N_5H).

Anal. Calcd. for $C_{33}H_{28}N_4O_9S$: C, 60.36; H, 4.30; N, 8.53; S, 4.88. Found: C, 60.26; H, 4.25; N, 8.43; S, 4.87.

6-Amino-3-methoxy-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**18**).

To a solution of **17** (8.9 g, 13.5 mmoles) in dichloromethane (300 ml) was added 3-chloroperoxybenzoic acid (85%, 4.73 g, 23 mmoles) and stirred at room temperature for two hours whereupon another 300 mg of the oxidizing agent was added. The suspension was stirred overnight, and then cooled to −20°, after which the oxidizing agent was removed by filtration. The filtrate was evaporated to dryness and the resulting foam was combined with methanolic ammonia (saturated at −10°, 250 ml), and sealed in a steel reaction vessel. The reaction mixture was heated at 110° for 16 hours, and the product was isolated by flash column chromatography (using methanol:dichloromethane (1:6) as eluent) to yield 2.5 g (60%) of **18** [7], mp 241-243° (lit [7] 241-242°).

Anal. Calcd. for $C_{11}H_{15}N_5O_6 \cdot \frac{1}{2}H_2O$: C, 41.00; H, 5.00; N, 21.73. Found: C, 40.94; H, 4.83; N, 21.41.

6-Amino-3-methoxy-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**19**).

To a suspension of **18** (8.73 g, 27.8 mmoles) in acetonitrile (300 ml) was added acetic anhydride (50 ml, 520 mmoles) and 4-dimethylaminopyridine (120 mg, 1 mmole) and the resulting solution was stirred at room temperature for 3 hours. The solution was evaporated to a syrup whereupon water (200 ml) was added and the resulting solid filtered. Crystallization from ethanol gave 10.4 g (85%) of **19**, mp 274-275°; ir: ν max 3460, 3360 (NH_2), 1750 (C=O) cm^{-1}; uv (*p*H 1): λ max 223 nm (ε 24,300), 254 (7,600); (*p*H 7): 224 nm (ε 23,700), 256 (7,100); (*p*H 11): 220 nm (sh) (ε 24,000), 254 (7,900); ^1H nmr (deuteriochloroform): δ 3.88 (s, 3H, OCH_3), 6.22 (d, J = 2.1 Hz, 1H, $C_1{\cdot}H$), 10.9 (s, 1H, N_5H).

Anal. Calcd. for $C_{17}H_{21}N_5O_9$: C, 46.47; H, 4.82; N, 15.94. Found: C, 46.34; H, 4.70; N, 15.72.

6-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]-pyrimidine-3,4(2*H*,5*H*)-dione (**20**).

Nucleoside **19** (4.9 g, 11 mmoles) was combined with sodium iodide (6.7 g, 44.6 mmoles), finely ground molecular sieves (4 Å, 6 g) and dry acetonitrile (250 ml). Chlorotrimethylsilane (5.6 ml, 44 mmoles) was slowly added to the reaction mixture which was then heated at 70° for 6 days. The reaction mixture was filtered while still hot, and the resulting solid was washed with hot ethanol (3 x 50 ml), followed by hot ethyl acetate/ethanol (1:1, v/v, 100 ml). The combined washings were evaporated to dryness, and successively triturated with concentrated aqueous solutions of sodium thiosulfate (80 ml) and brine (80 ml). The resulting solid was taken up in a hot solution of ethyl acetate and ethanol (1:1), combined with silica gel (60-200 mesh, 25 g), and evaporated to dryness. The silica gel mixture was placed atop a flash column and eluted with 7% methanol in dichloromethane. Evaporation of appropriate fractions gave 2.7 g of **20** (57%), mp >320°; ir: ν max 1740 (C=O) cm^{-1}; uv (*p*H 1): λ max 230 nm (ε 26,100), 262 (10,600); (*p*H 7): 232 nm (ε 25,800), 261 (sh) (7,100); (*p*H 11): 233 nm (ε 28,300); ^1H nmr (DMSO-d_6): δ 5.94 (d, J = 3.75, 1H, $C_1{\cdot}H$), 6.89 (br s, 2H, NH_2), 11.4 (br s, 1H, N_5H); ms: (FAB) 426.128 (MH^+).

6-Amino-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine-3,4(2*H*,-5*H*)-dione (**21**).

