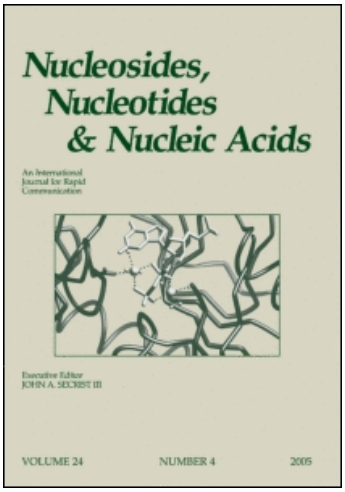

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Studies on the Chemical Synthesis of Potential Antimetabolites. 31.[1] A Novel Synthesis of 1-Deazaadenosine and Its Conversion to 5'-Deoxy-5'-Isobutylthio-1-Deazaadenosine (1-Deaza-Siba) and S-(1-Deazaadenosyl)-Homocysteine (1-DEAZA-SAH)

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STUDIES ON THE CHEMICAL SYNTHESIS OF POTENTIAL ANTIMETABOLITES. 31.[1] A NOVEL SYNTHESIS OF 1-DEAZAADENOSINE AND ITS CONVERSION TO 5'-DEOXY-5'-ISOBUTYLTHIO-1-DEAZAADENOSINE(1-DEAZA-SIBA) AND S-(1-DEAZAADENOSYL)-HOMOCYSTEINE(1-DEAZA-SAH)

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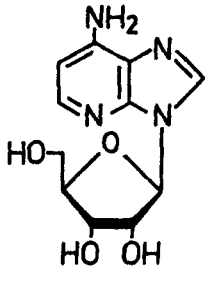
Abstract — A novel route for the preparation of 7-amino-3-(β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine(1-deazaadenosine) has been developed. Synthesis of 5'-deoxy-5'-isobutylthio-1-deazaadenosine(1-deazaSIBA) and S-(1-deazaadenosyl)-homocysteine(1-deazaSAH) is also described.

In view of current interest in chemotherapeutic and biological properties of adenosine and deazaadenosine derivatives[viz, 5'-deoxy-5'-isobutylthioadenosine(SIBA, 2a), S-adenosylhomocysteine(SAH, 3a), and the 3-deaza-counterpart, 2b or 3b],[2] we have been seeking an efficient preparation of 1-deazaadenosine(1), whose derivatives of biological interest such as compounds, 2c and 3c, have been a missing link in this area. This is because low overall yields of reported syntheses[3]



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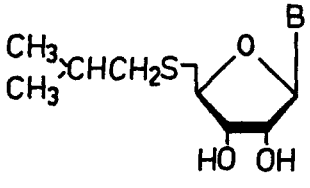
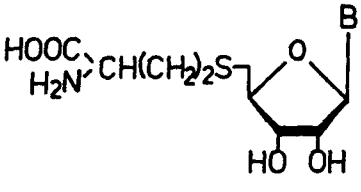
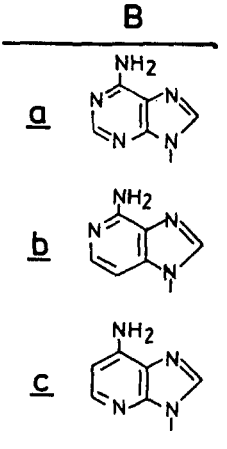


2a-c



3a-c



of 1 have rendered the availability of adequate quantities of analogs of 1-deazaadenosine series difficult and have hampered comparative studies on biochemical or biophysical properties among each counterpart.

In a preliminary communication we briefly described a new and efficient synthesis of 1[4], utilizing some recent advances in both aromatic amine N-oxides[1] and nucleoside chemistry[5], and a full description of this work along with the conversion of 1 to 5'-alkylthio-5'-deoxy-derivatives(2c and 3c) is now given.

The trimethylsilyl derivative(5), prepared from imidazo[4,5-b]-pyridine 4-oxide(4)[1,6] with hexamethyldisilazane in pyridine, was condensed with 1.2 equiv of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose(TAR, 6) in acetonitrile in the presence of stannic chloride[7] for 6 hours to give 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1H-imidazo[4,5-b]pyridine 4-oxide(7) in 82.2 % yield, which in turn was treated with methanolic ammonia to give a deacetylated nucleoside, 8. The site of glycosylation of 7 and 8 was elucidated by comparison of their uv absorption spectra with those of the corresponding N-methyl derivatives(see TABLE 1).

