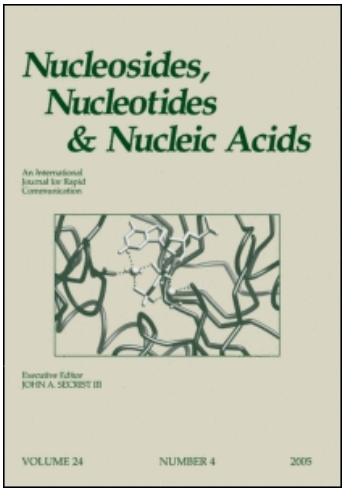

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Synthesis and Biological Evaluation of Some Acyclic Pyridine C-Nucleosides. Part One

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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME ACYCLIC PYRIDINE C-NUCLEOSIDES. PART ONE.

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ABSTRACT.

The reaction between 3-bromo-5-chloromethylpyridine hydrochloride (4) with the mono sodium salt of ethylene glycol was investigated. 3-Bromo-5-(2-hydroxyethoxymethyl)-pyridine (5) was synthesized and converted to the 3-carboxy analogue using butyllithium and CO_2. Subsequent treatment with diazomethane and ammonolysis gave the corresponding acyclic nicotinamide C-nucleosides. The latter compounds were converted into the thioamide analogues by reaction with Lawesson's reagent. The pyridine N-oxide derivatives were obtained by treatment with peracetic acid or hydrogen peroxide. All compounds were identified with the aid of ^{1}H- and ^{13}C-NMR and mass spectrometry. The acyclic pyridine C-nucleosides were evaluated against a number of viral strains and cancer cell lines but no significant biological activity was found.

I. INTRODUCTION.

Nucleoside analogues represent an important group of compounds with biological activity[1,2]. Amongst these, nucleosides with an acyclic carbohydrate moiety have been shown to possess antiviral activity[3,4,5].

Acyclovir (9-(2-hydroxyethoxymethyl)guanine, Zovirax®) is a potent antiherpetic

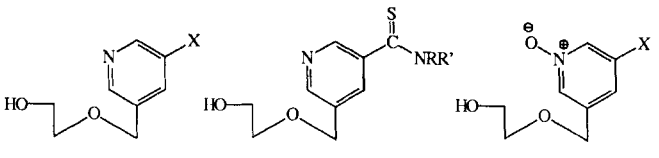
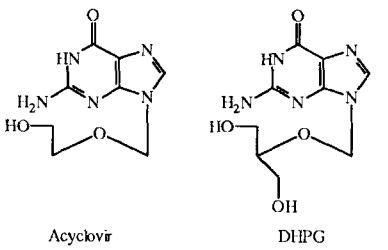


FIGURE 1.

agent with activity against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV) and Epstein-Barr virus (EBV). Ganciclovir [9-[(1,3-dihydroxy-2-propoxy)methyl]guanine, DHPG] has a broader spectrum of antiherpetic activity, also encompassing cytomegalovirus (CMV)[6,7,8,9]. Its activity against EBV is about sixfold higher than that of acyclovir[10,11,12].



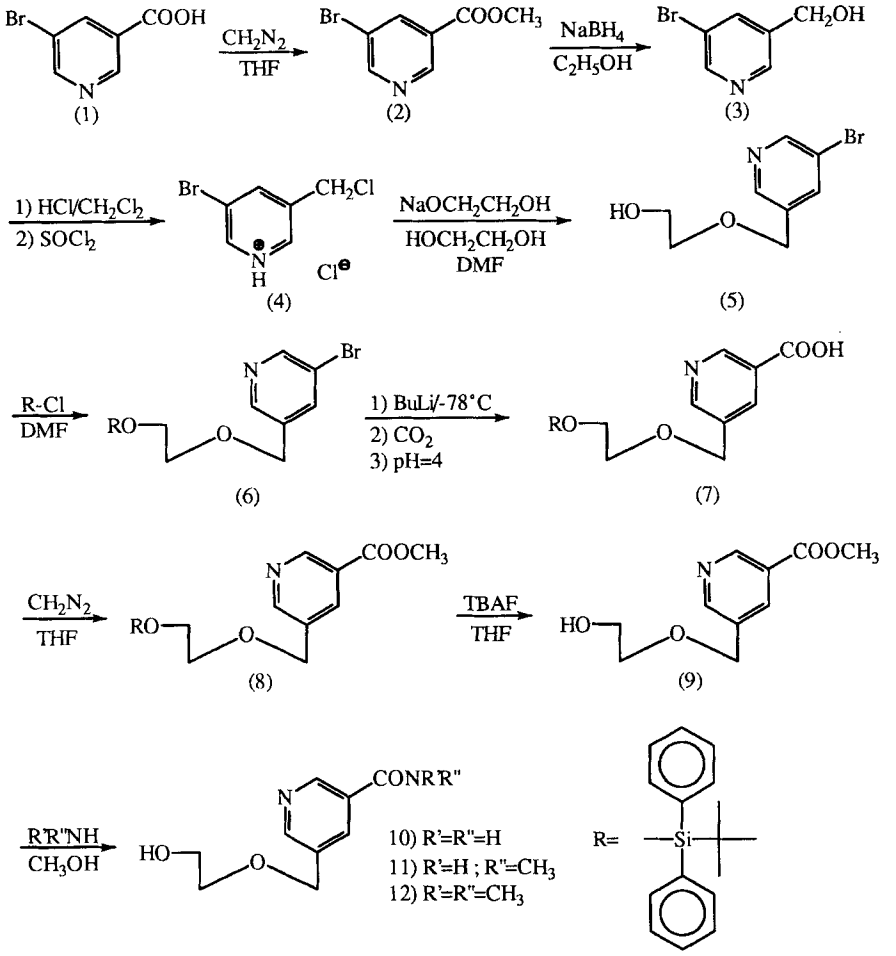
Our laboratory has been involved in the synthesis of pyridine C-nucleosides in attempts to develop novel compounds with cytostatic and/or antiviral properties. Several of such compounds have been reported by us[13,14,15,16,17] and others[18,19,20], some of them show modest *in vitro* cytostatic activity.

We now wish to report on the synthesis and biological evaluation of some acyclic pyridine C-nucleosides (FIGURE 1).

II. RESULTS AND DISCUSSION.

II.a. AMIDES.

The methodology summarized in SCHEME 1 was developed to obtain the pyridine C-nucleosides showed in Fig. 1.



SCHEME 1.

