Synthetic Studies of Potential Antimetabolites. XIII. Synthesis of 7-Amino-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridine (1-Deazaadenosine) and Related Nucleosides (1a).

Tokuo Itoh, Shigeru Kitano, and Yoshihisa Mizuno (1b)

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

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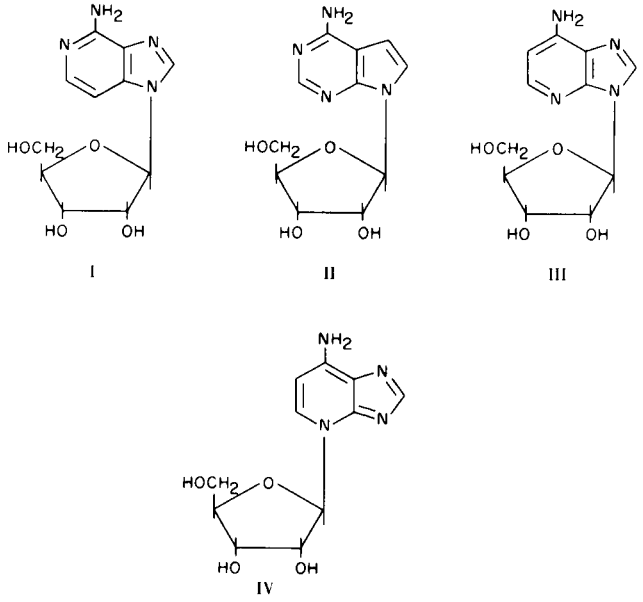
7-Amino-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridine (III, 1-deazaadenosine) was synthesized in 32% yield from the diacetyl derivative prepared from 7-aminoimidazo[4,5-*b*]pyridine (1-deazaadenine) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribose by the fusion method. A synthesis of 7-amino-4-β-D-ribofuranosyl-4*H*-imidazo[4,5-*b*]pyridine (IV) was also achieved.

A number of antibiotics of the deazapurine series have been isolated from various sources in recent years. Among them, tubercidin, toyocamycin, and formycin, possessing a ring system isomeric or isosteric with purine, are of interest because their nucleoside analogs have been useful as models for conformational studies, nmr and ord measurements (2). They have also been equally important as biochemical tools in cellular reactions as illustrated in those studies which have aided the elucidation of the complex steps involved in reading the genetic message on the ribosomes for protein synthesis (2).



Out of three possible deazaadenosine analogs, 7-deazaadenosine (II) (tubercidin) (3), and 3-deazaadenosine (I) (1a,4) have been already synthesized. The synthesis of 1-deazaadenosine (III) by the heavy metal procedure was reported by Jain, Chatterjee, and Anand in 1966 (5), without adequate characterization of the nucleosidic product, especially with regard to the position of glycosidation.

In this paper we wish to report a synthesis of 1-deazaadenosine (7-amino-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridine, III), 7-amino-4-D-ribofuranosyl-4*H*-imidazo-[4,5-*b*]pyridine (IV) (1-deaza-3-isoadenosine) and related nucleosides.

In addition to the condensation of an appropriate base with a sugar derivative, an alternate possible route to the nucleoside was considered, starting with 6-bromo-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridine (Va) (6) *via* a hetaryne intermediate which appeared quite promising (7).

However, the latter approach has been reserved for further investigation since a model experiment with 6-

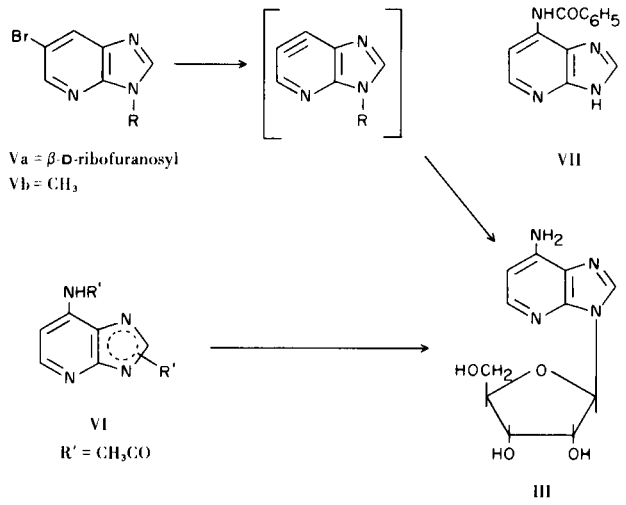


CHART 1

bromo-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (Vb) showed that treatment of Vb with sodium-liquid ammonia resulted in debromination to afford the 3-methyl derivative (9-methyl-1-deazapurine).

