Studies on the Chemical Synthesis of Potential Antimetabolites. 30. Regioselective Introduction of a Chlorine Atom into the Imidazo[4,5-*b*]pyridine Nucleus (1)

Tokuo Itoh*, Kazuo Ono, Tomokazu Sugawara and Yoshihisa Mizuno

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Received October 5, 1981

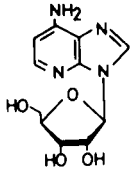
Reactions of some imidazo[4,5-*b*]pyridine 4-oxides with phosphoryl chloride are described. Treatment of *N*-1-substituted imidazo[4,5-*b*]pyridine 4-oxides with phosphoryl chloride led to the predominant formation of 7-chloro derivatives. This feature was successfully applied to the preparation of a chloroimidazo[4,5-*b*]pyridine nucleoside, which served as an important precursor of 1-deazaadenosine.

J. Heterocyclic Chem., **19**, 513 (1982).

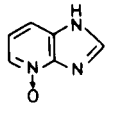
In view of the interesting biological and pharmacological properties of the deazapurine nucleosides, such as 3-deazaadenosine (2), tubercidin (7-deazaadenosine) (3) and some derivatives thereof, *viz.*, *S*-(3-deazaadenosyl)-homocysteine (4) and 5'-deoxy-5'-(isobutylthio)-3-deazaadenosine (5), we felt it a logical extension to also examine the biochemical and pharmacological properties of 1-deazaadenosine and derivatives thereof.

A number of papers dealing with the synthesis of the parent nucleoside, 1-deazaadenosine (**1**), have been published (6,7,8). However, an overall yield of **1**, from appropriate commercially available starting materials of each synthesis, is too low to secure ample amounts of the adenosine analog for a variety of screening tests or related examinations. A bottleneck in our previous synthesis is the nitration of imidazo[4,5-*b*]pyridine 4-oxide (**2a**) to afford only a low yield of the 7-nitro derivatives (**3**).

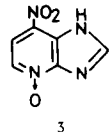
To circumvent the problem and to improve the overall yield from **2a** our effort has been to concentrate on the development of a new and efficient method for the



1



2a



3

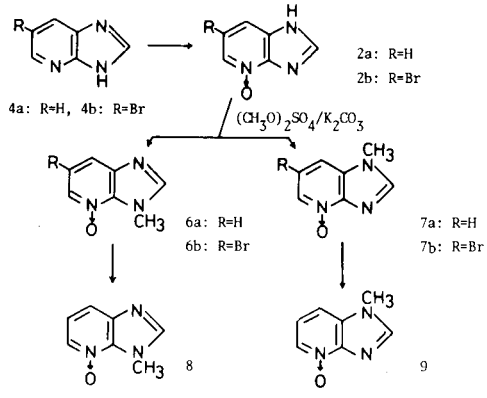
introduction of a substituent other than the nitro group on position 7 that is readily replaceable with nitrogen nucleophiles such as hydrazine or the azide ion.

We now wish to report the efficient synthesis of N-1 substituted 7-chloroimidazo[4,5-*b*]pyridine, involving reactions of imidazo[4,5-*b*]pyridine 4-oxides with phosphoryl chloride.

The 4-oxide **2a** was prepared from imidazo[4,5-*b*]-pyridine (see Scheme 1) by oxidation with hydrogen peroxide in acetic acid (9) or *m*-chloroperbenzoic acid (**5**) in about 95% yield. Oxidation of 6-bromoimidazo[4,5-*b*] pyridine with the peracid **5** gave the corresponding 4-oxide **2b** in 93.5% yield.

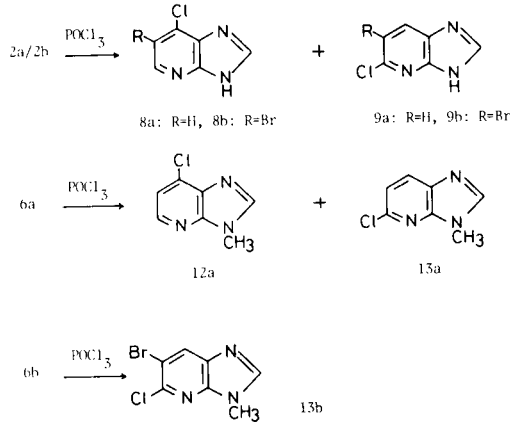
The 4-oxides, **2a** and **2b**, were converted to the corresponding 1-methyl-1*H*-**7a** and **7b** and 3-methyl-3*H*-**6a** and **6b** derivative by treatment with dimethyl sulfate in the presence of potassium carbonate. The site of methylation was elucidated by comparison of deoxigenated compounds **8** and **9** with the authentic samples (10).

