Nucleotides and Nucleosides: Direct Route to Condensed Pyridinethione Carbocyclic Nucleosides Related to 3-Deazauridine

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A novel synthesis of condensed pyridinethione carbocyclic glycosides utilizing pyridine-2(1*H*)-thiones and α-bromoglucose or α-bromogalactose tetraacetate as starting components is described.

Deazauridine, a pyrimidine nucleoside analogue that is an effective antitumour agent, must be activated to the di- and triphosphates (deazaUDP and deazaUTP) in order to exert its cytotoxic effects. 3-Deazauridine 5'-triphosphate, an active form of this antimetabolite, is a potent inhibitor of CTP synthetase (phosphocholine cytidyltransferase). DeazaUTP is a competitive inhibitor of this enzyme with respect to UTP. DeazaUDP is an inhibitor of ribonucleotide reductase activity. The net result of the inhibition at these sites is that the cells become deficient in cytidine and deoxycytidine nucleotides, causing inhibition of both RNA and DNA synthesis.[1] As part of our program directed towards the development of new, simple and efficient procedures for the synthesis of antimetabolites,[2–6] we report here the results of our investigation into the utility of the reaction of our previously reported pyridine-2(1*H*)-thiones **3**[7] with α-halogeno sugars for the synthesis of 3-deazapyrimidine glycosides. As far as we know this is the first coupling reaction of this type to be reported for pyridine-2(1*H*)-thiones. Compounds **3** were prepared by the reaction of 3-aryl-2-cyanothiopropenamide **1** with cycloalkanones **2** in boiling ethanol containing catalytic amounts of piperidine (Scheme 1). Compounds **3** reacted with 2,3,4,6 tetra-*O*-acetyl-α-D-gluco- and -galacto-pyranosyl bromides **4** in the presence of aq. potassium hydroxide to give the corresponding *N*-glucosides **5a–k** and *N*-galactosides **5l–s**, respectively. When compounds **1** were subjected to the reaction with bromides **4** and cycloalkanones **2a–c** in the presence of aq. potassium hydroxide, the corresponding pyridine-2-thione glycosides **5** were obtained. These compounds were shown to be the same as those obtained from the reaction of pyridine-2-thiones **3a–i** with bromides **4**. The structure of compounds **5** could be established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (UV, IR, ^{1}H NMR, ^{13}C NMR and MS). Analytical data for compound **5g** revealed a molecular formula $C_{28}H_{30}N_2O_{10}S$ (*m/z* 586). ^{1}H NMR spectroscopy was used to confirm this structure for the product. Thus, ^{1}H NMR spectroscopy revealed the presence of a doublet at δ 6.05 with spin–spin coupling constant 10.54 Hz which corresponds to the diaxial orientation of 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 3.94–5.50 region. The remaining four acetoxy groups appear as four singlets at δ 1.92–2.15 and the four methylene protons of the aglycone resonate at 1.73, 1.86, 2.74 and 2.98. ^{13}C NMR spectra were characterized by a signal at δ_C 80.6 corresponding to the C-1' atom of the β-D-glucopyranose. The four signals appearing at δ_C 169.3–169.9 are due to the four acetoxy carbonyl carbon atoms, while the four signals at δ_C 20.2–20.3 are attributed to the acetate methyl carbons. The four methylene carbon atoms of the aglycone resonated at δ_C 21.3, 21.8, 26.5 and 33.2. Another five signals at δ_C 61.4, 66.2, 67.6, 70.9 and 74.1 were assigned to C-6', -4', -2', -3' and -5', respectively. The IR spectrum of compound **5g** was characterized by the absence of signal for an NH group and the presence of acetoxy carbonyl groups at 1755 cm^{-1}. The UV spectra of compounds **5** 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 *S*-methyl derivative of compound **3g** shows two maxima at λ 278 and 346 nm, its *N*-glucosyl derivative exhibited three maximum absorption bands at λ 266, 335, 444 nm. Moreover, hydrolysis of compound **5g** with 9% aq. HCl afforded only the pyridin-2(1*H*)-thione derivative **3g** as the unique product (a 2-oxopyridine derivative is not formed) proving the existence of *N*-glycosides. The preparation of well crystalline 1-(β-D-glycopyranosyl)-3-cyanopyridine-2-thione derivatives **7a–p** was achieved by removal of the blocking acetyl groups on treatment with methanolic ammonia at 0 °C. TLC of compounds **7** showed that a single unique compound was produced, and their structures were further confirmed by elemental analysis and spectral data (MS, IR, UV, ^{1}H NMR, ^{13}C NMR). Thus, the analytical data for compound **7n** revealed a molecular formula $C_{23}H_{26}N_2O_6S$ *m/z* 458. The IR absorption spectra of this compound showed a characteristic band at 3650–3200 due to the hydroxy groups of the galactose moiety. ^{1}H NMR spectroscopy was used to confirm this structure for the product. Thus, the ^{1}H NMR spectra revealed the presence of a doublet at δ 5.53 ($J_{1',2'}$ 10.18 Hz), indicating the presence of only the β-D-galactopyranose moiety. The other six protons, of the galactose, appear as a multiplet at δ 3.37–3.77, while the four hydroxy groups of galactose moiety resonate at δ_C 4.53–5.32 (exchangeable by D_2O). ^{13}C NMR spectra were characterized by a signal at δ_C 83.9 corresponding to the C-1' atom of β-D-galactopyranose. Another five signals, at δ_C 60.2, 68.2, 68.6, 74.9 and 79.6, were assigned to C-6', -4', -2', -3' and -5' of the galactose part, respectively.

