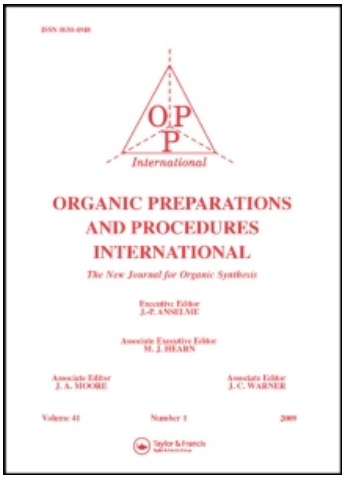

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NOVEL SYNTHESIS OF SOME PYRIDINETHIONE NUCLEOSIDES RELATED TO 3-DEAZAUREDINE

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NOVEL SYNTHESIS OF SOME PYRIDINETHIONE NUCLEOSIDES RELATED TO 3-DEAZAURIDINE

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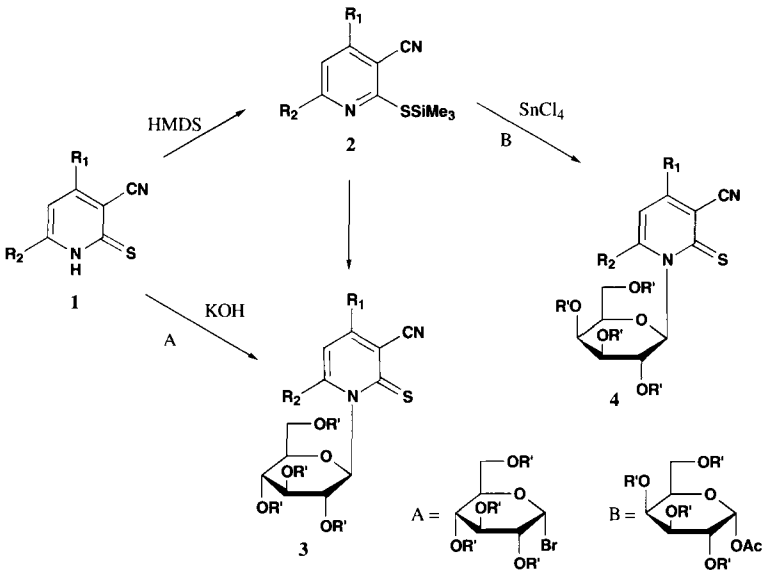
Among analogues of the naturally occurring pyrimidine nucleosides modified in the heterocycle, the 3-deaza analogues have demonstrated a broad spectrum of biological activity.[1,2] As part of our program directed towards the development of new, simple and efficient procedures for the synthesis of nucleosides and nucleotides,[3-7] we report here the results of our investigation into the utility of the reaction of our previously reported pyridine-2(1*H*)-thiones **1**[8,9] with acylated glycopyranosyl halides for the synthesis of 3-deazapyrimidine glycosides. Compounds **1** were prepared by the reaction of α-cyanothioacetamide with chalcones in boiling ethanol containing catalytic amounts of piperidine.

Compounds **1** reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galactopyranosyl bromides in the presence of aqueous potassium hydroxide to give the corresponding *N*-glucosyl (**3a-i**) and *N*-galactosyl compounds (**4a-i**). Although the coupling of **1** with the glycosyl bromides could also give the corresponding thioglycosides, the formation of (**3a-i**) and (**4a-i**) was proved chemically. Reaction of **1** with hexamethyldisilazane in the presence of ammonium sulfate gave the corresponding 2-trimethylsilylthiopyridines **2**, which were subsequently treated with peracylated sugars in the presence of redistilled $SnCl_4$ to afford the corresponding *N*-glycosyl compounds. All the previous literature reports that Lewis acid-induced coupling reactions of *S*-silylated heterocyclic bases with peracylated sugars gave the corresponding *N*-nucleosides as the sole product.[10,11]

