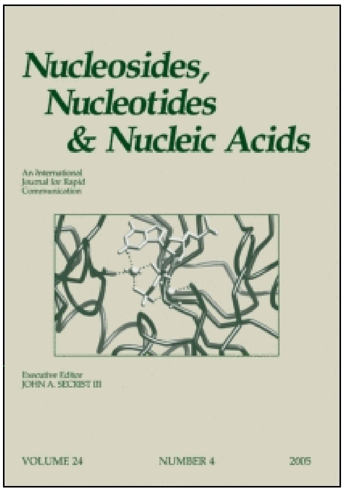

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Nucleic Acid Related Compounds: A Convenient Synthesis of 3-Deazauridine Analogues

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NUCLEIC ACID RELATED COMPOUNDS: A CONVENIENT SYNTHESIS OF 3-DEAZAURIDINE ANALOGUES.

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Abstract: A novel synthesis of 3-deazapyrimidine glycosides utilizing pyridine-2(1*H*)-ones or their sodium salts and α-halomonosugars namely D-glucose or D-galactose as starting components is described.

Important biological activity of deaza analogues of pyrimidine and its metabolites is anticipated from our increasing knowledge of pyrimidine nucleotide metabolism in microbial and mammalian system[1-2]. 3-Deazauridine inhibited the growth of microorganisms and of tumor cells in culture and was active against L1210 leukemia cells *in vivo*[3]. Also, 3-deazauridine is a potent inhibitor of CTP synthetase (phosphocholine cytidyltransferase). Deaza UTP is a competitive inhibitor of this enzyme with recpect to UTP. Deaza UTP 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 inhibtion of both RNA and DNA synthesis.[4,5]. As a part of our program directed for development of new, simple and efficient procedure for the synthesis of nucleosides and nucleoside bases[6-10], we report here the results of our investigation into the utility of the reaction of our previously reported pyridine-2(1*H*)-ones **7** or their sodium salts **3**[11] with α-halomonosugars for the synthesis of 3-deazapyrimidine glycosides. Compounds **7** can be prepared by the reaction of arylhydrazones **2** of both acetylacetone and benzoylacetone with cyanoacetamide **1** in boiling ethanolic sodium ethoxide. Compounds **3** reacted with 2, 3, 4, 6-tetra-*O*-acetyl-α-D-gluco- and D-galactopyranosyl bromides **4** in acetone to give the corresponding *N*-glucosides **5a-h** and *N*-galactosides **5i-l.**

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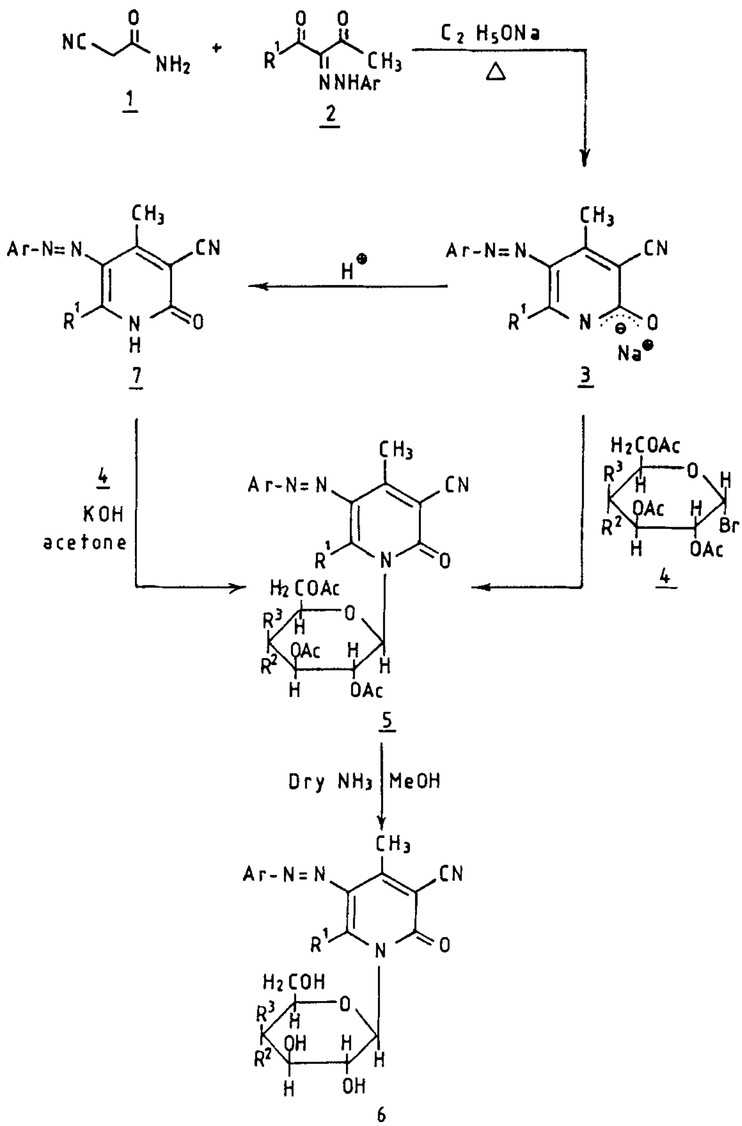

