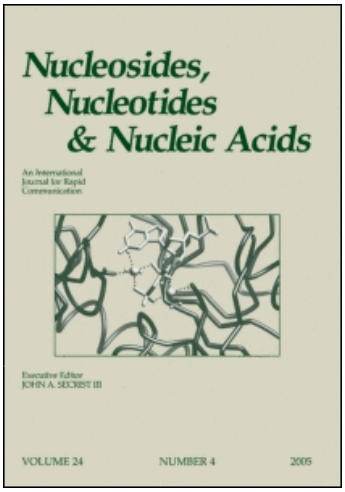

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A DIRECT ROUTE TO 2-(β-D-RIBOFURANOSYLTHIO)PYRIDINE GLYCOSIDES

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ABSTRACT

A novel synthesis of a new class of 2-(β-D-ribofuranosylthio)pyridine glycosides utilizing the reactions of substituted pyridine-2(1*H*)-thiones and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose as starting components is described.

Key Words: Pyridine thioglycosides; Pyridine-2(1*H*)-thiones; Coupling reactions; Biheterocyclic thioglycosides; Glycosides

Recently deazanucleoside analogues have been known to exhibit antitumour activity.[1] During our studies of nucleoside analogues with novel H-bonding patterns, a route for the synthesis of N-nucleosides bearing a substituted pyridine ring as the heterocyclic aglycone was desired.[2,3] Such a route could provide access to a variety of analogues of pyrimidine nucleosides with novel H-bonding patterns.[4,5] Such molecules might serve as components of an expanded genetic "alphabet" or display pharmaceutically useful antimetabolite activity.[6] We report here the results of an investigation into the

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utility of the reaction of our previously reported pyridine-2(1*H*)-thiones (**1a**–**c**)[7] with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**3**) for the synthesis of 2-ribofuranosylthiopyridine glycosides, compounds (**1a**–**c**) were prepared by the reaction of arylmethylidenecyanothioacetamides with acetylacetone in boiling ethanol containing catalytic amounts of piperidine. Compounds (**1a**–**c**) reacted with (**3**) in hexamethyldisilazane and ammonium sulfate in the presence of methylene chloride contaning a catalytic amount of trimethylsilyltrifluoro-methanesulfonate to give the corresponding thioribosides (**5a**–**c**). The structures of compounds (**5a**–**c**) were established and confirmed for the reaction products on the basis of their elemental analyses and spectral data (MS, IR, UV, ^{1}H NMR, ^{13}C NMR). The analytical data for (**5a**) revealed a molecular formula $C_{42}H_{34}N_2O_8S$ (m/z 726). ^{1}H NMR spectroscopy was used to confirm this structure for the product. Thus, ^{1}H NMR spectrum showed the anomeric proton as a dobulet at δ 6.65 with a spin-spin coupling constant ($J_{1'-2'} = 10.75$ Hz) corresponding to a trans orientation of H-1′ and H-2′ protons indicating the β-configuration. The ^{13}C NMR spectra were characterized by a signal at δ 85.5 corresponding to C-1′ of the β-D-ribofuranose. The IR spectrum of compound (**5a**) was characterized by the presence of benzoxy carbonyl groups at 1725 cm^{-1}. The formation of the *S*-ribosides (**5a**–**c**) was confirmed using ^{13}C NMR which revealed the absence of a signal at δ 178 ppm for the thione carbon[8] and the appearance of a signal at δ 161 for the C-2 carbon[9] which is of the same value observed for the corresponding methylthio derivatives (**2a**–**c**). Also, the UV spectra of compounds (**5a**–**c**) indicated that the reaction had led selectively to the formation of *S*-riboside derivatives since the corresponding *S*-methyl derivatives (**2a**–**c**) gave the same UV absoption maxima. Thus, the *S*-methyl derivative of compound (**2a**) shows three maxima at 216, 270 and 328 nm and its riboside derivative (**5a**) also exhibited three maximum absorption bands at 216, 267 and 333 nm. Compounds (**5a**–**c**) were deblocked through treatment with methanolic sodium methoxide and carbon dioxide to give the free ribosides (**6a**–**c**) after chromatographic purification. TLC of compounds (**6a**–**c**) showed that a single unique compound was produced in each case. The structures of these products were confirmed by their elemental analyses and spectral data. Thus, ^{1}H NMR spectroscopy was used to confirm this structure for the product. The ^{1}H NMR spectra revealed the presence of a doublet at δ 6.21 ($J_{1'-2'} =$ 10.75 Hz), indicating the presence of only the β-D-ribofuranoside. In summary, we have achieved a regioselective synthesis of interesting pyranosylthiopyridine glycosides by the reaction of substituted pyridinethiones with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose. These glycosides can be utilized as an excellent starting material for the synthesis of other carbohydrate derivatives and for biological evaluation studies.

