

A Convenient Synthesis of Pyrazolo[3,4-*b*]pyridine Nucleosides by Convenient Ring-Closure Procedures. X-Ray Crystal and Molecular Structure of 4-Amino-1-(β -D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-*b*]pyridin-6-one

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Practical syntheses of 1-(β -D-ribofuranosyl)pyrazolo[3,4-*b*]pyridines as purine antagonists, related to isoguanosine, guanosine, and xanthosine, are described for the first time. Ethyl 5-amino-1-(2,3-*O*-isopropylidene- β -D-ribofuranosyl)-1*H*-pyrazole-4-carboxylate (**10**) was converted into 5-amino-1-(2,3-*O*-isopropylidene- β -D-ribofuranosyl)-1*H*-pyrazole (**12**), which was in turn converted into 6-amino-1-(β -D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-*b*]pyridin-4-one (**4**) in four steps. 4-Amino-1-(β -D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-*b*]pyridin-6-one (**3**) was obtained in satisfactory overall yield from compound (**12**), prepared in four steps *via* a ring-closure procedure. The structure of compound (**3**) was established by a single-crystal X-ray study. 4-Hydroxy-1-(β -D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-*b*]pyridin-6-one (**5**) was obtained in three steps from the ester (**10**).

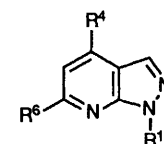
For a number of years, we^{1,2} and others³⁻¹² have been interested in the pyrazolo[3,4-*b*]pyridines as potential specific antagonists of nucleic acid metabolism, and in more recent years have evaluated derivatives of this ring system as substrate inhibitors of purine-requiring enzymes. Although several polysubstituted derivatives of this heterocycle have been synthesized¹³⁻¹⁹ as medicinal agents, such as etazolote, tracatolate, and cartazolote, only a few nucleosides possessing this ring system are known.¹⁻⁴ This may be due to the confusion and corrections^{4,7,9,11} over the identity of the pyrazolo[3,4-*b*]pyridine ring-closure product obtained from various pyrazole derivatives, and also due to the tedious preparation¹ of the precursor 5-amino-1-benzylpyrazole (**17**). Recently, we described a rather long but regio- and stereo-selective synthesis of compounds (**1**) and (**2**) from the amine (**17**) in several steps.^{1,2} It appeared that the most promising strategy which could lead to the desired 4- or 4,6-disubstituted *N*-1 nucleosides of this ring system would involve ring annulation of a preformed 5-aminopyrazole nucleoside such as 5-amino-1-(2,3-*O*-isopropylidene- β -D-ribofuranosyl)-1*H*-pyrazole (**12**), wherein regio- and stereo-chemistry is an inherent feature of the molecule. The present study now addresses the synthesis of the hitherto unreported and versatile nucleoside (**12**) onto which an appropriately substituted pyridine ring has now been successfully annulated.

Results and Discussion

In the preparation of the key intermediate ethyl 5-amino-1-(2,3-*O*-isopropylidene- β -D-ribofuranosyl)-1*H*-pyrazole-4-carboxylate (**10**), we used the procedure first introduced by Schmidt *et al.*^{20,21} Anhydrous 1-deoxy-1-hydrazinyl-2,3-*O*-isopropylidene- β -D-ribose, was regioselectively condensed with the unsymmetrical β -dicarbonyl derivative ethyl cyano(ethoxymethylene)acetate in absolute ethanol to furnish the pyrazole (**10**) as the major product in 55% yield.^{22,23} Subsequently, alkaline hydrolysis of the ester functionality of compound (**10**) was achieved in 98% yield to furnish the free acid (**11**). High-temperature decarboxylation of acid (**11**) in diphenyl ether gave the pyrazole (**12**) as a crystalline solid in 84% yield.

A literature¹⁹ survey revealed that considerable confusion has remained over the identity of certain pyrazolo[3,4-*b*]pyridines synthesized by the ring closure of 1-substituted

	R ¹	R ⁴	R ⁶
(1)	Rib	OH*	H
(2)	Rib	NH ₂	H
(3)	Rib	NH ₂	OH*
(4)	Rib	OH*	NH ₂
(5)	Rib	OH	OH*
(6)	Rib	OH*	SMe
(7)	Bn	OH*	NH ₂
(8)	Bn	NH ₂	OH*
(9)	Bn	OH	OH*



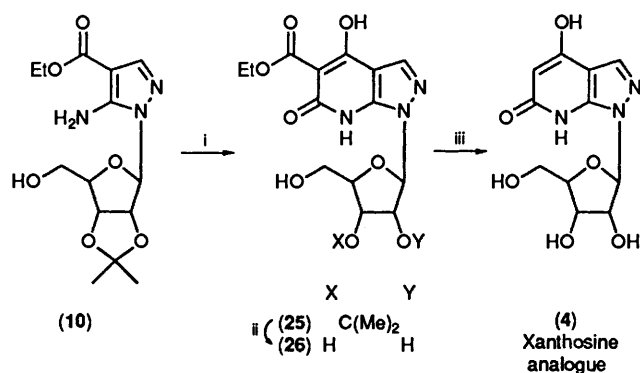
Rib = 1- β -D-ribofuranosyl

Bn = Benzyl

* Preferred as the oxo tautomer

5-aminopyrazoles with unsymmetrical 1,3-dicarbonyl compounds. Subsequent re-investigation of these reactions by various groups^{4,7,11} has changed the assignments of the reaction products. In one example, Dorn and Zubek¹² attempted to synthesize the guanine analogue (**7**), erroneously assigning the 6-oxo derivative (**8**) as the 4-oxo isomer (**7**). Therefore, the desired compound (**7**) was never obtained. No significant progress has been made since Dorn's original conception of this idea on using pyrazolo[3,4-*b*]pyridines as purine antagonists. We, therefore, investigated the possibility of preparing pyrazolo[3,4-*b*]pyridines (**3**)–(**5**) as isoguanosine, guanosine, and xanthosine analogues, directly. If Dorn and Zubek's compound is correctly assigned as having structure (**8**) then the most simple strategy could be the synthesis of 4-amino-1-(β -D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-*b*]pyridin-6-one (**3**) from the pyrazole (**12**) by utilization of the 4-step procedure depicted in Scheme 1. Treatment of compound (**12**) with the sodium salt of diethyl oxalacetate in glacial acetic acid afforded compound (**13**) in 98% yield. The latter compound was allowed to react with excess of hydrazine hydrate to give the required 6-hydroxy-1-(2,3-*O*-isopropylidene- β -D-ribofuranosyl)-1*H*-pyrazolo[3,4-*b*]pyridine-4-carbohydrazide (**14**) as a yellow solid in almost quantitative yield. Treatment of compound (**14**) in AcOH with NaNO₂ furnished the azide derivative (**15**) as the putative product. The latter compound (**15**) undergoes a Curtius rearrangement on treatment with glacial acetic acid at reflux temperature to give a mixture of the

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Scheme 3. Reagents and conditions: i, CH₂(CO₂Et)₂, NaOEt, EtOH, reflux; ii, aq. TFA; iii, aq. NaOH, reflux.