The commercially available, 5-bromonicotinic acid (1), was chosen which can be readily converted into its methylester (2) by diazomethane. Reduction of 2 with $NaBH_4$ gave 3-bromo-5-hydroxymethylpyridine (3) in 69% yield. The latter compound was purified by vacuum distillation before it was converted to the corresponding chloromethyl derivative (4). Prior to the treatment with $SOCl_2$, (3) was converted into its hydrochloride in order to avoid undesirable side reactions. 3-Bromo-5-chloromethylpyridine hydrochloride[21] was used as such without any attempt of further purification and was reacted with 2.2 eq. of the mono sodium

salt of ethylene glycol in DMF. 3-Bromo-5-(2-hydroxyethoxymethyl)pyridine (5) was obtained in 70% yield. This compound could be purified by distillation under reduced pressure and was obtained as a colourless oil. As already shown by Verberckmoes *et al.*[22], one should be able to introduce a carboxylic acid function by treatment of an intermediate lithiopyridine with dry ice. Therefore 3-bromo-5-(2-hydroxyethoxymethyl)pyridine (5) was dissolved in dry THF. Three equivalents of BuLi were introduced at -78°C, and after 5 minutes the reaction mixture was poured onto a large excess of freshly prepared dry ice. The pH of the reaction mixture was adjusted to 4 with 5N HCl and extracted several times with CH_2Cl_2. After evaporation of the combined organic layers the obtained residue was analysed by NMR and DCI-mass spectrometry. From these results we could conclude that the introduction of a carboxylic acid function at the 3-position failed and that the bromo atom had been replaced by an hydrogen atom. This is a phenomenon which normally can be explained by the presence of moisture. However, the same results were obtained if the reaction was repeated several times, taken every precaution possible to avoid moisture.

An experiment where 5 was treated with 1.1 eq. of NaH prior to lithiation and carboxylation did not solve this problem either. However, if 3-bromo-5-(2-hydroxyethoxymethyl)pyridine (5) was protected at the C-5'-position by a *tert*-butyldiphenylsilyl moiety, which can easily be introduced by reaction of 5 with *tert*-butyldiphenylsilylchloride in DMF, compound 6 could be lithiated and carboxylated as described above. Compound 7 was isolated by extraction with CH_2Cl_2 after the pH had been adjusted to 4. This extraction proceeds very efficiently because of the presence of the hydrophobic moiety at C-5'.

An explanation for the observations described above is not straightforward but it cannot be denied that protection of the OH-function is required in order to obtain the carboxylic acid in good yield.

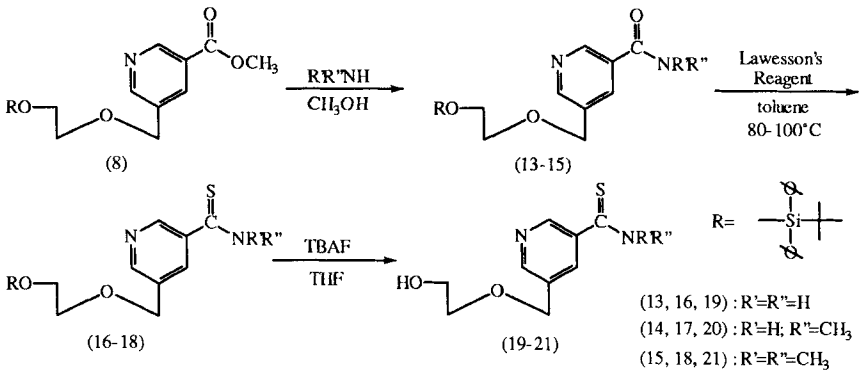
After evaporation of the solvent compound 7 was reacted immediately with CH_2N_2 in THF giving 3-methoxycarbonyl-5-(2-*tert*-butyldiphenylsilyloxyethoxymethyl)pyridine (8). The overall yield for the convertion of 6 to 8 varied from 52 to 74%.

Removal of the silyl protecting group was done by a standard procedure using TBAF in THF at room temperature. 3-Methoxycarbonyl-5-(2-hydroxyethoxy-methyl)pyridine (9) was obtained in 74% yield. The ester (9) was then suspended in methanol saturated with either NH_3, CH_3NH_2 or $(CH_3)_2NH$ and stirred for 2 days. After evaporation of the solvent, the acyclic nucleosides 10 to 12 were obtained in a nearly quantitative yield.

II.b. THIOAMIDES.

For the synthesis of the corresponding thioamide nucleosides, we initially used the procedure described by Scheibye *et al.*[23] Following this methodology the amides were dissolved in HMPA and heated for a few hours at 80°C for the primary amide 10 and at 100°C for the *sec.* and *tert.* amides 11 and 12 respectively in the presence of 0.5 eq. Lawesson's Reagent. After working up, no thioamides could be detected. This was in contrast with the results of Scheibye *et al.*, who transformed nicotinamide in its thioamide with a yield of 87%.

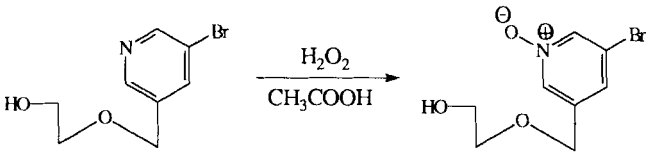
Since the removal of HMPA is difficult, an alternative synthesis of thioamides described by Tanaka *et al.*[24] was chosen.



Treatment of the protected amides 13 to 15 with 0.5 eq. Lawesson's Reagent in toluene produced the corresponding thioamides in 58 to 79% yield. Deprotection with TBAF/THF resulted in the formation of the target compounds 19 to 21.

II.c. N-OXIDE COMPOUNDS.

Taylor *et al.*[25] described the synthesis of nicotinamide-1-oxide by treatment of nicotinamide with H_2O_2 in glacial acetic acid in 78% yield. We used this method for the N-oxidation of 3-bromo-5-(2-hydroxyethoxymethyl)pyridine (5).

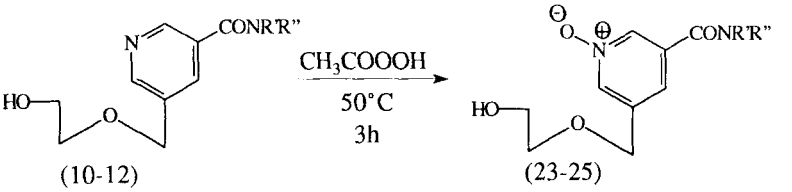


(5) (22)

After purification by preparative CCTLC, 22 was obtained as a white solid in 20% yield. Also isolated were 3-bromo-5-(2-acetyloxyethoxymethyl)pyridine (29%) and a small amount of 3-bromo-5-(2-acetyloxyethoxymethyl)pyridine-1-oxide.