		Ar	R^1	R^2	R^3
5	**a,**	C_6H_5	CH_3	OAc	H
	b,	$4\text{-}ClC_6H_4$	CH_3	OAc	H
	c,	$4\text{-}CH_3C_6H_4$	CH_3	OAc	H
	d,	$4\text{-}CH_3OC_6H_4$	CH_3	OAc	H
	e,	C_6H_5	C_6H_5	OAc	H
	f,	$4\text{-}ClC_6H_4$	C_6H_5	OAc	H
	g,	$4\text{-}CH_3C_6H_4$	C_6H_5	OAc	H
	h,	$4\text{-}CH_3OC_6H_4$	C_6H_5	OAc	H

	i,	C_6H_5	CH_3	H	OAc
	j,	$4\text{-}ClC_6H_4$	CH_3	H	OAc
	k,	$4\text{-}CH_3C_6H_4$	CH_3	H	OAc
	l,	$4\text{-}CH_3OC_6H_4$	CH_3	H	OAc
6	a,	C_6H_5	CH_3	OH	H
	b,	$4\text{-}ClC_6H_4$	CH_3	OH	H
	c,	$4\text{-}CH_3C_6H_4$	CH_3	OH	H
	d,	$4\text{-}CH_3OC_6H_4$	CH_3	OH	H
	e,	C_6H_5	C_6H_5	OH	H
	f,	$4\text{-}ClC_6H_4$	C_6H_5	OH	H
	g,	$4\text{-}CH_3C_6H_4$	C_6H_5	OH	H
	h,	$4\text{-}CH_3OC_6H_4$	C_6H_5	OH	H
	i,	C_6H_5	CH_3	H	OH
	j,	$4\text{-}ClC_6H_4$	CH_3	H	OH
	k,	$4\text{-}CH_3C_6H_4$	CH_3	H	OH
	l,	$4\text{-}CH_3OC_6H_4$	CH_3	H	OH

Compounds **5a-l** could also be obtained in good yield by the reaction of 2 (1*H*)-pyridineones **7** with **4** in the presence of aqueous potassium hydroxide. The chemical structure of the prepared compounds **5** were elucidated with elemental analyses and by studying IR, ^1H NMR, ^{13}C NMR as well as mass spectra. Compound **5i** serves as an example for the series. The analytical data for compound **5i** revealed a molecular formula $C_{28}H_{30}N_4O_{10}$ (m/z 582). The ^1H NMR spectrum showed the anomeric proton as a doublet at δ 6.43 ppm with spin-spin coupling constant equal to 9.4 Hz which corresponds to the diaxial orientation of H-1' and H-2' protons indicating the presence of only β-configuration. The other six protons of the galactopyranosyl ring resonates at δ 4.09-5.51 ppm region. The remaining four acetoxy groups appear as four singlets at δ 1.96, 1.98, 1.99 and 2.18 ppm. On the other hand, the two methyl groups of algycone resonate at δ 2.59 and 2.64 ppm (cf. Table 2). The ^{13}C NMR spectrum was characterized by a signal at δ 93.8 ppm corresponding to C-1' atom of the β-D-galactopyranose. Four signals appear at δ 168.8, 169.3, 169.6 and 169.8 ppm due to the four acetoxy carbonyl carbon atoms of the sugar moiety, with four additional signals at δ 20.2, 20.3, 22.5 and 26.2 ppm attributed to the acetoxy methyl carbons. The two methyl carbon atoms of aglycone appear at δ 17.2 and 19.6 ppm with another five signals at δ 61.1, 67.2, 67.9, 69.9 and 70.9 ppm assigned as C-6', C-4', C-2', C-3' and C-5' of galactose, respectively. On the other hand, the carbonyl carbon atom of pyridone appears at δ 159.3 ppm with the nitrile carbon atom at δ 116.1 ppm. The preparation of the crystalline 1-(β-D-glycopyranosyl)-3-cyanopyridine-2-one derivatives **6a-l** was achieved by removing the blocking acetyl groups with methanolic ammonia at 0^oC. The structure of compounds **6** were established

