A NOVEL SYNTHESIS OF 1-DEAZAADENOSINE[1]

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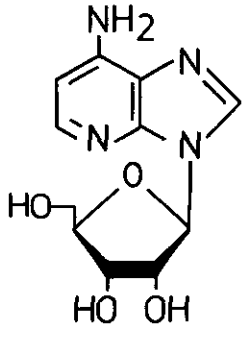
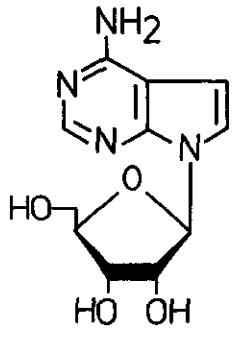
Abstract — A novel route for the synthesis of 7-amino-3-(β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine(1-deazaadenosine) has been developed, as illustrated in accompanying flow sheet, starting from imidazo[4,5-b]pyridine 4-oxide in much improved overall yield(20%).

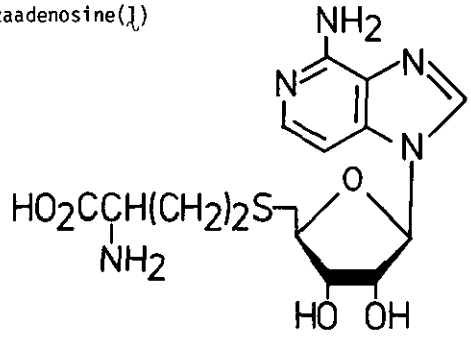
In view of current interest in chemotherapeutic and biological properties of deazaadenosines and derivatives thereof(*viz.*, tubercidin and 3-deazaadenosyl-homocysteine)[2], we have been seeking an efficient preparation of 1-deazaadenosine(1) whose derivatives of biological interest such as 5'-isobutylthio-5'-deoxy-1-deazaadenosine and 1-deazaadenosyl-L-homocysteine have been missing link in this area.



1-Deazaadenosine(1)

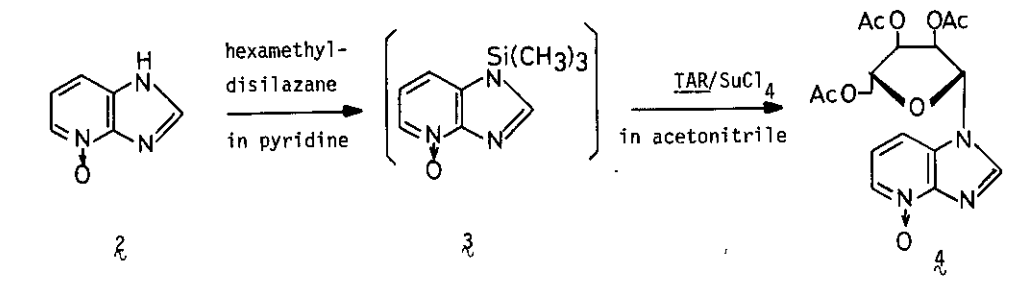


Tubercidin

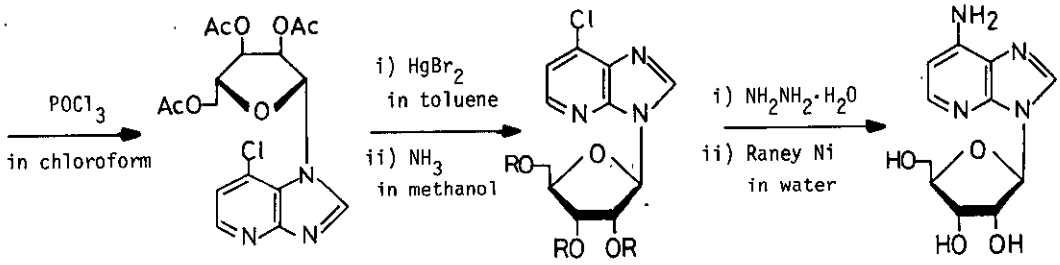


3-Deazaadenosyl-homocysteine

Dedicated to the 75th birthday of Prof. Kyosuke Tsuda.