The structures of the reaction products **3** and **4** were established and confirmed by their elemental analyses and spectral data (MS, IR, UV, ^{1}H NMR, ^{13}C NMR). Analytical data for compound **3f** revealed a molecular formula $C_{34}H_{34}N_2SO_{10}$ (m/z 662). ^{1}H NMR spectroscopy was used to confirm this structure for the product. Thus, the ^{1}H NMR spectrum showed the anomeric proton as a doublet at δ 6.28 with a spin-spin coupling constant 10.54 Hz which corresponds to a diaxial orientation for 1'-H and 2'-H protons, indicating the presence of only the β-configuration. The other six protons of the glucopyranosyl ring resonated in the δ 4.08- 5.74 region. The remaining four acetoxy



		R_1	R_2	R'		R_1	R_2	R'
3, 4	a	C_6H_5	C_6H_5	Ac	j	C_6H_5	C_6H_5	H
	b	C_6H_5	*p*-ClC_6H_4	Ac	k	C_6H_5	*p*-ClC_6H_4	H
	c	C_6H_5	*p*-$CH_3C_6H_4$	Ac	l	C_6H_5	*p*-$CH_3C_6H_4$	H
	d	*p*-$CH_3OC_6H_4$	C_6H_5	Ac	m	*p*-$CH_3OC_6H_4$	C_6H_5	H
	e	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	Ac	n	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	H
	f	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	Ac	o	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	H
	g	2-furyl	C_6H_5	Ac	p	2-furyl	C_6H_5	H
	h	2-furyl	*p*-$CH_3C_6H_4$	Ac	q	2-furyl	*p*-$CH_3C_6H_4$	H
	i	2-furyl	*p*-$CH_3OC_6H_4$	Ac	r	2-furyl	*p*-$CH_3OC_6H_4$	H

groups appear as four singlets at δ 1.64-2.05, while the methyl protons of the aglycone resonate at δ 2.43 and those of the methoxy protons at δ 3.87 (cf. Table 2). The ^{13}C NMR spectra for compound **3f** was characterized by a signal at 80.1 corresponding to the C-1' atom of the β-D-glucopyranose. The four signals appearing at δ 168.8-169.2 are due to the four acetoxy carbonyl carbon atoms, while the four signals at 19.4-19.8 are attributed to the acetate methyl carbons. Another five signals at 61.4, 67.7, 68.3, 72.4 and 74.5 were assigned to C-6', C-4', C-2', C-3' and C-5', respectively. The UV spectra of compounds **3** and **4** confirmed that the reaction takes place at the nitrogen atom of the pyridine ring, leading selectively to the formation of *N*-glycosides and excludes substitution at the sulfur atom. Thus, whereas the 2-(methylthio)pyridine derivative corresponding to pyridinethione **1f** shows one maximum at 278 nm, its *N*-glucosyl derivative **3f** exhibits two different UV absorption maxima at 274 and 329 nm.