Table 1 Physical and analytical data for compounds **5a-l** and **6a-l**.

Compd.	Mp	Yield %		Mol. formula	Found/calcd. (%)			
	°C	(a)	(b)		C	H	N	m/z
5a	173	60	53	$C_{28}H_{30}N_4O_{10}$	57.4	5.5	9.3	582
				(582)	57.7	5.2	9.6	
5b	139	64	55	$C_{28}H_{29}N_4ClO_{10}$	54.2	4.9	9.3	616
				(616.5)	54.5	4.7	9.1	
5c	136	63	54	$C_{29}H_{32}N_4O_{10}$	58.6	5.5	9.6	596
				(596)	58.4	5.4	9.4	
5d	187	62	50	$C_{29}H_{32}N_4O_{11}$	56.7	5.4	9.4	612
				(612)	56.9	5.2	9.2	
5e	142	67	56	$C_{33}H_{32}N_4O_{10}$	61.3	4.8	8.5	644
				(644)	61.5	5.0	8.7	
5f	208	66	55	$C_{33}H_{31}N_4ClO_{10}$	58.7	4.8	8.5	
				(678.5)	58.4	4.6	8.3	
5g	198	68	57	$C_{34}H_{34}N_4O_{10}$	62.3	5.4	8.8	658
				(658)	62.0	5.2	8.5	
5h	136	65	53	$C_{34}H_{34}N_4O_{11}$	60.3	5.1	8.1	674
				(674)	60.5	5.0	8.3	
5i	181	61	54	$C_{28}H_{30}N_4O_{10}$	57.9	5.4	9.8	582
				(582)	57.7	5.2	9.6	
5j	201	60	51	$C_{28}H_{29}N_4ClO_{10}$	54.7	4.5	9.4	616
				(616.5)	54.5	4.7	9.1	
5k	203	62	53	$C_{29}H_{32}N_4O_{10}$	58.1	5.6	9.2	
				(596)	58.4	5.4	9.4	
5l	193	64	52	$C_{29}H_{32}N_4O_{11}$	57.1	5.3	9.1	612
				(612)	56.9	5.2	9.2	

on the basis of elemental analyses and spectral data (MS, IR, ^1H NMR, ^{13}C NMR). Thus, the analytical data for **6e** revealed a molecular formula $C_{25}H_{24}N_4O_6$ (m/z 476). The ^1H NMR spectra showed the anomeric proton as a doublet at δ 6.04 ppm (J_{1-2} = 9.6 Hz) indicating the presence of only the β-configuration. The other six protons of the glucose ring appear as a multiplet at δ 3.35 - 3.81 ppm, while the four hydroxyl groups resonates at δ 4.56, 4.94 and 5.56 ppm (exchangeable by D_2O). The ^{13}C NMR spectra was characterized by a signal at δ 96.8 ppm corresponding to the C-1⁻ atom ofβ-D-glucopyranose. Another five signals at δ 61.4, 69.6, 72.7, 76.9 and 78.0 ppm were assigned as C-6⁻, C-4⁻, C-2⁻, C-3⁻ and C-5⁻ of the glucose moiety,

Table 1 (Continued)