1-Deazaadenine hydrochloride (XVI) was converted into the corresponding 6-*N*-benzoyl derivative (VII) which in turn was converted into the chloro-mercuri salt. Unexpectedly, by the usual procedure using boiling xylene as solvent, the mercuri-salt failed to be condensed with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (XVII). 6-*N*-Benzoyl compound was recovered quantitatively. We have no reasonable explanation for the unusual behavior of the mercuri salt.

Accordingly, we tried two additional procedures: "fusion procedure" (8) which has been successfully applied to the syntheses of some deazapurine β-D-ribofuranosides (9) and Yamaoka, *et al.*'s "Mercuri cyanide procedure" (10).

Synthesis of 1-deazaadenosine (III) was achieved by the former method. Thus, diacetyl-1-deazaadenine (VI) (5) was treated with tetra-*O*-acetyl-β-D-ribofuranose in the presence of a catalytic amount of *p*-toluenesulfonic acid at 150-165° *in vacuo* for 2 hours. Crude nucleosidic products obtained were purified on a silicic acid column. Fractions were obtained by washing the column with ethyl acetate containing increasing proportions of ethanol (up to 19:1 v/v) which afforded 40% yield of blocked nucleoside (VIII). Subsequent deblocking gave a nucleoside, which was found to be indistinguishable from Jain *et al.*'s nucleoside (5) on the criteria of the melting point, Rf-values and the ultraviolet absorption properties. This nucleoside, pK_a 4.70 was characterized as follows.

With III a negative Cotton effect was observed in the ord curve and the nucleoside (III) possessed a large negative specific rotation $[\alpha]_D^{18}$ -72°, which suggested that the anomeric configuration of III might be β. Ultraviolet absorption spectra of III were quite similar to those of 7-amino-3-(2-hydroxyethyl)-3*H*-imidazo[4,5-*b*]pyridine (XV), prepared by an unambiguous route (Chart 3). This demonstrated that the nucleoside was a 3-ribosyl derivative (9-D-ribosyl-1-deazaadenine). In nmr, chemical shifts due to sugar protons were quite similar to those of adenosine.

Confirmation of the structure of the nucleoside (III) was achieved by the formation of 3,5′-cyclonucleoside: N^6-acetyl-1-deazaadenosine (IX), prepared by partial deacetylation of N^6-2′,3′,5′-tetra-*O*-acetyl derivative (VIII) with methanolic sodium methoxide was converted to the 2′,3′-*O*-isopropylidene-5′-*O*-*p*-toluenesulfonyl derivative (XI) (uv max in ethanol 271 nm) *via* 2′,3′-*O*-isopropylidene-1-deazaadenosine (X) by a conventional procedure. On heating XI in acetone, an acetone-insoluble and water-soluble cyclonucleoside (XII) was obtained, whose absorption maxima showed a bathochromic shift and paper electrophoretic mobility was found to be similar to that of a cyclonucleoside (11) which originated from adenosine. The formation of a cyclonucleoside established that the nucleoside (III) is 9-β-D-ribofuranoside. The yield of III was 32% and quite satisfactory. However, "mercuric-cyanide procedure" was also tried as another promising route to 1-deazaadenosine.