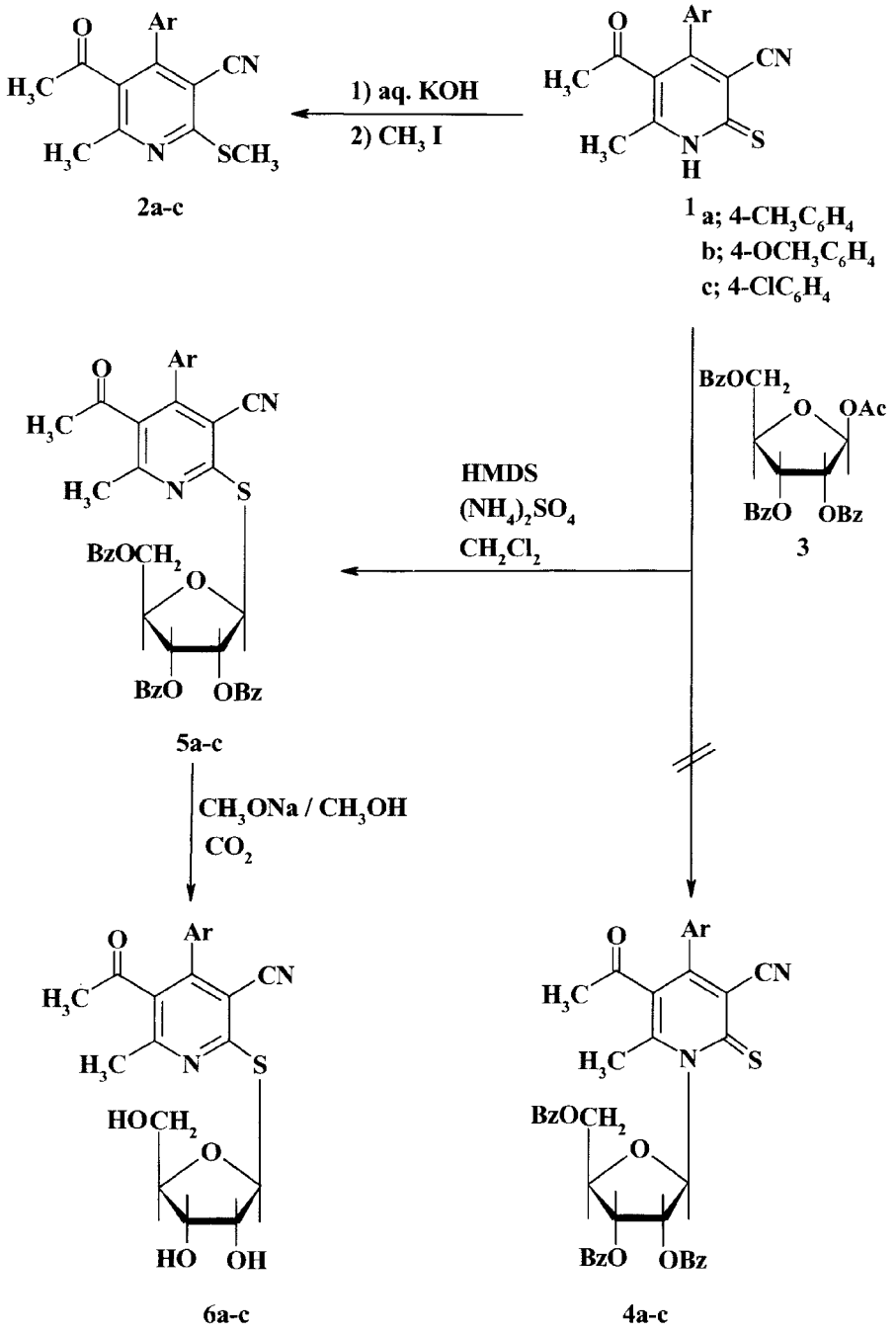

Chart 1.

EXPERIMENTAL

All evaporations were carried out under reduced pressure at 40°C. M.p.s are uncorrected. Aluminium sheets coated with silica gel F_{254} (Merck) were used for TLC. Detection was effected by viewing under a short-wavelength UV lamp. IR spectra were obtained (KBr disk) 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 solution in $CDCl_3$ or $(CD_3)_2SO$ with $SiMe_4$ as an 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.

5-Acetyl-3-cyano-6-methylpyridine-2(1*H*)-thiones (**1a**–**c**) were prepared following literature procedures.[7]

5-Acetyl-4-aryl-6-methyl-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylthio)pyridine-3-carbonitriles (5a–c)

General Procedures

A mixture of (**1a**–**c**) (0.01 mol) in hexamethyldisilazane (20 mL) and ammonium sulfate was heated at reflux for 12 h. The resulting clear solution was concentrated in vacuo under anhydrous conditions to yield silylated pyridinethione as colourless oil. To a solution of the silylated pyridinethione in dry methylene chloride (5 mL) were added a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**3**) (0.01 mol) in dry methylene chloride (5 mL) and trimethylsilyltrifluoromethanesulfonate (0.5 mL). The reaction mixture was heated at reflux for 2 h and quenched with saturated solution of anhydrous sodium carbonate Na_2CO_3 (10 mL). The organic layers were separated and the aqueous layer was extracted with methylene chloride (90 mL). The combined organic layer was washed with saturated anhydrous sodium carbonate and water and then dried with anhydrous sodium sulfate (Na_2SO_4). After filtration, the filtrate was concentrated and the residue was separated by silica gel chromatography (chloroform/methanol, 20:1). The products were crystallized from methanol.

(**5a**): brown; m.p. 175°C; yield (75%). UV: λ_{max} 216; 267; 333. IR: ν_{max}/cm^{-1}(KBr) 2221 (CN); 1725 (C=O). ^{1}H NMR: δ 1.60 (s, 3H, CH_3); 1.86 (s, 3H, CH_3); 2.41 (s, 3H, CH_3); 4.59 (m, 2H, H-5′); 4.78 (m, 1H, H-4′); 6.09 (m, 1H, H-3′); 6.16 (m, 1H, H-2′); 6.65 (d, $J_{1'-2'} = 10.75$ Hz, 1H, H-1′); 7.21–8.19 (m, 19H, C_6H_4, $3 \times C_6H_5$). MS: m/e = 726. Anal. Calcd. for ($C_{42}H_{34}N_2O_8S$): C, 69.42; H, 4.68; N, 3.85; S, 4.40. Found: C, 69.2; H, 5.0; N, 3.6; S, 4.7%. (**5b**): yellow; m.p. 108°C; yield (70%); UV: λ_{max} 210; 278; 319. IR: ν_{max}/cm^{-1} (KBr) 2220 (CN); 1720 (C=O). ^{1}H NMR: δ 1.99 (s, 3H, CH_3); 2.12 (s, 3H, CH_3); 3.99 (s, 3H, OCH_3); 4.49 (m, 2H, H-5′); 4.70 (m, 1H, H-4′); 6.00 (m, 1H, H-3′); 6.10 (m, 1H, H-2′); 6.59 (d, $J_{1'-2'} = 10.00$ Hz, 1H, H-1′); 7.10–8.10 (m, 19H, C_6H_4, $3 \times C_6H_5$). Anal. Calcd. for ($C_{42}H_{34}N_2O_9S$): C, 67.98; H, 4.37; N, 3.44; S, 4.37. Found: C,

