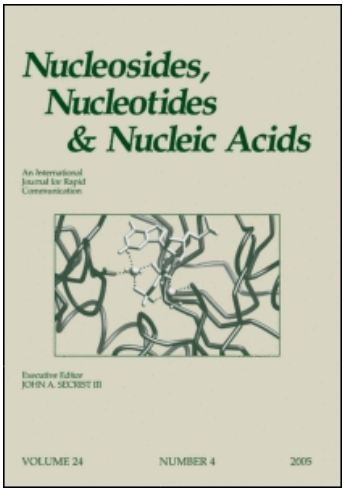

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Synthesis of Some Pyridine Ribosides and Their Biological Activity

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SYNTHESIS OF SOME PYRIDINE RIBOSIDES AND THEIR BIOLOGICAL ACTIVITY

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Abstract: A synthesis of 1-(β-D-ribofuranosyl)-pyridin-2-thiones *via* reaction of 3-cyanopyridin-2(1*H*)-thiones with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide under basic conditions, followed by hydrolysis with methanolic ammonia is reported .

A number of dideoxy- and deaza-pyrimidine nucleosides have been synthesized as potential antiviral agents.[1-3] Among them, 3`-azido-3`-deoxythymidine (AZT), 2`,3`-dideoxyinosine (DDI) and 2`,3`-dideoxycytidine (DDC) have been introduced in clinical use for the treatment of HIV infection diseases. As a part of our program directed toward the synthesis of nucleosides and nucleotides[4-7] with considerable biological and medicinal activity, we report here the synthesis of some 3-deazapyrimidine ribosides. Thus, it has been reported that the reaction of α-cyanothioacetamide with chalcones in boiling ethanol containing a catalytic amount of piperidine gave 4,6-disubstituted-3-cyanopyridin-2(1*H*)-thiones **1**.[8-9] Compounds **1** reacted with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide **3** in the presence of potassium hydroxide in acetone-water mixture to give the corresponding *N*-ribosides **4** (method A). Compounds **4** could also be obtained by the reaction of **1** with silver nitrate in aqueous