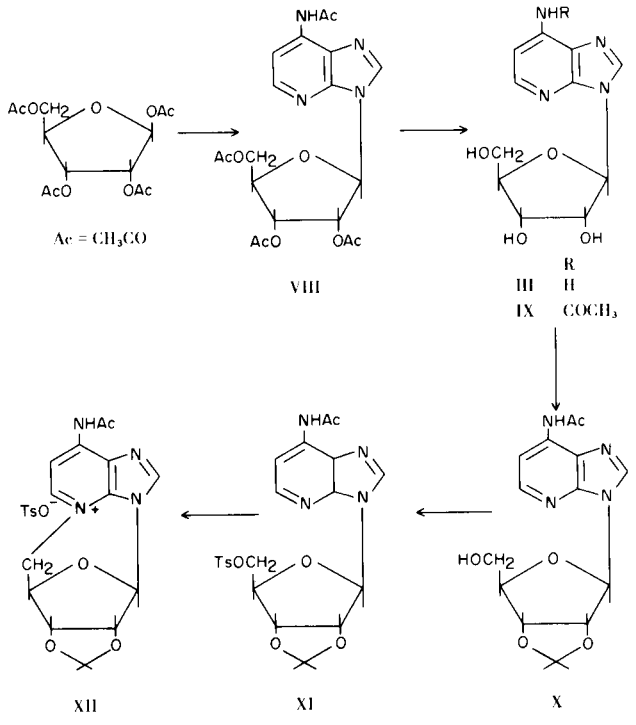


CHART 2

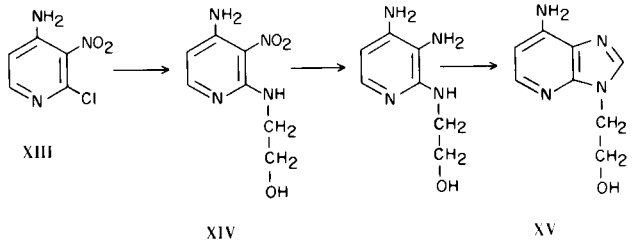


CHART 3

1-Deazaadenine hydrochloride (XVI) was treated with 2,3,5-tri-*O*-benzoyl-D-ribosyl chloride in the presence of mercuri cyanide in nitromethane. The crude blocked nucleosides obtained were chromatographed on an alumina column. Elution with benzene and benzene containing increasing proportions of ethyl acetate (95:5 up to 9:1 v/v) gave non-nitrogenous material which was discarded. Subsequent elution with benzene-ethyl acetate (8:2 v/v) gave blocked nucleoside (3%) which was treated

TABLE I

Physical Properties of Adenosine and Deazaadenosines and Related Nucleosides

Nucleosides	Adenine Series, Lit.	1-Deazaadenine Series
9-β-D-Ribofuranosyl	λ max 260 nm H_2O (13) *p*H 6.4 pK_a 3.62	λ max 262.5 nm (*p*H 7.40) 282 (*p*H 1.15) pK_a 4.70
3-β-D-Ribofuranosyl	λ max 277 nm H_2O (14) *p*H 6.4 274 (0.1NHCl) pK_a 5.50	λ max 292 nm (*p*H 11.0) 288.5 (*p*H 4.65) pK_a 7.10
7-β-D-Ribofuranosyl	λ max 270 nm 0.1*N* NaOH (15) 272 (0.1 NHCl) pK_a 3.68	

with methanolic sodium methoxide to give 1-deazaadenosine (III).

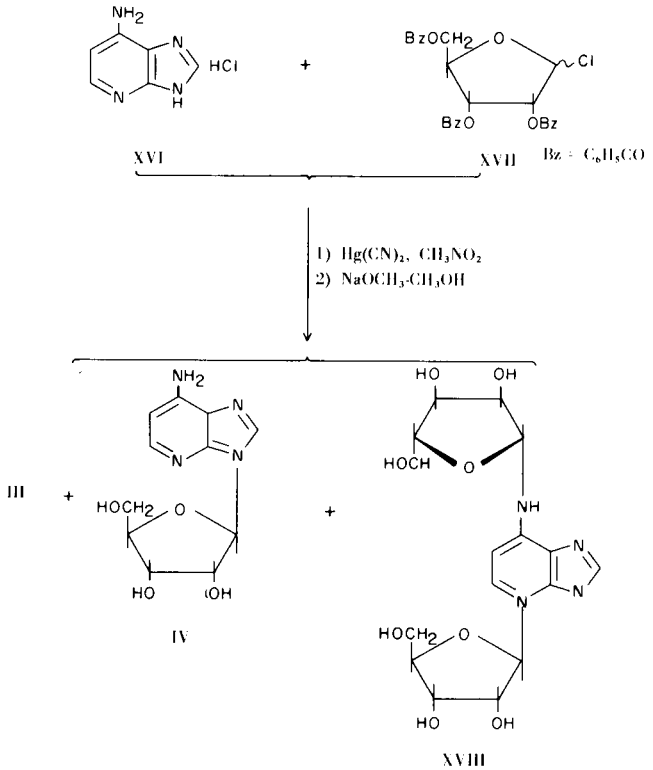


CHART 4

A small amount of gummy substance obtained in *ca.* 1% yield from the ethyl acetate fraction was treated with methanolic sodium methoxide to give a nucleosidic substance whose structure could not be determined because of a small quantity. However, judging from the uv spectra it was highly probable that the nucleoside was 4-β-D-ribofuranosyl-7-β-D-ribofuranosylamino-4*H*-imidazo[4,5-*b*]pyridine (XVIII).