67.7; H, 4.1; N, 3.8; S, 4.1%. (**5c**): yellow; m.p. 119°C; yield (65%). IR: ν_{max}/cm^{-1} (KBr) 2218 (CN); 1725 (C=O). UV: λ_{max} 219; 272; 315. ^{1}H NMR: δ 2.00 (s, 3H, CH_3); 2.48 (s, 3H, CH_3); 4.62 (m, 2H, H-5′); 4.88 (m, 1H, H-4′); 6.00 (m, 1H, H-3′); 6.18 (m, 1H, H-2′); 6.61 (d, $J_{1'-2'} = 9.85$ Hz, 1H, H-1′), 7.40–8.15 (m, 19H, C_6H_4, $3 \times C_6H_5$). ^{13}C NMR: δ 23.0 (CH_3), 26.0 (CH_3), 63.0 (C-5″), 66.2 (C-4′), 75.2 (C-2′), 79.8 (C-3′), 84.4 (C-1′), 105 (C-3′), 119 (CN), 128–135 (C_6H_5), 164.5–166 ($3 \times CO$). Anal. Calcd. for ($C_{41}H_{31}ClN_2O_8S$): C, 65.90; H, 4.15; N, 3.75; S, 4.28. Found : C, 65.6; H, 4.4; N, 3.5; S, 4.0%.

5-Acetyl-4-aryl-6-methyl-2-(β-D-ribofuoranosylthio)-pyridine-3-carbonitrile (6a–c)

General Procedures

Pyridinethione glycosides (**5a**–**c**) (0.01 mol) were stirred in 0.5 N $NaOCH_3$-CH_3OH (5 mL) at room temperature for 3 h and then neutrallized with CO_2 and evaporated to dryness. The products were isolated by silica gel chromatography (9:1 chloroform/methanol) and crystallized from methanol.

(**6a**): yellow; m.p. 260°C; yield (60%). IR: ν_{max}/cm^{-1} (KBr) 2215 (CN); 1710 (C=O). ^{1}H NMR: δ 1.29 (s, 3H, CH_3); 1.92 (s, 3H, CH_3); 2.39 (s, 3H, CH_3); 3.39 (m, 2H, H-5′); 3.85–4.29 (m, 3H, 4′,3′,2′-H); 4.90 (m, 2H, 2′,3′-OH); 5.31 (d, 1H, 5′-OH); 6.21 (d, $J_{1'-2'} = 9.70$ Hz, 1H, H-1′); 7.29–7.75 (m, 4H, C_6H_4). Anal. Calcd. for ($C_{21}H_{22}N_2O_5S$): C, 60.86; H, 5.31; N, 6.76; S, 7.72. Found: C, 60.8; H, 5.0; N, 7.0; S, 7.5%. (**6b**): White; m.p. 192°C ; yield (60%). IR: ν_{max}/cm^{-1} (KBr) 2222 (CN); 1700 (C=O). ^{1}H NMR: δ 1.99 (s, 3H, CH_3); 2.42 (s, 3H, CH_3); 3.42 (m, 2H, H-5′); 3.78 (s, 3H, OCH_3); 3.88–4.32 (m, 3H, 4′,3′,2′-H); 4.95 (m, 2H, 2′,3′-OH); 5.35 (d, 1H, 5′-OH); 6.13 (d, $J_{1'-2'} = 9.90$ Hz, 1H, H-1′); 7.09–7.90 (m, 4H, C_6H_4). Anal. Calcd. for ($C_{21}H_{22}N_2O_6S$): C, 58.60; H, 5.11; N, 6.51; S, 7.44. Found: C, 58.3; H, 4.9; N, 6.2; S, 7.8%. (**6c**): yellow; m.p. 218°C; yield (60%). IR: ν_{max}/cm^{-1} (KBr) 2222 (CN); 1710 (C=O). ^{1}H NMR: δ 1.97 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 3.50 (m, 2H, H-5′); 3.88–4.30 (m, 3H, 4′,3′,2′-H); 4.94 (m, 2H, 2′,3′-OH); 5.29 (d, 1H, 5′-OH); 6.47 (d, $J_{1'-2'} = 9.96$ Hz, 1H, H-1′); 7.00–7.70 (m, 4H, C_6H_4). Anal. Calcd. for ($C_{20}H_{19}ClN_2O_5S$): C, 55.25; H, 4.37; N, 6.44; S, 7.36. Found: C, 54.9; H, 4.1; N, 6.8; S, 7.0%.