However, if the same method was used for the preparation of the N-oxides of the amides 10 to 12, the reaction failed. DCI-mass spectrometry analysis of the reaction mixture only showed the presence of the acylated product. Variation of reaction time, temperature and concentration of H_2O_2 were unsuccessful. Based on the results reported by Ochiai[26], hydrogen peroxide in a solution of trifluoro-acetic acid was selected. The amides (10-12) were mixed with trifluoroacetic acid and 30% aqueous hydrogen peroxide and refluxed for 3 hours[27]. But, again no N-oxide formation was observed.

Finally, good results were obtained by treatment of the amide nucleosides 10 to 12 with peracetic acid.



(10-12) (23-25)

10, 23 : R'=R"=H
11, 24 : R'=H; R"=CH_3
12, 25 : R'=R"=CH_3

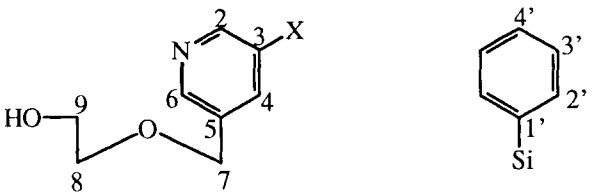
Here the nucleosides 10 to 12 were treated with peracetic acid and stirred at 50°C. After 3 hours the reaction was completed. After evaporation, the N-oxides 23 to 25 were obtained in 40-50% yield.

III. STRUCTURE IDENTIFICATION BY NMR.

Structure identification was done by 400 MHz ^{1}H-NMR spectroscopy, 100 MHz ^{13}C-NMR spectroscopy (15, 18, 20, 22, 23 and 25) and 25 MHz ^{13}C-NMR spectroscopy (all other compounds). The spectra were recorded in $CDCl_3$ or CD_3OD solutions, using the residual solvent signal or TMS as internal reference. In the case of the residual solvent signal we used δ = 77.00 ppm for $CDCl_3$ and δ = 49.00 ppm for CD_3OD in the case of ^{13}C-NMR and δ = 7.3 ppm ($C\underline{H}Cl_3$) for $CDCl_3$ and δ = 3.3 ppm ($CD_2\underline{H}OD$) for CD_3OD in the case of ^{1}H-NMR.

In most ^{1}H-NMR spectra the methylene (H-7) signal occurred as a doublet with a coupling constant ranging from 0.3 to 0.6 Hz.

Basic numbering of our compounds was done as follows:



The assignment of the carbon atoms of the acyclic chain was accomplished using the data of Sadtler Standard (Carbon-13 NMR Spectra) for a similar compound, i.e. 2-hydroxyethoxymethylbenzene ($C_9H_{12}O_2$; n° 17915). 2D HETCOR spectroscopy was used to assign the corresponding protons.

The carbon atoms of the phenyl rings were assigned partly by 2D HETCOR spectroscopy which clearly showed the quaternary C-1'. The other signals were assigned using results reported in the literature[28,29].

TABLE 1 : ^{13}C-NMR data of the amides, the thioamides and the N-oxides : δ-values in ppm.

	5	10	11	12	19	20	21	22	23	24	25
Solvent	$CDCl_3$	CD_3OD	CD_3OD	CD_3OD	CD_3OD	CD_3OD	$CDCl_3$	$CDCl_3$	CD_3OD	CD_3OD	CD_3OD
Reference	TMS	Solvent	Solvent	Solvent	Solvent	Solvent	Solvent	TMS	Solvent	Solvent	Solvent
C-2	149.86	151.96	151.59	150.43	151.16	150.64	148.09	139.50	140.77	140.56	139.43
C-3	120.74	131.00	131.49	133.62	135.63	138.81	140.05	120.11	134.89	135.20	136.88
C-4	137.92	136.24	135.75	135.75	135.51	135.45	135.73	127.77	127.73	127.28	127.13
C-5	135.67	136.24	136.18	136.30	135.51	135.71	138.77	138.81	140.83	140.80	141.06
C-6	146.76	148.54	148.06	147.51	147.87	147.51	144.80	136.96	138.57	138.25	137.60
C-7	69.75	70.87	70.87	70.87	70.93	70.96	69.57	69.03	69.89	69.83	69.82
C-8	72.43	73.37	73.37	73.43	73.43	73.38	72.49	72.91	73.73	73.73	73.72
C-9	61.47	62.16	62.16	62.22	62.22	62.22	61.65	61.65	62.18	62.16	62.16
C=O	-	169.74	168.04	170.66	-	-	-	-	166.75	165.24	167.64
C=S	-	-	-	-	200.57	197.14	194.70	-	-	-	-
NH-$\underline{CH_3}$	-	-	26.89	-	-	33.85	-	-	-	27.01	-
N-$\underline{(CH_3)_2}$	-	-	-	35.72;39.92	-	-	43.37;44.41	-	-	-	35.74;39.69

TABLE 2 : ^{1}H-NMR data of the amides, the thioamides and the N-oxides : δ-values in ppm, coupling constants in Hz.

	5	10	11	12	19	20	21	22	23	24	25
Solvent	$CDCl_3$	CD_3OD	CD_3OD	CD_3OD	CD_3OD	CD_3OD	$CDCl_3$	$CDCl_3$	CD_3OD	CD_3OD	CD_3OD
Reference	TMS	Solvent	Solvent	Solvent	Solvent	Solvent	Solvent	TMS	Solvent	Solvent	Solvent
H-2	8.48 d	8.69 d	8.67 d	8.54 d	8.62 d	8.59 d	8.48 d	8.18 br	8.48 d	8.46 d	8.35 d
H-4	7.86 t	8.30 t	8.24 t	7.93 t	8.28 t	8.16 t	7.71 t	7.32 br	8.01 t	7.95 t	7.64 t
H-6	8.61 d	8.94 d	8.87 d	8.63 d	8.94 d	8.81 d	8.54 d	8.20 br	8.65 d	8.60 d	8.42 d
H-7	4.57 d	4.68 d	4.67 d	4.67 d	4.66 d	4.65 d	4.61 d	4.46 d	4.66 d	4.65 d	4.64 d
H-8	3.80 t	3.74 t	3.74 t	3.73 t	3.74 t	3.75 t	3.81 t	3.74 t	3.75 t	3.75 t	3.74 t
H-9	3.64 t	3.65 t	3.64 t	3.64 t	3.64 t	3.65 t	3.66 t	3.59 t	3.66 t	3.66 t	3.65 t
NH-$\underline{CH_3}$	-	-	2.94 s	-	-	3.26 s	-	-	-	2.93 s	-
N-$\underline{(CH_3)_2}$	-	-	-	3.02 s 3.13 s	-	-	3.22 s 3.62 s	-	-	-	3.03 s 3.11 s
J(2,4)	1.7	1.7	2.1	2.0	2.0	2.0	1.5	-	1.8	1.9	1.9
J(4,6)	2.3	1.8	2.1	2.0	2.3	2.3	1.7	-	1.9	1.9	1.8
J(8,9)	4.6	4.6	4.8	4.7	4.5	4.6	4.5	4.5	4.6	4.7	4.8

TABLE 3.