Table 1. Physical and Analytical Data of Compounds **3** and **4**

Compd.	mp. (°C)	Yield (%) Method a	Method b	Found (Calcd.) C	H	N	M^+ m/z
3a	200	70	38	62.28 (62.13)	5.09 (4.85)	4.61 (4.53)	618
3b	203	73	44	58.76 (58.85)	4.50 (4.44)	4.46 (4.29)	
3c	204	72	46	62.53 (62.65)	5.01 (5.06)	4.44 (4.43)	632
3d	222	68	35	61.35 (61.11)	4.74 (4.93)	4.14 (4.32)	648
3e	188	71	43	57.94 (58.02)	4.52 (4.54)	4.26 (4.10)	
3f	212	70	42	61.78 (61.63)	5.26 (5.13)	4.30 (4.22)	662
3g	209	66	34	59.45 (59.21)	4.64 (4.60)	4.52 (4.60)	608
3h	217	68	36	60.03 (59.80)	4.80 (4.82)	4.57 (4.50)	622
3i	207	72	45	58.55 (58.30)	4.64 (4.70)	4.65 (4.38)	638
3j	217	87		63.84 (64.00)	4.93 (4.88)	6.40 (6.22)	450
3k	232	83		59.61 (59.44)	4.48 (4.33)	5.62 (5.77)	
3l	230	85		64.54 (64.65)	5.36 (5.17)	6.18 (6.03)	464
3m	236	81		62.33 (62.50)	5.15 (5.00)	5.74 (5.83)	480
3n	203	84		58.50 (58.36)	4.54 (4.47)	5.52 (5.44)	514
3o	230	82		63.45 (63.15)	5.40 (5.26)	5.64 (5.66)	494
3p	237	85		60.12 (60.00)	4.62 (4.54)	6.60 (6.36)	440
3q	265	80		61.02 (60.79)	4.70 (4.84)	6.45 (6.16)	454
3r	239	83		58.44 (58.72)	4.82 (4.68)	5.90 (5.95)	
4a	158	71	40	62.21 (62.13)	5.14 (4.85)	4.70 (4.53)	618
4b	192	70	39	59.06 (58.85)	4.61 (4.44)	4.42 (4.29)	652
4c	180	73	41	62.85 (62.65)	5.14 (5.06)	4.48 (4.43)	
4d	162	72	42	61.18 (61.11)	5.04 (4.93)	4.50 (4.32)	
4e	190	67	36	58.25 (58.02)	4.66 (4.54)	4.04 (4.10)	682
4f	122	70	41	61.74 (61.63)	5.07 (5.13)	4.36 (4.22)	662
4g	210	68	37	59.14 (59.21)	4.78 (4.60)	4.63 (4.60)	608
4h	198	66	35	59.64 (59.80)	4.90 (4.82)	4.41 (4.50)	622
4i	217	70	40	58.13 (58.30)	4.74 (4.70)	4.55 (4.38)	638
4j	229	89		64.18 (64.00)	5.02 (4.88)	6.08 (6.22)	450
4k	213	84		59.68 (59.44)	4.44 (4.33)	5.90 (5.77)	484
4l	210	86		64.81 (64.65)	5.22 (5.17)	6.14 (6.03)	464
4m	238	81		62.36 (62.50)	5.20 (5.00)	6.03 (5.83)	480
4n	220	83		58.55 (58.36)	4.61 (4.47)	5.33 (5.44)	
4o	201	84		63.14 (63.15)	5.48 (5.26)	5.73 (5.66)	494
4p	230	85		59.88 (60.00)	4.62 (4.54)	6.60 (6.36)	
4q	222	82		60.67 (60.79)	4.80 (4.84)	6.34 (6.16)	454
4r	231	88		58.89 (58.72)	4.88 (4.68)	6.12 (5.95)	470

Preparation of highly crystalline 3-cyano-1-(β-D-glycopyranosyl)pyridine-2-thione derivatives (**3j-r**) and (**4j-r**) was achieved by removal of the acetyl groups on treatment with ammonia in methanol at 0°. TLC of the obtained free glycosides showed that a single unique compound was produced, and their structures were further confirmed by elemental analyses and spectral data. Thus, the ^{1}H NMR spectrum of compound **4r** showed the anomeric proton as a doublet at δ 5.63 ($J_{1,2}$ = 9.84 Hz), indicating the presence of only the β-D-galactopyranose. The other six galactose protons appeared as a multiplet at δ 3.26-3.78, while the four hydroxy groups resonated at δ 4.56-5.44 (exchangeable by D_2O) (cf. Table 2). The ^{13}C NMR spectrum of **4r** contained a signal at δ 96.1 corresponding to the C-1' atom of the β-D-galactopyranose. Another five signals at δ 60.9, 68.0, 74.4, 79.4 and 83.8 were assigned to C-6', C-4', C-2', C-3' and C-5' of the galactose moiety, respectively.
Compounds **3j-r** and **4j-r** showed no activity against Human Immunodeficiency Virus (HIV) in MT-4 cells.

EXPERIMENTAL SECTION

All evaporations were carried out under reduced pressure at 40°. Melting points are uncorrected. TLC aluminium sheets silica gel 60 F_{254} (Merck) was used for thin layer chromatography; detection by short-wave length UV light. IR spectra were obtained (KBr disc) with a pye Unicam Spectra-1000. ^{1}H NMR and ^{13}C NMR spectra were measured in (CD3)2SO with a Wilmad 270 MHz or a Varian 400 MHz spectrometer using $SiMe_4$ as internal standard. Mass spectra were recorded with a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