Compound **20** (0.4 g, 0.9 mmole) was combined in a pressure bottle with methanolic ammonia (saturated at −5°, 80 ml) and stirred at room temperature overnight. A white solid formed which was collected by filtration, dissolved in water, neutralized with glacial acetic acid, and evaporated to dryness. The product was purified by semi-preparative scale hplc (elution with 2% acetonitrile/water followed by lyophylization) to give 210 mg of **21** (75%), mp >340°; ir: ν max 1710, 1700 (C=O); uv (*p*H 1): λ max 229 nm (ε 40,000), 253 (15,500); (*p*H 7): 232 nm (ε 38,600), 255 (sh)

(10,300); (*p*H 11): 233 nm (ε 39,100), 268 (sh) (8,100); ^{1}H nmr (DMSO-d_6): δ 5.75 (d, 1H, J = 4.8 Hz, $C_{1'}H$), 6.56 (br s, 2H, NH_2), 10.35 and 10.65 (2 br s, 2H, N_5H and N_2H); mass spec. (FAB) 300.095 (MH^+).

Anal. Calcd. for $C_{10}H_{13}N_5O_6 \cdot H_2O$: C, 37.86; H, 4.77; N, 22.08. Found: C, 37.72; H, 4.75; N, 22.22.

4-Amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]-pyrimidin-3(2*H*)-one (**24**).

A mixture of **11** (3.2 g, 21 mmoles) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (16 g, 31.7 mmoles) in dry nitromethane (250 ml) was heated to reflux temperature whereupon boron trifluoride ethyl etherate (4 ml, 32 mmoles) was added through the top of the condenser. After 15 minutes of heating, the reaction flask was removed from the heat source, and the contents were evaporated to dryness. Analysis of the reaction by tlc showed that two main products had formed. The resulting black mass was dissolved in ethyl acetate (500 ml) and washed with saturated aqueous sodium bicarbonate (300 ml) followed by water (100 ml). After drying (sodium sulfate), the organic phase was combined with silica gel and evaporated to dryness. The solid was then placed atop a silica gel column and eluted with dichloromethane followed by 8% methanol in dichloromethane. The fractions containing the faster-eluting product, **24** were pooled. Fractions which contained a mixture of both products were evaporated to dryness and treated with methanol which caused a preferential precipitation of **24**. The remaining filtrate contained an inseparable mixture (3.3 g) of **24** and **25**. The total yield of pure **24** was 4.7 g (37%), mp 264-265°; uv (ethanol): λ max 230 nm (ε 58,600), 276 (9,300); ^{1}H nmr (DMSO-d_6): δ 6.54 (d, 1H, J = 2.4 Hz, $C_{1'}H$), 6.88 and 7.76 (2 br s, 2H, NH_2), 7.4-7.9 (m, 15H, benzoyl aromatics), 8.13 (s, 1H, C_6H), 11.8 (br s, 1H, N_2H).

Anal. Calcd. for $C_{31}H_{25}N_5O_8$: C, 62.52; H, 4.23; N, 11.76. Found: C, 62.37; H, 4.12; N, 11.66.

4-Amino-3-hydroxy-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (**26**) and 4-Amino-2-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-3(7*H*)-one (**27**).

Compound **24** (3.08 g, 5.1 mmoles) was combined with dry methanol (200 ml) and sodium methoxide (0.86 g, 16 mmoles) and the resulting solution was stirred overnight at room temperature. The solution was neutralized using Dowex-50 H^+ resin and quickly decanted. The solution was allowed to stand at room temperature for 10 minutes whereupon a precipitate formed. The precipitate was collected by filtration and crystallized from aqueous methanol to give 1.29 g (82%) of **26**, mp 234°; uv (*p*H 1): λ max 230 nm (ε 30,200), 270 (sh) (5,200); (*p*H 7): 207 nm (17,000), 231 (27,000), 285 (sh) (4,200); (*p*H 11): 231 nm (28,500), 290 (sh) (4,200); ^{1}H nmr (DMSO-d_6): δ 5.92 (d, J = 4.8, 1H, $C_{1'}H$), 6.7 and 7.6 (2 br s, 2H, NH_2), 8.1 (s, 1H, C_6H), and 11.4 (br s, 1H, N_2H).

Anal. Calcd. for $C_{10}H_{13}N_5O_5$: C, 42.41; H, 4.63; N, 24.73. Found: C, 42.28; H, 4.51; N, 24.69.

An enriched mixture of **25** (containing a small amount of **24**) was treated with methanolic sodium methoxide as described above for compound **26**. After several hours, a precipitate formed which was collected by filtration, dissolved in water, and neutralized with glacial acetic acid. The resulting neutral solution was evaporated down to a small volume whereupon a precipitate formed. Recrystallization of the collected solid from water gave light green needles of **27**, mp >330°; ir: ν max 1670 (C=O) cm^{-1}; uv (*p*H 1): λ max 236 nm (ε 26,400); (*p*H 7): 238 nm (ε 23,200), 317 (1,900); (*p*H 11): 222 nm (ε 20,400), 239 (17,900), 320 (3,000); ^{1}H nmr (DMSO-d_6): δ 5.69 (d, J = 4.4 Hz, 1H, $C_{1'}H$), 7.6 and 8.05 (2 br s, 2H, NH_2), 12.2 (br s, 1H, N_7H).