Table 1. Positional parameters for all atoms in compound (3).

Atom	x	y	z
N(1)	0.333 5(2)	0.432 16(7)	0.296 06(13)
N(2)	0.397 1(2)	0.381 46(7)	0.204 7(2)
C(3)	0.365 2(2)	0.407 89(9)	0.081 2(2)
C(4)	0.212 7(2)	0.526 43(9)	-0.007 8(2)
C(5)	0.139 3(2)	0.588 13(9)	0.046 6(2)
C(6)	0.124 6(2)	0.601 13(8)	0.189 6(2)
N(7)	0.189 2(2)	0.549 27(7)	0.279 65(14)
C(8)	0.265 2(2)	0.488 92(8)	0.227 3(2)
C(9)	0.281 1(2)	0.475 08(8)	0.088 4(2)
N(10)	0.223 9(2)	0.512 59(9)	-0.143 67(14)
O(11)	0.054 8(2)	0.656 36(6)	0.242 11(12)
C(1')	0.341 4(2)	0.418 83(8)	0.441 8(2)
C(2')	0.292 4(2)	0.342 19(8)	0.483 27(15)
C(3')	0.373 8(2)	0.337 46(8)	0.626 70(15)
C(4')	0.534 9(2)	0.387 03(9)	0.613 9(2)
C(5')	0.710 9(3)	0.350 82(10)	0.608 6(2)
O(2')	0.110 5(2)	0.327 44(7)	0.484 22(13)
O(3')	0.259 1(2)	0.366 34(7)	0.728 57(12)
O(4')	0.517 4(2)	0.425 15(7)	0.485 14(15)
O(5')	0.841 7(2)	0.405 75(7)	0.593 01(15)
O(W1)	0.127 2(3)	0.243 54(9)	0.087 7(2)
O(W2)	0.524 4(2)	0.235 56(8)	0.174 3(2)
H(3)	0.393(3)	0.380 2(12)	-0.002(2)
H(5)	0.088(3)	0.622 9(11)	-0.011(2)
H(7)	0.196(3)	0.560 3(11)	0.362(2)
H(10A)	0.170(3)	0.541 4(12)	-0.198(2)
H(10B)	0.248(3)	0.469(2)	-0.171(3)
H(1')	0.259(3)	0.455 8(10)	0.488(2)
H(2')	0.355(3)	0.307 8(10)	0.420(2)
H(3')	0.412(3)	0.285 1(11)	0.649(2)
H(4')	0.526(3)	0.420 1(12)	0.691(2)
H(5'A)	0.732(4)	0.324 4(14)	0.694(3)
H(5'B)	0.720(4)	0.318 5(14)	0.534(3)
H(O2')	0.067(4)	0.337(2)	0.400(3)
H(O3')	0.184(4)	0.333 0(13)	0.751(2)
H(O5')	0.936(4)	0.382(2)	0.585(3)
H(W1A)	0.081(5)	0.279(2)	0.134(3)
H(W1B)	0.237(6)	0.241(3)	0.109(5)
H(W2A)	0.576(4)	0.243(2)	0.089(3)
H(W2B)	0.520(4)	0.281(2)	0.211(3)

Single-crystal X-Ray Diffraction Analysis of Compound (3).—Atomic co-ordinates are presented in Table 1. Atom labelling and molecular conformation are illustrated in Figure 1. The compound crystallizes as the dihydrate. The tautomeric proton resides on N(7) of the pyridine moiety as observed in the structure of 1-(2-deoxy-β-D-erythro-pentofuranosyl)-1,7-dihydropyrazolo[3,4-b]pyridin-4-one and that of its arabinofuranosyl congener recently reported from our laboratory.^{1,25}

Table 2. Bond lengths (Å), bond angles (°), and selected torsion angles (°) in (3).

Atom			Bond lengths 1-2	Bond angle 1-2-3
1	2	3		
N(2)	N(1)	C(8)	1.383(2)	110.42(13)
C(8)	N(1)	C(1')	1.353(2)	129.52(13)
C(1')	N(1)	N(2)	1.440(2)	120.03(12)
C(3)	N(2)	N(1)	1.320(2)	105.44(13)
C(9)	C(3)	N(2)	1.405(2)	111.72(15)
C(5)	C(4)	C(9)	1.381(2)	116.76(14)
C(9)	C(4)	N(10)	1.434(2)	119.25(15)
N(10)	C(4)	C(5)	1.349(2)	124.0(2)
C(6)	C(5)	C(4)	1.416(2)	123.36(14)
N(7)	C(6)	O(11)	1.392(2)	117.23(14)
N(7)	C(6)	C(5)		118.11(14)
O(11)	C(6)	C(5)	1.264(2)	124.65(14)
C(8)	N(7)	C(6)	1.361(2)	119.09(13)
C(9)	C(8)	N(1)	1.381(2)	107.69(13)
C(9)	C(8)	N(7)		123.84(14)
N(1)	C(8)	N(7)		128.45(14)
C(3)	C(9)	C(4)		136.47(15)
C(3)	C(9)	C(8)		104.72(14)
C(4)	C(9)	C(8)		118.80(14)
C(2')	C(1')	O(4')	1.528(2)	103.32(12)
C(2')	C(1')	N(1)		114.23(12)
O(4')	C(1')	N(1)	1.406(2)	108.65(13)
C(3')	C(2')	O(2')	1.528(2)	112.30(12)
C(3')	C(2')	C(1')		101.31(12)
O(2')	C(2')	C(1')	1.408(2)	114.99(13)
C(4')	C(3')	O(3')	1.537(2)	108.45(12)
C(4')	C(3')	C(2')		102.30(12)
O(3')	C(3')	C(2')	1.424(2)	111.46(13)
C(5')	C(4')	O(4')	1.497(3)	105.86(14)
C(5')	C(4')	C(3')		116.27(14)
O(4')	C(4')	C(3')	1.445(2)	106.98(15)
O(5')	C(5')	C(4')	1.432(2)	107.48(15)
C(1')	O(4')	C(4')		107.81(13)