Compound	L1210	FM3A	Molt/4F	CEM/0
	IC_{50} (μg/ml)			
21	98.7 ± 20.6	152 ± 33	127 ± 14	120 ± 29

IV. BIOLOGICAL STUDIES.

Nucleosides 12 and 19 to 25 were evaluated for their inhibitory effect on the replication of: herpes simplex virus-1 (strain KOS), herpes simplex virus-2 (strain G), vaccinia virus, vesicular stomatitis virus (VSV), thymidine kinase-deficient (TK^-) strains (herpes simplex virus-1 B2006 and VMW1837 in E_6SM cell cultures; VSV, Coxsackie virus B4 and polio virus-1 in HeLa cell cultures; and parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4 and Semliki forest virus in Vero cell cultures. The minimum inhibitory concentration (i.e. the compound concentration required to reduce the virus-induced cytopathogenicity by 50%) (MIC_{50}) was higher than 400 μg/ml. The minimum cytotoxic concentration (i.e. the compound concentration required to cause a microscopically detectable alteration of normal cell morphology) was also higher than 400 μg/ml [except for compound 21 where it was higher than 200 μg/ml]. Neither anti-HIV-1 nor anti-HIV-2-activity were observed in MT-4 cells (MIC_{50})200 μg/ml).

Only compound 21 showed cytostatic activity against murine leukemia cells (L1210), murine mammary carcinoma cells (FM3A) and human lymphocyte cells (Molt/4F and CEM/0) at concentrations up to 200 μg/ml (TABLE 3).

V. EXPERIMENTAL.

General methods.

^{1}H-NMR spectra were recorded on a 400 MHz Varian Unity 400 spectrometer. ^{13}C-NMR spectra were recorded on a Jeol JNM PFT-PS-100 spectrometer (25 MHz) connected to

a TI-980B computer system or on the Varian spectrometer. DCI-mass spectra were run on a Ribermag 10-10B quadrupole mass spectrometer, equipped with a Sidar data system. Primary ionisation was performed by 70 eV electrons using an emission current of 0.08 mA. The pressure in the ion source was 0.1 mmHg.

Separations on silica gel were performed by preparative centrifugal circular thin layer chromatography (CCTLC) on a Chromatotron® (Harrison Research, Palo Alto, CA). Stationary phase: Kieselgel 60 PF_{254} gipshaltig, Merck, Darmstadt, layer thickness 2mm, flow rate 5 ml/min.

Elemental analyses were recorded at Janssen Pharmaceutica (Beerse, Belgium).

Reactions involving organometallic reagents were performed in oven-dried glassware under N_2-atmosphere. THF was dried by distillation from sodium/benzophenone ketyl prior to use. DMF was dried by distillation from CaH_2 under reduced pressure. 5-Bromonicotinic acid, BuLi (1.6 M in hexane), TBAF (1 M in THF), Lawesson's reagent and *tert*-butyldiphenylsilylchloride were purchased from Janssen Chimica (Beerse, Belgium).

The cytostatic and antiviral assays were carried out according to previously published procedures[30,31,32,33].

Synthesis.

3-Bromo-5-methoxycarbonylpyridine (2).

In a 1l flask 5-bromonicotinic acid (1) (20 g, 99 mmol) was suspended in 300 ml THF and cooled to 0 °C. Then an excess (2.5 eq.) of ethereal diazomethane (50 g Diazogen in 460 ml ether added to 60 ml ethanol, 11.6 g KOH and 18 ml H_2O) was added. After 2 hours of stirring at room temperature the solvent was evaporated. The residue was then dissolved in CH_2Cl_2 and filtrated. Evaporation of the solvent gave 2 as a light brown solid (20.7 g, 97%). This solid was used in the next reaction step without further purification.

^{13}C-NMR ($CDCl_3$, TMS) : δ 164.42 (C=O), 154.49 (C-2), 148.83 (C-6), 139.45 (C-4), 127.38 (C-5), 120.56 (C-3), 52.70 (O-$\underline{C}H_3$).

^{1}H-NMR ($CDCl_3$, TMS) : δ 9.13 (1H, d, J=1.7 Hz, H-6), 8.84 (1H, d, J=2.3 Hz, H-2), 8.43 (1H, dd, H-4), 3.97 (3H, s, -O-$\underline{CH}_3$).

DCI-mass spectrometry (NH_3) : m/z = 216 ($[MH]^+(^{79}Br)$, 100%).

Elemental analysis for $C_7H_6BrNO_2$: calc. C, 38.92%; H, 2.80%; Br, 36.99%; N, 6.48%. Found : C, 38.84%; H, 2.78%; Br, 36.86%; N, 6.54%.

3-Bromo-5-hydroxymethylpyridine (3).

A three necked flask of 500 ml, equipped with a reflux condenser and a $CaCl_2$ tube, was filled with 3-bromo-5-methoxycarbonylpyridine (20.65 g, 96 mmol) dissolved in 150 ml absolute ethanol. This solution was cooled to 0 °C and $NaBH_4$ (8.3 g, 0.22 mol) was added in portions within 15 min. After stirring at 0 °C for 1 hour, the ice bath was removed and stirring was continued at room temperature for 3 hours. Finally, the solution was refluxed for 10 hours.

After cooling down of the solution, the solvent was evaporated and 100 ml acetone was added. After some stirring the acetone was evaporated and 100 ml of a saturated K_2CO_3-solution was added, and the mixture was refluxed for 1 hour. The solvent was evaporated and the residue was dissolved in 400 ml H_2O. The aqueous layer was then extracted continuously for 10 hours with CH_2Cl_2 (800 ml). After evaporation of the solvent the residue was purified by a distillation under reduced pressure to give 3-bromo-5-hydroxymethylpyridine (3) as a pale yellow oil (12.4 g, 69%, b.p. : 154 °C /4 mmHg).

^{13}C-NMR ($CDCl_3$, TMS) : δ 149.56 (C-2), 146.09 (C-6), 138.59 (C-5), 137.56 (C-4), 120.99 (C-3), 61.59 (-$\underline{CH_2}$-OH).

^{1}H-NMR ($CDCl_3$, TMS) : δ 8.57 (1H, d, J=2.1 Hz, H-6), 8.47 (1H, d, J=1.8 Hz, H-2), 7.90 (1H, t, H-4), 4.73 (2H, d, J=0.5 Hz, -$\underline{CH_2}$-OH).