We have shown that in the reaction of 1-substituted-1H-imidazo-[4,5-b]pyridine 4-oxides with phosphoryl chloride a chlorine atom was selectively introduced into the position 7[1]. This precedented feature was successfully applied to the preparation of 7-chloro-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1H-imidazo[4,5-b]pyridine(9). Thus, treatment of the oxide(7) with phosphoryl chloride or Vilsmeier reagent(phosphoryl chloride and dimethylformamide) led to the exclusive formation of a chlorinated nucleoside 9 in an excellent yield. As shown in TABLE 2, the anomeric protons in the pmr of 9 and its deacetylated nucleoside(10) appeared at comparatively lower field(6.75 and 6.40 ppm, respectively), suggesting that the chlorine atom was introduced in the vicinity of the anomeric proton, that is, in the position 7. It is worthy of note that, in the case where the Vilsmeier reagent was used as the chlorinating agent, an increased yield of the desired nucleoside(9) was obtained with a reduced reaction time. To our knowledge, this is the first successful example of the reaction of the Vilsmeier reagent with aromatic amine oxides.

It has been established in our laboratory[5] that in the presence of an appropriate Lewis acid an equilibrium between 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1H-imidazo[4,5-b]pyridine(A) and its 3-glycosyl-3H-

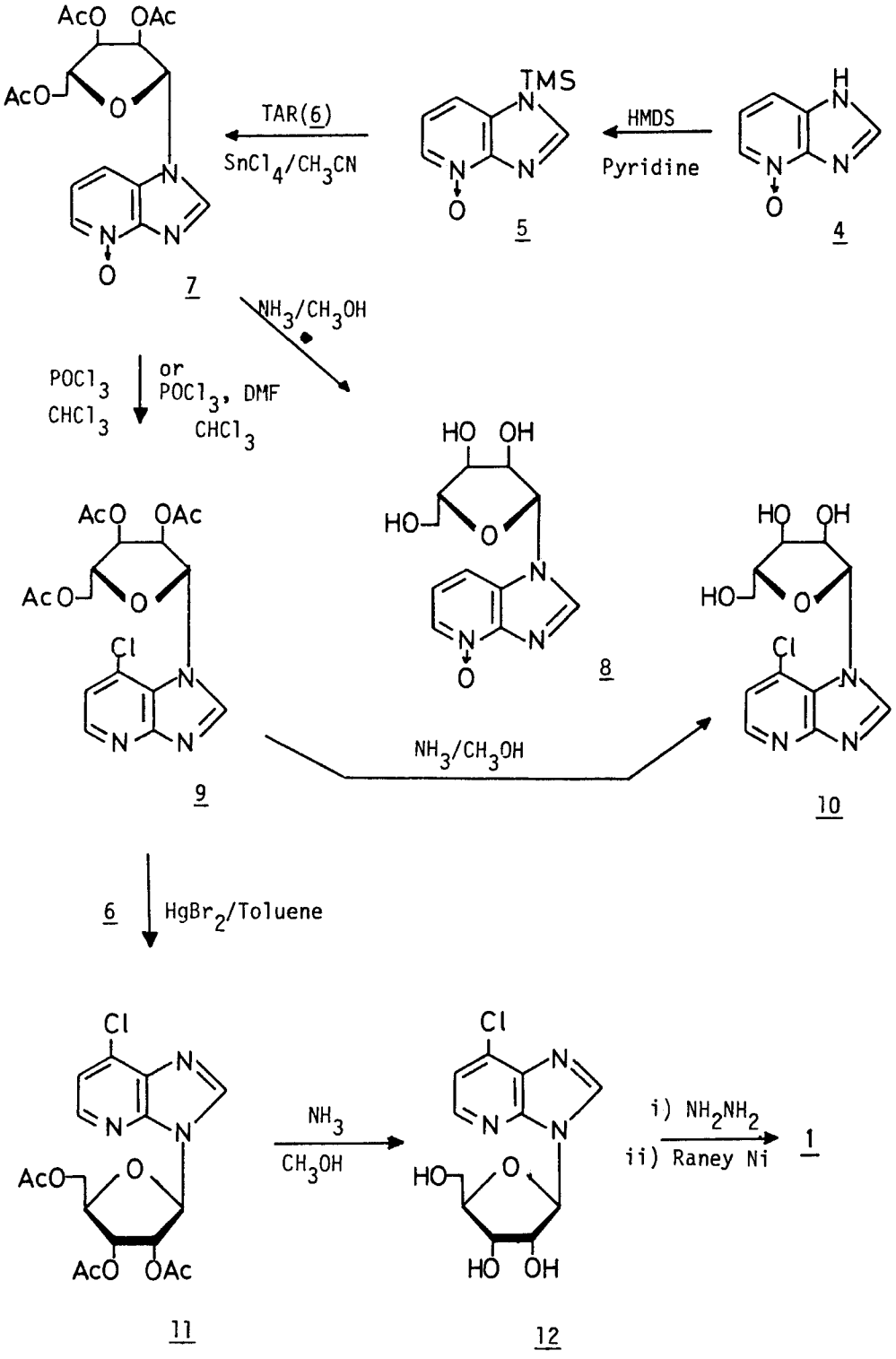
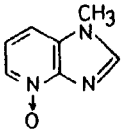
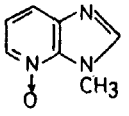
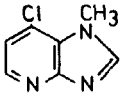
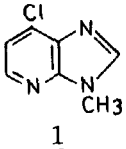
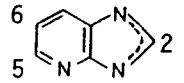