3-Cyano-1-(2', 3', 4', 6'-tetra-*O*-acetyl-β-D-gluco- and galactopyranosyl)-2-pyridine-thiones (3a-i and 4a-i). General Coupling Procedures.- Method A.- To a solution of one of the 3-cyanopyridine-2(1*H*)-thiones **1** (0.01 mol) in aqueous potassium hydroxide [0.56 g (0.01 mol) in 6 mL of distilled water], a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or galactopyranosyl bromide (4.521 g, 0.011 mol) in acetone (30 mL) was added. The mixture was stirred at room temperature until the reaction was judged complete by TLC using chloroform : petroleum ether 9:1, v/v, (R_f 0.72-0.76 region) (2 to 6h), then evaporated under reduced pressure at 40° and the residue washed with distilled water to remove KBr. The product was dried and crystallized from EtOH to afford pale yellow crystals (cf. Table 1).
Method B. A 3-cyanopyridine-2(1*H*)-thione **1** (0.01 mol) was stirred and refluxed for 48 hrs under anhydrous conditions with hexamethyldisilazane (25 mL) and ammonium sulfate (0.02 g). Excess HMDS was removed under diminished pressure, providing the silylated bases **2** as a colorless oils. To a solution of silylated base in dry acetonitrile (20 mL) was added a solution of α-D-glucose- or galactose pentaacetate (0.011 mol) in dry MeCN (10 mL) followed by $SnCl_4$ (1.6 mL). The mixture was stirred at room temperature until reaction was judged complete by TLC (6 to 12 hrs), then poured into saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude nucleosides which were purified by recrystallization from EtOH to afford pale yellow crystals (cf. Table 1).

TABLE 2. Spectral Data of Selected Compounds Listed in Table (1)