In summary, we have achieved a regiospecific synthesis of interesting condensed pyridine-2-thione nucleosides by the reaction of condensed pyridine-2(1*H*)-thiones with α-halogeno sugars. These nucleosides can be utilized as an excellent starting material for the synthesis of other carbohydrate derivatives and for biological evaluation studies.

Experimental

All evaporations were carried out under reduced pressure at 40 °C. M.p.s are uncorrected. Aluminium sheets coated with silica gel 60 F_{254} (Merck) were used for TLC. Detection was effected by viewing under a short-wavelength UV lamp.

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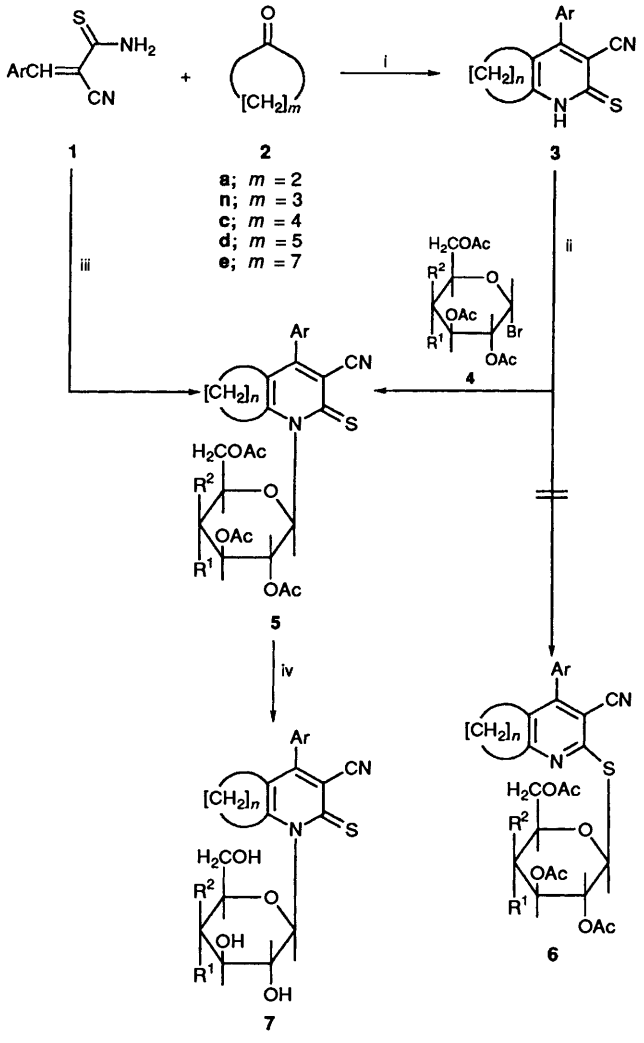

		Ar	n	R^1	R^2
5	a;	4-ClC_6H_4	3	OAc	H
	b;	4-$MeOC_6H_4$	3	OAc	H
	c;	2-furyl	3	OAc	H
	d;	1-naphthyl	3	OAc	H
	e;	4-ClC_6H_4	4	OAc	H
	f;	4-$MeOC_6H_4$	4	OAc	H
	g;	2-furyl	4	OAc	H
	h;	1-naphthyl	4	OAc	H
	i;	4-ClC_6H_4	5	OAc	H
	j;	4-ClC_6H_4	6	OAc	H
	k;	4-ClC_6H_4	8	OAc	H
	l;	4-ClC_6H_4	3	H	OAc
	m;	4-$MeOC_6H_4$	3	H	OAc
	n;	2-furyl	3	H	OAc
	o;	1-naphthyl	3	H	OAc
	p;	4-ClC_6H_4	4	H	OAc
	q;	$MeOC_6H_4$	4	H	OAc
	r;	2-furyl	4	H	OAc
	s;	1-naphthyl	4	H	OAc
7	a;	4-ClC_6H_4	3	OH	H
	b;	4-$MeOC_6H_4$	3	OH	H
	c;	2-furyl	3	OH	H
	d;	1-naphthyl	3	OH	H
	e;	4-ClC_6H_4	4	OH	H
	f;	4-$MeOC_6H_4$	4	OH	H
	g;	2-furyl	4	OH	H
	h;	1-naphthyl	4	OH	H
	i;	4-ClC_6H_4	3	H	OH
	j;	4-$MeOC_6H_4$	3	H	OH
	k;	2-furyl	3	H	OH
	l;	1-naphthyl	3	H	OH
	m;	4-ClC_6H_4	4	H	OH
	n;	4-$MeOC_6H_4$	4	H	OH
	o;	2-furyl	4	H	OH
	p;	1-naphthyl	4	H	OH