Selected torsion angles (°)

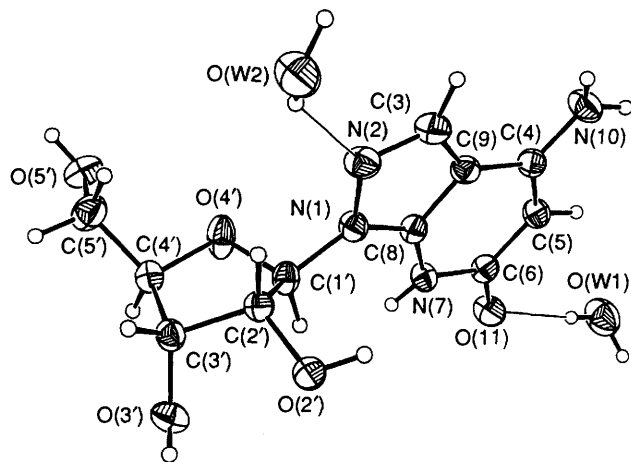
χ _{CN}	C(8)-N(1)-C(1')-O(4')	-109.5(2)
χ' _{CN}	N(2)-N(1)-C(1')-O(4')	72.8(2)
τ ₀	C(1')-C(2')-C(3')-C(4')	-31.46(14)
τ ₁	C(2')-C(3')-C(4')-O(4')	10.6(2)
τ ₂	C(3')-C(4')-O(4')-C(1')	16.9(2)
τ ₃	C(4')-O(4')-C(1')-C(2')	-37.5(2)
τ ₄	O(4')-C(1')-C(2')-C(3')	42.96(15)
φ _{OO}	O(4')-C(4')-C(5')-O(5')	59.9(2)
φ _{CO}	C(3')-C(4')-C(5')-O(5')	178.48(14)

Bond lengths, bond angles, and selected torsion angles are shown in Table 2. Bond lengths are in reasonable ranges for both the base ring system and the ribose moiety; the amino C-N bond is short and the oxo C=O bond is long, consistent with conjugation of these groups with the heteroaromatic ring system. The amino group is slightly nonplanar [N(10) is 0.115(2) Å out of the plane of its bonded atoms]. The pyridine-pyrazole dihedral angle is 0.78(6)°; the rms deviation of the fused-ring atoms from their mean plane is 0.009 Å.

The glycosidic bond length of 1.440(2) Å is consistent with other pyrazolo[3,4-*b*]pyridine nucleosides.²⁵ The glycosidic torsion angle, χ_{CN} = O(4')-C(1')-N(1)-C(8), is -109.5(2)°; thus, the glycosyl conformation is in the 'mid-anti' range. This conformation brings N(2) into close proximity to H(2') of the glycone, a feature which has been observed by Sprang *et al.*²⁶ in 8-azapurine nucleosides, and by Anderson *et al.*²⁷ in 3-oxopyrazolo[3,4-*d*]pyrimidine nucleosides. The two pyrazolo[3,4-*b*]pyridine nucleoside structures that do not exhibit

Table 3. Hydrogen bonding in compound (3).

D-H...A	Symmetry of A relative to D	d(D...A) (Å)	d(H...A) (Å)	∠(D-H...A) (°)
N(7) H(7) O(5')	1 - x, 1 - y, z	3.169(2)	2.35(2)	170(2)
N(10) H(10A) O(5')	1 - x, 1 - y, z - 1	3.019(2)	2.26(2)	148(2)
N(10) H(10B) O(3')	x, y, z - 1	3.004(2)	2.14(3)	167(2)
O(2') H(O2') O(11)	x, 1 - y, z	2.685(2)	1.79(3)	168(3)
O(3') H(O3') O(W2)	x - 0.5, 0.5 - y, 1 - z	2.768(2)	1.90(3)	172(2)
O(5') H(O5') O(2')	1 + x, y, z	2.721(2)	1.93(3)	154(3)
O(W1) H(W1A) O(11)	-x, 1 - y, z	2.763(2)	1.90(3)	169(3)
O(W1) H(W1B) O(W2)	x, y, z	3.134(3)	2.28(5)	178(4)
O(W2) H(W2A) O(W1)	0.5 + x, 0.5 - y, -z	2.693(2)	1.78(3)	168(3)
O(W2) H(W2B) N(2)	x, y, z	2.897(2)	2.09(3)	146(2)

**Figure 1.** Perspective drawing of compound (3) illustrating atom labelling and molecular conformation. Waters of hydration hydrogen bonded to N(2) and O(11) are also shown. Thermal ellipsoids are drawn at the 50% probability level.

this feature have the *syn* conformation and an intramolecular hydrogen bond between N(7) and O(5').²⁵ The sugar has a C^{1'}-*exo*/C^{2'}-*endo* conformation with a pseudorotation angle²⁸ P of 138.1° and an amplitude of pucker²⁸ τ_m of 42.2°. This conformation is distinct from the four different conformations reported for the pyrazolo[3,4-*b*]pyridine nucleosides.²⁵ The C(5')-O(5') side-chain has the *gauche-trans* orientation.

Table 3 details the hydrogen-bonding geometry, and Figure 2 illustrates the crystal packing. Every N-H and O-H hydrogen participates in hydrogen bonding. The sugar hydroxy hydrogen atoms and one hydrogen of each water molecule participate in fairly strong hydrogen-bonding interactions [$d(\text{H}\cdots\text{A}) < 2.00 \text{ \AA}$]. The base planes are approximately parallel to the (1,1,0) and (-1,1,0) crystallographic planes stacked along the *a* direction in a slanted fashion with interplanar distances of 3.4 Å. Interactions along the *b* direction between stacks of molecules are facilitated *via* the waters of hydration which form hydrogen-bonded, zig-zagged chains in the *a* direction between the nucleoside stacks. In the *c* direction, however, stacks interact [*via* N(10)⋯O(ribose) hydrogen bonds] with adjacent stacks related by translation along *c*. Each nucleoside is doubly hydrogen-bonded to each neighbour in a stack; hence, to one neighbour there exist reciprocating N(7)-H(7)⋯O(5') intermolecular hydrogen bonds [as observed in 1-(2-deoxy-β-D-erythro-pentofuranosyl)-1,7-dihydropyrazolo[3,4-*b*]pyridin-4-one],²⁵ and to the other neighbour there exist reciprocating O(2')-H(O2')⋯O(11) intermolecular hydrogen bonds. Another intrastack interaction

is the O(5')-HO(5')⋯O(2') intermolecular hydrogen bond which links molecules related by unit translation along the *a* direction.