Compd	IR (KBr)/cm^{-1}	^{1}H NMR (δ/ppm)
3a	2216 (CN), 1748 (CO)	1.61-2.06 (4s, 12H, 4CH_3CO), 4.06 (d, 2H, H-6', 6"), 4.42 (m, 1H, H-5'), 5.03 (t, 1H, H-4'), 5.31 (t, 1H, H-3'), 5.80 (t, 1H, H-2'), 6.32 (d, J_{1-2}= 10.56 Hz, 1H, H-1'), 7.61 (m, 5H, Ar-H), 7.78 (m, 3H, Ar-H), 8.06 (s, 1H, Pyridine 5-H), 8.44 (m, 2H, Ar-H)
3e	2218 (CN), 1750 (CO)	1.66-2.05 (4s, 12H, 4CH_3CO), 3.88 (s, 3H, OCH_3), 4.08 (d, 2H, H-6', 6"), 4.38 (m, 1H, H-5'), 5.01 (t, 1H, H-4'), 5.28 (t, 1H, H-3'), 5.72 (t, 1H, H-2'), 6.30 (d, J_{1-2} = 10.51 Hz, 1H, H-1'), 7.18 (d, 2H, Ar-H), 7.68 (dd, 4H, Ar-H), 8.02 (s, 1H, pyridine 5-H), 8.46 (d, 2H, Ar-H)
3f	2212 (CN), 1746 (CO)	1.64-2.05 (4s, 12H, 4CH_3CO), 2.43 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 4.08 (m, 2H, H-6', 6"), 4.35 (m, 1H, H-5'), 5.05 (t, 1H, H-4'), 5.24 (t, 1H, H-3'), 5.74 (t, 1H, H-2'), 6.28 (d, J_{1-2} = 10.54 Hz, 1H, H-1'), 7.18 (d, 2H, Ar-H), 7.42 (d, 2H, Ar-H), 7.74 (d, 2H, Ar-H), 7.96 (s, 1H, Pyridine 5-H),8.30 (d, 2H, Ar-H)
3h	2215 (CN), 1754 (CO)	1.61-2.02 (4s, 12H, 4CH_3CO), 2.28 (s, 3H, CH_3), 4.02 (d, 2H, H-6', 6"), 4.32 (m, 1H, H-5'), 5.00 (t, 1H, H-4'), 5.24 (t, 1H, H-3'), 5.76 (t, 1H, H-2'), 6.22 (d, J_{1-2} = 10.56 Hz, 1H, H-1'), 6.88 (d, 1H, furan 4-H), 7.62 (d, 2H, Ar-H), 7.73 (d, 1H, furan 3-H), 8.12 (d, 1H, furan 5-H), 8.20 (s, 1H, Pyridine 5-H), 8.44 (d, 2H, Ar-H)
3i	2218 (CN), 1756 (CO)	1.62-2.12 (4s, 12H, 4CH_3CO), 3.88 (s, 3H, OCH_3), 4.04 (m, 2H, H-6', 6"), 4.36 (m, 1H, H-5'), 5.01 (t, 1H, H-4'), 5.20 (t, 1H, H-3'), 5.72 (t, 1H, H-2'), 6.25 (d, J_{1-2} = 10.58 Hz, 1H, H-1'), 6.85 (d, 1H, furan 4-H), 7.18 (d, 2H, Ar- H), 7.68 (d, 1H, furan 3-H), 8.08 (d, 1H, furan 5-H), 8.12 (s, 1H, pyridine 5-H), 8.36 (d, 2H, Ar-H)
3j	3600-3180 (OH), 2215 (CN)	3.24-3.67 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'), 4.61 (t, 1H, 2'-OH), 5.15 (d, 1H, 3'-OH), 5.28 (t, 1H, 4'-OH), 5.59 (t, 1H, 6'-OH), 5.68 (d, J_{1-2} = 9.35 Hz, 1H, H-1'), 7.56 (t, 5H, Ar-H), 7.76 (d, 3H, Ar-H), 7.93 (s, 1H, pyridine 5-H), 8.28 (d, 2H, Ar-H)
3q	3660-3200 (OH), 2212 (CN)	2.18 (s, 3H, CH_3), 3.20-3.61 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'), 4.54 (t, 1H, 2'-OH), 5.08 (d, 1H, 3'-OH), 5.21 (d, 1H, 4'-OH), 5.50 (d, 1H, 6'-OH), 5.64 (d, J_{1-2} = 9.84 Hz, 1H, H-1') 6.85 (m, 1H, furan 4-H), 7.55 (d, 2H, Ar-H), 7.70 (d, 1H, furan 3-H), 8.08 (m, 2H, furan 5-H and pyridine 5-H), 8.24 (d, 2H, Ar-H)
3r	3640-3180 (OH), 2218 (CN)	3.90 (s, 3H, OCH_3), 3.16-3.77 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'), 4.50 (t, 1H, 2'-OH), 4.98 (d, 1H, 3'-OH), 5.15 (d, 1H, 4'-OH), 5.28 (m, 1H, 6'-OH), 5.66 (d, J_{1-2} = 9.16 Hz, 1H, H-1'), 6.80 (d, 1H, furan 4-H), 7.15 (d, 2H, Ar-H), 7.65 (d, 1H, furan 3-H), 8.05 (s, 1H, pyridine 5-H), 8.20 (d, 1H, furan 5-H), 8.34 (d, 2H, Ar-H)
4a	2214 (CN), 1748 (CO)	1.54-2.14 (4s, 12H, 4CH_3CO), 4.07 (m, 2H, H-6', 6"), 4.58 (t, 1H, H-5'), 5.26 (t, 1H, H-4'), 5.42 (d, 1H, H-3'), 5.66 (dd, 1H, H-2'), 6.25 (d, J_{1-2} = 10.63 Hz, 1H, H-1'), 7.58 (m, 5H, Ar-H), 7.76 (m, 3H, Ar-H), 8.05 (s, 1H, pyridine H-5), 8.40 (t, 2H, Ar-H)