Scheme 1



It has been well documented that the reaction of aromatic amine oxides, such as pyridine and quinoline 1-oxides, with phosphoryl chloride or sulfuryl chloride may give chlorinated derivatives with loss of the *N*-oxide group, usually, a mixture of α- and γ-chloro heterocycles being formed (11). Treatment of the oxides **2a** and **2b** with phosphoryl chloride at reflux temperature for two hours

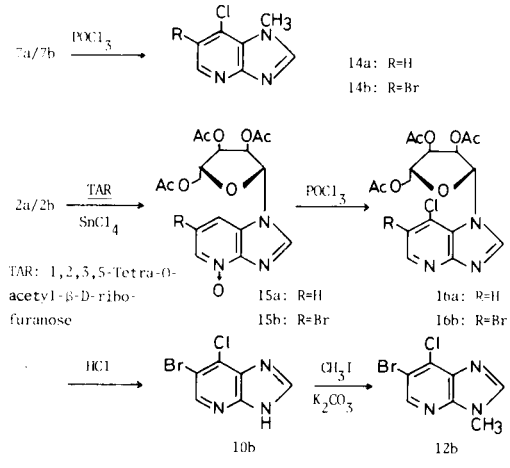
Scheme 2



gave rise to a mixture of comparable amounts of the corresponding 7-chloro-**10a** and **10b** and 5-chloro-**11a** and **11b** derivatives. Although we failed to separate the isomers, the ratios for formation of **8a/9a** and **8b/9b** could be determined by the pmr technique. Reaction of 3-methyl-3*H*-imidazo[4,5-*b*]pyridine 4-oxide (**6a**) also gave a mixture of 7-chloro-**12a** and 5-chloro-**13a** derivatives, which was isolated in the pure state by preparative thin layer chromatography, the yield being 40.5 and 20%, respectively. The structure of **12a** was confirmed by the presence of a doublet at lower field (δ 8.26 ppm) for H-5 with a fairly small coupling constant ($J_{5,6}$ = 5 Hz) (12). The isomer **13a** was assigned the structure on the basis of the presence of a larger doublet ($J_{5,6}$ = 8 Hz) for H-7 at 8.00 ppm. Treatment of **6b** with phosphoryl chloride in chloroform yielded a chlorinated product **13b** which was found to be not identical with 6-bromo-7-chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (**12b**). Thus, in the pmr spectrum of **12b** in chloroform-d, two singlets appeared at 8.05 and 8.53 ppm, which should be assigned to H-2 and H-5, respectively, whereas with **13b** singlets at 8.04 and 8.28 ppm were observed, which must be due to H-2 and H-7, respectively. Therefore, the structure of **13b** could be assigned as 6-bromo-5-chloro-3-methyl-3*H*-imidazo[4,5-*b*]-pyridine.

In the case of the N-1 methylated 4-oxides **7a** and **7b**, the results obtained deserve some comments. Thus, reactions of the 1-methyl-1*H*-isomers with phosphoryl chloride under comparable conditions, *vide supra*, led to the predominant formation of 7-chloro derivatives **14a** and **14b**. In the pmr spectrum of **14a**, a coupling between H-5 and H-6 was found to be 5.3 Hz. Furthermore, the signal due to the methyl group was observed at a much lower field (4.14 ppm for **14a** and 4.11 ppm for **14b**) than others, showing that the chlorine atom has been introduced in the position adjacent to the N-1 methyl group, that is position 7. The compounds, **15a** and **15b**, having the 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl) residue in place of a methyl group also reacted with phosphoryl chloride to yield the corresponding 7-chloro derivatives **16a** and **16b**. Compound **16a** turned out to be the useful intermediate for the synthesis of 1-deazaadenosine (**1**) (1).