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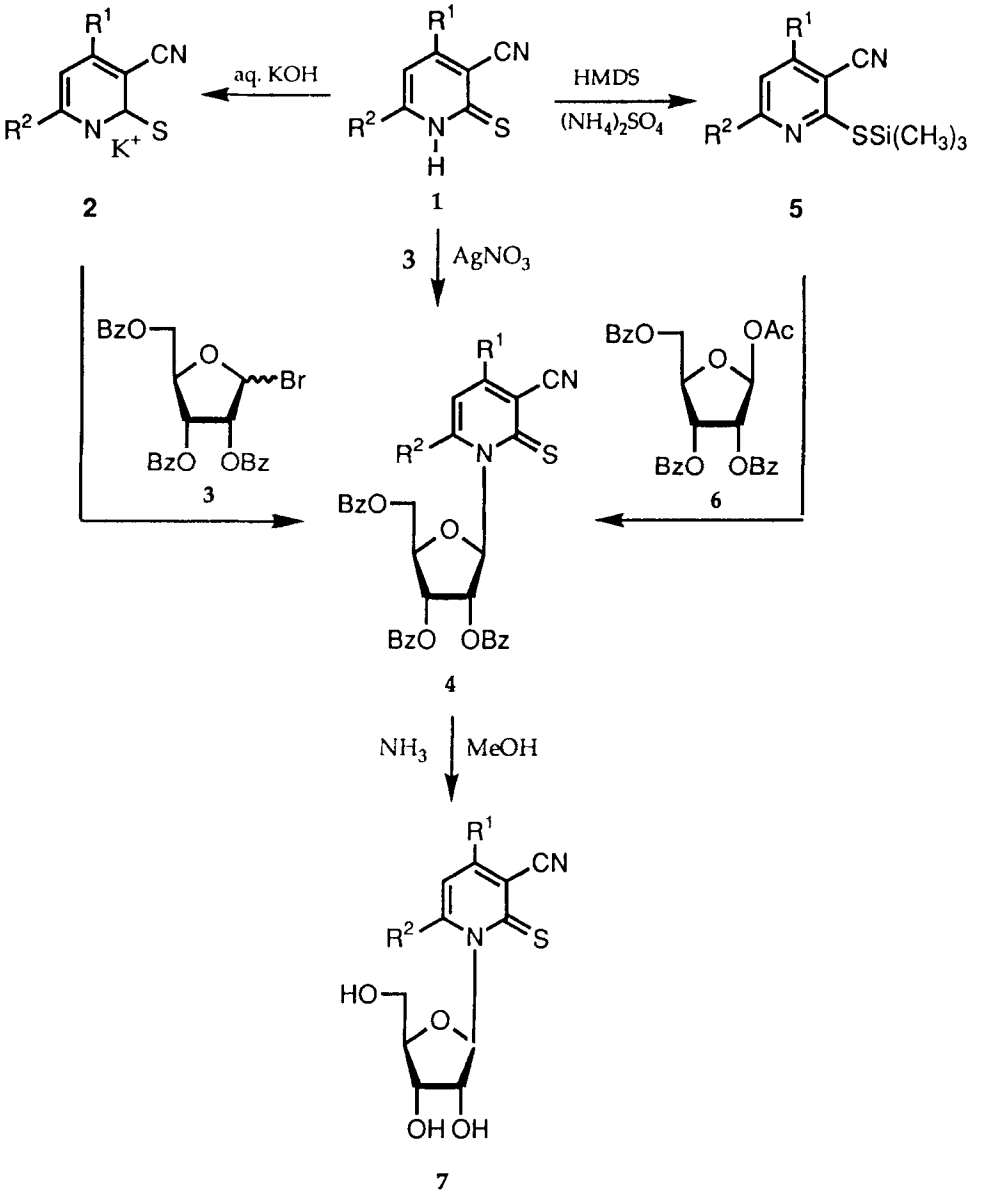
acetone, followed by coupling of the resultant silver salt with **3** at room temperature (method B). Although the coupling of **1** with the ribosyl bromide **3** could also give the corresponding thioribosides, the formation of **4** was proved chemically. Reaction of **1** with hexamethyldisilazane (HMDS) in the presence of ammonium sulphate gave the corresponding 2-trimethylsilylthiopyridines **5**, which were subsequently treated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **6** in the presence of $SnCl_4$ according to the method of Vorbruggen et al.[10-12] to afford the corresponding *N*-ribosides **4** (method C). The structures of the ribosides **4** were identified using elemental analysis and spectral data . The ^{1}H-NMR spectrum of **4b** showed a doublet at δ 5.90 (*J* 8.06 Hz) assigned to the anomeric proton of the ribose moiety, which is strongly indicative of the β-configuration. On the other hand, the methyl protons of the aglycone resonate at δ 2.28 , in addition to the pyridine H-5 singlet at δ 7.48 . The UV spectrum of **4b** proved that the reaction had led selectively to the formation of *N*-ribosides. Thus whereas the *S*-methyl derivative of **1b** showed one maximum at 278 nm, its *N*-riboside **4b** exhibited two maxima at 282 and 330 nm. The removal of the benzoyl groups was accomplished by the treatment of **4** with methanolic ammonia to furnish 1-(β-D-ribofuranosyl)-pyridin-2-thiones **7**. The ^{1}H-NMR spectrum of **7c** showed the anomeric proton as a doublet at δ 6.08 (*J* 7.86 Hz), indicating the presence of only the β-D-ribofuranose. The ^{13}C-NMR spectrum of **7c** was characterized by a signal at δ 91.3 corresponding to the C-1` atom of β-D-ribofuranose. Another four signals at δ 60.6, 68.7, 74.5, and 85.2 were assigned to C-5`, C-3`, C-2`, and C-4` of the ribose moiety, respectively. The ribosides obtained through these results constitute an important and versatile class of compounds for potential application in the synthesis of other carbohydrate derivatives.

The compounds $\mathbf{4_{a-d}}$ and $\mathbf{7_{a-d}}$ were evaluated for their inhibitory effect on Human Immunodeficiency Virus type 1 (HIV-1) induced cytopathogenicity in human T-Lymphocyte (MT-4) cells. None of the compounds tested proved inhibitory to the cytopathogenicity of HIV-1 at a concentration of 100 μg/mL. None of the compounds showed cytotoxicity at this concentration. They were also devoid of any activity against different types of tumor virus.

