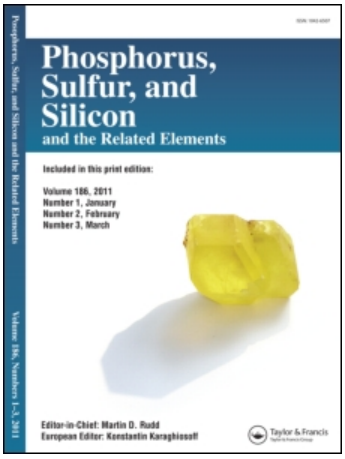

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Novel Synthesis of Condensed Pyridinethione Carbocyclic Glycosides

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NOVEL SYNTHESIS OF CONDENSED PYRIDINETHIONE CARBOCYCLIC GLYCOSIDES

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A novel synthesis of several new condensed pyridinethione carbocyclic glycosides via the reaction of condensed pyridine-2(1*H*)-thiones with α-halogeno sugars is described.

Key words: Glycosides, pyridinethione, pyrimidine nucleosides.

The function of various 3-deaza analogues of pyrimidine nucleosides in biological systems has been the subject of considerable comment and speculation.[1,2] The synthesis of pyridine-2(1*H*)-thiones and their condensed derivatives from the reactions of arylmethylenecyanothioacetamides with appropriate active methylene compounds[3,7] have been previously reported. The novel reaction of cycloalkylidenemalononitriles **1** with arylmethylenecyanothioacetamides **2** to produce the unexpected condensed pyridine-2(1*H*)-thiones **3**[8] by a sequence initiated by the exchange reaction between the cycloalkylidene group of **1** and the arylmethylene group of **2** has been described. In conjunction with this work, the results of our investigation into the utility of the reaction of pyridine-2(1*H*)-thiones **3** with α-halogeno sugars for the synthesis of pyridinethione glycosides are now reported. This is the first coupling reaction of this type to be reported for pyridine-2-(1*H*)-thiones. It has been found that compounds **3** reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galactopyranosyl bromides **4** in the presence of aqueous potassium hydroxide to afford the corresponding the acetates of the *N*-glucosides **5a–d** and *N*-galactosides **5e–h**, respectively. It may be argued that the coupling reaction of **3** with **4** happened on the sulfur atom to give the corresponding *S*-glycosides **6**. The formation of **5** was proven chemically by treating the pyridine-2(1*H*)-thiones **3** with hexamethyldisilazane (HMDS) in the presence of ammonium sulphate to give the corresponding 2-trimethylsilylthiopyridines **7**, treatment of the latter with peracetylated sugars **8** in dry acetonitrile and in the presence of redistilled $SnCl_4$ gave the corresponding *N*-glycosides **5**. All previous literature reports that the coupling reaction of *S*-silylated nitrogen bases with peracetylated sugars in the

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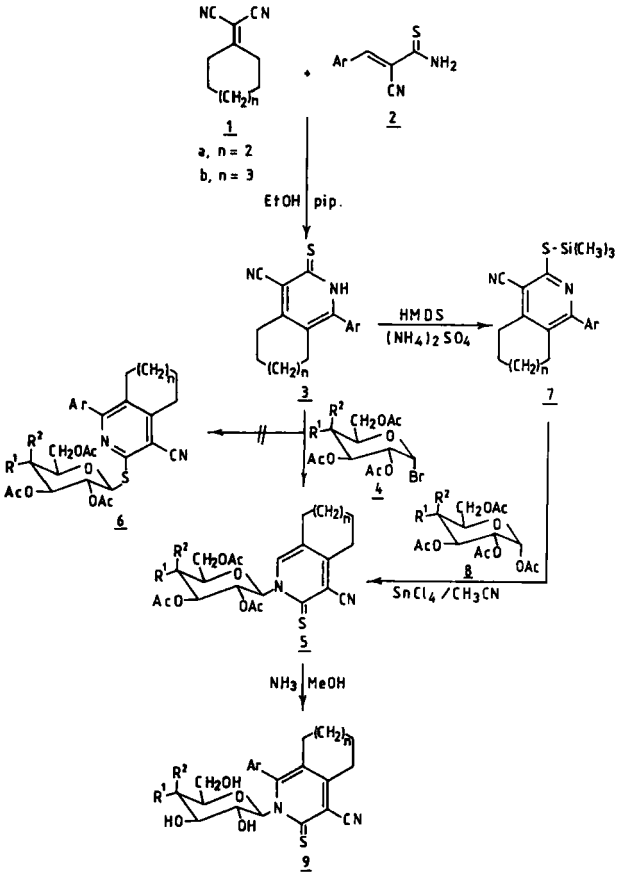