Scheme 1 *Reagents and conditions:* i, piperidine, EtOH, reflux; ii, aq. KOH; iii, **2a–c**, **4**, aq. KOH; iv, NH_3, MeOH

IR spectra were obtained (KBr disc) on a Pye Unicam Spectra-1000. ^1H NMR and ^{13}C NMR spectra were measured on a Wilmad 270 MHz or on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2SO$ with $SiMe_4$ as internal standard. *J* Values are given in Hz. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

1-(2′,3′,4′,6′-*Tetra*-O-*acetyl*-β-D-*gluco- and -galacto-pyranosyl*)*cycloalkane Ring-fused* 4-*Aryl*-3-*cyanopyridine*-2-*thiones* **5**. *General Procedures*.—To a solution of condensed pyridine-2(1*H*)-thione **3** (0.01 mol) in aq. potassium hydroxide [0.56 g, 0.01 mol, in distilled water (6 cm^3)] was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or -galacto-pyranosyl bromide **4** (4.521 g, 0.011 mol) in acetone (30 cm^3). The reaction mixture was stirred at room temperature until reaction was judged complete by TLC (30 min to 2 h). The mixture was evaporated under reduced pressure at 40 °C and the residue was washed with distilled water to remove the potassium bromide formed. The product was dried, and crystallized from the appropriate solvent.

Compound **5a**. Yellow crystals, m.p. 108 °C (from EtOH) (74%); ν_{max}/cm^{-1} 2220 and 1755; λ_{max}/nm 265, 322, 378 and 394; δ_H 1.94–2.14 (12 H, 4 s, 4 × AcO), 2.05 (2 H, t, CH_2), 2.74 (2 H, t, CH_2), 3.05 (2 H, t, CH_2), 4.18 (2 H, m, 6′-H_2 and 1 H, 5′-H), 5.12 (2 H, m, 4′- and 3′-H), 5.50 (1 H, t, 2′-H), 6.15 (1 H, d, $J_{1',2'}$ 9.98, 1′-H) and 7.60 (4 H, s, ArH); *m*/*z* 617 (Found: C, 56.8; H, 4.9; N, 4.8. $C_{29}H_{29}ClN_2O_9S$ requires C, 56.4; H, 4.7; N, 4.5%).

Compound **5b**. Yellow crystals, m.p. 165 °C (from EtOH) (76%); ν_{max}/cm^{-1} 2222 and 1758; δ_H 1.90–2.20 (12 H, 4 s, 4 × AcO), 2.08 (2 H, t, CH_2), 2.85 (2 H, t, CH_2), 3.05 (2 H, t, CH_2), 3.89 (3 H, s, OMe), 4.18 (2 H, m, 6′-H_2 and 1 H, 5′-H), 5.28 (2 H, m, 4′- and 3′-H), 5.53 (1 H, t, 2′-H), 6.11 (1 H, d, $J_{1',2'}$ 9.80, 1′-H), 7.08 (2 H, d, ArH) and 7.51 (2 H, d, ArH); *m*/*z* 612 (Found: C, 59.1; H, 5.1; N, 4.9. $C_{30}H_{32}N_2O_{10}S$ requires C, 58.8; H, 5.2; N, 4.6%).

Compound **5c**. Buff crystals, m.p. 127 °C (from EtOH) (78%); ν_{max}/cm^{-1} 2215 and 1750; δ_H 1.93–2.13 (12 H, 4 s, 4 × AcO), 2.02 (2 H, t, CH_2), 2.78 (2 H, t, CH_2), 2.96 (2 H, t, CH_2), 4.05 (2 H, m, 6′-H_2 and 1H, 5′-H), 5.10 (2 H, m, 4′- and 3′-H), 5.03 (1 H, t, 2′-H), 6.08 (1 H, d, $J_{1',2'}$ 9.89, 1′-H), 6.85 (1 H, m, furan 4-H), 7.33 (1 H, d, furan 3-H) and 8.10 (1 H, s, furan 5-H) δ_C[$(CD_3)_2(Me_2SO)$] 20.3–21.6 (4 × Me), 31.3–34.5 (3 × CH_2), 61.7 (C-6′), 68.9 (C-4′), 70.6 (C-2′), 74.9 (C-3′), 76.7 (C-5′), 80.5 (C-1′), 106.0 (C-3), 112.8 (CN), 115.8 (furan C-4), 117.6 (furan C-3), 132.1 (C-5), 135.7 (C-6), 139.4 (C-4), 146.7 (furan C-5), 158.3 (furan C-2), 169.2–170.4 (4 × CO) and 177.1 (C=S); *m*/*z* 572 (Found: C, 56.9; H, 5.1; N, 5.3. $C_{27}H_{28}N_2O_{10}S$ requires C, 56.6; H, 4.9; N, 4.9%).