The fraction eluted by ethanol gave, after removal of the solvent, solid form, which consisted mainly of a third (blocked) nucleoside in a yield of *ca.* 30%. The deblocked nucleoside (IV) showed double melting points, $[\alpha]_D^{18}$ -76.8°, pK_a 7.10. Combustion values were found to be compartible with those of monoribosyl derivative. The nucleoside absorbed ultraviolet light at a longer wavelength than III and its absorption spectra was quite similar to those of the 3-alkyl substituted adenine obtained by acid cleavage of N^9-glycosyl bond of the cyclonucleoside (XII). The nucleoside (IV) was more basic than III by 2.4 p*K* units (Table I). By analogy with the fact that, among 3-, 7- and 9-substituted derivatives, 3- and 7-alkyl derivatives absorb the light at longer wavelength than 9-alkyladenines, including adenosine and since 3-ribofuranosyladenine is the most basic among these three derivatives of adenine, the 3-D-ribofuranosyl structure was assigned to the nucleoside (IV).

Although the "mercuri-cyanide procedure" failed to afford a good yield of 1-deazaadenosine (III), this is another case to show that alkylation of 1-deazaadenine in aprotic solvents takes place predominantly at *N*-3 (12).

TABLE II

Physical Properties of Deazaadenosines

Nucleosides	max (nm)	$[\alpha]_D$	pK_a	Lit.
Adenosine	260 (neutral) 257 (cationic)	-60.4°	3.62	(14)
I	265 (n.) 262 (c.)	-46.5°	6.80	(4) (1a)
II	270 (n.) 272 (c.)	-60.7°	5.25	(16)
III	262.5 (n.) 282 (c.)	-72.0°	4.70	

As shown in Table II, it is evident that the differences in absorption maxima of neutral and cationic species of 3-deazaadenosine (I), 7-deazaadenosine (II) and adenosine are slight (*ca.* 2-3 nm), whereas the difference in 1-deazaadenosine (III) is comparatively large (*ca.* 20 nm). This might be a reflection of the difference in the site of protonation, because 1-deazaadenosine (III) is lacking a nitrogen atom at position one, where protonation may take place in adenosine, presumably also in 3-deazaadenosine (I) as well as 7-deazaadenosine (II).

EXPERIMENTAL

Unless otherwise stated, melting points were taken on Prism-scope melting point deterinator, Mitamura Co. Ultraviolet absorption spectra were determined on Hitachi Spectrophotometer type T-4. Optical rotations were determined on a polarimeter Hitachi No. 106-3, ir spectra were determined on Spectrophotometer, Model DS-701 G Nippon Bunko Co. Thin layer chromatography (tlc) was run on glass plates coated with silicic acid. Unless otherwise stated, paper chromatography was carried out by the use of ascending technique. Solvents used were: solvent A, 1-butanol saturated with water; solvent B, 5% ammonium sulfate-2-propanol (19:1 v/v); solvent C, ethanol-concentrated ammonia hydroxide-ether (80:4:16 v/v). Microanalyses were performed by Miss A. Maeda, Miss H. Kakizaki, and Miss T. Obara, Faculty of Pharmaceutical Sciences, Hokkaido University.

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

To a suspension of 1.98 g. of 6-bromoimidazo[4,5-*b*]pyridine in 50 ml. of aqueous methanol (2:1 v/v) was added 1 *N* methanolic sodium methoxide until a clear solution resulted. To the solution was added 2 ml. of methyl iodide at room temperature and the solution was allowed to stand at ambient temperature. The solution was concentrated to dryness and residue was dissolved in 30 ml. of water. The solution was subjected to chloroform extraction. The organic layer was washed with water and dried over sodium sulfate. Removal of the solvent left 1.5 g. of a crude product which was crystallized from aqueous ethanol (1:2 v/v) to give 1.1 g. (52%) of an analytical sample, m.p. 137°.

