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Note

Synthesis of some *N*-hexopyranosyl-2-pyridones and -2-pyridinethiones

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An important series of antimetabolites bearing a structural resemblance to the naturally occurring pyrimidine nucleosides uridine, cytidine, and thymidine consists of their 3-deaza analogues [1,2]. Although a number of *N*-glycosylpyridines have been prepared, no pyridinethione nucleosides have been synthesized or biologically evaluated. As a part of our program directed towards new, simple, and efficient procedures for the synthesis of antimetabolites [3–6], we report here a novel synthesis of 3-deazapyrimidine nucleosides **3** and **4** utilizing our previously reported 2-pyridones and their corresponding thiones **1** [7,8] as starting materials. Compounds **1** reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and -galacto-pyranosyl bromides in the presence of aqueous potassium hydroxide to give the corresponding *N*-glucosyl (**3a–d**) and *N*-galactosyl compounds (**4a–d**). Although the coupling of **1c** and **1d** with the glycosyl bromides could also give the corresponding thioglycosides, the formation of **3c**, **3d**, **4c**, and **4d** was proved chemically. Reaction of **1c** and **1d** with hexamethyldisilazane (HMDS) in the presence of ammonium sulfate gave the corresponding 2-trimethylsilylthiopyridines **2c** and **2d**, which were subsequently treated with peracetylated 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 peracetylated sugars gave the corresponding *N*-nucleosides as the sole heterocyclic product [9–11]. The structures of the reaction products **3** and **4** were

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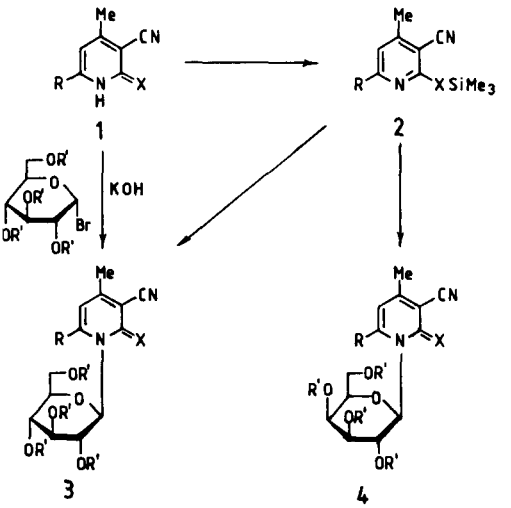
Table 1
Characterization data for compounds **3a–h** and **4a–h**

Compound	mp (°C)	Yield (%)		Mol. formula	Found/Calcd (%)			M^+ (m/z)
					C	H	N	
3a	131	60 [a]	43 [b]	$C_{22}H_{26}N_2O_{10}$ (478)	55.5 55.2	5.6 5.5	5.7 5.9	478
3b	162	64 [a]	46 [b]	$C_{27}H_{28}N_2O_{10}$ (540)	60.3 60.0	5.3 5.2	5.4 5.2	540
3c	180	73 [a]	49 [b]	$C_{22}H_{26}N_2SO_9$ (494)	53.5 53.4	5.5 5.3	5.4 5.7	494
3d	176	78 [a]	48 [b]	$C_{27}H_{28}N_2SO_9$ (556)	58.1 58.3	5.1 5.1	4.8 5.0	
3e	295	90		$C_{14}H_{18}N_2O_6$ (310)	54.5 54.2	5.9 5.9	9.2 9.0	310
3f	308	88		$C_{19}H_{20}N_2O_6$ (372)	61.0 61.3	5.5 5.4	7.7 7.5	
3g	263	86		$C_{14}H_{18}N_2SO_5$ (326)	51.8 51.5	5.6 5.5	8.5 8.6	
3h	281	89		$C_{19}H_{20}N_2SO_5$ (388)	59.1 58.8	5.1 5.2	7.5 7.2	388
4a	224	63 [a]	41 [b]	$C_{22}H_{26}N_2O_{10}$ (478)	55.3 55.2	5.5 5.5	6.1 5.9	478
4b	212	68 [a]	45 [b]	$C_{27}H_{28}N_2O_{10}$ (540)	60.2 60.0	5.4 5.2	5.5 5.2	540
4c	190	75 [a]	44 [b]	$C_{22}H_{26}N_2SO_9$ (494)	53.1 53.4	5.4 5.3	5.8 5.7	
4d	170	79 [a]	47 [b]	$C_{27}H_{28}N_2SO_9$ (556)	58.6 58.3	5.3 5.1	5.2 5.0	556
4e	291	84		$C_{14}H_{18}N_2O_6$ (310)	54.3 54.2	6.0 5.9	9.1 9.0	
4f	301	88		$C_{19}H_{20}N_2O_6$ (372)	61.6 61.3	5.6 5.4	7.8 7.5	372
4g	250	84		$C_{14}H_{18}N_2SO_5$ (326)	51.3 51.5	5.7 5.5	8.8 8.6	326
4h	201	86		$C_{19}H_{20}N_2SO_5$ (388)	59.0 58.8	4.5 5.2	7.4 7.2	388