Scheme 3



It is particularly worthy of note that in the reaction of N-1 substituted imidazo[4,5-*b*]pyridine 4-oxides with phosphoryl chloride, the chlorine atom was introduced exclusively into the more sterically hindered 7 position. To our knowledge, presumably this is the first example of introduction of a chlorine atom into the position *para* to the ring nitrogen in a case when the *ortho* position is vacant (11b). Bechman and Cooper reported that, in the quinoline 1-oxides, the 2- and 4-chloro isomers produced on treatment with phoshoryl chloride in variable ratios (0.6:1 to 3.5:1) were affected by the substituents already present in the benzenoid ring (13). We have no reasonable explana-

Table 1

PMR Spectral Data of Imidazo[4,5-*b*]pyridine

Compound	Solvent	Chemical Shifts (δ in ppm)					Coupling Constants (Hz)		
		H-2	H-5	H-6	H-7	N-CH_3	$J_{5,6}$	$J_{6,7}$	$J_{5,7}$
4a	Dimethylsulfoxide-d_6	8.45 s	8.32 dd	7.12 dd	7.96 dd		4.5	8.5	1.5
2a	Dimethylsulfoxide-d_6	8.50 s	8.35 dd	7.41 dd	7.94 dd		6.0	8.5	~1.0
10a	Dimethylsulfoxide-d_6	8.52 s	8.32 d	7.36 d			5.2		
11a	Dimethylsulfoxide-d_6	8.52 d		7.18 d	8.08 d			9.0	
8	Chloroform-d	8.02 s	8.50 dd	7.16 dd	7.66 dd	3.85 s	5.0	8.0	~1.0
6a	Dimethylsulfoxide-d_6	8.33 s	8.17 d	7.22 dd	7.72 d	4.25 s	6.3	8.3	
	Chloroform-d	7.94 s	8.18 d	7.15 dd	7.76 d	4.40 s	6.0	8.0	
12a	Chloroform-d	8.05 s	8.26 d	7.25 d		3.90 s	5.0		
13a	Chloroform-d	8.01 s		7.25 d	8.00 d	3.94 s		8.0	
9a	Chloroform-d	8.13 s	8.59 d	7.24 dd	7.77 d	3.88 s	5.0	8.0	
7a	Dimethylsulfoxide-d_6	8.41 s	8.22 dd	7.26 dd	7.68 dd	3.91 s	6.3	8.3	1.0
	Chloroform-d	7.99 s	8.31 dd	7.18 dd	7.37 dd	3.92 s	6.3	8.3	0.7
14a	Dimethylsulfoxide-d_6	8.46 s	8.30 d	7.30 d		4.04 s	5.0		
	Chloroform-d	8.06 s	8.41 d	7.19 d		4.14 s	5.2		

Table 2

Spectral Data of Brominated Imidazo[4,5-*b*]pyridines

Compound	Solvent	Chemical Shifts (δ in ppm)				Coupling Constants
		H-2	H-5	H-7	N-CH_3	$J_{5,7}$ (Hz)
4b	Dimethylsulfoxide-d_6	8.47 s	8.44 d	8.28 d		2.5
2b	Dimethylsulfoxide-d_6	8.50 s	8.50 d	7.96 d		1.5
6b	Dimethylsulfoxide-d_6	8.32 s	8.38 d	7.92 d	4.16 s	1.5
	Chloroform-d	7.87 s	8.25 d	7.84 d	4.32 s	1.2
12b	Chloroform-d	8.07 s	8.53 s		3.92 s	
13b	Chloroform-d	8.04 s		8.28 s	3.88 s	
7b	Dimethylsulfoxide-d_6	8.39 s	8.43 d	8.02 d	3.87 s	1.5
	Chloroform-d	7.94 s	8.40 d	7.51 d	3.89 s	1.5
14b	Chloroform-d	7.99 s	8.50 s		4.11 s	

tion for the above-mentioned unusual regioselectivity.