Compound **5d**. Pale yellow crystals, m.p. 117 °C (from

EtOH) (73%); ν_{max}/cm^{-1} 2215 and 1750; *m/z* 632 (Found: C, 63.1; H, 5.3; N, 4.6. $C_{33}H_{32}N_2O_9S$ requires C, 62.7; H, 5.1; N, 4.4%).

Compound **5e**. Pale yellow crystals, m.p. 187 °C (from EtOH) (78%); ν_{max}/cm^{-1} 2225 and 1756; *m/z* 631 (Found: C, 57.4; H, 4.7; N, 4.7. $C_{30}H_{31}ClN_2O_9S$ requires C, 57.1; H, 4.9; N, 4.4%).

Compound **5f**. Pale yellow crystals, m.p. 126 °C (from EtOH) (76%); ν_{max}/cm^{-1} 2226 and 1758; *m/z* 626 (Found: C, 59.8; H, 5.6; N, 4.8. $C_{31}H_{34}N_2O_{10}S$ requires C, 59.4; H, 5.4; N, 4.5%).

Compound **5g**. Pale brown crystals, m.p. 170 °C (from EtOH) (74%); ν_{max}/cm^{-1} 2222 and 1755; λ_{max} 266, 335 and 444; δ_H 1.73 (2 H, t, CH_2), 1.86 (2 H, t, CH_2), 1.92–2.15 (12 H, 4 s, 4 × AcO), 2.74 (2 H, t, CH_2), 2.98 (2 H, m, CH_2), 4.03 (2 H, m, 6′-H_2), 4.38 (1 H, t, 5′-H), 5.24 (1 H, t, 4′-H), 5.39 (1 H, d, 3′-H), 5.48 (1 H, dd, 2′-H), 6.05 (1 H, d, $J_{1',2'}$ 10.54, 1′-H), 6.78 (1 H, dd, furan 4-H), 7.10 (1 H, d, furan 3-H) and 8.03 (1 H, d, furan 5-H); δ_C 20.2–20.3 (4 × Me), 21.3–33.2 (4 × CH_2), 61.4 (C-6′), 66.2 (C-4′), 67.6 (C-2′), 70.9 (C-3′), 74.1 (C-5′), 80.6 (C-1′), 102.5 (C-3), 112.1 (CN), 115.2 (furan C-4), 116.4 (furan C-3), 127.3 (C-5), 140.8 (C-6), 145.4 (C-4), 145.7 (furan C-5), 155.1 (furan C-2), 162.2 (C=S) and 169.3–169.9 (4 × CO); *m/z* 586 (Found: C, 57.6; H, 5.3; N, 5.1. $C_{28}H_{30}N_2O_{10}S$ requires C, 57.3; H, 5.1; N, 4.8%).

Compound **5h**. Pale yellow crystals, m.p. 196 °C (from EtOH) (72%); ν_{max}/cm^{-1} 2220 and 1755; *m/z* 646 (Found: C, 63.5; H, 5.5; N, 4.6. $C_{34}H_{34}N_2O_9S$ requires C, 63.2; H, 5.3; N, 4.3%).

Compound **5i**. Yellow crystals, m.p. 156 °C (from EtOH) (79%); ν_{max}/cm^{-1} 2216 and 1758; δ_H 1.42 (2 H, s, CH_2), 1.58 (2 H, s, CH_2), 1.72 (2 H, s, CH_2), 1.88–2.0 (12 H, 4 s, 4 × AcO), 2.41 (2 H, m, CH_2), 2.88 (2 H, m, CH_2), 4.0 (2 H, m, 6′-H_2), 4.29 (1 H, t, 5′-H), 5.13 (1 H, t, 4′-H), 5.28 (1 H, d, 3′-H), 5.43 (1 H, d, 2′-H), 6.0 (1 H, d, 1′-H) and 7.22–7.62 (4 H, m, ArH); *m/z* 645 (Found: C, 57.4; H, 5.3; N, 4.5. $C_{31}H_{33}ClN_2O_9S$ requires C, 57.7; H, 5.1; N, 4.3%).

Compound **5j**. Yellow crystals, m.p. 167 °C (from EtOH) (75%); ν_{max}/cm^{-1} 2220 and 1756; δ_H 1.28 (4 H, m, 2 × CH_2), 1.57 (2 H, s, CH_2), 1.93–2.05 (12 H, 4 s, 4 × AcO), 2.37 (2 H, m, CH_2), 2.47 (2 H, s, CH_2), 2.85 (2 H, m, CH_2), 4.0 (2 H, m, 6′-H_2), 4.41 (1 H, t, 5′-H), 5.15 (1 H, m, 4′-H), 5.38 (1 H, d, 3′-H), 5.46 (1 H, m, 2′-H), 6.11 (1 H, d, 1′-H) and 7.17–7.72 (4 H, m, ArH); *m/z* 659 (Found: C, 58.6; H, 5.5; N, 4.6. $C_{32}H_{35}ClN_2O_9S$ requires C, 58.3; H, 5.3; 4.3%).