DCI-mass spectrometry (NH_3) : m/z = 188 ($[MH]^+(^{79}Br)$, 100%).

Elemental analysis for C_6H_6BrNO : calc. C, 38.51%; H, 3.23%; Br, 42.21%; N, 7.49%. Found : C, 38.62%; H, 3.24%; Br, 42.14%; N, 7.45%.

3-Bromo-5-chloromethylpyridine hydrochloride (4).

The alcohol (3) (12 g, 63 mmol) was dissolved in dry CH_2Cl_2 saturated with HCl-gas. After 5 min stirring the solvent was evaporated. To this solid residue 44 ml $SOCl_2$ was added at 0 °C after which the solvent was refluxed for 2 hours. After this period the solution was cooled to room temperature and 120 ml cyclohexane was added. The arisen precipitate was filtrated and washed several times with cyclohexane. This gave 4

(11.9 g, 49 mmol) as a pale yellow solid, which was used in the next reaction step without further purification. Yield (crude) : 77%.

3-Bromo-5-(2-hydroxyethoxymethyl)pyridine (5).

In a flask of 50 ml, 25 ml ethylene glycol was stirred with 1.05 g Na-metal until H_2-formation was over.

A three necked flask of 500 ml, equipped with a $CaCl_2$ tube, was filled with 100 ml dry DMF. Then 11.8 ml (2.2 eq.) of the above described $NaOCH_2CH_2OH/HOCH_2CH_2OH$-mixture was added. To this solution, 4 (2.02 g, 9.8 mmol) dissolved in some dry DMF was added dropwise, and the whole mixture was stirred ar room temperature for 24 hours. After evaporation of the solvent the obtained yellow oil was suspended in H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced presurre and the obtained oil was purified by a distillation under reduced pressure. This gave 3-bromo-5-(2-hydroxyethoxymethyl)-pyridine (5) (61%, b.p. : 117 °C/0.06 mmHg).

DCI-mass spectrometry (NH_3) : m/z = 232 ($[MH]^+(^{79}Br)$, 100%).

Elemental analysis for $C_8H_{10}BrNO_2$: calc. C, 41.56%; H, 4.36%; Br, 34.17%; N, 6.06%. Found : C, 41.53%; H, 4.27%; Br, 34.03%; N, 6.01%.

3-Bromo-5-(2-*tert*-butyldiphenylsilyloxyethoxymethyl)pyridine (6).

3-Bromo-5-(2-hydroxyethoxymethyl)pyridine (5) (640 mg, 2.8 mmol) was dissolved in dry DMF (20 ml), and *tert*-butyldiphenylsilylchloride (0.83 g, 0.79 ml, 1.1 eq.) and imidazole (0.49 g, 2.2 eq.) were added. The solution was stirred at room temperature for 6 hours, after which it was poured in a saturated $NaHCO_3$-solution. This solution was then extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent an oil was obtained, which was purified by preparative CCTLC (CH_2Cl_2/CH_3OH (99:1)). This gave 6 as a colorless oil (1.2 g, 91%).

^{13}C-NMR ($CDCl_3$, TMS) : δ 149.99 (C-2), 146.82 (C-6), 137.62 (C-4), 135.91 (C-1'), 135.61 (C-2'), 133.54 (C-5), 129.70 (C-4'), 127.69 (C-3'), 120.80 (C-3), 72.19 (C-8), 69.81 (C-7), 63.48 (C-9), 26.87 (-C-$(\underline{CH_3})_3$), 19.19 (-$\underline{C}$-$(CH_3)_3$).

^{1}H-NMR ($CDCl_3$, TMS) : δ 8.61 (1H, d, J=2.3 Hz, H-6), 8.45 (1H, d, J=1.8 Hz, H-2), 7.85 (1H, t, H-4), 7.65-7.69 (4H, m, H-2'), 7.34-7.44 (6H, m, H-3' and H-4'), 4.55 (2H,

d, J=0.6 Hz, H-7), 3.86 (2H, t, J=5.0 Hz, H-8), 3.63 (2H, t, J=5.0 Hz, H-9), 1.06 (9H, s, -C-$(CH_3)_3$).

DCI-mass spectrometry (NH_3) : m/z = 470 ($[MH]^+$ (^{79}Br), 100%).

Elemental analysis for $C_{24}H_{28}BrNO_2Si$: calc. C, 61.39%; H, 6.02%; Br, 16.82%; N, 2.99%. Found : C, 61.28%; H, 6.07%; Br, 16.79%; N, 2.94%.

5-(2-*tert*-Butyldiphenylsilyloxyethoxymethyl)-3-methoxycarbonylpyridine (8).

a) A three necked flask of 100 ml, equipped with a dropping funnel, $CaCl_2$ tube and dry N_2 inlet system, was filled with 6 (1.2 g, 2.6 mmol) dissolved in 80 ml dry THF. The solution was cooled in a CO_2/acetone bath to -78 °C, and 2 ml BuLi (1.2 eq.) was added while stirring. After 5 minutes the contents were poured on a large excess of dry ice (200 g). After evaporation of the CO_2, the reaction mixture was evaporated in vacuo to dryness and the residue was dissolved in H_2O. This aqueous solution was acidified to pH=4 (HCl) and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to obtain 7 as a white solid.

DCI-mass spectrometry (NH_3) : m/z = 436 ($[MH]^+$,100%).

b) The carboxylic acid (7) (900 mg, 2 mmol) was dissolved in THF, cooled to 0 C and an excess (2.5 eq.) of ethereal diazomethane was added. After evaporation of the solvent, the residue was purified by preparative CCTLC (CH_2Cl_2/CH_3OH (99:1)) and (8) was collected (600 mg, 52%).

^{13}C-NMR ($CDCl_3$, TMS) : δ 165.70 (C=O), 152.48 (C-2), 149.99 (C-6), 136.10 (C-4), 135.61 (C-2'), 134.88 (C-1'), 133.60 (C-5), 129.64 (C-4'), 127.63 (C-3'), 125.86 (C-3), 72.19 (C-8), 70.24 (C-7), 63.48 (C-9), 52.33 (-O-CH_3), 26.80 (-C-$(CH_3)_3$), 19.19 (-C-$(CH_3)_3$).