TABLE 2. Continued

Compd	IR (KBr)/cm^{-1}	^{1}H NMR (δ/ppm)
4h	2218 (CN), 1752 (CO)	1.56-2.08 (4s, 12H, 4 CH_3CO), 2.38 (s, 3H, CH_3), 4.01 (m, 2H, H-6', 6"), 4.54 (m, 1H, H-5'), 5.28 (t, 1H, H-4'), 5.42 (d, 1H, H-3'), 5.66 (dd, 1H, H-2'), 6.20 (d, J_{1-2} = 10.54 Hz, 1H, H-1'), 6.82 (m, 1H, furan 4-H), 7.41 (d, 2H, Ar-H), 7.70 (d, 1H, furan 3-H), 8.12 (d, 1H, furan 5-H), 8.18 (s, 1H, pyridine 5-H), 8.25 (d, 2H, Ar-H)
4i	2220 (CN), 1750 (CO)	1.58-2.12 (4s, 12H, $4CH_3CO$), 3.86 (s, 3H, OCH_3), 4.00 (m, 2H, H-6', 6") 4.56 (t, 1H, H-5'), 5.28 (t, 1H, H-4'), 5.45 (d, 1H, H-3'), 5.70 (dd, 1H, H-2'), 6.20 (d, J_{1-2} = 10.64 Hz, 1H, H-1'), 6.84 (d, 1H, furan 4-H), 7.18 (d, 2H, Ar-H), 7.70 (d, 1H, furan 3-H), 8.08 (d, 1H, furan 5-H), 8.16 (s, 1H, pyridine 5-H), 8.36 (d, 2H, Ar-H)
4j	3680-3200 (OH), 2213 (CN)	3.24-3.81 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'), 4.60 (d, 1H, 2'-OH), 4.69 (t, 1H, 3'-OH), 5.04 (d, 1H, 4'-OH), 5.43 (d, 1H, 6'-OH), 5.68 (d, J_{1-2} = 10.06 Hz, 1H, H-1'), 7.59 (m, 5H, Ar-H), 7.74 (m, 3H, Ar-H), 7.93 (s, 1H, pyridine 5-H), 8.29 (m, 2H, Ar-H)
4m	3600-3150 (OH), 2210 (CN)	3.24-3.65 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'), 3.86 (s, 3H, OCH_3), 4.64 (d, 2H, 2'-OH and 3'-OH), 5.02 (s, 1H, 4'-OH), 5.48 (s, 1H, 6'-OH), 5.67 (d, J_{1-2} = 8.10 Hz, 1H, H-1'), 7.18 (d, 2H, Ar-H), 7.46-7.96 (m, 6H, Ar-H and pyridine 5-H), 8.28 (d, 2H, Ar-H)
4q	3680-3190 (OH), 2218 (CN)	2.36 (s, 3H, CH_3), 3.23-3.74 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'), 4.58 (d, 1H, 2'-OH), 4.61 (t, 1H, 3'-OH), 5.01 (d, 1H, 4'-OH), 5.38 (d, 1H, 6'-OH), 5.66 (d, J_{1-2} = 7.93 Hz, 1H, H-1'), 6.83 (d, 1H, furan 4-H), 7.39 (d, 2H, Ar-H), 7.68 (d, 1H, furan 3-H), 8.08 (m, 2H, furan 5-H and pyridine 5-H), 8.16 (d, 2H, Ar-H)
4r	3600-3160 (OH), 2220 (CN)	3.26-3.78 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'), 3.83 (s, 3H, OCH_3), 4.62 (m, 2H, 2'-OH and 3'-OH), 5.06 (d, 1H, 4'-OH), 5.44 (d, 1H, 6'-OH), 5.63 (d, J_{1-2} = 9.84 Hz, 1H, H-1'), 6.81 (m, 1H, furan 4-H), 7.12 (d, 2H, Ar-H), 7.64 (d, 1H, furan 3-H), 7.98 (s, 1H, pyridine 5-H), 8.04 (d, 1H, furan 5-H), 8.19 (d, 2H, Ar-H)

3-Cyano-1-(β-D-gluco- and galactopyranosyl)-2-pyridinethiones (3j-r and 4j-r). General Procedure for Nucleoside Deacylation.- Dry gaseous ammonia was passed through a solution of a protected nucleoside (0.5 g of **3a-i** and **4a-i**) in dry methanol (20 mL) at 0° for about 0.5 hr, and the reaction mixture was then stirred until TLC [using chloroform: methanol 8:2, v/v, (R_f 0.66-0.69 region)] indicated complete conversion (8 to 12 hrs). The resulting reaction mixture was subsequently concentrated under reduced pressure at 40° to afford a solid residue which was crystallized from methanol to furnish colorless crystals (cf. Table 1).

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