Compound **5k**. Yellow crystals, m.p. 142 °C (from EtOH) (76%); ν_{max}/cm^{-1} 2218 and 1755; *m/z* 687 (Found: C, 59.7; H, 5.9; N, 4.4. $C_{34}H_{39}ClN_2O_9S$ requires C, 59.4; H, 5.7; N, 4.1%).

Compound **5l**. Yellow crystals, m.p. 178 °C (from EtOH) (75%); ν_{max}/cm^{-1} 2222 and 1750; *m/z* 617 (Found: C, 56.7; H, 4.5; N, 4.8. $C_{29}H_{29}ClN_2O_9S$ requires C, 56.4; H, 4.7; N, 4.5%).

Compound **5m**. Yellow crystals, m.p. 193 °C (from EtOH) (74%); ν_{max}/cm^{-1} 2218 and 1756; *m/z* 612 (Found: C, 58.5; H, 5.4; N, 5.0. $C_{30}H_{32}N_2O_{10}S$ requires C, 58.8; H, 5.2; N, 4.6%).

Compound **5n**. Buff crystals, m.p. 198 °C (from EtOH) (76%); ν_{max}/cm^{-1} 2224 and 1755; *m/z* 572 (Found: C, 56.8; H, 4.7; N, 5.2. $C_{27}H_{28}N_2O_{10}S$ requires C, 56.6; H, 4.9; N, 4.9%).

Compound **5o**. Yellow crystals, m.p. 103 °C (from EtOH) (74%); ν_{max}/cm^{-1} 2218 and 1758; *m/z* 632 (Found: C, 62.9; H, 4.9; N, 4.7. $C_{33}H_{32}N_2O_9S$ requires C, 62.7; H, 5.1; N, 4.4%).

Compound **5p**. Pale yellow crystals, m.p. 212 °C (from EtOH) (78%); ν_{max}/cm^{-1} 2222 and 1758; *m/z* 631 (Found: C, 57.5; H, 5.1; N, 4.7. $C_{30}H_{31}ClN_2O_9S$ requires C, 57.1; H, 4.9; N, 4.4%).

Compound **5q**. Pale yellow crystals, m.p. 222 °C (from EtOH) (77%); ν_{max}/cm^{-1} 2227 and 1750; *m/z* 626 (Found: C, 59.6; H, 5.6; N, 4.7. $C_{31}H_{34}N_2O_{10}S$ requires C, 59.4; H, 5.4; N, 4.5%).

Compound **5r**. Pale brown crystals, m.p. 204 °C (from EtOH) (77%); ν_{max}/cm^{-1} 2222 and 1755; δ_H 1.73 (2 H, t, CH_2), 1.84 (2 H, t, CH_2), 1.92–2.14 (12 H, 4 s, 4 × AcO), 2.72 (2 H, m, CH_2), 2.98 (2 H, m, CH_2), 4.02 (2 H, m, 6′-H_2), 4.37 (1 H, t, 5′-H), 5.24 (1 H, t, 4′-H), 5.38 (1 H, d, 3′-H), 5.47 (1 H, dd, 2′-H), 6.04 (1 H, d, $J_{1',2'}$ 10.57, 1′-H), 6.77 (1 H, m, furan 4-H), 7.14 (1 H, dd, furan 3-H) and 8.02 (1 H, s, furan 5-H); δ_C 20.1–20.2 (4 × Me), 21.3–33.1 (4 × CH_2), 61.4 (C-6′), 66.3 (C-4′), 67.6 (C-2′), 70.9 (C-3′), 74.1 (C-5′), 80.7 (C-1′), 102.6 (C-3), 112.0 (CN), 115.3 (furan C-4), 116.5 (furan C-3), 127.3 (C-5), 140.8 (C-6), 145.7 (C-4), 152.7 (furan C-5), 155.1 (furan C-2), 162.2 (C=S), 169.2–169.8 (4 × CO); *m/z* 586 (Found: C, 57.6; H, 5.2; N, 4.9. $C_{28}H_{30}N_2O_{10}S$ requires C, 57.3; H, 5.1; N, 4.8%).