TABLE 1 Uv Absorption Maxima (nm) (and $\varepsilon x10^{-3}$) of Imidazo[4,5-b]pyridines

Compound	Solvent	0.1N HCl			0.1N NaOH		
7	ethanol	223.5	293		224.5	299	
8	water	217.5	293.5		218.5	294.5	
	water		295			296.5	304sh
	water	280sh	301.5		273	304	309sh
9	ethanol	277sh	284	287sh	257	280.5	286sh
10	water	276sh	283 (11.1)	287sh	257 (6.98)	280 (10.4)	285sh
	water	277sh	283	288sh	261sh	280	284sh
11	ethanol	249	275	280sh	257	278.5	285sh
12	water	250	274	281.5	256.5	279	285sh
	water	247	273	281.5	259	280.5	287sh
1	water		266sh	282.5		262.5	278
13	water		265sh	283		263	278.5
2c	water		267sh	284 (16.9)		263 (14.4)	278 (10.7)
3c	water		265sh	283 (22.8)		263 (14.0)	278 (11.0)

sh: shoulder

TABLE 2 Pmr Chemical Shifts of Imidazo[4,5-b]pyridine Derivatives(*1)



(Coupling Constants)

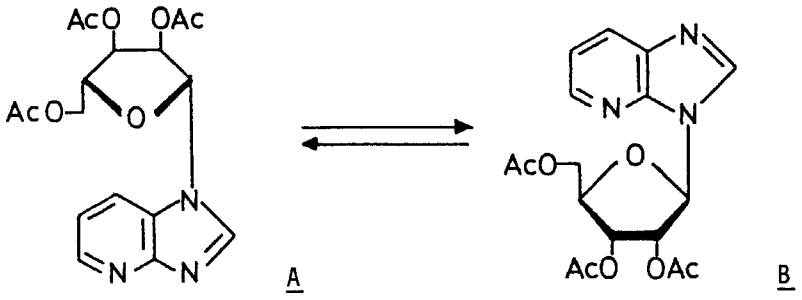
Compd.	Solvent	H-2	H-5	H-6	H-7	H-1'	H-2'	H-3'	H-4'	H-5'	Other Protons(*2)		
7	$CDCl_3$	8.40s	8.30d ($J_{5,6}$=6.3Hz)	7.21dd ($J_{6,7}$=7.6Hz)	7.70d	6.16d ($J_{1,2}$=5.9Hz)	5.57t	5.38t	4.57m	4.47m	2.16s (Ac)	2.14s (Ac)	
8	DMSO-d_6	8.66s	8.23d ($J_{5,6}$=5.9Hz)	7.26dd ($J_{6,7}$=7.8Hz)	7.87d	5.91d ($J_{1,2}$=6.3Hz)	4.34t	4.13t	4.02m	3.66m			
9	$CDCl_3$	8.65s	8.51d ($J_{5,6}$=5.4Hz)	7.32d	-	6.75d ($J_{1,2}$=4.2Hz)	5.65t	5.43t	4.52m	4.44m	2.20s (Ac)	2.13s (Ac)	
10	DMSO-d_6	9.02s	8.39d ($J_{5,6}$=5.4Hz)	7.44d	-	6.40d ($J_{1,2}$=4.5Hz)	4.43q	4.25q	4.00m	3.66m			
11	$CDCl_3$	8.30s	8.31d ($J_{5,6}$=5.4Hz)	7.34d	-	6.28d ($J_{1,2}$=5.1Hz)	6.03t	5.71t	4.43m		2.15s (Ac)	2.12s (Ac)	2.09s (Ac)
12	DMSO-d_6	8.82s	8.35d ($J_{5,6}$=5.0Hz)	7.50d	-	6.07d ($J_{1,2}$=5.4Hz)	4.63	4.19q	3.99q	3.63m			
1	DMSO-d_6	8.22s	7.75d ($J_{5,6}$=5.4Hz)	6.35d		5.85d ($J_{1,2}$=6.3Hz)	4.68q	4.11q	3.96m	3.58m	6.47s (NH_2)		