[a] Method A.
[b] Method B.

established and confirmed by their elemental analyses (Table 1) and spectral data (MS, IR, UV, ^{1}H NMR, ^{13}C NMR) (Table 2). Thus, the analytical data for **4b** revealed a molecular formula $C_{27}H_{28}N_2O_{10}$ (m/z 540). The ^{1}H NMR spectrum showed the anomeric proton as a doublet at δ 6.55 with a spin–spin coupling constant of 8.36 Hz corresponding to a diaxial orientation of H-1′ and H-2′ protons indicating the β configuration, while the other six galactose protons resonated at δ 4.06–5.51. The four acetyl groups appeared as four singlets at δ 1.78–2.16 and the methyl protons of the aglycon resonated at δ 2.32. The ^{13}C NMR spectrum of **4b** contained a signal at δ 93.8 corresponding to the C-1′ atom of the β configuration. Four signals appeared at δ 168.8–169.9 due to the ester carbonyl carbon atoms, while signals appearing at δ 20.1–20.7 were attributed to the acetoxy methyl carbons. Another five signals at δ 61.5, 67.5, 67.8, 70.1, and 71.1 were assigned to C-6′, C-4′, C-2′, C-3′, and C-5′, respectively. The UV spectrum of **3c** proved that the reaction had led selectively to the formation of *N*-glucosyl derivatives and excluded substitution at the sulfur atom. Thus, whereas the *S*-methyl derivative of **1c** showed two maxima at 271 and 311 nm, its *N*-glucosyl derivative exhibited three maxima at 263, 308, and 392 nm. Removal of the acetyl groups with ammonia in methanol gave the free glycosides **3e–h** and **4e–h** after chromatographic purification. The structures of compounds **3** and **4** were confirmed by their elemental analyses and spectral data. The ^{13}C NMR spectrum of **4g** contained a signal at δ 84.8 corresponding to the C-1′ atom of β-D-galactopyranose. Another five signals at δ 60.2, 68.3, 68.7, 74.9, and 79.6 were assigned to C-6′, C-4′, C-2′, C-3′, and C-5′ of the galactose moiety, respectively.



Key for 1 and 2

	X	R
a	O	Me
b	O	Ph
c	S	Me
d	S	Ph

Key for 3 and 4

	X	R	R'
a	O	Me	Ac
b	O	Ph	Ac
c	S	Me	Ac
d	S	Ph	Ac
e	O	Me	H
f	O	Ph	H
g	S	Me	H
h	S	Ph	H

Scheme 1.

In summary, we have achieved a regiospecific synthesis of 3-deazapyrimidine nucleosides by the reaction of 2-pyridones and their corresponding thiones with protected glycosyl bromides. These nucleosides can be utilized as starting materials for the synthesis of other carbohydrate derivatives and for biological evaluation studies.