Compound **5s**. Yellow crystals, m.p. 163 °C (from EtOH) (73%); ν_{max}/cm^{-1} 2218 and 1758; δ_H 1.59 (2 H, t, CH_2), 1.84 (2 H, t, CH_2), 1.96–2.15 (12 H, 4 s, 4 × AcO), 2.22 (2 H, m, CH_2), 3.03 (2 H, m, CH_2), 4.06 (2 H, m, 6′-H_2), 4.44 (1 H, t, 5′-H), 5.24 (1 H, m, 4′-H), 5.41 (1 H, d, 3′-H), 5.49 (1 H, m, 2′-H), 6.14 (1 H, d, $J_{1',2'}$ 10.66, 1′-H), 7.27–7.69 (4 H, m, ArH) and 8.08 (3 H, t, ArH); δ_C 20.3 (4 × Me), 21.5–32.9 (4 × CH_2), 61.3 (C-6′), 66.2 (C-4′), 67.5 (C-2′), 70.9 (C-3′), 74.06 (C-5′), 80.5 (C-1′), 105.8 (C-3), 114.6 (CN), 123.9–132.9 (Ar carbons), 152.4 (C-6), 156.6 (C-4), 161.9 (C=S) and 169.3–169.9 (4 × CO); *m/z* 646 (Found: C, 63.4; H, 5.5; N, 4.7. $C_{34}H_{34}N_2O_9S$ requires C, 63.2; H, 5.3; N, 4.3%).

1-(β-D-*Gluco- and -galacto-pyranosyl*)*cycloalkane Ring-fused* 4-*Aryl*-3-*cyanopyridine*-2-*thiones* **7**. *General Procedures*.—Dry gaseous ammonia was passed through a solution of a protected nucleoside **5** (0.5 gm) in dry methanol (20 cm^3) at 0 °C for *ca.* 0.5 h, then the mixture was stirred at 0 °C until reaction was judged to be complete by TLC (2–6 h). The mixture was evaporated under reduced pressure at 40 °C to give a solid residue, which was crystallized from the appropriate solvent.

Compound **7a**. Pale yellow crystals, m.p. 157 °C (from MeOH) (88%); ν_{max}/cm^{-1} 3600–3200 and 2220, δ_H 2.03 (2 H, t, CH_2), 2.45 (2 H, t, CH_2), 2.95 (2 H, t, CH_2), 3.23–3.76 (6 H, m, 6′-H_2, 5′-, 4′-, 3′- and 2′-H), 4.51 (2H t, 2′- and 3′-OH), 5.08 (1 H, d, 4′-OH), 5.37 (1 H, d, 6′-OH), 5.73 (1 H, d, $J_{1',2'}$ 9.76, 1′-H) and 7.65 (4 H, s, ArH); δ_C 22.4–34.7 (3 × CH_2), 60.6 (C-6′), 69.6 (C-4′), 71.8 (C-2′), 76.6 (C-3′), 78.4 (C-5′), 81.5 (C-1′), 103.6 (C-3), 115.6 (CN), 128.7–133.4 (Ar carbons), 134.4 (C-5), 147.8 (C-6), 159.6 (C-4) and 163.4 (C=S); *m/z* 449 (Found: C, 56.5; H, 4.9; N, 6.4. $C_{21}H_{21}ClN_2O_5S$ requires C, 56.2; H, 4.7; N, 6.2%).

Compound **7b**. Pale yellow crystals, m.p. 197 °C (from MeOH) (86%); ν_{max}/cm^{-1} 3600–3180 and 2226; δ_H 2.02 (2 H, t, CH_2), 2.83 (2 H, t, CH_2), 3.01 (2 H, t, CH_2), 3.21–3.76 (6 H, m, 6′-H_2, 5′-, 4′-, 3′- and 2′-H), 3.88 (3 H, s, OMe), 4.44 (2 H, d, 2′- and 3′-OH), 4.98 (1 H, d, 4′-OH), 5.18 (1 H, d, 6′-OH), 5.61 (1 H, d, $J_{1',2'}$ 9.87, 1′-H), 7.08 (2 H, d, ArH) and 7.49 (2 H, d, ArH); *m/z* 444 (Found: C, 59.8; H, 5.2; N, 6.6. $C_{22}H_{24}N_2O_6S$ requires C, 59.5; H, 5.4; N, 6.3%).

Compound **7c**. Pale yellow crystals, m.p. 261 °C (from MeOH) (89%); ν_{max}/cm^{-1} 3640–3180 and 2228; δ_H 2.09 (2 H, t, CH_2), 2.78 (2 H, t, CH_2), 2.96 (2 H, t, CH_2), 3.20–3.67 (6 H, m, 6′-H_2, 5′-, 4′-, 3′- and 2′-H), 4.41 (2 H, t, 2′- and 3′-OH), 5.00 (1 H, d, 4′-OH), 5.21 (1 H, d, 6′-OH), 5.58 (1 H, d, $J_{1',2'}$ 9.84, 1′-H), 6.81 (1 H, m, furan 4-H), 7.34 (1 H, d, furan 3-H) and 8.1 (1 H, d, furan 5-H); δ_C 22.4, 31.2 and 34.6 (3 × CH_2), 60.7 (C-6′), 69.6 (C-4′), 71.9 (C-2′), 76.7 (C-3′), 78.5 (C-5′), 81.4 (C-1′), 106.0 (C-3), 112.7 (CN), 115.4 (furan C-4), 117.6 (furan C-3), 135.7 (C-5), 145.7 (C-6), 146.6 (C-4), 147.0 (furan C-5), 159.4 (furan C-2) and 160.7 (C=S); *m/z* 404 (Found: C, 56.8; H, 5.2; N, 6.6. $C_{19}H_{20}N_2O_6S$ requires C, 56.4; H, 5.0; N, 6.9%).