13	DMSO-d_6	8.25s	7.81d ($J_{5,6}$=5.6Hz)	6.36d	-	5.95d ($J_{1,2}$=5.9Hz)	4.76q	4.20q	4.06m	3.87m	6.38s (NH_2)		
2c	DMSO-d_6	8.27s	7.82d ($J_{5,6}$=5.4Hz)	6.38d	-	5.92d ($J_{1,2}$=5.9Hz)	4.78q	4.14q	4.00m	2.80m	6.34s (NH_2) 0.87q (CH_3)	2.38q (SCH_2-)	1.69m (CH)
3c	D_2O	8.35s	7.95d ($J_{5,6}$=5.7Hz)	6.63d	-	6.08d ($J_{1,2}$=5.5Hz)	*3	4.39t	4.31m	2.96m	2.55t (SCH_2-)	1.78m (CH_2CH)	3.22q (CH)

*1. Signals are designated as s(singlet), d(doublet), t(triplet), q(quartet), and m(multiplet).

*2. Signals due to hydroxyl groups of the unblocked nucleosides are not given.

*3. The signal was buried in HOD-peak.

isomer(B) exists in solution and that the ratio of A to B may depend on the solvent used. Thus, in acetonitrile or nitromethane a mixture of



A B

comparable amounts of the isomers may be obtained, whereas in refluxing toluene the thermodynamically more stable product may be the isomer B. A similar transglycosylation took place with compound 9. Thus, treatment of 9 with mercuric bromide in toluene in the presence of 6 gave rise to a transglycosylated product 11 in 75.9 % yield.[5b]

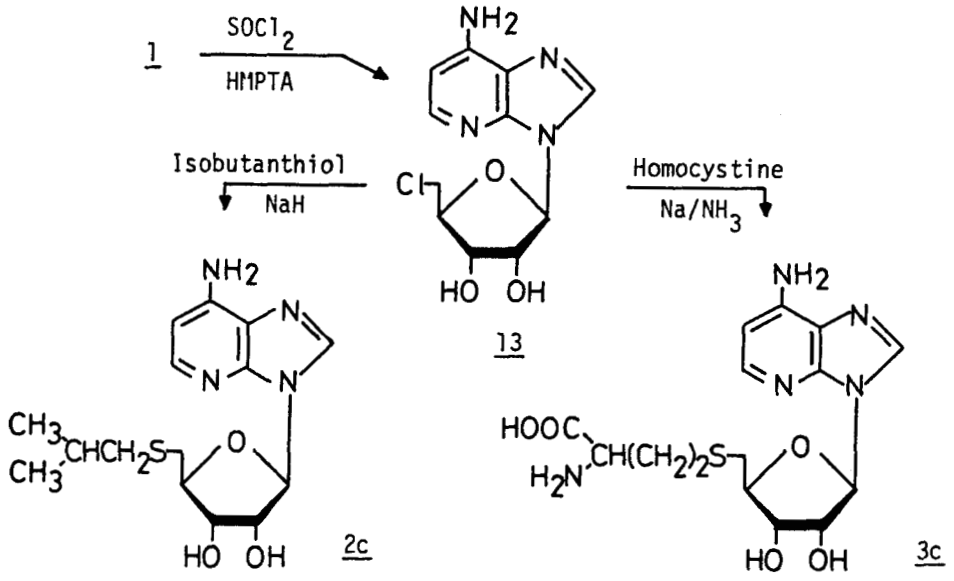
7-Amino-3-(β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine(1-deazaadenosine, 1) was obtained from the deblocked nucleoside(12) in 61.5 % yield by treatment with hydrazine hydrate under nitrogen atmosphere at refluxing temperature, followed by Raney nickel reduction.[3b,8]

Physical properties of 12 and 1 were virtually identical with those reported.[3]

The present route for the synthesis of 1-deazaadenosine, with an overall yield of about 25 % based on 4 and involving several new reactions(7→9→11), was found to represent much improvement in yield and procedure.