The pmr chemical shifts of imidazo[4,5-*b*]pyridines are summarized in Tables 1 and 2. It is worthy of note that, in the pmr spectra, the H-2 signals appeared at around 8 ppm in chloroform-d and further downfield (around 8.5 ppm) in dimethylsulfoxide-d_6 although signals due to the other protons were not affected. Elguero *et al.*, has also observed similar solvent effects with imidazo[4,5-*b*]-pyridines (14). This solvent-dependent shift may be a common tendency in imidazoles fused with another heterocycle.

EXPERIMENTAL

Melting points were taken on a Yamato melting point apparatus, Type MP-1, and are uncorrected. The uv spectra were taken on a Hitachi Recording Spectrophotometer 323. The pmr spectra were determined on a JEOL JNM-FX100 FT NMR Spectrometer; signals are designated as s (singlet), d (doublet), t (triplet or pseudo-triplet), dd (double doublet) and m (multiplet).

Imidazo[4,5-*b*]pyridine 4-Oxide (**2a**).

To a solution of 3.57 g (30 mmoles) of **4a** in 65 ml of acetic acid, 10.4 g (60 mmoles) of *m*-chloroperbenzoic acid (**5**, 80% purity) was added and the mixture was allowed to stand for one hour. Compound **2a** began to precipitate from the reaction mixture. After an hour the precipitate was collected by filtration and washed with 50 ml of ether. Recrystallization from 30 ml of water gave 3.85 g (95%) of **2a**, which was identical with an authentic sample (9).

6-Bromoimidazo[4,5-*b*]pyridine 4-Oxide (**2b**).

Compound **4b** (5.96 g, 30 mmoles) was oxidized with **5** in a procedure similar to that used to prepare **2a**. Crude **2b** oxide, obtained in 93.5% yield, was recrystallized from acetic acid to afford 4.1 g (63.9 %) of **2b**, mp 282-284°; uv (*p*H 1): λ max nm 223, 285, 309, 318.5; (*p*H 12), 227, 290, 322.5.

Anal. Calcd. for $C_6H_4BrON_3$: C, 33.67; H, 1.88; N, 19.63; Br, 37.34. Found: C, 33.76; H, 1.90; N, 19.48; Br, 37.06.

Methylation of **2a**.

To a suspension of 1.33 g (10 mmoles) of **2a** and 1.42 g (20.6 mmoles) of potassium carbonate in 40 ml of dimethylformamide, 0.97 ml (1.33 g, 10.3 mmoles) of dimethyl sulfate was added and the mixture was stirred at room temperature. After an hour another equimolar amount of dimethyl sulfate was added and the reaction mixture was stirred until it became a clear solution (usually three days). The solvent was evaporated *in vacuo* to give an oily residue which was dissolved in 50 ml of water. The aqueous solution was extracted with three 50 ml portions of chloroform and the organic layer was dried over magnesium sulfate. The dried solution was concentrated *in vacuo* to leave 3-methyl-3*H*-imidazo-[4,5-*b*]pyridine 4-oxide (**6a**) which was purified by alumina column chromatography. Evaporation of the chloroform-ethanol fraction (19:1, 70 ml) gave **6a** in the pure state, mp 153-156°; uv (*p*H 1.2): λ max nm 276 sh; 302 (*p*H 12.6): 273, 304, 307 sh.

Anal. Calcd. for $C_7H_7ON_3$: C, 56.37; H, 4.69; N, 28.18. Found: C, 56.57; H, 4.78; N, 28.16.

The aqueous layer, from which **6a** had been extracted, was concentrated *in vacuo* to afford a gray residue, which was extracted with three 20 ml portions of boiling chloroform. Concentration of the extract *in vacuo* gave a brown gum, which was crystallized from 5 ml of chloroform to give 0.551 g (36%) of 1-methyl-1*H*-imidazo[4,5-*b*]pyridine 4-oxide (**7a**), mp 113-118°; uv (*p*H 1.7): λ max nm 295; (*p*H 12.6) 296, 304 sh.

Anal. Calcd. for $C_7H_7ON_3$: C, 56.37; H, 4.69; N, 28.18. Found: C, 56.24; H, 4.80; N, 27.97.

Methylation of **2b**.