^{1}H-NMR ($CDCl_3$, TMS) : δ 9.15 (1H, d, J=2.0 Hz, H-6), 8.72 (1H, d, J=2.1 Hz, H-2), 8.27 (1H, t, J=2.1 Hz, H-4), 7.66-7.70 (4H, m, H-2'), 7.34-7.43 (6H, m, H-3' and H-4'), 4.62 (2H, d, J=0.5 Hz, H-7), 3.94 (3H, s, -O-CH_3), 3.87 (2H, t, J=5.0 Hz, H-8), 3.65 (2H, t, J=5.0 Hz, H-9), 1.06 (9H, s, -C-$(CH_3)_3$).

DCI-mass spectrometry (NH_3) : m/z = 450 ($[MH]^+$, 100%).

Elemental analysis for $C_{26}H_{31}NO_4Si$: calc. C, 69.46%; H, 6.96%; N, 3.12%. Found : C, 69.39%; H, 7.01%; N, 3.07%.

5-(2-Hydroxyethoxymethyl)-3-methoxycarbonylpyridine (9).

The ester (8) (500 mg, 1.1 mmol) was dissolved in 80 ml dry THF and 2.2 ml (2 eq.) $(Bu)_4NF$ (TBAF, 1 M in THF) were added. The solution was stirred at room temperature for 30 min. The THF was evaporated in vacuo and the residue dissolved in H_2O (100 ml). This aqueous solution was extracted with CH_2Cl_2 and the organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by preparative CCTLC (CH_2Cl_2/CH_3OH (95:5)), and compound 9 was obtained as a colorless oil (173 mg, 74%).

^{13}C-NMR ($CDCl_3$, TMS) : δ 165.64 (C=O), 152.60 (C-2), 150.05 (C-6), 136.34 (C-4), 133.78 (C-5), 125.92 (C-3), 72.37 (C-8), 70.24 (C-7), 61.71 (C-9), 52.45 (-O-$\underline{CH_3}$).

^{1}H-NMR ($CDCl_3$, TMS) : δ 9.16 (1H, d, J=2.0 Hz, H-6), 8.78 (1H, d, J=2.3 Hz, H-2), 8.33 (1H, t, J=2.1 Hz, H-4), 4.66 (2H, s, H-7), 3.97 (3H, s, -O-$\underline{CH_3}$), 3.82 (2H, t, J=4.6 Hz, H-8), 3.67 (2H, t, J=4.6 Hz, H-9).

DCI-mass spectrometry (NH_3) : m/z = 212 ($[MH]^+$, 100%).

Elemental analysis for $C_{10}H_{13}NO_4$: calc. C, 56.85%; H, 6.21%; N, 6.63%.

Found : C, 56.91%; H, 6.16%; N, 6.62%.

3-Carbamoyl-5-(2-hydroxyethoxymethyl)pyridine (10).

The methyl ester (9) (170 mg, 0.9 mmol) was dissolved in CH_3OH (50 ml), cooled to 0 C, and saturated with NH_3. The mixture was stirred at room temperature for 2 days. After evaporation of the solvent, the residue was purified by preparative CCTLC (CH_2Cl_2/CH_3OH (85:15)), giving the amide (10) as a white solid (160 mg, 99%).

DCI-mass spectrometry (NH_3) : m/z = 197 ($[MH]^+$, 100%).

Elemental analysis for $C_9H_{12}N_2O_3$: calc. C, 55.09%; H, 6.16%; N, 14.28%.

Found : C, 54.96%; H, 6.17%; N, 14.19%.

3-(N-methylcarbamoyl)-5-(2-hydroxyethoxymethyl)pyridine (11) and 3-(N,N-dimethylcarbamoyl)-5-(2-hydroxyethoxymethyl)pyridine (12).

The methylamide (11) and the dimethylamide (12) were synthesised following the same procedure as for 10, but using CH_3NH_2 and $(CH_3)_2NH$ instead of NH_3 as reagent gas. The obtained compounds were purified by preparative CCTLC (CH_2Cl_2/CH_3OH (90:10)).

Yields : (11) : 97%.

(12) : 95%.

DCI-mass spectrometry (NH_3) : m/z = 211 (11) and m/z = 225 (12)($[MH]^+$, 100%).
Elemental analysis for $C_{10}H_{14}N_2O_3$ (11) : calc. C, 57.12%; H, 6.72%; N, 13.33%.
Found : C, 56.91%; H, 6.86%; N, 13.30%.
Elemental analysis for $C_{11}H_{16}N_2O_3$ (12) : calc. C, 58.90%; H, 7.20%; N, 12.50%.
Found : C, 58.79%; H, 7.13%; N, 12.42%.

3-Carbamoyl-5-(2-*tert*-butyldiphenylsilyloxyethoxymethyl)pyridine (13), 3-(N-methylcarbamoyl)-5-(2-*tert*-butyldiphenylsilyloxyethoxymethyl)pyridine (14) and 3-(N,N-dimethylcarbamoyl)-5-(2-*tert*-butyldiphenylsilyloxyethoxymethyl)pyridine (15).

The methylester (8) (200 mg) was suspended in CH_3OH (50 ml), cooled to 0 C and saturated with NH_3, CH_3NH_2 or $(CH_3)_2NH$. The mixture was then stirred at room temperature for 2 days. After evaporation of the solvent in vacuo, the residues were purified by CCTLC (CH_2Cl_2/CH_3OH (95:5)), yielding the amides 13 to 15 nearly quantitatively.

^{13}C-NMR.

(13) : ($CDCl_3$, solv. ref.) : δ 167.28 (C=O), 151.69 (C-2), 147.64 (C-6), 135.56 (C-2'), 134.24 (C-3 and C-5), 134.13 (C-4), 133.63 (C-1'), 129.70 (C-4'), 127.67 (C-3'), 72.27 (C-8), 70.21 (C-7), 63.52 (C-9), 26.85 (-C-$(CH_3)_3$), 19.23 (-C-$(CH_3)_3$).

(14) : (CD_3OD, solv. ref.) : δ 167.92 (C=O), 151.53 (C-2), 148.00 (C-6), 136.60 (C-2'), 136.11 (C-5), 135.69 (C-4), 134.65 (C-1'), 131.55 (C-3), 130.75 (C-4'), 128.68 (C-3'), 73.25 (C-8), 70.99 (C-7), 64.60 (C-9), 29.95 (-NH-CH_3), 27.37 (-C-$(CH_3)_3$), 19.94 (-C-$(CH_3)_3$).

(15) : ($CDCl_3$, solv. ref.) : δ 168.41 (C=O), 148.91 (C-2), 146.44 (C-6), 135.26 (C-2'), 134.61 (C-5), 133.83 (C-1'), 133.30 (C-4), 131.74 (C-3), 129.40 (C-4'), 127.39 (C-3'), 71.94 (C-8), 69.33 (C-7), 63.23 (C-9), 39.13 and 35.10 (-N-$(CH_3)_2$), 26.59 (-C-$(CH_3)_3$), 18.77 (-C-$(CH_3)_3$).