1-Deazaadenosine(1) was successfully converted to 5'-alkylthio-5'-deoxy-derivatives, 2c and 3c, via 5'-chloro-5'-deoxy-1-deazaadenosine (13). Thus, treatment of 1 with thionyl chloride in hexamethylphosphoramide[9] gave rise to the 5'-chloro-nucleoside(13) in 70.9 % yield, which was unstable enough to afford a 3,5'-cyclonucleoside on heating for a short time.

The reaction of 13 with isobutanethiol in the presence of sodium hydride in dimethylformamide afforded 5'-deoxy-5'-isobutylthio-1-deazaadenosine(1-deazaSIBA, 2c) in 84 % yield. S-(1-Deazaadenosyl)homocysteine(1-deazaSAH, 3c) was obtained from 13 by treatment with L-homocystine in liquid ammonia[10] in 42.6 % yield.



Ultraviolet absorption maxima and pmr chemical shifts of these compounds are summarized in TABLE 1 and 2.

Biological and biochemical effects of the nucleosides described herein are under examination, and the results will be the subject of a forthcoming paper.

EXPERIMENTAL

Melting points were determined with a Yamato melting point apparatus, Type MP-1, and are uncorrected. Ultraviolet absorption spectra were taken on a Hitachi Recording Spectrophotometer 323. Pmr spectra were obtained on JEOL FX-100 and FX-200 Spectrometers using tetramethylsilane as an internal standard. Circular dichroism spectra were taken on a JASCO J-40 Spectropolarimeter. Mass spectra were taken on a JMS-D-300 JEOL Mass Spectrometer and FD mass spectra were obtained on a JEOL JMS-OISG-2 Mass Spectrometer.

1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-1H-imidazo[4,5-b]pyridine 4-oxide(7)

A suspension of 13.85 g(71.5 mmoles) of 4(acetate) and 0.5 g of ammonium sulfate in 60 mL of hexamethyldisilazane and 100 mL of pyridine

was refluxed for 3 hours. The mixture was concentrated in vacuo to provide the trimethylsilyl derivative 5 as a colorless solid. This was dissolved in 200 mL of anhydrous acetonitrile and 25.0 g(79.0 mmoles) of TAR(6) was added to the solution, followed by 10.0 mL(86.4 mmoles) of anhydrous stannic chloride. The solution was stirred for 6 hours at room temperature. The reaction mixture was poured into sodium bicarbonate solution(60 g in 600 mL of water) and the suspension was extracted successively with two 300-mL portions and three 50-mL portions of chloroform. The dried(Na_2SO_4) organic layer was evaporated in vacuo to give a foam, which was purified with a silica gel column(ϕ 3.7 cm x 44 cm). Concentration of a fraction eluted with ethanol-chloroform(1:9 v/v) gave 23.1 g(82.2 %) of 7 as a foam.

Anal. Calcd. for $C_{17}H_{19}N_3O_8 \cdot 1/2H_2O$: C, 50.74; H, 5.00; N, 10.44. Found: C, 50.87; H, 5.04; N, 10.15.

1-(β-D-ribofuranosyl)-1H-imidazo[4,5-b]pyridine 4-oxide(8)

A solution of 980 mg (2.43 mmoles) of 7 in about 60 mL of methanolic ammonia was allowed to stand overnight at room temperature. The mixture was concentrated in vacuo to give a yellow oil, which was crystallized from 95 % ethanol to give 610 mg(88.1 %) of 8, mp 170-171°.

Anal. Calcd. for $C_{11}H_{13}N_3O_5 \cdot H_2O$: C, 46.31; H, 5.30; N, 14.73. Found: C, 46.10; H, 5.33; N, 14.52.