Anal. Calcd. for $C_7H_6BrN_3$: C, 39.65; H, 2.72; N, 19.81. Found: C, 39.80; H, 2.79; N, 19.81.

N^7-Benzoylamino-3*H*-imidazo[4,5-*b*]pyridine Hydrochloride (VII·HCl).

To a solution of 300 mg. of 7-amino-3*H*-imidazo[4,5-*b*]pyridine hydrochloride (5) in 10 ml. of pyridine was added 0.6 ml. of benzoyl chloride. The solution was refluxed for 3 hours during which time pyridine hydrochloride separated. After cooling, the salt was filtered. The crude product was crystallized from aqueous ethanol, m.p. 230°, yield 180 mg. (40%); uv max nm 285 (water); 296 (0.1 *N* hydrochloric acid); 294.4 (0.1 *N* sodium hydroxide).

Anal. Calcd. for $C_{13}H_{10}N_4O\cdot HCl$: C, 56.84; H, 4.04; N, 20.40. Found: C, 57.04; H, 4.32; N, 20.26.

Mercurichloride Salt of N^7-Benzoylamino-3*H*-imidazo[4,5-*b*]pyridine.

To a suspension of 1.37 g. of N^7-benzoylamino compound (VII) in 100 ml. of water was added 5 ml. of 2 *N* sodium hydroxide solution. To the solution was added with stirring an ethanol solution containing 1.35 g. of mercuric chloride. The solid which separated was collected, washed successively with water, ethanol, and ether and dried, yield 2.10 g. (89%).

Anal. Calcd. for $C_{13}H_9ClHgN_4O$: N, 11.84. Found: N, 11.99.

Ribosylation of the above mercurichloride (950 mg.) with XVII, prepared from 1 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose was attempted according to a standard procedure (18) (100 ml. of xylene was used for solvent at refluxing temperature for 3 hours). After working-up as usual, N^7-benzoylamino-3*H*-imidazo[4,5-*b*]pyridine was recovered almost quantitatively.

1-Deazaadenosine (III).

The diacetyl derivative (5) of 7-aminoimidazo[4,5-*b*]pyridine (876 mg., 4.02 mmoles) was fused with 1,2,3,5-tetra-*O*-acetyl-D-ribose (2.54 g., 7.98 mmoles) at 165°, and while hot, 31 mg. of *p*-toluenesulfonic acid (monohydrate) was added to the melt and the mixture was heated again under reduced pressure (10-14 mm Hg) at 162-165° (bath temperature, this temperature range was critical) for 2 hours. After cooling, the mixture was dissolved in chloroform. The solution was washed successively with a 5% aqueous solution of sodium bicarbonate, with water and dried over sodium sulfate. Removal of the solvent left 2.895 g. of crude products, which were separated by silicic acid column chromatography (weight of silicic acid 100 g., column size 2.6 x 32 cm).

Fraction A eluted by benzene containing increasing proportions of acetate (3:1 to 1:5 v/v, 1.8 l.) gave a non-nitrogenous substance (1.55 g.).

Fraction B eluted by ethyl acetate containing increasing proportions of ethanol (up to 19:1 v/v, 1.5 l.) gave after removal of the solvent 0.698 g. (39.6%) of nucleosidic substance (N^6-2′,3′,5′-tetra-*O*-acetyl-1-deazaadenosine VIII).

To a solution of 668 mg. of blocked nucleoside in 40 ml. of absolute methanol was added 1.5 ml. of 1 *N* methanolic sodium methoxide solution. The mixture was refluxed for 2 hours. The solution was cooled and neutralized with IRC 50 (H^+ form). The resin was removed by filtration and the filtrate concentrated to dryness to yield 331 mg. (81% yield). The residue was twice recrystallized from water, m.p. 258.5°; pK_a determined spectrophotometrically (19) 4.70 $[\alpha]_D^{18}$ -72° (c, 0.5, DMSO); uv max nm 265 (12.200 sh), 282 (17.050) at *p*H 1.05; 262 (14.000), 278 (10.300) at *p*H 7.17; R_f in water (*p*H 10) 0.49; R_f-values by descending technique in solvent A 0.42, R(Ad) (relative mobility with respect with adenosine) 1.20 (a reported value (6) 0.51; R(Ad) 1.00), in solvent B 0.55; R(Ad) 1.01 (a reported R_f 0.657; R(Ad) 1.03).