Experimental

M.p.s were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Robertson Laboratory. TLC was carried out on Merck silica gel 60 F₂₅₄ plates. E. Merck silica gel (230-400 mesh) was used for flash column chromatography. All solvents used were reagent grade. Detection of nucleoside components in TLC was by UV light and with 10% H₂SO₄ in MeOH spray followed by heating. Evaporation was conducted under diminished pressure with the bath temperature <30 °C. IR spectra were recorded with a Beckman Acculab 2 spectrophotometer and UV spectra ($\epsilon \times 10^{-3}$) were recorded on a Beckman DU-50 spectrophotometer. ¹H NMR spectra were recorded with an IBM NR/300 spectrometer. The chemical-shift values are expressed in δ-values relative to Me₄Si as internal standard. The chemical-shift values for certain exchangeable protons are not reported due to their broad resonance. The presence of water, AcOH, and NaOMe, as indicated by elemental analysis, was verified by ¹H NMR spectroscopy. All solvent ratios are v/v.

5-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-1H-pyrazole-4-carboxylic Acid (11).—A solution of ethyl 5-amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-1H-pyrazole-4-carboxylate^{22,23} (10) (6.3 g, 19.2 mmol) in aq. NaOH (4.4 g, 110 mmol in 20 ml) was heated at gentle reflux (bath temperature 110 °C) for 4 h and cooled to room temperature. The clear solution was neutralized with Dowex-50 H⁺ resin and filtered. The resin was washed successively with hot water (2 × 50 ml) and EtOH (2 × 50 ml). The combined filtrates were concentrated under reduced pressure and the gummy residue was placed in a vacuum desiccator (over P₂O₅) for 12 h connected under high-vacuum (0.01 mmHg) pump to remove last traces of water. The hygroscopic solid (11) (5.65 g, 98%) thus obtained was pure enough for subsequent reaction. A small portion of the title acid (11) was crystallized from acetone-hexanes to furnish analytically pure *needles*; m.p. 146 °C (Found: C, 48.1; H, 5.75; N, 13.8. C₁₂H₁₇N₃O₆ requires C, 48.15; H, 5.72; N, 14.04%); λ_{max} (99% EtOH, qualitative) (pH 1) 234 and 254 nm; (pH 7) 240 nm; (pH 11) 238 nm; ν_{max} (KBr) 1 375 and 1 545 cm⁻¹ (C=O); δ_{H} [(CD₃)₂SO] 1.30 (3 H, s, Me), 1.48 (3 H, s, Me), 3.32 (2 H, m, 5'-H₂), 4.05 (1 H, m, 4'-H), 4.80 (1 H, d, 3'-H), 4.93 (1 H, br s, 5'-OH), 5.22 (1 H, d, 2'-H), 6.06 (1 H, s, 1'-H), 6.58 (2 H, s, NH₂), 7.51 (1 H, s, 3-H), and 12.01 (1 H, br s, CO₂H).

5-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-1H-pyrazole (12).—To a stirred melt of Ph₂O (3 ml) heated at

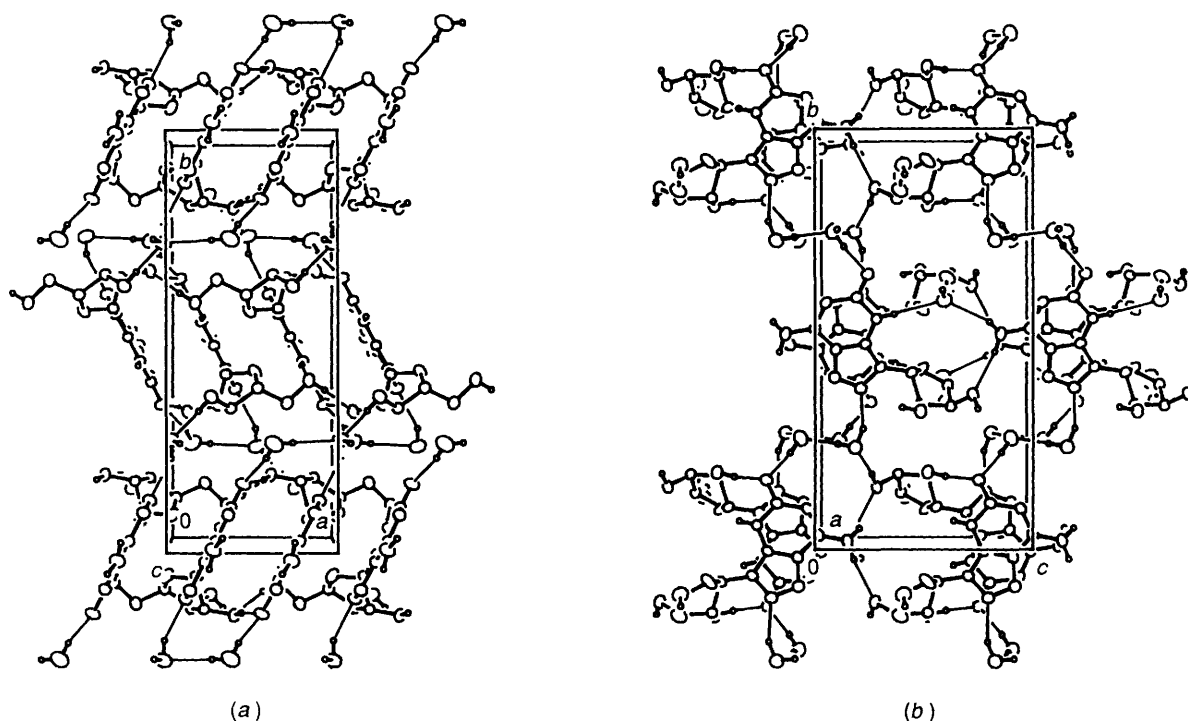


Figure 2. Packing diagrams for compound (3) showing hydrogen bonding. (a) View along the *c* direction illustrating slant-stacking of base planes. (b) View along *a* direction; molecular pairs at $y = \frac{1}{2}$ interact *via* reciprocated N(7)–H...O(5') hydrogen bonds, whereas molecular pairs at $y = 0$ and $y = 1$ interact *via* O(2')–H...O(11) hydrogen bonds.