2 3 4



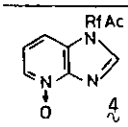
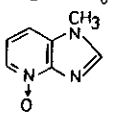
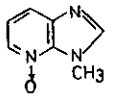
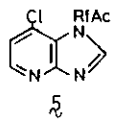
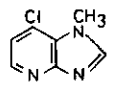
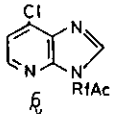
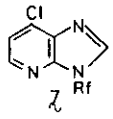
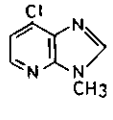
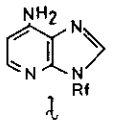
5 6: R = Ac
7: R = H 1

In the synthesis reported here we utilized some recent advances in both aromatic N-oxide chemistry[3] and nucleoside chemistry[4] to overcome low overall yields associated with the previous synthesis of (1).[5]

The trimethylsilyl derivative(3), prepared from imidazo[4,5-b]pyridine 4-oxide[6](2, 72 mmoles) with hexamethyldisilazane in pyridine, was condensed with 1,2,3,5 -tetra-O-acetyl-β-D-ribofuranose (TAR, 144 mmoles) in acetonitrile(300 ml) in the presence of stannic chloride(147 mmoles)[7] at room temperature for 5 h to give a homogeneous sample of a nucleoside(4)(68.1%) which was characterized as 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1H-imidazo[4,5-b]pyridine 4-oxide by comparison of its uv spectra with those of the corresponding N-methyl derivatives[3](see Table).

It has been established in our laboratory that treatment of imidazo[4,5-b]pyridine 4-oxide and 3H-3-methyl-derivative with phosphoryl chloride may give rise to comparable amounts of mixture of 5-chloro- and 7-chloroimidazopyridines, whereas a chlorine atom can be exclusively introduced at position 7 in the reaction of 1-methyl-1H-imidazo[4,5-b]pyridine 4-oxide.[3] This feature was successfully applied to the preparation of 7-chloronucleoside(5), which was smoothly converted to 7-chloro-3-(β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine(7), a key intermediate to 1-deazaadenosine(1).

Table Uv and Pmr Spectra of Imidazo[4,5-b]pyridines

Compound*1	λ_{max}^{water} (nm) 0.1NHCl	0.1NNaOH	Pmr*2 chemical shift, δ in ppm (coupling constant) H-2	H-5	H-6	H-7	CH_3	H-1'	H-2'	H-3'	H-4'	H-5'
 4	293	299	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
	295	296.5 304sh	7.99s	8.31dd ($J_{5,6}$ = 6.3Hz) ($J_{5,7}$ = 0.7Hz)	7.18dd ($J_{6,7}$ = 8.3Hz)	7.37dd	3.91s	—	—	—	—	—
	276sh	273 304 307sh	7.94s	8.18d ($J_{5,6}$ = 5.4Hz)	7.15dd ($J_{6,7}$ = 8.0Hz)	7.76d	4.40s	—	—	—	—	—
 5	277sh 284 287sh	257 280.5 286sh	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
	277sh 283 288sh	261sh 280 284sh	8.06s	8.41d ($J_{5,6}$ = 5.2Hz)	7.19d	—	4.14s	—	—	—	—	—
 6	249 275 280sh	257 278.5 285sh	8.30s	8.31d ($J_{5,6}$ = 5.4Hz)	7.34d	—	—	6.28d ($J_{1',2'}$ = 5.1Hz)	6.03t	5.71t	4.43m	
 7	250 275 281.5	256.5 279 285sh	8.82s	8.35t ($J_{5,6}$ = 5.2Hz)	7.50d	—	—	6.07d ($J_{1',2'}$ = 5.4Hz)	4.63q	4.91q	3.99q	3.63m
	247 273 281.5	259 280.5 287sh	8.05s	8.26d ($J_{5,6}$ = 5.0Hz)	8.25d	—	3.90s	—	—	—	—	—
 1	222 256sh 282.5	221 262.5 278	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

*1 R: β-D-ribofuranosyl, RfAc: 2,3,5-tri-O-acetyl-β-D-ribofuranosyl.