7-Chloro-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1H-imidazo[4,5-b]-pyridine(9)

(a) To a solution of 19.0 g(48.3 mmoles) of 7 in 70 mL of chloroform was added Vilsmeyer reagent, prepared from 9.0 mL(96.7 mmoles) of phosphoryl chloride and 7.5 mL(96.7 mmoles) of dimethylformamide, at 0°. The mixture was stirred at room temperature for an hour, poured into sodium bicarbonate solution(60 g in 500 mL of water), and extracted with three 100-mL portions of chloroform. The dried(Na_2SO_4) organic layer was concentrated in vacuo to give a syrup, which was purified with a silica gel column(ϕ 3.7 cm x 45.3 cm). Evaporation of a fraction eluted with ethanol-chloroform(5:95 v/v) gave 15.26 g(76.9 %) of 9, which was crystallized from hexane, mp 88-92°. MS: 411/413(M^+), 259 (M-B), 153/155(B+H).

Anal. Calcd. for $C_{17}H_{18}N_3O_7Cl \cdot 1/3H_2O$: C, 48.87; H, 4.50; N, 10.06; Cl, 8.49. Found: C, 48.98; H, 4.39; N, 9.78; Cl, 8.45.

(b) To a solution of 5.95 g(15.1 mmoles) of 7 in 100 mL of chloroform was added 2.0 mL(21.6 mmoles) of phosphoryl chloride and 1.0 g of molecular sieves 4A and the mixture was stirred at 30-33° for 24 hours. The reaction mixture was worked up by the same procedure described above to give 5.18 g of a brown syrup. A part of the crude sample(1.56g) was purified with a silica-gel column to give 1.21 g(64.8 %) of 9, which was identical with the sample obtained above.

7-Chloro-1-(β-D-ribofuranosyl)-1H-imidazo[4,5-b]pyridine(10)

A solution of 50 mg(0.12 mmole) of 9 in 5 mL of methanolic ammonia was allowed to stand overnight at room temperature. Evaporation of the solvent gave a white powder, which was crystallized from water to give 21 mg(61.2 %) of 10, mp 204-205°. MS: 285/287(M^+), 196/198(B+44), 182/184(B+30), 154/156(B+2H), 153/155(B+H).

Anal. Calcd. for $C_{11}H_{12}N_3O_4Cl$: C, 46.24; H, 4.23; N, 14.70; Cl, 12.41. Found: C, 46.21; H, 4.19; N, 14.56; Cl, 12.18.

7-Chloro-3-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-3H-imidazo[4,5-b]-pyridine(11)

A solution of 14.26 g(34.7 mmoles) of 9 and 11.0 g(34.6 mmoles) of 6 in 200 mL of toluene was refluxed for 3.5 hours in the presence of 12.5 g(34.7 mmoles) of mercuric bromide. The solvent was distilled off in vacuo to give a residue, to which was added 300 mL of chloroform and 250 mL of 30 % potassium iodide. The organic layer was washed with another 250 mL of 30 % potassium iodide and then with 300 mL of water. Concentration of the dried(Na_2SO_4) chloroform solution gave a foam, which was purified with a silica gel column(ϕ 4.2 cm x 42.7 cm). Evaporation of the chloroform fraction gave 10.83 g(75.9 %) of 11 as a pale yellow foam. MS: m/e 411/413(M^+), 259(M-B), 153/155(B+H).

7-Chloro-3-(β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine(12)

A solution of 10.83 g(26.3 mmoles) of 11 in about 300 mL of methanolic ammonia was allowed to stand overnight at room temperature. The solvent was evaporated in vacuo to give 6.14 g(81.8 %) of 12 as a white powder, which was crystallized from water, mp 196-197° MS: 285/287(M^+), 255/257(M-30), 196/198(B+44), 182/184(B+30), 154/156(B+2H), 153/155(B+H).

Anal. Calcd. for $C_{11}H_{12}N_3O_4Cl$: C, 46.24; H, 4.23; N, 14.70; Cl, 12.41. Found: C, 46.27; H, 4.19; N, 14.78; Cl,12.24.