^{1}H-NMR.

(13) : (CD_3OD, solv. ref.) : δ 8.94 (1H, d, J=2.1 Hz, H-6), 8.66 (1H, d, J=2.0 Hz, H-2), 8.07 (1H, t, H-4), 7.64-7.68 (4H, m, H-2'), 7.32-7.40 (6H, m, H-3' and H-4'), 6.1 (2H, broad, -NH_2), 4.60 (2H, d, J=0.5 Hz, H-7), 3.86 (2H, t, J=4.9 Hz, H-8), 3.64 (2H, t, J=4.9 Hz, H-9), 1.03 (9H, s, -C-$(CH_3)_3$).

(14) : ($CDCl_3$, TMS) : δ 8.83 (1H, d, J=1.8 Hz, H-6), 8.58 (1H, d, J=1.7 Hz, H-2), 7.95

(1H, t, H-4), 7.59-7.63 (4H, m, H-2'), 7.26-7.35 (6H, m, H-3' and H-4'), 6.08 (1H, broad, NH-CH_3), 4.54 (2H, s, H-7), 3.80 (2H, t, J=5.0 Hz, H-8), 3.59 (2H, t, J=5.0 Hz, H-9), 2.91 (3H, d, J=4.7 Hz, NH-CH_3), 0.99 (-C-$(CH_3)_3$).

(15) : ($CDCl_3$, solv. ref.) : δ 8.61 (2H, broad, H-2 and H-6), 7.76 (1H, t, J=1.7 Hz, H-4), 7.67-7.71 (4H, m, H-2'), 7.35-7.43 (6H, m, H-3' and H-4'), 4.62 (2H, d, J=0.3 Hz, H-7), 3.88 (2H, t, J=5.0 Hz, H-8), 3.66 (2H, t, J = 5.0 Hz, H-9), 2.98 and 3.13 (6H, s, N-$(CH_3)_2$), 1.06 (9H, s, -C-$(CH_3)_3$).

DCI-mass spectrometry (NH_3).

(13) : m/z = 435 ($[MH]^+$, 100%).

(14) : m/z = 449 ($[MH]^+$, 100%).

(15) : m/z = 463 ($[MH]^+$, 100%).

Elemental analysis for $C_{25}H_{30}N_2O_3Si$ (13) : calc. C, 69.09%; H, 6.96%; N, 6.45%. Found : C, 69.02%; H, 7.03%; N, 6.39%.

Elemental analysis for $C_{26}H_{32}N_2O_3Si$ (14) : calc. C, 69.61%; H, 7.20%; N, 6.25%. Found : C, 69.70 %; H, 7.03%; N, 6.19%.

Elemental analysis for $C_{27}H_{34}N_2O_3Si$ (15) : calc. C, 70.09%; H, 7.41%; N, 6.06%. Found : C, 70.01%; H, 7.35%; N, 6.11%.

3-Thiocarbamoyl-5-(2-*tert*-butyldiphenylsilyloxyethoxymethyl)pyridine (16).

To a solution of 13 (250 mg) in toluene (3.6 ml) was added Lawesson's reagent (117 mg, 0.29 mmol), and the mixture was stirred at 80 C for 1.5 h. The solution was allowed to cool to room temperature, poured into a saturated $NaHCO_3$-solution (30 ml), and extracted with EtOAc (3 x 30 ml). The organic layers were washed with saturated $NaHCO_3$-solution (3 x 30 ml) and then with brine (3 x 30 ml). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by preparative CCTLC (CH_2Cl_2/CH_3OH (95:5)) to give the desired thioamide (16) as a yellow oil (58%).

^{13}C-NMR ($CDCl_3$, solv. ref.) : δ 199.44 (C=S), 150.90 (C-2), 146.02 (C-6), 135.42 (C-2'), 134.75 (C-5), 134.08 (C-4), 133.84 (C-3), 133.41 (C-1'), 129.64 (C-4'), 127.62 (C-3'), 72.19 (C-8), 70.06 (C-7), 63.35 (C-9), 26.80 (-C-$(CH_3)_3$), 19.13 (-C-$(CH_3)_3$).

^{1}H-NMR (CD_3OD, solv. ref.) : δ 8.92 (1H, d, J=2.3 Hz, H-6), 8.56 (1H, d, J=2.0 Hz, H-2), 8.22 (1H, t, H-4), 7.66-7.70 (4H, m, H-2'), 7.34-7.42 (6H, m, H-3' and H-4'), 4.62

(2H, d, J=0.5 Hz, H-7), 3.87 (2H, t, J=4.7 Hz, H-8), 3.70 (2H, t, J=4.7 Hz, H-9), 1.03 (9H, s, -C-$(CH_3)_3$).

DCI-mass spectrometry (NH_3) : m/z = 451 ($[MH]^+$, 100%), 417 ($[MH^+ - H_2S]$, 28%).

Elemental analysis for $C_{25}H_{30}N_2O_2SSi$: calc. C, 66.64%; H, 6.72%; N, 6.22%; S, 7.10%. Found : C, 66.55%; H, 6.75%; N, 6.15%; S, 7.02%.

3-(N-methylthiocarbamoyl)-5-(2-*tert*-butyldiphenylsilyloxyethoxymethyl)pyridine (17) and 3-(N,N-dimethylthiocarbamoyl)-5-(2-*tert*-butyldiphenylsilyloxyethoxymethyl)pyridine (18).

The thioamides 17 and 18 were synthesized by stirring a solution of 14 or 15 in toluene with Lawesson's reagent at 100 C for 2 h. The obtained mixtures were then treated by the same procedure as described for the synthesis of 16. This gave the thioamides 17 (79%) and 18 (77%) as a yellow oil.

^{13}C-NMR.

(17) : (CD_3OD, solv. ref.) : δ 196.85 (C=S), 150.43 (C-2), 147.14 (C-6), 138.55 (C-3), 136.54 (C-2'), 135.57 (C-5), 135.44 (C-4), 134.59 (C-1'), 130.69 (C-4'), 128.68 (C-3'), 73.25 (C-8), 70.93 (C-7), 64.60 (C-9), 33.89 (NH-CH_3), 27.37 (-C-$(CH_3)_3$), 19.94 (-C-$(CH_3)_3$).

(18) : ($CDCl_3$, solv. ref.) : δ 197.31 (C=S), 148.24 (C-2), 145.08 (C-6), 138.86 (C-3), 135.43 (C-2'), 134.74 (C-5), 133.48 (C-1'), 132.48 (C-4), 129.55 (C-4'), 127.54 (C-3'), 72.14 (C-8), 70.10 (C-7), 63.38 (C-9), 43.98 and 43.12 (N-$(CH_3)_2$), 26.57 (-C-$(CH_3)_3$), 18.92 (-C-$(CH_3)_3$).