Compound **2b** (2.14 g 10 mmoles) was allowed to react essentially as described for the methylation of **2a**. 6-Bromo-3-methyl-3*H*-imidazo[4,5-*b*]-pyridine 4-oxide (**6b**) (0.42 g, 18.4%) was obtained, mp 178-179°; uv (*p*H 1.7): λ max nm 228, 282.5, 319; (*p*H 12.6): 228, 281.5, 318.5.

Anal. Calcd. for $C_7H_6BrON_3$: C, 36.86; H, 2.65; N, 18.43. Br, 35.04. Found: C, 36.83; H, 2.66; N, 18.58; Br, 35.03.

Recrystallization of a crude sample of 1-methyl-1*H*-imidazo[4,5-*b*]-pyridine 4-oxide (**7b**) gave 0.37 g (16.2%) of pure material, mp 251-253°; uv (*p*H 1.7): λ max nm 227.5, 291, 311, 321.5 (*p*H 12.6): 228.5, 291, 311, 321.5.

Anal. Calcd. for $C_7H_6BrON_3$: C, 36.86; H, 2.65; N, 18.43. Br, 35.04. Found: C, 36.82; H, 2.65; N, 18.52. Br, 34.92.

Reaction of **2a** with Phosphoryl Chloride.

A suspension of 2.66 g (20 mmoles) of **2a** in 20 ml of phosphoryl chloride was refluxed for two hours. The phosphoryl chloride was removed *in vacuo* to give an oily substance, which was neutralized with 50 ml of saturated sodium bicarbonate solution. The mixture was concentrated *in vacuo* to leave a white residue, which was extracted with chloroform using a Soxhlet apparatus. Evaporation of the solvent gave 2.27 g (74%) of a white solid which was found to be a mixture of **10a** and **11a** (the ratio = 3.5) by pmr spectra (DMSO-d_6): 8.52 (s, H-2), 8.32 (d, H-5, $J_{5,6}$ = 5.2 Hz) and 7.36 (d, H-6, $J_{5,6}$ = 5.2 Hz) for **10a**; 8.52 (s, H-2), 8.08 (d, H-7, $J_{6,7}$ = 9.0 Hz), 7.18 (d, H-6, $J_{6,7}$ = 9.0 Hz) for **11a**. It is difficult to separate the isomer mixture.

Reaction of **2b** with Phosphoryl Chloride.

Compound **2b** (4.1 g, 17.9 mmoles) was treated under the same conditions used to methylate **2a**. The reaction mixture was concentrated *in*

vacuo to give a gum, which was neutralized with 6 g of sodium bicarbonate in 100 ml of water. The white powder which precipitated was collected by filtration and 4.2 g (93.5%) of product mixture was obtained. Two substances (Rf 0.85, λ max 292 nm and Rf 0.75, λ max 300 nm) were observed upon tlc with a silica-gel plate (solvent system: 40% ethanol in chloroform). The pmr spectrum in dimethylsulfoxide-d_6 showed that the precipitate was a mixture of **10b** and **11b**, but they could not be separated from each other.

7-Chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (**12a**) and 5-Chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (**13a**).

To a solution of 149 mg (1 mmole) of **6a** in 5 ml of chloroform, 0.50 ml of phosphoryl chloride and three pieces of molecular sieve 4A were added and the mixture was heated at 50° for 19 hours. The solution was concentrated *in vacuo* to give a colorless material to which was added sodium bicarbonate solution (0.5 g in 10 ml of water) and then extracted with three 10 ml portions of chloroform. The combined extracts were dried over magnesium sulfate and the dried solution was concentrated *in vacuo* to give a mixture of **12a** and **13a**, which could be separated on alumina plates (developed with benzene-ethyl acetate = 1:2). From the upper band (Rf *ca* 0.54) 70 mg (40.5%) of **12a** was obtained, mp 118-121°; uv (*p*H 1.4): λ max nm 247, 250 sh 273.5, 281.5 (*p*H 12.6): 259, 280.5, 287; ms: 167/169 (M^+).

Anal. Calcd. for $C_7H_6ClN_3$: C, 50.16; H, 3.61; N, 25.07; Cl, 21.05. Found: C, 50.11; H, 3.58; N, 25.02; Cl, 21.03.

Compound **13a** (33.4 mg, 20%) was obtained from the slower moving band (Rf *ca* 0.44), mp 84-86°; ms: 167/169 (M^+).