Anal. Calcd. for $C_{10}H_{13}N_5O_5$: C, 42.41; H, 4.63; N, 24.73. Found: C, 42.09; H, 4.70; N, 24.45.

1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine-3,4(2*H*,5*H*)-dione (**28**).

Method A.

Compound **26** (195 mg, 0.7 mmole) was combined with Tris-buffer (5 ml, 200 m*M*, *p*H 7.4) and water (10 ml) and the *p*H of the resulting solution was adjusted to 7.4 by adding 1 *N* sodium hydroxide. Adenosine deaminase (50 μl, 130 units) was added and the solution stirred overnight at 37°. Additional enzyme (100 μl) was added on each of two succeeding days. After 4 days total reaction time, the resulting suspension was evaporated to dryness and triturated with hot methanol. The product was purified by semi-preparative hplc (water as eluent) and the collected homogeneous fractions lyophilized to give 90 mg (46%) of **28** as a hygroscopic powder, mp 190-193° (softens), 217° (effervesces); uv (*p*H 1): λ max 218 nm (ε 16,300), 264 (3,300); (*p*H 7): 228 nm (ε 13,800), 275 (3,000); (*p*H 11): 227 nm (ε 16,000), 277 (3,500); ^{1}H nmr (DMSO-d_6): δ 5.91 (d, J = 4.6 Hz, 1H, $C_{1'}H$), 7.93 (s, 1H, C_6H), and other sugar protons.

Anal. Calcd. for $C_{10}H_{12}N_4O_6 \cdot 3H_2O$: C, 35.51; H, 5.36; N, 16.56. Found: C, 35.28; H, 5.38; N, 16.93.

Method B.

Purine nucleoside phosphorylase (1 unit, 10 μl of 3.2 *M* ammonium sulfate suspension) was added to a *p*H 7.4 solution of **8** (10 mg, 0.065 mmole) in 20 ml of 10 m*M* Tris-chloride buffer. Ribose-1-phosphate (40 mg, 0.09 mmole) was added in increments with additional units of PNPase over 72 hours at ambient temperature to yield 80% conversion to **28** as determined by hplc. The entire solution was evaporated to a small volume and applied to a preparative tlc plate. Elution of the plate with ethyl acetate:ethanol:water (2:1:1) gave 20 mg of crude product which was determined by nmr, uv, and hplc analysis to be identical to the product obtained by method A.

X-ray Diffraction Analysis.

Suitable crystals of **26** and **27** were obtained by slow evaporation of aqueous solutions of the respective compounds. Crystals of **26** were large colorless plates and crystals of **27** were very thin, nearly-square colorless plates. Crystal and experimental data for both are summarized in Table 6. Initial positions of all non-hydrogen atoms for both structures were obtained by direct methods (SHELXS86 [21]). Positions of hydrogen atoms were obtained from electron density difference maps (for **26**, peaks were 0.38-0.82 e $Å^{-3}$ and R = 0.056; for **27**, peaks were 0.36-0.80 e $Å^{-3}$ and R = 0.051). The structure of **26** was refined in two blocks, each block composed of one unique nucleoside molecule and the water of solvation. Possible disorder in molecule **B** at the O5' position was ultimately neglected except that certain constraints were imposed on the geometry of this hydroxymethyl group. Thus, the hydrogen atoms on C5'B were idealized [d(C-H) = 1.00 Å; ∠H-C-H = 109.5°] and the O5'B-HO5'B bond distance was constrained to 0.95 Å. Constraints were also imposed on the water of solvation. Thus, d(OW-HOW) was constrained to 0.93

Å, ∠H-OW-H was fixed at 104°, and the isotropic thermal parameters [U(HOW)] for the hydrogen atoms were refined as a single variable. The structure of **27** had slight disorder present in OW1. Hence, the OW1 and OW1D refined occupancies were 0.921(5) and 0.079(5), respectively. An isotropic thermal parameter for OW1D was fixed at 0.056, a value approximately equal to the average Ueq of OW1 and OW2. Both structures were refined using the least-squares program SHELX76 [22]. All atomic positions, anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms were varied except where constraints took priority. Atomic scattering factors and anomalous-dispersion corrections for non-hydrogen atoms were taken from the "International Tables for X-ray Crystallography" [23]. Scattering factors for hydrogen atoms were taken from Stewart, Davidson and Simpson [24]. Figures were drawn with ORTEPII [25]. Least-squares planes were calculated with the program PLANES [26].

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