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.43; H, 5.27; N, 20.88.

N^6-Acetyl-1-deazaadenosine (IX).

To a solution of tetraacetyl-1-deazaadenosine (VIII, 713 mg., 1.64 mmoles) in methanol (30 ml.) was added 0.3 ml. of 1 *N* methanolic sodium methoxide solution. The solution was magnetically stirred at room temperature for 2 hours during which time crystals separated. The crystals were collected, yield 286 mg. (57%), m.p. 237-240°; uv max nm 272 (ε, 21,400), 282 (ε, 18,000); uv min nm (ε, 1,850); R_f in solvent C 0.58; R_f in solvent A 0.53.

Anal. Calcd. for $C_{13}H_{16}N_4O_5$: C, 50.64; H, 5.22; N, 18.18. Found: C, 50.49; H, 5.23; N, 17.95.

N^6-Acetyl-2′,3′-*O*-isopropylidene-1-deazaadenosine (X).

To a solution of N^6-acetyl-1-deazaadenosine (IX, 343 mg., 1.11 mmoles) in dry acetone (55 ml.) and 2,2-dimethoxypropane (1.1 ml.) was added *p*-toluenesulfonic acid monohydrate (1.97 g.). The solution was stirred at room temperature for 2 hours. The

solution was neutralized with solid potassium carbonate (2.80 g.) and then concentrated to dryness. The residue was extracted with ten 50-ml. portions of chloroform. Evaporation of the solvent left the crude product, which was crystallized from water. A yield was 194 mg. (50%), m.p. 190-192°; uv max (ethanol) nm 271 (ϵ, 21,500), 281.5 (ϵ, 17,900); un min (ethanol) 237 (ϵ, 2,630). R_f in solvent C 0.75; R_f in solvent A 0.81; ir max (potassium bromide), 1710 (carbonyl of acetamido group).

Anal. Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.79; N, 16.08. Found: C, 54.91; H, 5.95; N, 16.02.

N^6-Acetyl-2′,3′-*O*-isopropylidene-5-*O*′-*p*-tolylsulfonyl-1-deazaadenosine (XI).

A solution of X (72.5 mg., 0.208 mole) in 1 ml. of dry pyridine was treated with *p*-toluenesulfonyl chloride (75.9 mg., 0.397 mole) overnight at room temperature. The solution was neutralized with 1 ml. of a saturated solution or sodium bicarbonate, and extracted with three 5-ml. portions of chloroform. The organic layer was separated and successively washed with two 5-ml. portions of cold saturated solution of sodium hydrogen sulfate and with 5-ml. portions of cold water, dried over sodium sulfate. The salt was filtered and washed with chloroform. The combined chloroform solution was concentrated to dryness, yield 51.6 mg.; uv max nm 271 (ethanol).

Preparation of Cyclonucleoside (XII).

A solution of XI (8.6 mg.) in dry acetone (2 ml.) was heated in an oil bath for 40 minutes at reflux temperature, during which time a white precipitate separated on the surface of the flask. The precipitate was collected and washed with a small amount of cold acetone, yield 2.9 mg.; uv max nm 297 (methanol) (bathochromic shift by 28 nm as compared with max of the original nucleoside); R_f in solvent A 0.47; on paper electrophoresis (0.36 *M* formate buffer, *p*H 3.5; 70 volts/1 cm), the quaternized cyclonucleoside travelled toward the cathode by 4.9 cm. Under the same conditions, 2′,3′-*O*-isopropylidene-3′,5′-cyclonucleoside (11) travelled the same distance, whereas the starting material (XI) did not move; ir max (potassium bromide) 1730 (carbonyl of acetamido group).

Acid Hydrolysis of XII (17).

A solution of XII (0.6 mg.) in 0.6 ml. of 1 *N* hydrochloric acid was heated on a boiling water bath for 30 minutes. (These conditions were used for partial hydrolysis of a purinecyclonucleoside) (17). The ultraviolet absorption spectra of the solution was similar than those of 1-deazaadenine-3-riboside (IV); uv max nm 223, 267, 287.5 at acidic *p*H (< 1), 293 at *p*H 11.9.