220 °C under N₂ was added the acid (11) (1.0 g, 3.34 mmol) in 4 portions during 10 min. The mixture was stirred for another 10 min and the solution was then cooled to room temperature. Hexanes (50 ml) were added to the reaction mixture, the solution was stirred, and the hexanes were decanted off to leave a gummy residue in the flask. This procedure was repeated 3 times to remove most of the Ph₂O from the product. The residue was purified on a flash silica gel column (2.5 × 25 cm) with EtOAc as eluant, which provided syrupy amine (12) (0.72 g, 84%) (turned dark on exposure to light and air but kept well under N₂ in a dark bottle), which was sublimed under high vacuum (0.01 mmHg) to give the *title amine* as needles; m.p. 87 °C (Found: C, 51.6; H, 6.65; N, 16.2. C₁₁H₁₇N₃O₄ requires C, 51.75; H, 6.71; N, 16.46%); λ_{max}(pH 1) 207 (3.0) and 249 nm (8.0); (pH 7) 232 nm (6.3); (pH 11) 232 nm (6.4); δ_H(CDCl₃) 1.34 (3 H, s, Me), 1.57 (3 H, s, Me), 3.62 (2 H, br s, NH₂), 3.7 (2 H, m, 5'-H₂), 4.47 (1 H, br s, 4'-H), 5.05 (1 H, m, 3'-H), 5.17 (1 H, m, 2'-H), 5.54 (1 H, s, 4-H, exchanged slowly in D₂O), 5.80 (1 H, br s, 5'-OH), 5.87 (1 H, s, 1'-H), and 7.31 (1 H, s, 3-H).

Ethyl 6-Hydroxy-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (13).—To a stirred solution of the free amine (12) (5.10 g, 20 mmol) in glacial AcOH (100 ml) was added the sodium salt of diethyl oxalacetate (8.4 g, 40 mmol) in one portion and the mixture was heated to reflux for 1 h. The yellow reaction mixture was evaporated and the residue was dissolved in EtOAc (250 ml) and washed with water (2 × 100 ml). After drying (MgSO₄), the solvent was evaporated off and the residue was purified on a flash silica gel column (5 × 60 cm) with EtOAc as eluant, which provided the *title ester* (13) (7.42 g, 98%) as a pale yellow gum (this was pure enough for the next step). A small portion of the gum was crystallized from EtOAc–hexanes as analytically pure sample of compound (13), m.p. 158 °C (Found: C, 53.9; H, 5.4; N, 11.0. C₁₇H₂₁N₃O₇ requires C, 53.81; H, 5.58; N, 11.07%); λ_{max}(pH 1) 211 (10.4) and 332 nm (4.4); (pH 7) 239 (5.8), 300sh (1.9), and 344 nm (4.2); (pH 11) 219 (14.0), 238 (11.2), and 323 nm (7.1);

δ_H(CDCl₃) 1.35 (3 H, s, Me), 1.42 (3 H, t, CH₂Me), 1.64 (3 H, s, Me), 3.85 (2 H, m, 5'-H₂), 4.42 (2 H, q, CH₂), 4.53 (1 H, br s, 4'-H), 5.03 (1 H, m, 3'-H), 5.13 (1 H, m, 2'-H), 6.47 (1 H, d, J_{1',2'} 3.2 Hz, 1'-H), 7.05 (1 H, s, 5-H), and 8.16 (1 H, s, 3-H).

6-Hydroxy-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-1H-pyrazolo[3,4-b]pyridine-4-carbohydrazide (14).—A mixture of the ester (13) (3.79 g, 10 mmol) and 70% hydrazine hydrate (10 ml) was heated under reflux for 24 h, during which time the reaction mixture became homogeneous. After the mixture had cooled to room temperature, the hydrazine was removed by coevaporation with EtOH (3 × 50 ml) and toluene (2 × 50 ml). The yellow residue was dissolved in EtOH (50 ml) and neutralized by dropwise addition of AcOH to pH ~ 6.5 which produced a yellow precipitate. Warming of the solution redissolved the precipitate. The crude product was adsorbed onto silica gel (10 g) and purified by silica gel column chromatography with EtOAc–water–propan-1-ol (4:1:2, upper phase) as eluant. Pooling and evaporation of the appropriate fractions furnished the *hydrazide* (14) as a yellow solid (3.60 g, 98%); m.p. 198 °C (Found: C, 49.3; H, 5.2; N, 19.0. C₁₅H₁₉N₅O₆ requires C, 49.31; H, 5.24; N, 19.17%); λ_{max}(pH 1) 208 (21.5), 234sh (11.8), and 325 nm (8.3); (pH 7) 217 (18.6), 236 (14.3), and 325 nm (9.4); (pH 11) 240 (8.3), 293 (2.5), and 345 nm (5.6); δ_H[(CD₃)₂SO] 1.33 (3 H, s, Me), 1.51 (3 H, s, Me), 3.44 (2 H, m, 5'-H₂), 4.11 (1 H, m, 4'-H), 4.95 (1 H, d, 3'-H), 5.35 (1 H, d, 2'-H), 6.36 (1 H, s, 1'-H), 6.81 (1 H, s, 5-H), 8.15 (1 H, s, 3-H), and 10.0 (1 H, br s, NH).

4-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-b]pyridin-6-one (16).—To a cold (0 °C), stirred solution of the hydrazide (14) (2.14 g, 5.8 mmol) in glacial AcOH (50 ml) was added a solution of NaNO₂ (3.45 g, 50 mmol) in water (5 ml) during 30 min. The mixture was stirred for 30 min at 5 °C and was then concentrated under reduced pressure to furnish a yellow residue of crude azide (15).

The crude azide (15) was suspended in cold (10 °C) water (50

ml) and the suspension was filtered. The yellow, residual solid azide (**15**) was dissolved in aq. AcOH (95%; 50 ml) and the solution was heated under reflux for 40 min, then evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (4 × 35 cm) with EtOAc–water–propan-1-ol (4:1:2, upper phase) as eluant to furnish two products in the order described: (i) *compound (16)* (1.01 g, 53.5%) as a powder; m.p. 165 °C (softened) (Found: C, 50.7; H, 5.7; N, 16.7. C₁₄H₁₈N₄O₅·0.4 H₂O requires C, 51.02; H, 5.74; N, 17.00%); δ_H[(CD₃)₂SO] 1.32 (3 H, s, Me), 1.50 (3 H, s, Me), 3.35 (2 H, m, 5'-H₂), 4.09 (1 H, m, 4'-H), 4.88 (1 H, m, 3'-H), 4.90 (1 H, br s, 5'-OH), 5.26 (1 H, m, 2'-H), 5.28 (1 H, s, 5-H, exchanged slowly in D₂O), 6.26 (1 H, s, 1'-H), 6.68 (2 H, br s, NH₂), 7.95 (1 H, s, 3-H), and 10.8 (1 H, br s, NH).