Compound **7d**. Pale yellow crystals, m.p. 179 °C (from MeOH) (85%); ν_{max}/cm^{-1} 3650–3200 and 2220; δ_H 2.02 (2 H, t, CH_2), 2.58 (2 H, t, CH_2), 3.06 (2 H, t, CH_2), 3.18–3.96 (6 H, m, 6′-H_2, 5′-, 4′-, 3′- and 2′-H), 4.48 (2 H, m, 2′- and 3′-OH), 5.05 (1 H, d, 4′-OH), 5.26 (1 H, d, 6′-OH), 5.63 (1 H, d, $J_{1',2'}$ 9.93, 1′-H) and 7.56 (7 H, m, ArH); *m/z* 464 (Found: C, 65.0; H, 5.4; N, 6.3. $C_{25}H_{24}N_2O_5S$ requires C, 64.7; H, 5.2; N, 6.0%).

Compound **7e**. Pale yellow crystals, m.p. 223 °C (from MeOH) (89%); ν_{max}/cm^{-1} 3600–3150 and 2220; *m/z* 463 (Found: C, 57.4; H, 5.2; N, 6.3. $C_{22}H_{23}ClN_2O_5S$ requires C, 57.1; H, 5.0; N, 6.1%).

Compound **7f**. Pale yellow crystals, m.p. 287 °C (from MeOH) (86%); ν_{max}/cm^{-1} 3640–3180 and 2220; *m/z* 458 (Found: C, 60.6; H, 5.9; N, 6.4. $C_{23}H_{26}N_2O_6S$ requires C, 60.3; H, 5.7; N, 6.1%).

Compound **7g**. Pale yellow crystals, m.p. 220 °C (from MeOH) (84%); ν_{max}/cm^{-1} 3630–3160 and 2216; *m/z* 418 (Found: C, 57.7; H, 5.5; N, 6.5. $C_{20}H_{22}N_2O_6S$ requires C, 57.4; H, 5.3; N, 6.7%).

Compound **7h**. Pale yellow crystals, m.p. 215 °C (from MeOH) (86%); ν_{max}/cm^{-1} 3640–3150 and 2215; *m/z* 478 (Found: C, 65.6; H, 5.6; N, 6.1. $C_{26}H_{26}N_2O_5S$ requires C, 65.3; H, 5.4; N, 5.9%).

Compound **7i**. Pale yellow crystals, m.p. 247 °C (from MeOH) (86%); ν_{max}/cm^{-1} 3650–3200 and 2216; δ_H 2.07 (2 H, q, CH_2), 2.82 (2 H, t, CH_2), 3.03 (2 H, m, CH_2), 3.23–3.77 (6 H, m, 6′-H_2, 5′-, 4′-, 3′- and 2′-H), 4.55 (2 H, t, 2′- and 3′-OH), 4.99 (1 H, d, 4′-OH), 5.39 (1 H, d, 6′-OH), 5.60 (1 H, d, $J_{1',2'}$ 10.1, 1′-H) and 7.61 (4 H, m, ArH); *m/z* 449 (Found: C, 56.5; H, 4.5; N, 6.4. $C_{21}H_{21}ClN_2O_5S$ requires C, 56.2; H, 4.7; N, 6.2%).

Compound **7j**. Pale yellow crystals, m.p. 209 °C (from MeOH) (84%); ν_{max}/cm^{-1} 3620–3180 and 2215; *m/z* 444 (Found: C, 59.7; H, 5.5; N, 6.0. $C_{22}H_{24}N_2O_6S$ requires C, 59.5; H, 5.4; N, 6.3%).

Compound **7k**. Pale yellow crystals, m.p. 213 °C (from MeOH) (86%); ν_{max}/cm^{-1} 3600–3200 and 2218; δ_H 2.09 (2 H, t, CH_2), 3.04 (4 H, m, 2 × CH_2), 3.20–3.85 (6 H, m, 6′-H_2, 5′-, 4′-, 3′- and 2′-H), 4.57 (2 H, m, 2′- and 3′-OH), 4.98 (1 H, t, 4′-OH), 5.38 (1 H, t, 6′-OH), 5.64 (1 H, d, $J_{1',2'}$ 9.77, 1′-H), 6.84 (1 H, m, furan 4-H), 7.31 (1 H, d, furan 3-H) and 8.08 (1 H, dd, furan 5-H); *m/z* 404 (Found: C, 56.6; H, 5.1; N, 7.2. $C_{19}H_{20}N_2O_6S$ requires C, 56.4; H, 5.0; N, 6.9%).