5–Acetyl–4–aryl–6-methyl–2-(methylthio)pyridine–3-carbonitrile (2a–c)

General Procedures

To a solution of (**1a**–**c**) (0.01 mol) in methylene chloride was added potassium hydroxide [0.56 g. (0.01 mol)], the reaction mixture was stirred at room temperature (30 min to 3 h). A solution of methyl iodide (0.01 mol) was added and the reaction mixture was stirred for 3 h. The mixture was left to cool at room temperature and the resultant precipitate was filtered off and crystallized from the appropriate solvent.

(**2a**): white, from EtOH; m.p. $>300°C$; yield (70%). UV: λ_{max} 216; 270; 328. IR: ν_{max}/cm^{-1}(KBr) 2221 (CN); 1718 (C=O). ^1H NMR: δ 1.90 (s, 3H, CH_3); 2.09 (s, 3H, CH_3); 2.41 (s, 3H, CH_3); 2.62 (s, 3H, SCH_3); 7.12–7.80 (m, 4H, C_6H_4). Anal. Calcd. for ($C_{17}H_{16}N_2OS$): C, 68.94; H, 5.40; N, 9.45; S, 10.81. Found: C, 68.6; H, 5.2; N, 9.5; S, 10.5%. (**2b**): white, from EtOH; m.p. $>300°C$; yield (70%). UV: λ_{max} 220; 275; 327. IR: ν_{max}/cm^{-1} (KBr) 2221 (CN); 1710 (C=O). ^1H NMR: δ 2.10 (s, 3H, CH_3); 2.39 (s, 3H, CH_3); 2.58 (s, 3H, SCH_3); 3.90 (s, 3H, OCH_3); 7.05–7.72 (m, 4H, C_6H_4). Anal. Calcd for ($C_{17}H_{16}N_2O_2S$): C, 65.38; H, 5.12; N, 8.9; S, 10.25. Found : C, 65.1; H, 5.2; N, 8.6; S, 9.9%. (**2c**): white, from EtOH; m.p. $>300°C$; yield (65%). UV: λ_{max} 211; 259; 320. IR: ν_{max}/cm^{-1} (KBr) 2221 (CN); 1700 (C=O). ^1H NMR: δ 2.11 (s, 3H, CH_3); 2.45 (s, 3H, CH_3); 2.55 (s, 3H, SCH_3); 6.98–7.70 (m, 4H, C_6H_4). Anal. Calcd. for ($C_{16}H_{14}ClN_2OS$): C, 60.47; H, 4.40; N, 8.81; S, 10.07. Found: C, 60.5; H, 4.5; N, 9.1; S, 10.1%.

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