Anal. Calcd. for $C_7H_6ClN_3$: C, 50.16; H, 3.61; N, 25.07; Cl, 21.05. Found: C, 50.35; H, 3.65; N, 24.90; Cl, 21.00.

6-Bromo-5-chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (**13b**).

Compound **6b** (114 mg, 0.5 mmole) was treated by the same procedure used to prepare **12a** and **13a**. The solvent was evaporated *in vacuo* to give a colorless material to which was added sodium bicarbonate solution (250 mg in 10 ml of water). The mixture was shaken with two 25 ml portions of chloroform. After drying the extract over magnesium sulfate, the chloroform was evaporated *in vacuo* to give 122 mg (99%) of **13b** which was crystallized from 4 ml of ethanol, mp 202°; uv λ max (ethanol): 245, 303, 309 sh.

Anal. Calcd. for $C_7H_5BrClN_3$: C, 34.12; H, 2.05; N, 17.06; Br, 32.38; Cl, 14.38. Found: C, 34.06; H, 2.06; N, 17.06; Br, 32.52; Cl, 14.34.

7-Chloro-1-methyl-1*H*-imidazo[4,5-*b*]pyridine (**14a**).

Compound **14a** (594 mg, 92%) was obtained by the treatment of 597 mg (4 mmoles) of **7a** with phosphoryl chloride essentially as described for the preparation of **13b**, mp 148-151° (benzene): uv (*p*H 1.35): λ max nm 275 sh, 283, 288 (*p*H 12.6): 261 sh, 280, 284: ms: 167/169 (M^+).

Anal. Calcd for $C_7H_6ClN_3$: C, 50.16; H, 3.61; N, 25.07; Cl, 21.05. Found: C, 50.36; H, 3.59; N, 25.48; Cl, 20.74.

6-Bromo-7-chloro-methyl-1*H*-imidazo[4,5-*b*]pyridine (**14b**).

Compound **14b** (106 mg, 86%) was obtained by the treatment of 114 mg (0.5 mmole) of **7b** with phosphoryl chloride essentially as described for the preparation of **13b**, mp 161-164° (ethanol): uv (ethanol): λ max nm 271 sh, 297.5.

Anal. Calcd. for $C_7H_5BrClN_3$: C, 34.12; H, 2.05; N, 17.06; Br, 32.38; Cl, 14.38. Found: C, 34.08; H, 2.03; N, 16.87; Br, 32.34; Cl, 14.26.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-imidazo[4,5-*b*]pyridine 4-Oxides (**15a**).

A mixture of 2.0 g (14 mmoles) of **2a**, 50 ml of hexamethyldisilazane, 30 ml of pyridine and 50 mg of ammonium sulfate was refluxed for 4 hours. The resulting clear solution was concentrated *in vacuo* to give a crude trimethylsilylated derivative of **2a**, which was azeotropically dried with toluene (20 ml × 4) and could be used in subsequent ribosylation without further purification. To a suspension of the trimethylsilylated base in 50 ml of acetonitrile were added 6.4 g (20 mmoles) of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose and 2.5 ml (*ca* 20 mmoles) of stannic chloride (15) and the mixture was stirred at room temperature for 18 hours. The resulting clear solution was concentrated *in vacuo* to leave a brown syrup which was neutralized with sodium bicarbonate solution (10 g in 100 ml of water) and then extracted with three 100 ml portions of chloroform. The extract was dried over magnesium sulfate and concentrated *in vacuo* to leave 7.2 g of a crude sample of **15a**, which was purified with a silica-gel column (4 cm × 30 cm). After washing with 500 ml of chloroform and 475 ml of ethanol-chloroform (1:19), **15a** was eluted out with 1.5 l of ethanol-chloroform (1:19). Evaporation of the solvent gave 4.33 g (60%) of **15a** as a foam; uv (*p*H 2): λ max nm 293 (*p*H 12): 299; pmr (chloroform-d): δ 8.40 (s, H-2, 1H), 8.30 (d, H-5, 1H, $J_{5,6}$ = 6.3 Hz), 7.70 (d, H-7, 1H, $J_{6,7}$ = 7.6 Hz), 7.21 (dd, H-6, 1H, $J_{5,6}$ = 6.3 Hz, $J_{6,7}$ = 7.6 Hz), 6.16 (d, H-1′, 1H, $J_{1',2'}$ = 5.9 Hz), 5.57 (t, H-2′, 1H), 5.38 (t, H-3′, 1H), 4.57 (m, H-4′, 1H), 4.47 (m, H-5′, 2H), 2.16 (s, CH_3CO, 6H), 2.14 (s, CH_3CO, 3H).