4-Amino-2-(2-hydroxyethyl)amino-3-nitropyridine (XIV).

To a solution of 4-amino-2-chloro-3-nitropyridine (XIII, 240 mg.) (9) in nitromethane (5 ml.) was added 180 mg. of 2-hydroxyethylamine. The solution was heated for 1.5 hour. An amine hydrochloride separated and was removed by decantation. Removal of the solvent left a crude product which was crystallized from benzene-ethanol, m.p. 153-154°, yield 153 mg. (57%); uv max nm 235.

Anal. Calcd. for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.64; H, 5.30; N, 28.13.

7-Amino-3-(2-hydroxyethyl)-3*H*-imidazo[4,5-*b*]pyridine (XV).

To a solution of XIV (47 mg.) in ethanol (10 ml.) was added a spatulaful of Raney nickel. The solution was reduced in a hydrogen atmosphere at room temperature. Approximately 20 ml. of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate was concentrated to dryness, yield, 50 mg.; uv max nm 227, 282 at *p*H 1.0; 220 (sh), 288 at *p*H 13. To a solution of 50 mg. of the residue was added 60 mg. of formamidine acetate. The solution was refluxed for 1.5 hours and the solvent was removed *in vacuo*. The remaining solvent was removed by codistillation with water. The residue was crystallized from water, yield, 7 mg. m.p. 234°; pK_a 6.32 (19); uv max nm 266 (ϵ, 7,800, sh), 282.5 (ϵ, 10,200) at *p*H 1.25, nm 263 (ϵ, 8,500), 277 (ϵ, 7,100) at *p*H 8.86.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.45. Found: C, 53.60; H, 5.66; N, 31.09.

Ribosylation of XVI by Mercuri Cyanide Procedure (10).

A mixture of 3.5 g. of XVI, 2,3,5-tri-*O*-benzoyl-D-ribosyl chloride (XVII), prepared from 10 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose, 10 g. of mercuric cyanide and 8.0 g. of calcium sulfate in 300 ml. of nitromethane was azeotropically dried and then refluxed for 4 hours. The mixture was filtered and the inorganic salt was washed with 100 ml. of nitromethane. The combined filtrate and washings were concentrated to dryness. The residue was dissolved in chloroform and the inorganic material was filtered. The filtrate was washed successively with 100-ml. portions of 30% potassium iodide and two 100-ml. portions of water. The solution was dried over sodium sulfate. The solvent was removed *in vacuo* to leave 9.83 g. of a white foam. The residue was purified over alumina column (alumina 250 g., column size 3.8 x 27 cm). One fraction was *ca.* 300 ml.

Fraction-I (fraction No. 1-16) eluted by benzene and a mixture of benzene and ethyl acetate (9:1) gave, after removal of solvent, a non-nitrogenous substance (2.01 g.) which was discarded.

Fraction-II (fraction No. 17) obtained by washing the column with benzene-ethyl acetate (1:1 v/v) gave 0.35 g. of blocked nucleoside of III (yield, 3%).

Fraction-III (fraction No. 25) eluted by ethyl acetate gave 0.11 g. (1%) of blocked *bis*-ribosyl compound.

Fraction-IV (fraction No. 29-35) eluted by benzene containing increasing proportions of ethanol (1:4 to 1:1 v/v) gave 3.4 g. (30% yield) of benzoyl blocked nucleoside of IV.

Fraction-III was dissolved in 30 ml. of dry methanol added with 0.1 ml. of 2 *N* methanolic sodium methoxide. The solution was refluxed for about 1 hour. The solution was neutralized with resin IRC (H^+ form) and filtered. The filtrate was concentrated to dryness. The residue was crystallized from water, yield 68 mg. (57%). This sample was found to be indistinguishable from the sample of III described above based on the criteria of m.p., uv and nmr spectral properties.

4-β-D-Ribofuranosyl-7-β-D-ribofuranosyl-4*H*-imidazo[4,5-*b*]pyridine (XVIII).