Compound **7l**. Pale yellow crystals, m.p. 173 °C (from MeOH) (83%); ν_{max}/cm^{-1} 3600–3150 and 2216; δ_H 2.02 (2 H, t, CH_2), 2.78 (2 H, t, CH_2), 3.08 (2 H, t, CH_2), 3.21–3.94 (6 H, m, 6′-H_2, 5′-, 4′-, 3′- and 2′-H), 4.55 (2 H, t, 2′- and 3′-OH), 5.01 (1 H, d, 4′-OH), 5.38 (1 H, d, 6′-OH), 5.67 (1 H, d, $J_{1',2'}$ 9.98, 1′-H) and 7.73 (7 H, m, ArH); *m/z* 464 (Found: C, 64.9; H, 5.1; N, 6.4. $C_{25}H_{24}N_2O_5S$ requires C, 64.7; H, 5.2; N, 6.0%).

Compound **7m**. Pale yellow crystals, m.p. 275 °C (from MeOH) (86%); ν_{max}/cm^{-1} 3620–3200 and 2218; *m/z* 463 (Found: C, 57.3; H, 5.2; N, 6.4. $C_{22}H_{23}ClN_2O_5S$ requires C, 57.1; H, 5.0; N, 6.1%).

Compound **7n**. Pale yellow crystals, m.p. 273 °C (from MeOH) (86%); ν_{max}/cm^{-1} 3610–3180 and 2216; δ_H 1.65 (2 H, t, CH_2), 1.82 (2 H, t, CH_2), 2.38 (2 H, t, CH_2), 2.92 (2 H, t, CH_2), 3.37–3.77 (6 H, m, 6′-H_2, 5′-, 4′-, 3′- and 2′-H), 3.82 (3 H, s, OMe), 4.53 (2 H, s, 2′- and 3′-OH), 4.92 1 H, s, 4′-OH), 5.32 (1 H, s, 6′-OH), 5.53 (1 H, d, $J_{1',2'}$ 10.18, 1′-H), 7.09 (2 H, d, ArH) and 7.31 (2 H, d, ArH); δ_C 21.6–33.1 (4 × CH_2), 55.1 (OMe), 60.2 (C-6′), 68.2 (C-4′), 68.6 (C-2′), 74.9 (C-3′), 79.6 (C-5′), 83.9 (C-1′), 104.8 (C-3), 114.0 (CN), 126.9–129.6 (Ar carbons), 153.3 (C-5), 156.5 (C-6), 159.6 (C-4) and 161.2 (C=S); *m/z* 458 (Found: C, 60.4; H, 6.0; N, 6.4. $C_{23}H_{26}N_2O_6S$ requires C, 60.3; H, 5.7; N, 6.1%).

Compound **7o**. Pale yellow crystals, m.p. 238 °C (from MeOH) (85%); ν_{max}/cm^{-1} 3600–3180 and 2215; δ_H 1.70 (2 H, d, CH_2), 1.82 (2 H, d, CH_2), 2.68 (2 H, d, CH_2), 2.92 (2 H, d, CH_2), 3.34–3.75 (6 H, m, 6′-H_2, 5′-, 4′-, 3′- and 2′-H), 4.53 (2 H, s, 2′- and 3′-OH), 4.94 (1 H, s, 4′-OH), 5.33 (1 H, s, 6′-OH), 5.49 (1 H, d, $J_{1',2'}$ 10.19, 1′-H), 6.76 (1 H, m, furan 4-H), 7.05 (1 H, d, furan 3-H) and 8.0 (1 H, d, furan 5-H); *m/z* 418 (Found: C, 57.8; H, 5.4; N, 6.9. $C_{20}H_{22}N_2O_6S$ requires C, 57.4; H, 5.3; N, 6.7%).

Compound **7p**. Pale yellow crystals, m.p. 214 °C (from MeOH) (87%); ν_{max}/cm^{-1} 3620–3180 and 2216; δ_H 1.56 (2 H, d, CH_2), 1.80 (2 H, d, CH_2), 2.18 (2 H, m, CH_2), 2.99 (2 H, t, CH_2), 2.37–3.80 (6 H, m, 6′-H_2, 5′-, 4′-, 3′- and 2′-H), 4.55 (2 H, m, 2′- and 3′-OH), 4.99 (1 H, d, 4′-OH), 5.41 (1 H, d, 6′-OH), 5.61 (1 H, d, $J_{1',2'}$ 10.10, 1′-H), 7.28 (1 H, t, ArH), 7.60 (5 H, m, ArH) and 8.07 (1 H, t, ArH); δ_C 21.5–33.1 (4 × CH_2), 60.2 (C-6′), 68.2 (C-4′), 68.6 (C-2′), 74.8 (C-3′), 79.6 (C-5′), 83.8 (C-1′), 105.3 (C-3), 114.9 (CN), 123.8–132.9 (Ar carbons), 152.2 (C-5), 156.6 (C-6), 156.7 (C-4) and 161.5 (C=S); *m/z* 478 (Found: C, 65.4; H, 5.5; N, 6.2. $C_{26}H_{26}N_2O_5S$ requires C, 65.3; H, 5.4; N, 5.9%).

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