Anal. Calcd. for $C_{17}H_{19}N_3O_8 \cdot \frac{1}{2}H_2O$: C, 50.74; H, 5.00; N, 10.44. Found: C, 50.87; H, 5.04; N, 10.18.

6-Bromo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-imidazo[4,5-*b*]-pyridine 4-Oxide (**15b**).

Compound **15b** was prepared in 78.8% yield from **2b** by the same method used to obtain **15a**; uv (ethanol): λ max nm 238, 303 sh, 311, 322; pmr (chloroform-d): δ 8.42 (d, H-5, 1H, $J_{5,7}$ = 1.5 Hz), 8.27 (s, H-2, 1H), 7.83 (d, H-7, 1H, $J_{5,7}$ = 1.5 Hz), 6.03 (d, H-1′, 1H, $J_{1',2'}$ = 4.9 Hz), 5.48 (t, H-2′, 1H), 5.36 (t, H-3′, 1H), 4.50 (m, H-4′ and H-5′, 3H), 2.22 (s, CH_3CO, 3H), 2.16 (s, CH_3CO, 3H), 2.14 (s, CH_3CO, 3H).

Anal. Calcd. for $C_{17}H_{18}BrN_3O_8$: C, 43.23; H, 3.81; N, 8.89; Br, 16.96. Found: C, 43.42; H, 3.91; N, 8.57; Br, 17.01.

7-Chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-imidazo[4,5-*b*]pyridine (**16a**).

To a solution of 5.95 g (15.1 mmoles) of **15a** in 100 ml of chloroform were added 2.0 ml (21.6 mmoles) of phosphoryl chloride, 400 mg of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose and 1.0 g of molecular sieve 4A. The mixture was stirred at 30-33° for 24 hours. The solution was concentrated *in vacuo* to give a brown syrup, which was dissolved in 50 ml of chloroform. The solution was poured into sodium bicarbonate solution (15 g in 200 ml of water) under stirring. The aqueous layer was extracted with 100 ml of chloroform. The combined organic layer, after drying with sodium sulfate, was concentrated *in vacuo* to give 5.18 g of a brown syrup, which was purified by silica-gel chromatography. After elution with chloroform, **16a** was obtained by evaporation of 2% ethanol-chloroform (*ca* 1,000 ml) as light yellow foam; uv (ethanol): λ max nm 254, 281, 287; ms: 411/413 (M^+); pmr (chloroform-d): 8.65 (s, H-2, 1H), 8.51 (d, H-5, 1H, $J_{5,6}$ = 5.4 Hz), 7.32 (d, H-7, 1H, $J_{5,6}$ = 5.4 Hz), 6.75 (d, H-1′, 1H, $J_{1',2'}$ = 4.2 Hz), 5.65 (t, H-2′, 1H), 5.34 (t, H-3′, 1H), 4.52 (m, H-4′, 1H), 4.44 (m, H-5′, 2H), 2.20 (s, CH_3CO, 3H), 2.13 (s, CHCO, 6H).

Anal. Calcd. for $C_{17}H_{18}ClN_3O_7$: C, 49.58; H, 4.41; N, 10.20; Cl, 8.61. Found: C, 49.69; H, 4.36; N, 9.98; Cl, 8.27.

6-Bromo-7-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-imidazo-[4,5-*b*]pyridine (**16b**).

