

SYNTHESIS OF 5- AND 6-AMINO-IMIDAZO[4,5-b]PYRIDINE RIBONUCLEOSIDES

(A NEW TYPE OF ADENOSINE ANALOGS) BY COUPLING REACTIONS¹⁾

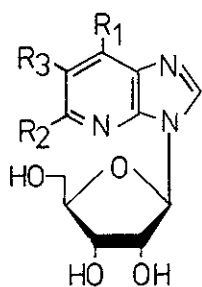
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Synthesis of 5- (2) and 6-amino-3-(β -D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine (3) is described. Ribosylation of 5-acetamidoimidazo[4,5-b]pyridine by "the mercuric cyanide-nitromethane" procedure gave rise to 3-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)-3H-derivative 5 (71.2% yield) together with a considerable amount (18.3%) of 1-isomer (7). A trimethylsilylated derivative of 6-nitroimidazo[4,5-b]pyridine (16) was also ribosylated in the presence of stannic chloride to yield 3-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)-3H-derivative (17) (35%) and its positional isomer (19) (10.8%). The blocked nucleosides (5, 7, 17, and 19) were converted into the corresponding free nucleosides (2, 9, 3, and 21). Physical properties (pKa-values, chemical shifts, uv absorption maxima, and CD-parameters) of the newly prepared nucleosides are also reported.

It is well known that adenosine is a constituent of many naturally occurring substances of biological importance ²⁾ (e.g., NAD, Coenzyme A, ATP, cAMP,

Dedicated to the 80th birthday of Prof. Shigehiko Sugasawa.