Fraction-II was treated as in the preparation of III. From 90 mg. of blocked nucleoside, 12 mg. of a nucleoside was obtained; uv max nm 225, 267, 290 at *p*H 10; nm 225, 270, 294 at *p*H 13. The nucleoside (1 mg.) was dissolved in 0.1 *N* hydrochloric acid solution. The solution was heated for 10 minutes. The uv spectra shifted initially to those of IV and after 60 minutes of heating, to those of XVI. Therefore, it was highly probable that the nucleoside was 4-β-D-ribofuranosyl-7-β-D-ribofuranosyl-4*H*-imidazo[4,5-*b*]pyridine. However, it was not further characterized.

7-Amino-4-β-D-ribofuranosyl-4*H*-imidazo[4,5-*b*]pyridine (IV).

Fraction-IV (629 mg.) was deblocked as above. The crude deblocked nucleoside was crystallized from water, yield 152 mg. (50%), m.p. (double melting points) 173-175°, 213-215°; R_f in water (*p*H 10) 0.45; pK_a 7.10 (19); uv max nm 280 (15,400,

sh), 294 (18,200) at *p*H 11.0; $[\alpha]_D^{18}$ -76.8° (c 1.25, DMF).

Anal. Calcd. for $C_{11}H_{14}N_4H_2O$: C, 46.47; H, 5.67; N, 19.72. Found: C, 46.61; H, 5.80; N, 19.62.

REFERENCES

(1a) XII of this series. Y. Mizuno, S. Tazawa, and K. Kageura, *Chem. Pharm. Bull.*, 16, 2011 (1968). (b) This investigation was supported in part by fund Research Contact, Cancer Chemotherapy, National Cancer Institute.

(2) R. J. Suhaldonik, "Nucleoside Antibiotics," John Wiley and Sons, Inc., New York, N. Y., 1970, pp. V, 301, 362.

(3) R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Am. Chem. Soc.*, 91, 2102 (1969).

(4) R. J. Rousseau, L. B. Townsend, and R. K. Robins, *Biochemistry*, 5, 756 (1966).

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

(6a) Nucleoside Va was already synthesized by Mizuno *et al.* (6b); (b) Y. Mizuno, N. Ikekawa, T. Itoh, and K. Saito, *J. Org. Chem.*, 30, 4066 (1965).

(7) R. H. J. Hertog and H. C. van der Plas, "Advances in Heterocyclic Chemistry," 4, 121 (1965). A. R. Katritzky, Ed., Academic Press, New York.

(8) R. Ishido, T. Shimadate, and T. Sato, *Bull. Chem. Soc. Japan*, 34, 1437 (1961); R. Ishido, T. Shimadate, and T. Sato, *Nippon Kagaku Zasshi* (Tokyo), 81, 1441 (1960).

(9) J. A. Montgomery and K. Hewson, *J. Med. Chem.*, 9, 354 (1966).

(10) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, 30, 149 (1965).

(11) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

(12) N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.*, 84, 2148 (1962).

(13) B. Shimizu and M. Miyaki, *Chem. Ind.* (London), 644 (1966).

(14a) M. Asai, M. Miyaki, and B. Shimizu, *Agr. Biol. Chem.*, 31, 319 (1967); (b) J. A. Montgomery and H. J. Thomas, *J. Am. Chem. Soc.*, 80, 2672 (1963); (c) J. A. Montgomery and H. J. Thomas, *ibid.*, 87, 5442 (1965); (d) N. J. Leonard and T. Fujii, *ibid.*, 85, 3719 (1965); (e) N. J. Leonard and J. A. Deyrup, *ibid.*, 82, 6202 (1960); (f) N. J. Leonard and J. A. Deyrup, *ibid.*, 84, 2148 (1962); (g) C. J. Abshire and L. Berlignet, *Can. J. Chem.*, 42, 1599 (1964).

(15) N. J. Leonard and R. A. Laursen, *Biochemistry*, 4, 3546 (1965).

(16) Y. Mizuno, M. Ikehara, K. A. Watanabe, S. Suzaki, and T. Itoh, *J. Org. Chem.*, 28, 3329 (1963).

(17) R. E. Holmes and R. K. Robins, *ibid.*, 28, 3483 (1963).

(18) J. Davoll and A. Lowy, *J. Am. Chem. Soc.*, 73, 1650 (1951).

(19) S. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, 9, 199 (1952).