Compound **16b** was obtained in 65% yield by treatment of **15b** with phosphoryl chloride essentially as described for the preparation of **16a**; uv (ethanol): λ max: 256, 297; pmr (chloroform-d): δ 8.70 (s, H-5, 1H), 8.58 (s, H-2, 1H), 6.74 (d, H-1′, 1H, $J_{1',2'}$ = 4.5 Hz), 5.66 (t, H-2′, 1H), 5.44 (t, H-3′, 1H), 4.42 (m, H-4′ and H-5′, 3H), 2.18 (s, CH_3CO, 3H), 2.12 (s, CH_3CO, 6H). Prolonged reaction led to the isomerization of **16b** to 3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-3*H*-derivative. The glycoside bond of **16b** was found to be unstable and to degrade to **10b** and a sugar.

6-Bromo-7-chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (**12b**).

To a solution of 100 mg of **16b** in ethanol, a drop of concentrated hydrochloric acid was added and the solution allowed to stand for 4 hours. Compound **10b** which precipitated from the reaction mixture was collected by suction to give 35 mg of compound, mp 260°; uv (*p*H 1): λ max nm 252, 293; (*p*H 7): 258, 293; (*p*H 12): 300. To a solution of **10b** (135 mg) in 10 ml of dimethylformamide was added 138 mg of potassium car-

bonate and 0.14 ml of methyl iodide and the mixture was stirred at room temperature for 20 hours. The solvent was evaporated *in vacuo* to give a syrup, which was dissolved in 20 ml of water. The solution was extracted with three 10 ml portions of chloroform, which was dried over magnesium sulfate. Evaporation of the solvent gave 40 mg of **12b**. Recrystallization from ethanol gave 25 mg of **12b** in the pure state, mp 169-170°; uv (*p*H 1): λ max nm 252.5, 292.5; (*p*H 12): 263.5, 296.

Anal. Calcd. for $C_7H_5BrClN_3$: C, 34.12; H, 2.05; N, 17.05; Br, 32.38; Cl, 14.38. Found: C, 34.02; H, 2.09; N, 17.09; Br, 32.24; Cl, 14.19.

Acknowledgement.

This research was supported in part by a grant-in-aid for special project from the Ministry of Education, Science and Culture, Japan.

REFERENCES AND NOTES

(1) For **29**, T. Itoh, T. Sugawara and Y. Mizuno, *Heterocycles*, **17**, 305 (1982).

(2a) P. K. Chiang and G. L. Cantoni, *Biochem. Pharmacol.*, **28**, 1897 (1979); (b) R. T. Borchardt, *J. Med. Chem.*, **23**, 347 (1980); (c) T. P. Zimmerman, G. Wolberg, C. R. Stopford and G. L. Duncan, "Transmethylation", Usdin, Borchardt, and Creveling, Elsevier, North Holland, 1978, pp 187-196.

(3) R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, John Wiley and Sons, Inc, New York, NY, 1970, pp 315-320.

(4) R. T. Borchardt, "The Biochemistry of Adensoylmethionine", Columbia University Press, New York, NY, 1977, pp 152-157.

(5) P. K. Chiang, G. L. Cantoni and J. P. Badex, *Biochem. Biophys. Res. Commun.*, **82**, 417 (1978).

(6) P. C. Jain, S. K. Chatterjee and N. Anand, *Ind. J. Chem.*, **4**, 403 (1966).

(7) K. B. De Roos and C. A. Salemink, *Rec. Trav. Chim.*, **90**, 654 (1971).

(8) T. Itoh, S. Kitano and Y. Mizuno, *J. Heterocyclic Chem.*, **9**, 465 (1972).

(9) Y. Mizuno, N. Ikekawa, T. Itoh and K. Saito, *J. Org. Chem.*, **30**, 4066 (1965).

(10) Y. Mizuno, M. Ikehara, T. Itoh and K. Saito, *ibid.*, **28**, 1837 (1963).

(11) E. Ochiai, "Aromatic Amine Oxides", Elsevier Publishing Company, Amsterdam·London·New York, 1967, pp 259-269; (b) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides", Academic Press, London and New York, 1971, pp 258-270.

(12) L. M. Jackman and S. Sterhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd Ed, Pergamon Press, London, 1969, pp 305-311.

(13) G. B. Bechman and D. E. Cooper, *J. Org. Chem.*, **9**, 302 (1944).

(14) J. Elguero, A. Frughier and S. Mignonag-Mondon, *Bull. Soc. Chim. France*, 2916 (1972).

(15) U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **39**, 3654 (1974).