6a	221	84	$C_{20}H_{22}N_4O_6$	58.3	5.5	13.4	414
			(414)	58.0	5.3	13.5	
6b	283	88	$C_{20}H_{21}N_4ClO_6$	53.8	4.6	12.8	
			(448.5)	53.5	4.7	12.5	
6c	285	89	$C_{21}H_{24}N_4O_6$	58.7	5.7	13.3	428
			(428)	58.9	5.6	13.1	
6d	271	85	$C_{21}H_{24}N_4O_7$	56.9	5.5	12.5	444
			(444)	56.8	5.4	12.6	
6e	255	90	$C_{25}H_{24}N_4O_6$	63.2	4.9	11.6	476
			(476)	63.0	5.0	11.8	
6f	265	90	$C_{25}H_{23}N_4ClO_6$	58.5	4.6	11.1	510
			(510.5)	58.8	4.5	11.0	
6g	241	89	$C_{26}H_{26}N_4O_6$	63.5	5.4	11.5	
			(490)	63.7	5.3	11.4	
6h	219	87	$C_{26}H_{26}N_4O_6$	61.8	5.3	11.3	506
			(506)	61.7	5.1	11.1	
6i	213	88	$C_{20}H_{22}N_4O_6$	58.2	5.1	13.7	414
			(414)	58.0	5.3	13.5	
6j	280	86	$C_{20}H_{21}N_4ClO_6$	53.6	4.9	12.7	448
			(448.5)	53.5	4.7	12.5	
6k	253	87	$C_{21}H_{24}N_4O_6$	59.2	5.8	13.3	428
			(428)	58.9	5.6	13.1	
6l	274	89	$C_{21}H_{24}N_4O_7$	56.6	5.5	12.8	444
			(444)	56.8	5.4	12.6	

respectively. The carbonyl carbon atom of the pyridone appears at δ 159.6 ppm with the nitrile carbon atom at δ 115.3 ppm.

In summary, we have achieved a regiospecific synthesis of interesting 3-deazapyrimidine nucleosides by the reaction of pyridine-2(1*H*)-ones or their sodium salts with α-halomonosugars. 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. Melting points are uncorrected. TLC aluminium 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

Table 2 Spectral data for selected compounds listed in Table 1.