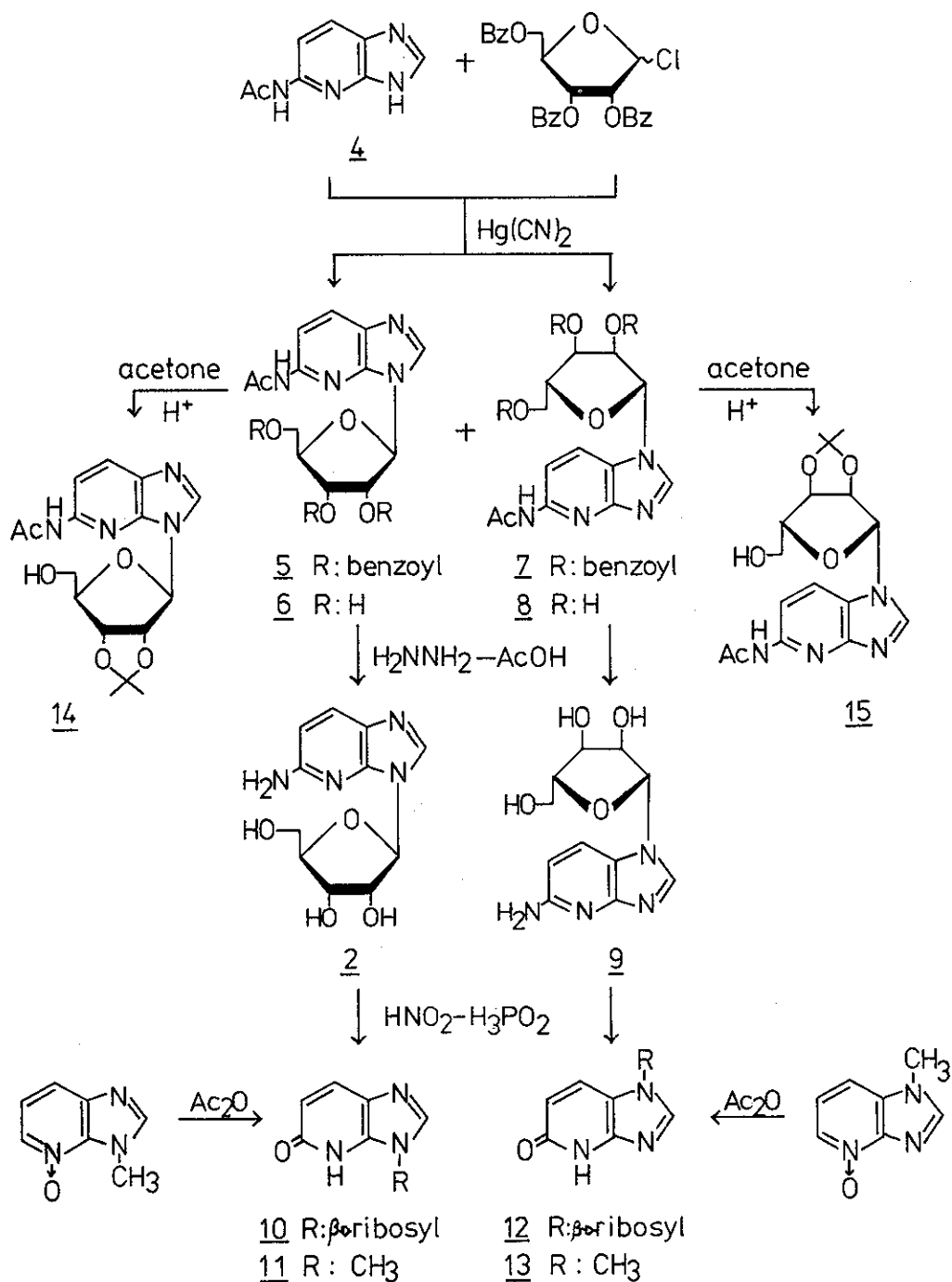


	R ₁	R ₂	R ₃	
<u>1</u>	NH ₂	H	H	(1-Deazaadenosine)
<u>2</u>	H	NH ₂	H	
<u>3</u>	H	H	NH ₂	

KNA, etc.). Synthesis of adenosine analogs has been extensively pursued to search potent antimetabolites or antagonists and not a few analogs turned out to show the wide-spectrum of chemotherapeutic activity.³⁾

Recently we have reported the synthesis of some deazapurine ribonucleosides.⁴⁾ Out of these, 1-deazaadenosine (1) phosphates showed the ability to act as a substrate or an activator for a number of adenosine-utilizing enzymes including cAMP-dependent protein kinase⁵⁾ and 5'-nucleotidase.^{4c)} 1-Deazakinetin ribonucleoside was found to exhibit potent cytokinin activity in the tobacco pitch callus bioassay.⁶⁾ Furthermore, 1 shows potent antileukemic activity.⁷⁾ In sharp contrast, the corresponding 3-deazaadenosine derivatives showed no such remarkable activities. These results prompted us to prepare other 1-deazaadenosine analogs. We now wish to report the synthesis of 5- and 6-amino-imidazo[4,5-b]-pyridine ribosides (2, 9, 3, and 21).

Condensation of 5-acetamido-imidazo[4,5-b]pyridine (4)⁸⁾ with 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride was achieved in the presence of mercuric cyanide and molecular sieve at refluxing temperature⁹⁾ for 3 hours to afford a mixture of two nucleosidic substances, 5 and 6, which could be isolated in pure state by the use of a silica gel column in 71.2% and 18.3% yield, respectively. Treatment of each nucleoside (5 and 6) with methanolic sodium methoxide



effected complete removal of O-benzoyl protecting groups (but not N-acyl group) to give 5-acetamido-imidazo[4,5-b]pyridine ribosides (6 and 8). Further removal of N-acetyl groups of 6 and 8 required treatment with hydrazine-acetic acid in pyridine ¹⁰⁾ at 70-75° to give 5-amino-imidazo[4,5-b]pyridine riboside (2 and 9) in 72 and 51% yields, respectively. The structures of these nucleosides were determined in the following ways. Nucleosides, 2 and 9, were each treated with sodium nitrite in hypophosphorous acid to yield imidazopyridone derivatives, 10 and 12, respectively, whose UV absorption spectra were found to be almost indistinguishable with those of corresponding 3- and 1-methyl counterparts. ¹¹⁾ On the basis of these data, the site of ribosylation in the nucleoside, 2 was determined to be N-3 and that of 9, N-1. The anomeric configuration was established to be β after the conversion into the corresponding isopropylidene derivative, 14 and 15, by invoking the "isopropylidene rule" ¹²⁾ ($\Delta\delta_{CH_3}$ 0.20 and 0.23 ppm, respectively). Ribosylation of 4 by alternate methods (the trimethylsilyl procedure ¹³⁾ or the fusion procedure ¹⁴⁾) gave a complex mixture of products. Out of these, 3- α -D-ribofuranosyl derivative could be detected.

The synthesis of another target nucleoside started with 6-nitro-imidazo[4,5-b]pyridine ¹⁵⁾ which was silylated with large excess of hexamethyldisilazane (HMDS) at refluxing temperature. The crude trimethylsilylated derivative which had been obtained by removal of HMDS was used for the subsequent step without further purification. Condensation of this silyl derivative (16) with 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribose in $SnCl_4/CH_3CN$ at room temperature for 12 hours afforded a complex mixture of nucleosidic products, from which a pair of monoglycosyl derivative (17 and 19) were isolated in 35% and 10.8% yield, respectively. Removal of the benzoyl groups with sodium methoxide followed by catalytic reduction of nitro group with 10% Pd-charcoal gave rise to 6-amino-imidazo[4,5-b]pyridine ribosides, 3 and 21, in 52 and 35% respective yield.