		Ar	n	R_1	R^1
5	**a**	4-$CH_3OC_6H_4$	2	OAc	H
	b	4-$CH_3OC_6H_4$	3	OAc	H
	c	4-$CH_3C_6H_4$	3	OAc	H
	d	4-ClC_6H_4	3	OAc	H
	e	4-$CH_3OC_6H_4$	2	H	OAc
	f	4-$CH_3OC_6H_4$	3	H	OAc
	g	4-$CH_3C_6H_4$	3	H	OAc
	h	4-ClC_6H_4	3	H	OAc

9	**a**	4-$CH_3OC_6H_4$	2	OH	H
	b	4-$CH_3OC_6H_4$	3	OH	H
	c	4-$CH_3C_6H_4$	3	OH	H
	d	4-ClC_6H_4	3	OH	H
	e	4-$CH_3OC_6H_4$	2	H	OH
	f	4-$CH_3OC_6H_4$	3	H	OH
	g	4-$CH_3C_6H_4$	3	H	OH
	h	4-ClC_6H_4	3	H	OH

presence of Friedel-Crafts catalyst gave the corresponding *N*-nucleosides as the sole product.[9-11] The structures of the reaction products **5** were established and confirmed by the correct analytical and spectral data (MS, IR, UV, ^{1}H NMR, ^{13}C NMR). The mass spectrum of **5d** was compatible with the molecular formula $C_{30}H_{31}ClN_2SO_9$ (m/z 630). The ^{1}H NMR spectrum showed a doublet at δ 6.13 ppm assigned to the anomeric proton of the glucose moiety with a spin-spin coupling constant equal to 10.14 Hz which corresponds to a diaxial orientation of H-1′ and H-2′ protons indicating the presence of only β-configuration and $^4C_1$ (D) conformation for this glucoside. The other protons of the glucopyranosyl ring resonates at δ 4.78–5.85 ppm region, while the four acetoxy groups appear as four singlets at δ 1.92–2.08 ppm region provided further verification of the favour $^4C_1$ (D) conformation with β-configuration, since these signals lie within the range expected for equatorial secondary acetoxy groups. The ^{13}C NMR spectrum of **5d** was characterized by a signal at δ 81.8 ppm corresponding to the C-l′ atom of the β-D-glucopyranose. Four signals appeared at δ 169.3, 169.4, 169.6 and 169.8 ppm due to the four acetoxy carbonyl carbon atoms of the acetates attached to the glucose, while the four signals appear at δ 20.3, 20.8, 21.5 and 21.7 ppm attributed to the methyl carbons of the acetate attached to the glucose. Another five signals at 61.4, 66.3, 67.8, 71.0 and 74.1 ppm were assigned to C-6′, C-4′, C-2′, C-3′ and C-5′, respectively. The UV spectrum of **5d** 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 **3d** showed two maxima at 298 and 329 nm, its *N*-glucosyl derivative exhibited three maxima at 311, 347 and 414 nm. The protected nucleosides (**5a–h**) were deblocked through treatment with methanolic ammonia to give the free glycosides (**9a–h**) after chromatographic purification. The structures of compounds **9** were confirmed by their elemental analyses and spectral data. Thus, the analytical data for **9d** revealed a molecular formula $C_{22}H_{23}ClN_2SO_5$ (m/z 462). The ^{1}H NMR spectrum showed the anomeric proton as a doublet at δ 5.67 ppm ($J_{1'-2'}$ = 10.01 Hz) indicating the presence of only the β-configuration. The other six glucose protons appeared as a multiplet at δ 3.21–3.78 ppm, while the four hydroxy groups resonated at δ 4.43–5.38 ppm (exchangeable by D_2O). The ^{13}C NMR spectrum of **9d** was characterized by a signal at δ 83.5 ppm corresponding to the C-1′ atom of β-D-glucopyranose. Another five signals at δ 60.6, 69.6, 71.7, 78.6 and 81.6 ppm were assigned to C-6′, C-4′, C-2′, C-3′ and C-5′ of the glucose moiety, respectively. The glycosides obtained through these results constitute an important and versatile class of compounds for potential application in the synthesis of other carbohydrate derivatives and for biological evaluation studies.