Compd.	IR(KBr)/cm^{-1}	^{1}H NMR (DMSO) δ/ppm
5a	2220 (CN), 1754 (CO ester), 1635 (CO pyridone)	1.94-2.12 (4s, 12H, 4 CH_3CO), 2.54 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 4.15 (m, 2H, H-6',6" and 1H, H-5'), 5.18 (m, 2H, H-4' and H-3'), 5.55 (t, J=8.7 Hz, 1H, H-2'), 6.34 (d, J_{1-2}=9.6 Hz, 1H, H-1'), 7.65 (m, 3H, Ar-H), 7.88 (m, 2H, Ar-H)
5b	2224 (CN), 1755 (CO ester), 1640 (CO pyridone)	1.92-2.16 (4s, 12H, 4 CH_3CO), 2.55 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 4.18 (m, 2H, H-6',6" and 1H, H-5'), 5.26 (m, 3H, H-4', H-3' and H-2'), 6.18 (d, J_{1-2}=9.4 Hz, 1H, H-1'), 7.74 (m, 4H, Ar-H)
5c	2224 (CN), 1757 (CO ester), 1640 (CO pyridone)	1.90-2.20 (4s, 12H, 4 CH_3CO), 2.35 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 4.19 (m, 2H, H-6',6" and 1H, H-5'), 5.13 (m, 2H, H-4' and H-3'), 5.52 (m, 1H, H-2'), 6.24 (d, J_{1-2}=9.8 Hz, 1H, H-1'), 7.45 (d, 2H, Ar-H), 7.81 (d, 2H, Ar-H).
5d	2226 (CN), 1758 (CO ester), 1642 (CO pyridone)	1.92-2.15 (4s, 12H, 4 CH_3CO), 2.55 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 4.06 (m, 2H, H-6',6" and 1H, H-5'), 5.12 (m, 2H, H-4' and H-3'), 5.50 (m, 1H, H-2'), 6.38 (d, J_{1-2} = 9.0 Hz, 1H, H-1'), 7.15 (d, 2H, Ar-H), 7.91 (d, 2H, Ar-H)
5e	2228 (CN), 1756 (CO ester), 1642 (CO pyridone)	1.88-2.16 (4s, 12H, 4 CH_3CO), 2.64 (s, 3H, CH_3), 4.08 (m, 2H, H-6',6" and 1H, H-5'), 5.23 (m, 2H, H-4' and H-3'), 5.64 (m, 1H, H-2'), 6.41 (d, J_{1-2} = 9.3 Hz, 1H, H-1'), 7.56 (m, 10H, Ar-H)
5f	2224 (CN), 1752 (CO ester), 1642 (CO pyridone)	1.92-2.14 (4s, 12H, 4 CH_3CO), 2.60 (s, 3H, CH_3), 4.08 (m, 2H, H-6', 6" and 1H, H-5'), 5.20 (m, 3H, H-4', H-3' and H-2'), 6.34 (d, J_{1-2} = 8.9 Hz, 1H, H-1'), 7.46 (m, 9H, Ar-H).
5g	2222 (CN), 1750 (CO ester), 1645 (CO pyridone)	1.90-2.15 (4s, 12H, 4 CH_3CO), 2.36 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.13 (m, 2H, H-6', 6" and 1H, H-5'), 5.26 (m, 3H, H-4', H-3' and H-2'), 6.48 (d, J_{1-2} = 8.7 Hz, 1H, H-1'), 7.35 (m, 9H, Ar-H).
5h	2223 (CN), 1752 (CO ester) 1640 (CO pyridone)	1.81-2.12 (4s, 12H, 4 CH_3CO), 2.61 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.25 (m, 2H, H-6', 6" and 1H, H-5'), 5.18 (m, 2H, H-4' and H-3'), 5.58 (m, 1H, H-2'), 6.45 (d, J_{1-2} = 9.5 Hz, 1H, H-1'), 7.46 (m, 9H, Ar-H).
5i	2226 (CN), 1757 (CO ester) 1641 (CO pyridone)	1.96, 1.98, 1.99 and 2.18 (4s, 12H, 4CH_3CO), 2.59 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.09 (m, 2H, H-6', 6"), 4.53 (t, J = 8.9 Hz, 1H, H-5'), 5.36 (m, 2H, H-4' and H-3'), 5.51 (m, 1H, H-2'), 6.43 (d, J_{1-2} = 9.4 Hz, 1H, H-1'), 7.62 (m, 3H, Ar-H), 7.89 (m, 2H, Ar-H).
5k	2227 (CN) 1758 (CO ester) 1643 (CO Pyridone)	1.84-2.18 (4s, 12H, 4CH_3CO), 2.27 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.01 (m, 2H, H-6', 6"), 4.48 (m, 1H, H-5'), 5.32 (m, 3H, H-4', H-3' and H-2'), 6.34 (d, J_{1-2} = 9.6 Hz, 1H, H-1'), 7.48 (d, 2H, Ar-H), 7.78 (d, 2H, Ar-H).

spectra were measured on a Wilmad 270 MHz or on a Varian 400 MHz spectrometer for solutions in (DMSO-d_6) using TMS as external standard. 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 D-galactopyranosyl)-5-arylazo-3-cyano-2(1*H*)-pyridineones 5.

General coupling procedures.

Method A. To a solution of 2(1*H*)-pyridineone sodium salts **3a-h** (0.01 mol) in acetone (10 ml), a solution of 2,3,4, 6-tetra-*O*-acetyl-α-D-gluco- or D-galactopyranosyl bromide **4** (4.521 gm,

Table 2 (Continued)