Table 1 Physical Properties of 5-, 6-, and 7-Amino-imidazo[4,5-b]pyridine
3-Ribosides (2, 3, and 1)

	melting point(°C)	pmr chemical shifts*(ppm) due to sugar protons H _{1'} H _{2'} H _{3'} H _{4'} 2H _{5'} (J _{1',2'}) (J _{2',3'}) (J _{3',4'})	absorption maxima(nm) (ε x10 ⁻³)	pKa**	elemental analysis*** (found)
<u>1</u>	258.5	5.89 4.76 4.12 4.03 3.6 (6.0) (5.0) (2.5)	(pH 7.17) (pH 1.05) 262(14.0) 265(12.2) 278(10.3) 282(17.0)	4.70	C: 49.43 H: 5.27 N: 20.88
<u>2</u>	164~6	5.88 4.59 4.14 3.88 3.6 (6.0) (5.1) (2.8)	(pH 8.15) (pH 1.70) 247(4.80) 240s(3.95) 310(10.4) 316(10.7)	4.14	C: 49.60 H: 5.38 N: 20.78
<u>3</u>	178~82	5.88 4.64 4.14 3.97 3.6 (6.0) (5.4) (2.5)	(pH 6.87) (pH 2.05) 250s(6.30) 270(8.90) 319(7.80) 274s(8.80) 325(4.75)	4.00	C: 49.42 H: 5.35 N: 20.78

*Measured in dimethyl sulfoxide-d₆ at room temperature.

**Determined spectrophotometrically according to D. Shugar and J. J. Fox; Biochim. Biophys. Acta, 9, 199(1952).

***Calcd. for C₁₁H₁₄N₄O₄; C: 49.62, H: 5.30, N: 21.04

Table 2 Pmr Chemical Shifts of the Blocked Nucleosides, 5 and 14, in Various Solvents (ppm)

compd. solvent		-NH-	H ₂	H ₆	H ₇	H _{1'}	H _{2'}	H _{3'}	H _{4'}	2H _{5'}
5	Chloroform-d	8.68	8.10		8.21	6.24	6.53	6.80	5.25	4.50
	Dimethyl sulfoxide-d ₆	10.46	8.60	8.10		6.62	6.70-6.20		4.86	
	Methanol-d ₄	failed to be assigned					6.50		4.80	
14	Chloroform-d	8.00	8.05	8.08	8.22	5.96	5.20	5.10	4.52	3.82 4.02
	Dimethyl sulfoxide-d ₆	10.39	8.95	8.07		6.24	5.41	5.14	4.17	3.52

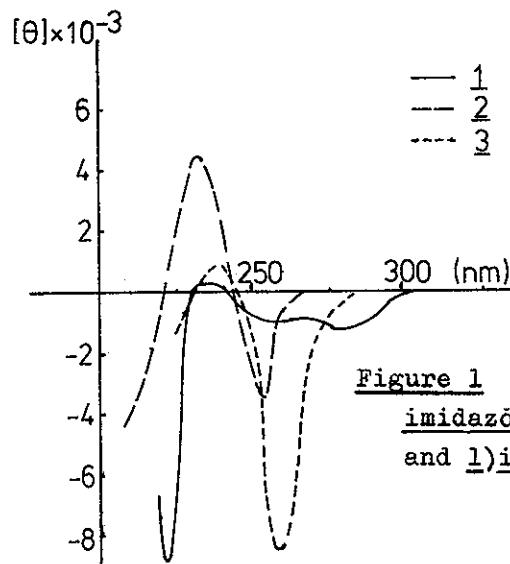


Figure 1 CD Spectra of 5-, 6-, and 7-Amino-
imidazo[4,5-b]pyridine 3-Ribosides(2, 3,
and 1)in Phosphate Buffer(pH 6.87)

The site of ribosylation was established by their conversion to the known nucleosides (22 and 23, respectively) ¹⁶⁾ and their anomeric configuration was assigned to be β on the basis of nmr spectral data [the observed chemical shifts ($\Delta\delta$) of the isopropylidene methyl groups in 24 and 25 were 0.24 and 0.23 ppm]. ¹²⁾

Physical properties of the newly prepared nucleosides, 2 and 3, are listed in Table 1 together with those of 1.

As regards the pmr spectra, signals due to H₂, of 2 and 3 appear at higher field by 0.17 and 0.12 ppm and those of H₄, by 0.15 and 0.06 ppm, respectively, than the corresponding signals of 1. These results may be explained by the assumption that the decrease in the proportion of syn to anti conformation about the glycosyl linkage is ordered as 1 > 3 > 2. ¹⁷⁾

Remarkable solvent effects in pmr spectra of the blocked nucleosides, 5 and 14, were observed as shown in Table 2. The corresponding positional isomers, 7 and 15, did not show such properties, indicating that the conformation of the 3-glycosyl isomers depends on the solvents to considerable extent.

CD spectra of 1, 2, and 3 are shown in Figure 1. It is to be noted that greater amplitudes of Cotton effects are observed in the latter two nucleosides, compared with that of the former.

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