^{1}H-NMR.

(17) : (CD_3OD, solv. ref.) : δ 8.79 (1H, d, J=2.1 Hz, H-6), 8.53 (1H, d, J=2.0 Hz, H-2), 8.11 (1H, t, H-4), 7.65-7.69 (4H, m, H-2'), 7.33-7.44 (6H, m, H-3' and H-4'), 4.54 (2H, d, J=0.4 Hz, H-7), 3.87 (2H, t, J=4.8 Hz, H-8), 3.68 (2H, t, J=4.8 Hz, H-9), 3.25 (3H, s, NH-CH_3), 1.03 (9H, s, -C-$(CH_3)_3$).

(18) : ($CDCl_3$, solv. ref.) : δ 8.53 and 8.49 (2H, s, broad, H-6 and H-2), 7.67-7.71 (4H, m, H-2'), 7.66 (1H, t, J=2.1 Hz, H-4), 7.35-7.45 (6H, m, H-3' and H-4'), 4.63 (2H, d, J=0.4 Hz, H-7), 3.88 (2H, t, J=5.0 Hz, H-8), 3.67 (2H, t, J=5.0 Hz, H-9), 3.60 and 3.16 (6H, s, N-$(CH_3)_2$), 1.07 (9H, s, -C-$(CH_3)_3$).

DCI-mass spectrometry (NH_3).

(17) : m/z = 465 ($[MH]^+$, 100%).

(18) : m/z = 479 ([MH]$^+$, 100%).

Elemental analysis for $C_{26}H_{32}N_2O_2SSi$ (17) : calc. C, 67.21%; H, 6.95%; N, 6.03%; S, 6.89%. Found : C, 67.18%; H, 6.90%; N, 5.95%; S, 6.93%.

Elemental analysis for $C_{27}H_{34}N_2O_2SSi$ (18) : calc. C, 67.75%; H, 7.17%; N, 5.86%; S, 6.69%. Found : C, 67.69%; H, 7.21%; N, 5.81%; S, 6.62%.

3-Thiocarbamoyl-5-(2-hydroxyethoxymethyl)pyridine (19), 3-(N-methylthiocarbamoyl)-5-(2-hydroxyethoxymethyl)pyridine (20) and 3-(N,N-dimethylthiocarbamoyl)-5-(2-hydroxyethoxymethyl)pyridine (21).

General procedure for the preparation of the unprotected thioamides 19 to 21.

To a solution of the protected thioamide (16,17,18) (0.33 mmol) in dry THF (25 ml), 2 eq. $(nBu)_4NF$ (0.66 ml) were added, and the mixture was stirred at room temperature for 1h. The solvent was evaporated in vacuo, and H_2O (50 ml) was added. This aqueous solution was extracted with EtOAc (4 x 50 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by preparative CCTLC (CH_2Cl_2/CH_3OH (90:10)) to give 19 to 21 as yellow oils.

Yields : (19) : 57%.
(20) : 51%.
(21) : 55%.

DCI-mass spectrometry (NH_3).

(19) : m/z = 213 ([MH]$^+$, 100%), 179 ([MH$^+$ - H_2S], 47%).

(20) : m/z = 227 ([MH]$^+$, 100%).

(21) : m/z = 241 ([MH]$^+$, 100%).

Elemental analysis for $C_9H_{12}N_2O_2S$ (19) : calc. C, 50.93%; H, 5.70%; N, 13.21%, S, 15.08%. Found : C, 50.95%; H, 5.64%; N, 13.18%; S, 15.00%.

Elemental analysis for $C_{10}H_{14}N_2O_2S$ (20) : calc. C, 53.08%; H, 6.24%; N, 12.39%; S, 14.14%. Found : C, 53.04%; H, 6.19%; N, 12.43%; S, 14.10%.

Elemental analysis for $C_{11}H_{16}N_2O_2S$ (21) : calc. C, 54.98%; H, 6.72%; N, 11.66%; S, 13.32%. Found : C, 54.87%; H, 6.75%; N, 11.59%; S, 13.28%.

3-Bromo-5-(2-hydroxyethoxymethyl)pyridine-1-oxide (22).

A mixture of 9 (500 mg, 2.3 mmol), 30% hydrogen peroxide (0.5 ml, 4.3 mmol) and glacial acetic acid (3 ml) was heated at 90 C for a period of 4 hours. It was then

diluted with 10 ml H_2O and evaporated to dryness under reduced pressure. The residue was dissolved in H_2O and the aqueous solution was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The obtained N-oxide was purified by preparative CCTLC (CH_2Cl_2/CH_3OH (95:5)). This gave 22 as a white solid (20%).

DCI-mass spectrometry (NH_3) : m/z = 248 ($[MH]^+$, 94.1%), m/z = 265 ($[MNH_4]^+$, 100%).

Elemental analysis for $C_8H_{10}BrNO_3$: calc. C, 38.87%; H, 4.08%; Br, 31.95%; N, 5.67%. Found : C, 38.75%; H, 3.90%; Br, 31.98%; N, 5.51%.

3-Carbamoyl-5-(2-hydroxyethoxymethyl)pyridine-1-oxide (23), 3-(N-methylcarbamoyl)-5-(2-hydroxyethoxymethyl)pyridine-1-oxide (24) and 3-(N,N-dimethylcarbamoyl)-5-(2-hydroxyethoxymethyl)pyridine-1-oxide (25).

General procedure for the synthesis of the N-oxides 23 to 25.

The amide nucleoside (10-12) (0.3 mmol) was dissolved in CH_3COOOH (32 wt. % solution in dilute acetic acid), and the mixture was stirred at 50 C for 3 hours. After this period the solvent was evaporated in vacuo and the residue was purified by preparative CCTLC (CH_2Cl_2/CH_3OH (85:15)). This gave the N-oxides (23-25) as a white solid (40 -50%).

Elemental analysis for $C_9H_{12}N_2O_4$ (23) : calc. C, 50.92%; H, 5.70%; N, 13.21%. Found : C, 50.87%; H, 5.72%; N, 13.15%.

Elemental analysis for $C_{10}H_{14}N_2O_4$ (24) : calc. C, 53.07%; H, 6.24%; N, 12.39%. Found : C, 52.98%; H, 6.20%; N, 12.36%.

Elemental analysis for $C_{11}H_{16}N_2O_4$ (25) : calc. C, 54.97%; H, 6.72%; N, 11.66%. Found : C, 55.02%; H, 6.78%; N, 11.60%.

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