(ii) *Compound (3)* (0.18 g, 10.8%), which was crystallized from water as fine needles, m.p. 247–248 °C (Found: C, 46.5; H, 4.9; N, 19.6. C₁₁H₁₄N₄O₅ requires C, 46.80; 4.99; N, 19.85%); λ_{max}(pH 1) 218 (20.5), 260sh (12.3), and 277 nm (15.8); (pH 7) 220 (18.6), 262 (10.9), and 285 nm (15.0); (pH 11) 225 (22.4), 272 (12.7), and 284 nm (13.1); δ_H[(CD₃)₂SO] 3.45 (2 H, m, 5'-H₂), 3.85 (1 H, m, 4'-H), 4.15 (1 H, m, 3'-H), 4.47 (1 H, m, 2'-H), 5.05 (1 H, d, 3'-OH), 5.20 (1 H, br s, 5-H, exchanged slowly in D₂O), 5.24 (1 H, d, 2'-OH), 5.97 (1 H, d, J_{1',2'} 4.5 Hz, 1'-H), 6.63 (2 H, s, NH₂), 7.90 (1 H, s, 3-H), and 10.80 (1 H, br s, NH).

4-Amino-1-(β-D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-b]pyridin-6-one (3).—A suspension of the protected nucleoside (**16**) (0.20 g, 0.62 mmol) in a mixture of TFA–water (9:1; 3 ml) was stirred at room temperature for 30 min. The TFA was evaporated off under a stream of argon, and the residue was coevaporated with EtOH (3 × 25 ml) and toluene (2 × 25 ml) and finally dried *in vacuo* to yield crude compound (**3**) (0.12 g), which was crystallized from water to give pure deprotected compound (**3**) (88 mg, 50%), identical in all respects with the sample obtained during the preparation of compound (**16**).

5-[1-Benzyl-1H-pyrazol-5-ylamino(methylthio)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (19).—A mixture of 5-[bis(methylthio)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**18**) (0.744 g, 3 mmol), the amine (**17**) (0.519 g, 3 mmol), and EtOH (5 ml) was heated to reflux (90 °C, bath temperature) for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography with EtOAc–hexanes (3:7) as eluant to furnish the *title compound (19)* (0.76 g, 68%), which was crystallized as yellow flakes from EtOAc–hexanes; m.p. 126 °C (Found: C, 58.2; H, 5.1; N, 11.3; S, 8.45. C₁₈H₁₉N₃O₄S requires C, 57.89; H, 5.12; N, 11.25; S, 8.58%); λ_{max}(pH 1) 218 (5.5) and 314 nm (7.3); (pH 7) 208 (11.5), 256 (15.8), and 300sh nm (6.0); (pH 11) 205 (37.3), 256 (15.1), and 300sh nm (6.0); δ_H(CDCl₃) 1.73 (6 H, s, Me), 2.07 (3 H, s, SMe), 5.32 (2 H, s, CH₂Ph), 6.33 (1 H, d, J 1.8 Hz, 4-H), 7.16–7.57 (5 H, m, Ph), 7.57 (1 H, d, J 1.8 Hz, 3-H), and 12.4 (1 H, br s, NH).

6-Amino-1-benzyl-1,7-dihydropyrazolo[3,4-b]pyridin-4-one (7).—To a stirred solution of compound (**19**) (0.37 g, 1 mmol) in dry THF (10 ml) was added NH₄OH (28%; 3 ml) followed by HgCl₂ (0.27 g, 1 mmol) and the mixture was stirred for 48 h at room temperature. The suspension was filtered and the residue was washed with CH₂Cl₂ (2 × 25 ml). The combined filtrates were washed with water (25 ml) and dried (MgSO₄). The solvent was evaporated off and the residue was purified by flash silica gel column chromatography (1 × 5 cm) with EtOAc as eluant to furnish 5-[amino-(1-benzyl-1H-pyrazol-5-ylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**20**) (0.20 g, 58%), which was crystallized from EtOH as needles; m.p. 96–98 °C; δ_H(CDCl₃) 1.71 (6 H, s, Me), 5.24 (2 H, s, CH₂Ph), 5.67 (1 H, s, NH₂), 6.23 (1 H, d, J 1.8 Hz, 4-H), 7.20–7.33 (5 H, m, Ph),

7.57 (1 H, d, J 1.8 Hz, 3-H), 9.46 (1 H, s, NH₂), and 11.35 (1 H, br s, NH).

A mixture of compound (**20**) (0.18 g, 0.5 mmol) in Ph₂O (10 ml) was immersed in a pre-heated oil-bath (270 °C) and the clear solution was stirred under gentle reflux for 15 min under argon. The mixture was then cooled to room temperature and hexanes (50 ml) were added to precipitate the product as a white solid. The product was washed with hexanes (3 × 25 ml) to remove most of the Ph₂O and was finally crystallized from EtOH–Et₂O to furnish *compound (7)* (0.10 g, 70%), m.p. 247 °C (Found: C, 64.5; H, 5.2; N, 23.1. C₁₃H₁₂N₄O requires C, 64.99; H, 5.03; N, 23.32%); λ_{max}(pH 1) 216 (27.6), 260sh (11.5), and 283 nm (16.4); (pH 7) 211 (29.2), 260sh (5.1), and 294 nm (17.8); (pH 11) 207 (35.6), 273sh (14.8), and 282 nm (15.8); δ_H[(CD₃)₂SO] 5.35 (2 H, s, CH₂Ph), 5.69 (1 H, d, 5-H, exchanged slowly in D₂O), 6.12 (2 H, s, NH₂), 7.11–7.30 (5 H, m, Ph), and 7.22 (1 H, d, 3-H).

6-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-b]pyridin-4-one (24).—A mixture of compound (**18**) (0.99 g, 4 mmol), the free amine (**12**) (0.765 g, 3 mmol), and dry EtOH (50 ml) was stirred at room temperature for 48 h under argon. The solvent was evaporated off (< 30 °C) and the residue was purified by silica gel column chromatography (2 × 10 cm) with EtOAc–hexanes (1:1) as eluant to furnish *compound (21)* (0.66 g, 48%) as a pale yellow, hygroscopic foam (decomposed on heating > 70 °C to give unidentified products); m.p. 66 °C (collapsed) (Found: C, 49.8; H, 5.7; N, 9.15. C₁₉H₂₅N₃O₈S requires C, 50.09; H, 5.53; N, 9.22%).