1. Experimental

All evaporations were carried out under reduced pressure at 40°C. Melting points are uncorrected. Precoated aluminium sheets of Silica Gel 60 F_{254} (Merck) were used for thin layer chromatography. Detection was effected by viewing under a short-wavelength UV lamp. IR spectra were obtained (KBr disc) on a Pye Unicam Spectra-1000. ^{1}H NMR and ^{13}C NMR spectra were measured on a Wilmad 270 MHz or on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2SO$, using $SiMe_4$ as internal standard. Mass spectra were recorded on 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 -galacto-pyranosyl)-2-pyridones and -2-pyridinethiones* **3a–d** *and* **4a–d**.—*General coupling procedures. Method A.* To a solution of 3-cyano-2-pyridones and their corresponding thiones **1** (0.01 mol) in aq

Table 2
IR and ^{1}H NMR data for compounds listed in Table 1

Compound	IR(KBr) (cm^{-1})	^{1}H NMR (Me_2SO)/δ
3a	2216 (CN), 1750 (CO ester), 1643 (CO pyridone)	1.96–2.08 (4 s, 12 H, 4 CH_3CO), 2.40 (s, 3 H, CH_3), 2.57 (s, 3 H, CH_3), 4.21 (m, 3 H, 2 H-6, H-5′), 5.08 (m, 2 H, H-4′ and H-3′), 5.53 (t, J 8.7 Hz, 1 H, H-2′), 6.40 (d, $J_{1,2}$ 8.89 Hz, 1 H, H-1′), 7.16 (s, 1 H, pyridine 5-H)
3b	2223 (CN), 1759 (CO ester), 1638 (CO pyridone)	1.78–2.01 (4 s, 12 H, 4 CH_3CO), 2.39 (s, 3 H, CH_3), 4.24 (m, 3 H, 2 H-6′, H-5′), 5.14 (m, 2 H, H-4′ and H-3′), 5.63 (t, J 8.41 Hz, 1 H, H-2′), 6.61 (d, $J_{1,2}$ 8.35 Hz, 1 H, H-1′), 7.44 (s, 1 H, pyridine 5-H), 7.81 (m, 3 H, Ar-H), 8.23 (m, 2 H, Ar-H)
3c	2218 (CN), 1758 (CO ester)	1.86–2.05 (4 s, 12 H, 4 CH_3CO), 2.31 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 4.16 (m, 3 H, 2 H-6′, H-5′), 5.01 (m, 2 H, H-4′ and H-3′), 5.55 (t, J 10.8 Hz, 1 H, H-2′), 6.19 (d, $J_{1,2}$ 10.34 Hz, 1 H, H-1′), 7.22 (s, 1 H, pyridine 5-H)
3d	2218 (CN), 1760 (CO ester)	1.90–2.04 (4 s, 12 H, 4 CH_3CO), 2.35 (s, 3 H, CH_3), 4.06 (m, 2 H, 2 H-6′), 4.51 (m, 1 H, H-5′), 5.50 (m, 3 H, H-4′, H-3′ and H-2′), 6.15 (d, $J_{1,2}$ 10.18 Hz, 1 H, H-1′), 6.88 (s, 1 H, pyridine 5-H), 7.54 (s, 5 H, Ar-H)
3e	3664–3134 (OH), 2216 (CN), 1664 (CO pyridone)	2.22 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 3.24–3.68 (m, 6 H, 2 H-6′, H-5′, H-4′, H-3′ and H-2′), 4.58 (t, J 8.5 Hz, 1 H, HO-2′), 5.06 (d, 2 H, HO-3′ and HO-4′), 5.40 (s, 1 H, HO-6′), 6.18 (d, $J_{1,2}$ 8.64 Hz, 1 H, H-1′), 7.05 (s, 1 H, pyridine 5-H)