*2 Pmr spectra were measured in chloroform-d except those of the unprotected nucleosides, 1 and 7, which were taken in dimethyl sulfoxide-d_6; signals are designated as s(singlet), d(doublet), dd(double doublet), t(triplet), q(quartet), and m(multiplet).

Thus, the reaction of (4, 15.1 mmoles) with phosphoryl chloride(2 ml, 21.6 mmoles) in chloroform (100 ml) in the presence of molecular sieves 4Å(40 g) at 30° for 18 h led to the predominant formation of a chlorinated nucleoside(5), whose anomeric proton signal in pmr appeared at comparatively downfield(see Table) suggesting that the chloride atom was introduced in the vicinity of the anomeric proton, that is, at the position 7. Treatment of (5) with mercuric bromide(1 eq.) in the presence of TAR(1 eq.) in refluxing toluene for 24 h gave rise to a transglycosylated product(6)[8](65.3%, based on 5) which was deacetylated with methanolic ammonia at room temperature to afford 7-chloro-3-(β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine(7)(90%), mp 199-201°. Physical properties of (7) were substantially identical with those of the reported.[5b]

7-Amino-3-(β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridine(1-deazaadenosine, 1), mp 251-252°, was obtained from (7)(1.87 g) by treatment with hydrazine hydrate (17 ml) under nitrogen atmosphere at 90° for 1 h followed by Raney Nickel(61.5%).

Uv and pmr spectra of the nucleosides, synthesized here, and some related N-methylated imidazo-[4,5-b]pyridine are summarized in Table.

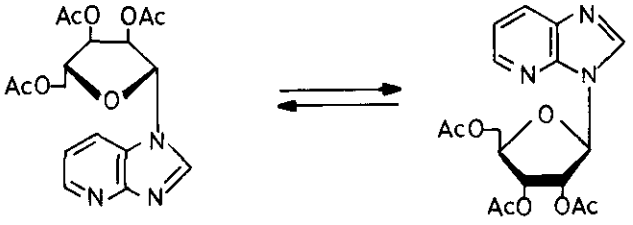
The route for the synthesis of (1), overall yield being about 20%, involving a couple of new reactions(4 → 5 → 6) was found to be much superior to that reported.[5]

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

References

1. Studies on Chemical Synthesis of Potential Antimetabolites. 29. For 28, T. Itoh, T. Yamaguchi, and Y. Mizuno, J. Carbohydr. Nucleosides Nucleotides, 1981, 8, 119.
2. For a comprehensive and leading review, see: R. T. Borchardt, J. Medicin. Chem., 1980, 23, 347.
3. T. Itoh, K. Ono, and Y. Mizuno, Abstracts of the 10th Congress of Heterocyclic Chemistry, Tukuba, Japan, 1977, pp 171-174. J. Heterocycl. Chem., in submission.
4. T. Itoh and Y. Mizuno, Heterocycles, 1976, 5, 285.
5. a. P. C. Jain, S. K. Chatterjee, and N. Anand, Indian J. Chem., 1966, 4, 403; b. K. B. De Roos and C. A. Salemink, Recueil, 1971, 90, 654; c. T. Itoh, S. Kitano, and Y. Mizuno, J. Heterocycl. Chem., 1972, 9, 465.
6. Y. Mizuno, N. Ikekawa, T. Itoh, and K. Saito, J. Org. Chem., 1965, 30, 4066.
7. U. Niedballa and H. Vorbrüggen, Ibid., 1974, 39, 3654.
8. It has been shown that in the presence of Lewis acid an equilibrium between 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1H-imidazo[4,5-b]pyridine(A) and its 3H-3-glycosyl- isomer exists in solution and that the ratio of (A) to (B) may depend on the solvent used. Thus, in acetonitrile

or nitromethane an equimolar mixture of the isomers may be obtained, whereas in refluxing toluene thermodynamically more stable product may be the 3-glycosyl isomer(B).[4]



(A) (B)

Received, 31st August, 1981