7-Amino-3-(β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine(1-deazaadenosine, 1)

A solution of 3.0 g(10.5 mmoles) of 12 in 24 mL of 80 % hydrazine hydrate was refluxed for an hour under nitrogen atmosphere. Evaporation of excess hydrazine in vacuo gave a colorless syrup, to which was added 10 mL of oxygen-free water and was evaporated to give a crude sample of 7-hydrazino-3-(β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine, λ_{max}: (at pH 1) 271sh, 282.5; (at pH 12) 265, 283.5. This was dissolved in 40 mL of oxygen-free water and the solution was added with 6 g of Raney nickel(W2). The mixture was refluxed for an hour under nitrogen atmosphere. The nickel was filtered off and the filtrate was concentrated in vacuo to give a crude sample of 1, which was recrystallized from water, 2.20 g(78.7 %), mp 250-251°. MS: 266(M^+), 236(M-30), 177(M-89), 163(B+30), 135(B+2H), 134(B+H). CD: λ(nm)([θ]) at pH 12.3; 280(-1,420), 262(-950), 238(+760), 225(-7,620).

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.62; H, 5.34; N, 21.03.

7-Amino-3-(5-chloro-5-deoxy-β-D-ribofuranosyl)-3H-imidazo[4,5-b]-pyridine(5'-chloro-5'-deoxy-1-deazaadenosine, 13)

To a mixture of 1.50 mL(3.75 mmoles) of thionyl chloride and 5 mL hexamethylphosphoramide was added 1.00 g(3.75 mmoles) of 1 and the reaction mixture was allowed to stand overnight at room temperature under nitrogen atmosphere. Water was added to the mixture to quench the reaction. After neutralizing with 1N ammonium hydroxide, concentration of the mixture gave a precipitate, which was applied to a Dowex 50W x 8(H^+ form) column(φ 2.2 cm x 30.7 cm). After washing the column with water, a crude sample of 13 was eluted out with 1N ammonium hydroxide. Concentration of the fraction gave a white solid, which was crystallized from ethanol, 877 mg(70.9 %), mp 127-128° and 185-187°(double melting). FD-MS: 284/286(M^+), 285/287(M+1).

Anal. Calcd. for $C_{11}H_{13}N_4O_3Cl \cdot 2/3C_2H_5OH$: C, 47.02; H, 5.44; N, 17.78; Cl, 11.25. Found: C, 46.84; H, 5.68; N, 17.62; Cl, 11.45.

7-Amino-3-(5-deoxy-5-isobutylthio-β-D-ribofuranosyl)-3H-imidazo[4,5-b]-pyridine(1-deazaSIBA, 2c)

To an ice-cooled solution of 0.20 mL(1.85 mmoles) of isobutanethiol and 60 mg of sodium hydride(60 % in paraffin, 1.50 mmoles) in 2.0 mL of

dimethylformamide was added 110 mg(0.39 mmole) of 13. The mixture was stirred at 0° for about 5 hours and was concentrated in vacuo to give a solid, which was purified on preparative silica-gel plates to provide 107 mg(81.4 %) of 2c. Recrystallization from ethanol, mp 138°. High Resolution MS Calcd. for $C_{15}H_{22}N_4O_3S$: 338.1408. Observed: 338.1408. CD: λ(nm)([θ]) at pH 12.5; 283(+3,780), 262(+5,830), 228(-11,100).

Anal. Calcd. for $C_{15}H_{22}N_4O_3S$: C, 53.23; H, 6.55; N, 16.55; S, 9.47. Found: C, 53.06; H, 6.45; N, 16.62; S, 9.41.

S-(1-Deazaadenosyl)-L-homocysteine(1-deazaSAH, 3c)

Sodium(0.1 g) and 330 mg(1.23 mmoles) of L-homocystine were dissolved in about 25 mL of liquid ammonia and a small amount of ammonium chloride was added until the mixture became colorless. After addition of 400 mg(1.41 mmoles) of 13, the mixture was allowed to stand at room temperature for a day in a sealed glass tube. Excess ammonia was evaporated to give a light brown foam, which was dissolved in 20 mL of water. After neutralization with 10 % acetic acid, the mixture was applied to a Dowex 50W(NH_4^+ form) column(φ 2.2 cm x 19.2 cm), which was eluted with water and then with 1N ammonium hydroxide. Evaporation of the latter fraction gave 230 mg(42.6 %) of 3c, mp 178°(dec.). FD-MS: 384 (M+1), 383(M^+), 340(M+1-CO_2), 339(M-CO_2), 282[M+1- $CH_2CH_2CH(NH_2)COOH$]. CD: λ(nm)([θ]) at pH 12.3; 282(+2,690), 262(+3,760), 228(-7,530).

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