Experimental

All evaporations were carried out under reduced pressure at 40 °C. Melting points are uncorrected. TLC was carried out on aluminum sheet silica gel 60 F_{254} (Merck) detected by short UV light. IR Spectra were obtained (KBr) using a Pye Unicam spectra 1000. ^{1}H-NMR and ^{13}C-NMR spectra were measured on a Varian Gemini 200 MHz spectrometer in $CDCl_3$ or DMSO-d_6 using $SiMe_4$ as internal standard. Analytical data obtained from the Microanalytical Center at Cairo University.



	R^1	R^2
1, 4, 7 a	C_6H_5	4-ClC_6H_4
b	C_6H_5	4-$CH_3C_6H_4$
c	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$
d	2-Furyl	4-$CH_3C_6H_4$

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-3-cyano-4,6-disubstituted-pyridin-2-thiones 4

Method A: To a solution of 3-cyano-4,6-disubstituted-pyridin-2(1*H*) thiones **1** (0.01mol) in aqueous potassium hydroxide [0.56 g (0.01mol) in 6 mL of distilled water], a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide **3** (0.011 mol) in acetone (30 mL) was added The reaction mixture was stirred at room temperature until completion (TLC, 4 to 6 h), using chloroform: petroleum ether 9:1 *v/v* (Rf, 0.66-0.68), then evaporated under reduced pressure at 40 °C and the residue was washed with distilled water to remove the formed potassium bromide. The resulting product was dried and crystallized from ethanol to give the products **4a-d** in 62-65 % yield.

Method B: To a solution of 3-cyano-4,6-disubstituted-pyridin-2(1*H*) thiones **1** (0.01 mol) in aqueous silver nitrate (0.01 mol in 6 mL of distilled water) and 10 mL acetone, a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide **3** (0.011 mol) in acetone (20 mL) was added. The reaction mixture was stirred at room temperature until judged complete by TLC (20 to 24 h). The reaction mixture was filtered to remove unreacted base, and the filtrate was evaporated under reduced pressure at 40 °C . The solid product was dried and crystallized from ethanol to give the products **4a-d** in 40-43 % yield.

Method C: 3-Cyano-4,6-disubstituted-pyridin-2(1*H*)-thione **1** (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 **5** as a colorless oil. To a solution of silylated base in dry acetonitrile (30 mL) was added a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **6** (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 (6 to 8 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 product which was crystallized from ethanol to give the products **4a-d** in 28-32 % yield.

4a: Yield 62%, mp 115 °C; IR 2212(CN), 1728(CO) cm^{-1}; m/z 766.5 (Found: C,68.8; H,3.9; N,3.9. $C_{44}H_{31}ClN_2SO_7$ requires C,68.9; H,4.0; N,3.9%).

4b: Yield 64%, mp 126 °C; IR 2215(CN), 1726(CO) cm^{-1}; ^{1}H-NMR δ 2.28 (s,3H,CH_3), 4.55(m,2H,2H-5`), 4.84(m,1H,H-4`), 5.71(d,1H,H-3`), 5.79(d,1H,H-2`), 5.90(d,$J_{1'-2'}$= 8.06 Hz,1H,H-1`), 7.35(m,3H,Ar-H), 7.48(s,1H, pyridine H-5), 7.58-7.72 (m,15H,Ar-H), 7.85 (d, 2H,Ar-H), 7.94(d,2H,Ar-H), 8.02(d,2H,Ar-H); m/z 746(Found: C, 72.2; H,4.5; N,3.7. $C_{45}H_{34}N_2SO_7$ requires C,72.4; H,4.6; N,3.8%).

4c: Yield 65%, mp 175 °C; IR 2211(CN), 1725(CO) cm^{-1}; m/z 776(Found: C,71.0; H,4.5; N,3.7. $C_{46}H_{36}N_2SO_8$ requires C,71.1; H,4.6; N,3.6%).