EXPERIMENTAL

All evaporations were carried out under reduced pressure at 40°C. Melting points are uncorrected. TLC aluminum sheets silica gel 60 F_{254} (Merck) was 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 galactopyranosyl)condensed pyridine-2-thiones **5**

General coupling procedures

Method A. To a solution of **3** (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** (4.521 g, 0.011 mol) in acetone (30 ml) was added. The reaction mixture was stirred at room temperature until judged complete by TLC (30 to 60 min), then evaporated under reduced pressure at 40°C and the residue washed with distilled water to remove the formed potassium bromide. The product was dried and crystallized from ethanol to afford pale yellow crystals.

Method B. Condensed pyridine-2(1*H*)-thiones **3** (0.01 mol) was boiled under reflux, with stirring, under anhydrous conditions for 48 hours with hexamethyldisilazane (25 ml) and ammonium sulphate (0.02 g). The excess of hexamethyldisilazane was removed under diminished pressure, providing the silylated bases **7** as a colorless oil. To a solution of silylated base in dry acetonitrile (30 ml) was added a solution of 1,2,3,4,6-penta-*O*-acetyl-α-D-gluco- or galactopyranose (0.011 mol) in dry acetonitrile (20 ml), followed by $SnCl_4$ (1.6 ml). The reaction mixture was stirred at room temperature until judged complete by TLC (3 to 6 h), 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 ethanol to afford pale yellow crystals.

5a. mp 126°C, yield 73%. IR (KBr) 2217, 1753 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.92 (t, 2H, CH_2), 1.96–2.04 (4s, 12H, $4CH_3CO$), 2.82, (t, 2H, CH_2), 3.08 (t, 2H, CH_2), 3.88 (s, 3H, OCH_3), 4.05 (m, 2H, H-6', 6'' and 1H, H-5'), 5.18 (m, 2H, H-4' and H-3'), 5.57 (t, 1H, H-2'), 6.16 (d, $J_{1'-2'}$ = 9.96 Hz, 1H, H-1'), 7.12 (d, 2H, Ar—H), 7.56 (d, 2H, Ar—H); m/z 612 (Found: C, 58.9; H, 5.3; N, 4.8. $C_{30}H_{32}N_2SO_{10}$ requires C, 58.8; H, 5.2; N, 4.6%).

5b. mp 138°C, yield 71%. IR (KBr) 2220, 1750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.48 (t, 2H, CH_2), 1.76 (t, 2H, CH_2), 1.92–2.06 (4s, 12H, $4CH_3CO$), 2.72 (s, 2H, CH_2), 2.98 (d, 2H, CH_2), 3.86 (s, 3H, OCH_3), 5.08 (m, 4H, H-6', 6'', H-5' and H-4'), 5.41 (d, 1H, H-3'), 5.68 (s, 1H, H-2'), 6.11 (d, $J_{1'-2'}$ = 10.06 Hz, 1H, H-1'), 7.08 (d, 2H, Ar—H), 7.38 (d, 2H, Ar—H); m/z 626 (Found: C, 59.6; H, 5.5; N, 4.7. $C_{31}H_{34}N_2SO_{10}$ requires C, 59.4; H, 5.4; N, 4.5%).

5c. mp 147°C, yield 69%. IR (KBr) 2215, 1754 cm^{-1}; m/z 610 (Found: C, 61.2; H, 5.5; N, 4.7. $C_{31}H_{34}N_2SO_9$ requires C, 61.0; H, 5.6; N, 4.6%).