Ammonolysis of compound (**21**) in the presence of HgCl₂ [as described for the preparation of compound (**7**)] gave the amine (**22**) in 53% yield; m.p. 172 °C (decomp.); δ_H[(CD₃)₂SO] 1.31 (3 H, s, Me), 1.46 (3 H, s, Me), 1.63 (6 H, s, Me), 3.30 (2 H, m, 5'-H), 4.06 (1 H, m, 4'-H), 4.85 (1 H, d, 3'-H), 5.39 (1 H, d, 2'-H), 5.89 (1 H, s, 1'-H), 6.42 (1 H, d, J = 1.5 Hz, 4-H), 7.66 (1 H, d, J = 1.5 Hz, 3-H), 7.76 (1 H, s, NH₂), 9.30 (1 H, s, NH₂), and 11.10 (1 H, br s, NH).

Compound (**22**) underwent cyclocondensation in boiling Ph₂O [as described above for the preparation of compound (**7**)] to give the *amine (24)* in a 71% yield; m.p. 144 °C (Found: C, 49.8; H, 5.4; N, 16.2. C₁₄H₁₈N₄O₅·H₂O requires C, 49.40; H, 5.92; N, 16.46%); δ_H[(CD₃)₂SO] 1.29 (3 H, s, Me), 1.48 (3 H, s, Me), 3.40 (2 H, m, 5'-H₂), 4.07 (1 H, m, 4'-H), 4.90 (1 H, d, 3'-H), 5.00 (1 H, br s, 5'-OH), 5.23 (1 H, d, 2'-H), 5.72 (1 H, s, 5-H, exchanged slowly in D₂O), 6.18 (1 H, d, J_{1',2'} 2.1 Hz, 1'-H), and 7.81 (1 H, s, 3-H).

6-Amino-1-(β-D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-b]pyridin-4-one (4).—Deisopropylideneation of compound (**24**) [as described for the preparation of compound (**3**) using aq. TFA] gave the *deprotected compound (4)* in 49% yield; m.p. 152–153 °C (decomp.) (Found: C, 46.4; H, 5.7; N, 17.45. C₁₁H₁₄N₄O₅·0.6AcOH requires C, 46.03; H, 5.20; N, 17.59%); λ_{max}(pH 1) 213 (21.3), 251 (4.0), and 293 nm (15.8); (pH 7) 223 (23.3), 266sh (12.1), and 280 nm (13.7); (pH 11) 225 (25.8), 270 (14.0), and 280 nm (13.9); δ_H[(CD₃)₂SO] 3.45 (2 H, m, 5'-H₂), 3.83 (1 H, m, 4'-H), 4.14 (1 H, m, 3'-H), 4.52 (1 H, m, 2'-H), 5.71 (1 H, s, 5-H), 6.01 (1 H, d, J_{1',2'} 4.6 Hz, 1'-H), 6.12 (2 H, br s, NH₂), and 7.77 (1 H, s, 3-H).

6-Methylthio-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-b]pyridin-4-one (23).—A stirred solution of compounds (**12**) (0.76 g, 3 mmol) and (**18**) (0.74 g, 3 mmol) in dry DMF (30 ml) was heated at 120 °C (bath) under argon for 6 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with EtOAc–hexanes (1:1) as eluant to furnish the *title compound (23)* (0.91 g, 86%) as needles after crystallization from diethyl

ether; m.p. 168 °C (Found: C, 51.2; H, 5.4; N, 13.8; S, 10.1. $C_{15}H_{19}N_3O_5S$ requires C, 51.21; H, 5.43; N, 13.41; S, 10.23%; λ_{max} (pH 1) 218 (15.2), 280 (10.0), and 303 nm (14.1); (pH 7) 237 (20.3), 279 (16.2), and 291 nm (15.7); (pH 11) 238 (20.1), 279 (16.0), and 291 nm (15.3); $\delta_H[(CD_3)_2SO]$ 1.31 (3 H, s, Me), 1.57 (3 H, s, Me), 2.49 (3 H, s, SMe), 3.85 (2 H, m, 5'-H₂), 4.49 (1 H, s, 4'-H), 5.07 (2 H, s, 2'- and 3'-H), 6.31 (1 H, s, 5-H), 6.63 (1 H, s, 1'-H), and 7.97 (1 H, s, 3-H).

6-Methylthio-1-(β -D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-b]pyridin-4-one (6).—Deisopropylidenation [as described for compounds (3) and (4)] of compound (23) with aq. TFA gave the free nucleoside (6) in 84% yield; m.p. 203–204 °C (Found: C, 45.7; H, 4.8; N, 13.3; S, 10.2. $C_{12}H_{15}N_3O_5S$ requires C, 45.99; H, 4.82; N, 13.41; S, 10.23%; λ_{max} (pH 1) 283sh (10.0) and 305 nm (21.3); (pH 7) 237 (29.4), 280 (23.3), and 292 nm (22.8); (pH 11) 237 (30.0), 280 (23.2), and 292 nm (22.7); $\delta_H[(CD_3)_2SO]$ 2.51 (3 H, s, SMe), 3.50 (2 H, m, 5'-H₂), 3.86 (1 H, m, 4'-H), 4.22 (1 H, m, 3'-H), 4.62 (1 H, m, 2'-H), 4.76 (1 H, br s, OH), 5.16 (1 H, br s, OH), 5.37 (1 H, br s, OH), 6.20 (1 H, d, $J_{1,2}$ 4.8 Hz, 1'-H), 6.40 (1 H, s, 5-H), 8.08 (1 H, s, 3-H), and 13.30 (1 H, br s, NH).

Ethyl 4-Hydroxy-1-(2,3-O-isopropylidene- β -D-ribofuranosyl)-6-oxo-6,7-dihydro-1H-pyrazolo[3,4-b]pyridin-5-carboxylate (25).—To a stirred solution of diethyl malonate (24 ml, 149 mmol) in a freshly prepared solution of NaOEt [Na (3.84 g, 160 mmol) in EtOH (100 ml)] was added a solution of the amino ester (10) (14 g, 42.8 mmol) in absolute EtOH (25 ml) during 10 min at room temperature. The resulting clear solution was refluxed for 15 h, during which time some white solid began to form, and which stayed until the end of reflux. The mixture was concentrated under reduced pressure and the white residue was dissolved in water (200 ml). The aqueous solution was then acidified (pH ~ 6) with glacial AcOH and extracted with EtOAc (2 × 100 ml). The combined extract was dried (MgSO₄) and evaporated to furnish a gummy residue. The residue was purified by flash silica gel column chromatography (5 × 50 cm) with EtOAc as the eluant to afford compound (25) (10.5 g, 62%) following crystallization from acetone; m.p. 161 °C (Found: C, 51.7; H, 5.25; N, 10.5. $C_{17}H_{21}N_3O_8$ requires C, 51.64; H, 5.35; N, 10.62%; $\delta_H[(CD_3)_2SO]$ 1.28 (3 H, t, CH₂Me), 1.32 (3 H, s, Me), 1.50 (3 H, s, Me), 3.37 (2 H, m, 5'-H₂), 4.10 (1 H, m, 4'-H), 4.26 (2 H, q, CH₂), 4.88 (1 H, d, 3'-H), 4.90 (1 H, br s, 5'-OH), 5.29 (1 H, d, 2'-H), 6.35 (1 H, s, 1'-H), 8.08 (1 H, s, 3-H), 12.2 (1 H, br s, NH), and 13.2 (1 H, br s, OH).