5l	2225 (CN), 1754 (CO ester), 1640 (CO Pyridone)	1.96, 1.97, 1.99 and 2.18 (4s, 12H, $4CH_3CO$), 2.56 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.88 (s, 3H< OCH_3), 4.09 (m, 2H, H-6', 6"), 4.51 (t, J=8.7 Hz, 1H, H-5'), 5.37 (m, 3H, H-4', H-3' and H-2'), 6.41 (d, $J_{1\text{-}2}$ = 9.4 Hz, 1H, H-1'), 7.17 (d, 2H, Ar-H), 7.91 (d, 2H, Ar-H).
6a	3600-3200 (OH), 2226 (CN), 1655 (CO pyridone)	2.54 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.34-3.72 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'), 4.50 (d, J = 8.5 Hz, 2H, 2'-OH and 3'-OH), 4.92 (s, 1H, 4'-OH), 5.48 (s, 1H,6'-OH), 6.05 (d, $J_{1\text{-}2}$ = 9.2 Hz, 1H, H-1'), 7.64 (m, 5H, Ar-H).
6e	3600-3200 (OH), 2227 (CN), 1659 (CO pyridone)	2.65 (s, 3H, CH_3), 3.35-3.81 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'),4.56 (d, J = 8.9 Hz, 2H, 2'-OH and 3'-OH), 4.94 (s, 1H, 4'-OH), 5.41 (s, 1H, 6'-OH), 6.04 (d, $J_{1\text{-}2}$ = 9.6 Hz, 1H, H-1'), 7.46 (m, 10H, Ar-H).
6h	3650-3200 (OH), 2224 (CN), 1654 (CO pyridone)	2.58 (s, 3H, CH_3), 3.24-3.73 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'), 3.90 (s, 3H, OCH_3), 4.48 (t, J = 8.7 Hz, 2H, 2'-OH and 3'-OH), 5.08 (d, J=9.3 Hz, 1H, 4'-OH), 5.46 (d, J=10.8 Hz, 1H, 6'-OH), 6.08 (d, $J_{1\text{-}2}$ = 8.8 Hz, 1H, H-1'), 7.16 (d, 2H, Ar-H), 7.48 (m, 5H, Ar-H), 7.74 (d, 2H, Ar-H)
6i	3600-3180 (OH), 2225 (CN), 1645 (CO pyridone)	2.59 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.35-3.78 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'), 4.54 (d, J=8.4 Hz, 2H, 2'-OH and 3'-OH), 4.99 (s, 1H, 4'-OH), 5.45 (s, 1H, 6'-OH), 5.60 (d, $J_{1\text{-}2}$ = 8.9 Hz, 1H, H-1'), 7.76 (m, 5H, Ar-H)
6l	3600-3150 (OH), 2226 (CN), 1644 (CO pyridone)	2.55 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.34-3.87 (m, 6H, H-6', 6", H-5', H-4', H-3' and H-2'), 3.88 (s, 3H, OCH_3), 4.56 (m, 2H, 2'-OH and 3'-OH), 4.97 (d, J=9.1 Hz, 1H, 4'-OH), 5.33 (d, J=10.6 Hz, 1H, 6'-OH), 5.58 (d, $J_{1\text{-}2}$ = 9.4 Hz, 1H, H-1'), 7.16 (d, 2H, Ar-H), 7.86 (d, 2H, Ar-H)

0.011 mol) in acetone (20 ml) was added. The reaction mixture was stirred at room temperature until judged complete by TLC (18 to 24 h). The mixture was evaporated under reduced pressure at 40^{o}C and the crude glycoside was washed with distilled water to remove the formed sodium bromide. The product was dried and crystallized from ethanol to afford yellow crystals (cf. Table 1).

Method B. To a solution of 2(1*H*)-pyridineones **7a-h** (0.01 mol) in aqueous potassium hydroxide (0.56 gm, 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 D-galactopyranosyl bromide **4** (4.521 gm, 0.011 mol) in acetone (30 ml). The reaction mixture was stirred at room temperature until judged complete by TLC (18 to 24 h) then processed as described above.

1-(β-D-Gluco- and D-galactopyranosyl)-3-cyano-2(1*H*)-pyridineones 6.

General Procedure for Nucleoside Deacylation.

Dry gaseous ammonia was passed through a solution of protected nucleosides **5** (0.5 gm) in dry methanol (20 ml) at 0^{o}C for about 0.5 hour. The reaction mixture was then stirred at 0^{o}C until judged complete by TLC (12 to 18 h). The mixture was evaporated under reduced pressure at 40

^{o}C giving a solid residue which was crystallized from methanol to afford yellow crystals (cf. Table 1).

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