5d. mp 127°C, yield 74%. IR (KBr) 2218, 1752 cm^{-1}; UV λ_{max} 311, 347 and 414 nm; ^1H NMR (DMSO-d_6) δ 1.58 (m, 4H, $2CH_2$), 2.32 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 1.92–2.08 (4s, 12H, $4CH_3CO$), 4.78–5.18 (m, 4H, H-6', 6'', H-5' and H-4'), 5.53 (t, 1H, H-3'), 5.85 (m, 1H, H-2'), 6.13 (d, $J_{1'-2'}$ = 10.14 Hz, 1H, H-1'), 7.31 (d, 2H, Ar—H), 7.54 (d, 2H, Ar—H); ^{13}C NMR (DMSO-d_6) δ 20.3, 20.8, 21.5 and 21.7 ($4CH_3$), 24.7, 26.1, 26.8 and 33.0 ($4CH_2$), 61.4 (C-6'), 66.3 (C-4'), 67.8 (C-2'), 71.0 (C-3'), 74.1 (C-5'), 81.8 (C-1'), 105.1 (C-3), 115.9 (CN), 127.9–134.0 (Ar-Carbons), 143.2 (C-5), 152.5 (C-4), 154.0 (C-6), 161.8 (C=S), 169.3, 169.4, 169.6 and 169.8 (4CO); m/z 630 (Found: C, 57.3; H, 5.1; N, 4.5. $C_{30}H_{31}ClN_2SO_9$ requires C, 57.1; H, 4.9; N, 4.4%).

5e. mp 174°C, yield 71%. IR (KBr) 2215, 1756 cm^{-1}; m/z 612 (Found: C, 59.0; H, 5.1; N, 4.6. $C_{30}H_{32}N_2SO_{10}$ requires C, 58.8; H, 5.2; N, 4.6%).

5f. mp 183°C, yield 70%. IR (KBr) 2216, 1750 cm^{-1}; m/z 626 (Found: C, 59.5; H, 5.6; N, 4.5. $C_{31}H_{34}N_2SO_{10}$ requires C, 59.4; H, 5.4; N, 4.5%).

5g. mp 189°C, yield 68%. IR (KBr) 2213, 1754 cm^{-1}; m/z 610 (Found: C, 60.8; H, 5.7; N, 4.7. $C_{31}H_{34}N_2SO_9$ requires C, 61.0; H, 5.6; N, 4.6%).

5h. mp 179°C, yield 73%. IR (KBr) 2214, 1751 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.73 (m, 4H, $2CH_2$), 1.90–2.10 (4s, 12H, $4CH_3CO$), 2.34 (t, 2H, CH_2), 2.96 (m, 2H, CH_2), 4.05 (m, 2H, H-6', 6''), 4.44 (t, 1H, H-5'), 5.32 (m, 3H, H-4', H-3' and H-2'), 6.08 (d, $J_{1'-2'}$ = 10.17 Hz, 1H, H-1'), 7.21–7.74 (m, 4H, Ar—H); m/z 630 (Found: C, 57.0; H, 5.0; N, 4.6. $C_{30}H_{31}ClN_2SO_9$ requires C, 57.1; H, 4.9; N, 4.4%).

3-Cyano-1-(β-D-gluco- and galactopyranosyl)condensed pyridine-2-thiones **9**

General procedure for nucleoside deacylation

Dry gaseous ammonia was passed through a solution of protected nucleosides **5** (0.5 g) in dry methanol (25 ml) at 0°C for about 0.5 hour, then the reaction mixture was stirred until judged complete by TLC (6–8 h). The resulting reaction mixture was evaporated under reduced pressure at 40°C giving a solid residue which was crystallized from methanol to afford colourless crystals.

9a. mp 218°C, yield 88%, IR (KBr) 3665–3140, 2215 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.01 (t, 2H, CH_2), 2.84 (t, 2H, CH_2), 2.97 (t, 2H, CH_2), 3.18–3.66 (m, 6H, H-6′, 6″, H-5′, H-4′, H-3′ and H-2′), 3.90 (s, 3H, OCH_3), 4.38 (d, 2H, 2′-OH and 3′-OH), 4.93 (d, 1H, 4′-OH), 5.14 (d, 1H, 6′-OH) 5.63 (d, $J_{1'-2'}$ = 9.89 Hz, 1H, H-1′), 7.13 (d, 2H, Ar—H), 7.46 (d, 2H, Ar—H); m/z 444 (Found: C, 59.7; H, 5.5; N, 6.5. $C_{22}H_{24}N_2SO_6$ requires C, 59.5; H, 5.4; N, 6.3%).