4-Hydroxy-1-(β -D-ribofuranosyl)-1,7-dihydropyrazolo[3,4-b]pyridin-6-one (5).—Ethyl 4,6-dihydroxy-1-(β -D-ribofuranosyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (26) was prepared by deisopropylidenation of compound (25) with aq. TFA in a similar manner as described for compound (3). Compound (25) (1.0 g, 2.53 mmol) gave the deprotected nucleoside (26) (0.51, 56%); m.p. 120 °C (foam); $\delta_H[(CD_3)_2SO]$ 1.27 (3 H, t, CH₂Me), 3.55 (2 H, m, 5'-H₂), 3.88 (1 H, m, 4'-H), 4.14 (1 H, m, 3'-H), 4.26 (2 H, q, CH₂), 4.45 (1 H, m, 2'-H), 5.10 (1 H, br s, 5'-OH), 5.11 (1 H, d, 3'-OH), 5.40 (1 H, d, 2'-OH), 6.02 (1 H, d, $J_{1,2}$ 4.3 Hz, 1'-H), 8.05 (1 H, s, 3-H), 12.20 (1 H, br s, NH), and 13.20 (1 H, br s, OH).

A solution of compound (26) (0.18 g, 0.5 mmol) in aq. NaOH (2M; 10 ml) was heated under reflux for 6 h, and cooled to room temperature. The reaction mixture was neutralized by the addition of Dowex-50 H⁺ resin and filtered. The resin was washed with MeOH (3 × 50 ml), and the combined filtrates were evaporated to dryness. The white residue was suspended in hot EtOH and the mixture was filtered. On cooling of the filtrate, compound (5) (70 mg, 41%) was collected as white powder; m.p. 280 °C (decomp.) (Found: C, 42.9; H, 4.5; N, 12.65. $C_{11}H_{13}N_3O_6 \cdot NaOMe$ requires C, 42.73; H, 4.78; N, 12.45%);

λ_{max} (pH 1) 250sh (6.7) and 283 nm (18.0); (pH 7) 256 (15.5) and 280 nm (23.3); (pH 11) 278 nm (22.4); $\delta_H[(CD_3)_2SO]$ 3.54 (2 H, m, 5'-H₂), 3.86 (1 H, m, 4'-H), 4.16 (1 H, m, 3'-H), 4.51 (1 H, m, 2'-OH), 4.94 (1 H, br s, 5'-OH), 5.07 (1 H, d, 3'-OH), 5.32 (1 H, d, 2'-OH), 5.63 (1 H, br s, 5-H), 6.03 (1 H, d, $J_{1,2}$ 4.3 Hz, 1'-H), 7.89 (1 H, s, 3-H), and 11.33 (2 H, br s, OH, NH).

X-Ray Crystallography.—Suitable crystals of compound (3) were obtained by slow evaporation of a butan-1-ol solution of the compound containing a drop of water.

Crystal Data.— $C_{11}H_{14}N_4O_5 \cdot 2H_2O$, $M = 318.29$. Orthorhombic, $a = 7.588$ 5(18), $b = 18.606$ (6), $c = 9.723$ 4(15) Å, $V = 1$ 372.9(6)° (determined by least-squares using setting angles of 25 reflections in the range $41.6^\circ < 2\theta < 59.9^\circ$, $\lambda = 1.541$ 78 Å), space group $P2_12_12$ (No. 18), $Z = 4$, $D_x = 1.540$ g cm⁻³. The specimen was a colourless, parallelepiped-shaped needle of dimensions 0.395 (100) × 0.12 (011,0 $\bar{1}$ 1) × 0.04 (001) mm (distances between face pairs), $\mu(Cu - K\alpha) = 10.644$ cm⁻¹.

Data Collection and Processing.—Enraf-Nonius CAD4 automated diffractometer, graphite-monochromated Cu-K α radiation, four octants of reciprocal space ($h = 0 \rightarrow 9$; $k = -23 \rightarrow 23$; $l = -12 \rightarrow 12$), $3.0 \leq 2\theta \leq 152^\circ$, ω - 2θ mode, ω scan width of $0.80 + 0.15 \tan\theta$ (in degrees), ω scan speed 1.4–16.5 deg min⁻¹, 6 152 reflections measured, 2 869 unique reflections (merging $R_{int} = 0.0221$ after correction for Lorentz and polarization effects, decay [correction range: 1.000–1.006; based on three check reflections (125, 273, 323)] and absorption [correction range: 0.763–0.966] using the SDP-Plus program package²⁹).

Structure Analysis and Refinement.—All non-hydrogen atom positions from direct methods using the program SHELXS86.³⁰ All hydrogen-atom positions from a difference map (peaks of 0.49–0.82 eÅ⁻³; $R = 0.062$). All positional and thermal (non-hydrogen atoms: anisotropic; hydrogens: isotropic) parameters and an extinction parameter were refined by full-matrix least-squares with the program SHELX76.³¹ Refinement was terminated with a maximum Δ/σ of 0.0012; the final $R = 0.0291$, $R = 0.0374$ and $S = 1.280$ for 2 583 observed reflections [$F \geq 4\sigma(F)$] and 272 variables. Reflection weighting scheme: $w^{-1} = \sigma^2(F) + 0.0004F^2$; $\sigma(F)$ obtained from counting statistics. The extinction parameter refined to a value of $1.38(12) \times 10^{-6}$. The extrema in the final difference map were 0.32 and -0.25 eÅ⁻³. Scattering factors and anomalous-dispersion corrections for non-hydrogen atoms were taken from International Tables for X-ray Crystallography;³² for hydrogen atoms, scattering factors were taken from Stewart, Davidson, and Simpson.³³ Figures were drawn with ORTEPII.³⁴

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