4d: Yield 64%, mp 130 °C; IR 2218(CN), 1730(CO) cm^{-1}; ^{1}H-NMR δ 2.32 (s,3H,CH_3), 4.50(m,2H,2H-5`), 4.86(m,1H,H-4`), 5.71(d,1H,H-3`), 5.79(d,1H,H-2`), 5.98(d,$J_{1'-2'}$= 7.90 Hz,1H,H-1`), 6.86(m,1H, furan H-4), 7.18(d,1H, furan H-3), 7.35(d,2H,Ar-H), 7.48(s,1H, pyridine H-5), 7.68-7.80(m,15H,Ar-H), 8.12(m,1H, furan H-5 and 2H,Ar-H); m/z 736(Found: C,70.0; H,4.4; N,3.7. $C_{43}H_{32}N_2SO_8$ requires C,70.1; H,4.3; N, 3.8%).

1-(β-D-Ribofuranosyl)-3-cyano-4,6-disubstituted-pyridin-2-thiones 7.

General procedure .

Dry gaseous ammonia was passed through a solution of protected nucleoside **4** (0.5 g) in dry methanol (20 mL) at 0 °C for 0.5 h. The reaction mixture was stirred till complete as shown by TLC (36-40 h) using $CHCl_3$: MeOH 9:1 *v:v* (Rf, 0.68-0.70). The resulting mixture was then concentrated under reduced pressure to afford a solid residue that was crystallized from methanol to furnish colorless crystals.

7a: Yield 76%, mp 240 °C; IR 3660-3428(OH), 2212(CN)cm^{-1}; m/z 454.5 (Found: C, 60.9; H,4.0; N,6.1. $C_{23}H_{19}ClN_2SO_4$ requires C,60.7; H,4.2; N,6.2%).

7b: Yield 74%, mp 215 °C; IR 3660-3430(OH), 2212(CN) cm^{-1}; ^{1}H-NMR δ 2.30(s,3H,CH_3), 3.20-3.78(m,5H,2H-5`,H-4`,H-3`, and H-2`), 4.04(m,1H,3`-OH), 5.20(d,1H,5`-OH), 5.64(t, 1H,2`-OH), 5.96(d,$J_{1'-2'}$ = 7.78 Hz,1H,H-1`), 7.36(d,2H,Ar-H), 7.58(s,1H, pyridine H-5), 7.72(m,5H,Ar-H), 7.96(d,2H,Ar-H); m/z 434 (Found: C,66.5; H,5.3; N,6.6. $C_{24}H_{22}N_2SO_4$ requires C,66.4; H,5.1; N, 6.5%).

7c: Yield 77%, mp 245 °C; IR 3668-3438(OH), 2218(CN)cm^{-1}; ^{1}H-NMR δ 2.36(s,3H,CH_3), 3.28-3.84(m,5H,2H-5`,H-4`,H-3` and H-2`), 3.88(s,3H,OCH_3), 4.48(m,1H,3`-OH), 4.84(m, 1H,5`-OH), 5.66(t,1H,2`-OH), 6.08(d,$J_{1'-2'}$ = 7.86 Hz,1H,H-1`), 7.18(d,2H,Ar-H), 7.36(d, 2H,Ar-H), 7.62(s,1H, pyridine H-5), 7.78(d,2H,Ar-H), 8.05(d,2H,Ar-H); ^{13}C-NMR δ 23.7(CH_3), 55.6(OCH_3), 60.6(C5`), 68.7(C3`), 74.5(C2`), 85.2(C4`), 91.3(C1`), 110.2(C3), 115.4(CN), 126.7-140.3(Ar-C), 145.8(C5), 147.2(C4), 157.1(C6), 171.1(C2); m/z 464 (Found: C,64.6; H,5.1; N,5.9. $C_{25}H_{24}N_2SO_5$ requires C,64.7; H,5.2; N,6.0%).

7d: Yield 75%, mp 230 °C; IR 3662-3430(OH), 2210(CN) cm^{-1}; m/z 424 (Found: C,62.2; H,4.8; N,6.8. $C_{22}H_{20}N_2SO_5$ requires C,62.3; H,4.7; N,6.6%).

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