9b. mp 191°C, yield 86%. IR (KBr), 3700–3200, 2212 cm^{-1}; m/z 458 (Found: C, 60.5; H, 5.6; N, 6.3. $C_{23}H_{26}N_2SO_6$ requires C, 60.3; H, 5.7; N, 6.1%).

9c. mp 198°C, yield 87%. IR (KBr) 3650–3100, 2212 cm^{-1}, m/z 442 (Found: C, 62.7; H, 6.1; N, 6.5. $C_{23}H_{26}N_2SO_5$ requires C, 62.4; H, 5.9; N, 6.3%).

9d. mp 208°C, yield 85%. IR (KBr) 3600–3150, 2215 cm^{-1}; UV λ_{max} 313, 349 and 415 nm; ^1H NMR (DMSO-d_6) δ 1.84 (t, 2H, CH_2), 2.06 (t, 2H, CH_2), 3.04 (m, 4H, $2CH_2$), 3.21–3.78 (m, 6H, H-6′, 6″, H-5′, H-4′, H-3′ and H-2′), 4.43 (t, 2H, 2′-OH and 3′-OH), 4.91 (d, 1H, 4′-OH), 5.38 (t, 1H, 6′-OH), 5.67 (d, $J_{1'-2'}$ = 10.01 Hz, 1H, H-1′), 7.62 (m, 4H, Ar—H); ^{13}C NMR (DMSO-d_6) δ 21.8, 26.1, 27.2 and 33.0 ($4CH_2$), 60.6 (C-6′), 69.6 (C-4′), 71.7 (C-2′), 78.6 (C-3′), 81.6 (C-5′), 83.5 (C-1′), 104.5 (C-3), 115.0 (CN), 125.4–133.9 (Ar-carbons), 144.3 (C-5), 152.3 (C-4), 156.4 (C-6), 161.6 (C=S); m/z 462 (Found: C, 57.3; H, 5.2; N, 6.3. $C_{22}H_{23}ClN_2SO_5$ requires C, 57.1; H, 5.0; N, 6.1%).

9e. mp 229°C, yield 83%. IR (KBr) 3600–3180, 2212 cm^{-1}; m/z 444 (Found: C, 59.8; H, 5.3; N, 6.4. $C_{22}H_{24}N_2SO_6$ requires C, 59.5; H, 5.4; N, 6.3%).

9f. mp 198°C, yield 85%. IR (KBr) 3680–3200, 2213 cm^{-1}; m/z 458 (Found: C, 60.4; H, 5.9; N, 6.2. $C_{23}H_{26}N_2SO_6$ requires C, 60.3; H, 5.7; N, 6.1%).

9g. mp 209°C, yield 81%. IR (KBr) 3700–3190, 2211 cm^{-1}; m/z 442 (Found: C, 62.3; H, 6.1; N, 6.6. $C_{23}H_{26}N_2SO_5$ requires C, 62.4; H, 5.9; N, 6.3%).

9h. mp 201°C, yield 84%. IR (KBr) 3600–3160, 2216 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.65 (t, 2H, CH_2), 1.88 (t, 2H, CH_2), 2.36 (t, 2H, CH_2), 2.98 (t, 2H, CH_2), 3.18–3.67 (m, 6H, H-6′, 6″, H-5′, H-4′, H-3′ and H-2′), 4.51 (m, 2H, 2′-OH and 3′-OH), 4.96 (d, 1H, 4′-OH), 5.43 (d, 1H, 6′-OH), 5.61 (d, $J_{1'-2'}$ = 10.1 Hz, 1H, H-1′), 7.66 (m, 4H, Ar—H); m/z 462 (Found: C, 57.2; H, 4.9; N, 6.4. $C_{22}H_{23}ClN_2SO_5$ requires C, 57.1; H, 5.0; N, 6.1%).

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