3f	3650–3200 (OH), 2217 (CN), 1667 (CO pyridone)	2.41 (s, 3 H, CH_3), 3.21–3.74 (m, 6 H, 2 H-6′, H-5′, H-4′, H-3′, and H-2′), 4.61 (t, J 8.73 Hz, 1 H, HO-2′), 5.18 (d, 2 H, HO-3′ and HO-4′), 5.46 (s, 1 H, HO-6′), 6.11 (d, $J_{1,2}$ 8.55 Hz, 1 H, H-1′), 6.81 (s, 1 H, pyridine 5-H), 7.70 (m, 3 H, Ar-H), 8.18 (m, 2 H, Ar-H)
3g	3650–3180 (OH), 2220 (CN)	2.29 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3), 3.13–3.64 (m, 6 H, 2 H-6′, H-5′, H-4′, H-3′, and H-2′), 4.70 (m, 3 H, HO-2′, HO-3′, and HO-4′), 5.56 (d, J 10.18 Hz, 1 H, HO-6′), 6.14 (d, $J_{1,2}$ 10.53 Hz, 1 H, H-1′), 7.12 (s, 1 H, pyridine 5-H)
3h	3640–3200 (OH), 2217 (CN)	2.43 (s, 3 H, CH_3), 3.18–3.71 (m, 6 H, 2 H-6′, H-5′, H-4′, H-3′, and H-2′), 4.12 (m, 2 H, HO-2′ and HO-3′), 4.51 (d, J 9.68 Hz, 1 H, HO-4′), 5.10 (d, J 10.03 Hz, 1 H, HO-6′), 5.62 (d, $J_{1,2}$ 10.31 Hz, 1 H, H-1′), 7.40 (s, 1 H, pyridine 5-H), 7.81 (m, 3 H, Ar-H), 8.15 (m, 2 H, Ar-H)
4b	2222 (CN), 1753 (CO ester), 1634 (CO pyridone)	1.78–2.16 (4 s, 12 H, 4 CH_3CO), 2.32 (s, 3 H, CH_3), 4.06 (m, 2 H, 2 H-6′), 4.65 (t, J 8.63 Hz, 1 H, H-5′), 5.46 (m, 3 H, H-4′, H-3′, and H-2′), 6.55 (d, $J_{1,2}$ 8.36 Hz, 1 H, H-1′), 7.64 (m, 1 H, pyridine 5-H; and 3 H, Ar-H), 8.25 (m, 2 H, Ar-H)
4c	2220 (CN), 1756 (CO ester)	1.85–2.15 (4 s, 12 H, 4 CH_3CO), 2.30 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 4.01 (d, 2 H, 2 H-6′), 4.40 (t, J 10.3 Hz, 1 H, H-5′), 5.34 (m, 3 H, H-4′, H-3′, and H-2′), 6.05 (d, $J_{1,2}$ 10.13 Hz, 1 H, H-1′), 7.21 (s, 1 H, pyridine 5-H)
4d	2223 (CN), 1759 (CO ester)	1.68–2.12 (4 s, 12 H, 4 CH_3CO), 2.45 (s, 3 H, CH_3), 4.03 (m, 2 H, 2 H-6′), 4.50 (t, J 10.17 Hz, 1 H, H-5′), 5.31 (m, 2 H, H-4′ and H-3′), 5.68 (m, 1 H, H-2′), 6.20 (d, $J_{1,2}$ 10.21 Hz, 1 H, H-1′), 7.09 (s, 1 H, pyridine 5-H), 7.74 (m, 3 H, Ar-H), 8.28 (m, 2 H, Ar-H)
4e	3640–3190 (OH), 2213 (CN)	2.21 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 3.15–3.68 (m, 6 H, 2 H-6′, H-5′, H-4′, H-3′ and H-2′), 4.41 (d, J 8.91 Hz, 2 H, HO-2′ and HO-3′), 4.98 (s, 1 H, HO-4′), 5.34 (s, 1 H, HO-6′), 5.58 (d, $J_{1,2}$ 8.69 Hz, 1 H, H-1′), 8.87 (s, 1 H, pyridine 5-H)

Table 2 (continued)

Compound	IR(KBr) (cm^{-1})	^1H NMR (Me_2SO)/δ
4f	3600–3200 (OH), 2221 (CN)	2.43 (s, 3 H, CH_3), 3.11–3.77 (m, 6 H, 2 H-6′, H-5′, H-4′, H-3′, and H-2′), 4.58 (s, 1 H, HO-2′), 5.23 (s, 1 H, HO-3′), 5.62 (d, *J* 9.6 Hz, 2 H, HO-4′ and HO-6′), 6.08 (d, $J_{1,2}$ 8.78 Hz, 1 H, H-1′), 6.78 (s, 1 H, pyridine 5-H), 7.59 (m, 3 H, Ar-H), 7.85 (m, 2 H, Ar-H)
4g	3650–3200 (OH), 2225 (CN)	2.34 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3), 3.14–3.71 (m, 6 H, 2 H-6′, H-5′, H-4′, H-3′, and H-2′), 4.43 (d, *J* 9.53 Hz, 2 H, HO-2′ and HO-3′), 4.98 (s, 1 H, HO-4′), 5.32 (s, 1 H, HO-6′), 5.58 (d, $J_{1,2}$ 9.86 Hz, 1 H, H-1′), 7.05 (s, 1 H, pyridine 5-H)
4h	3600–3150 (OH), 2220 (CN)	2.38 (s, 3 H, CH_3), 3.15–3.80 (m, 6 H, 2 H-6′, H-5′, H-4′, H-3′, and H-2′), 4.55 (m, 2 H, HO-2′ and HO-3′), 5.02 (d, *J* 9.1 Hz, 1 H, HO-4′), 5.35 (d, *J* 10.64 Hz, 1 H, HO-6′), 5.61 (d, $J_{1,2}$ 10.21 Hz, 1 H, H-1′), 6.80 (s, 1 H, pyridine 5-H), 7.55 (m, 3 H, Ar-H), 8.16 (m, 2 H, Ar-H)

KOH [0.56 g (0.01 mol) in 6 mL of distilled water] was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or -galacto-pyranosyl bromide (4.521 g, 0.011 mol) in acetone (30 mL). The mixture was stirred at room temperature until the reaction was judged complete by TLC (30 min to 20 h), then evaporated under reduced pressure at 40°C, and the residue washed with distilled water to remove KBr. The product was dried and crystallized from EtOH to afford pale-yellow crystals (see Table 1).

Method B. 3-Cyano-2-pyridones and their corresponding thiones **1** (0.01 mol) were boiled under reflux, with stirring, under anhydrous conditions for 48 h with hexamethyldisilazane (25 mL) and $(NH_4)_2SO_4$ (0.02 g). The excess of hexamethyldisilazane was removed under diminished pressure, providing the silylated bases **2a–d** as colourless oils. To a solution of silylated base in dry MeCN (30 mL) was added a solution of α-D-glucose or α-D-galactose pentaacetate (0.011 mol) in dry MeCN (20 mL) followed by $SnCl_4$ (1.6 mL). The mixture was stirred at room temperature until reaction was judged complete by TLC (3 to 6 h), then poured into satd aq $NaHCO_3$, 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 (see Table 1).

3-Cyano-1-(β-D-gluco- and -galacto-pyranosyl)-2-pyridones and their corresponding thiones **3e–h** *and* **4e–h**.—*General procedure for nucleoside deacylation.* Dry gaseous NH_3 was passed through a solution of protected nucleosides **3a–d** and **4a–d** (0.5 g) in dry MeOH (25 mL) at 0°C for ca. 0.5 h, then the mixture was stirred until the reaction was judged complete by TLC (4 to 18 h). The resulting mixture was evaporated under reduced pressure at 40°C giving a solid residue which was crystallized from MeOH to afford colourless crystals (see Table 1).

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