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# Nucleoside Peptides. 6. Synthesis of Certain *N*-[5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]amino Acids Related to Naturally Occurring Intermediates in the Purine Biosynthetic Pathway

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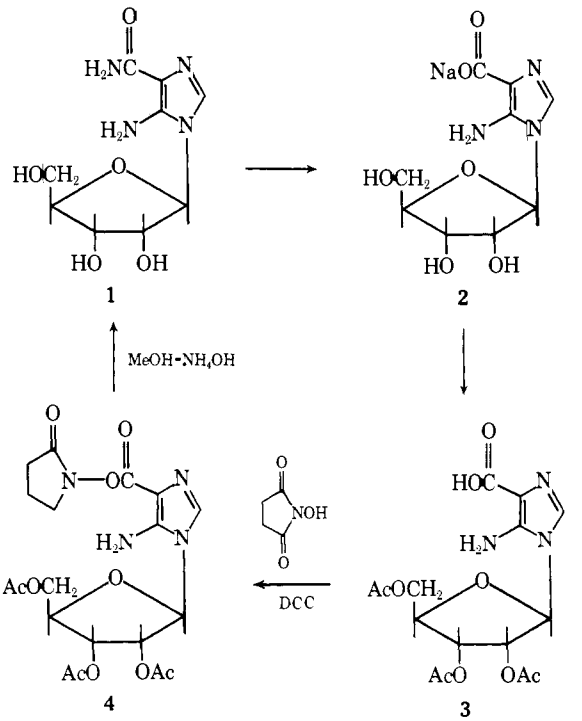
Alkaline hydrolysis of AICA ribonucleoside has provided a new synthesis of sodium 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate in good yield. Selective acetylation of this product afforded 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid. Various appropriately blocked amino acids have been coupled to the 4-carboxy group of this compound *via* the *N*-hydroxysuccinimidyl ester. Subsequent deblocking procedures have provided good yields of the title compounds.

AICAR [5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide 5′-phosphate],[1] an intermediate in the *de novo* purine biosynthetic pathway, has been synthesized enzymatically from 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylic acid 5′-phosphate *via* the amino acid nucleotide *N*-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]-L-aspartic acid 5′-phosphate.[2] These nucleotides, as well as the corresponding nucleosides, have been synthesized chemically, but in such small yields that the physical characteristics of these compounds for the most part have not yet been studied.† It was of interest to investigate the laboratory scale synthesis of the nucleoside analogs of these interesting imidazole intermediates, as well as a number of their amino acid and peptide derivatives. It seemed reasonable that these nucleoside peptides might well possess special biological properties which would provide useful medicinal agents as discussed in the first paper of this series.[4,5] The recent commercial availability of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide‡ (1, AICA ribonucleoside) provided the necessary source of starting material to initiate this study (Scheme I).

It is well known that conversion of carboxamides to carboxylic acids can be effected either by alkaline or acid conditions.[6] The use of acidic media was precluded because the glycosyl linkage of 1 (Scheme I) is acid labile.

Scheme I

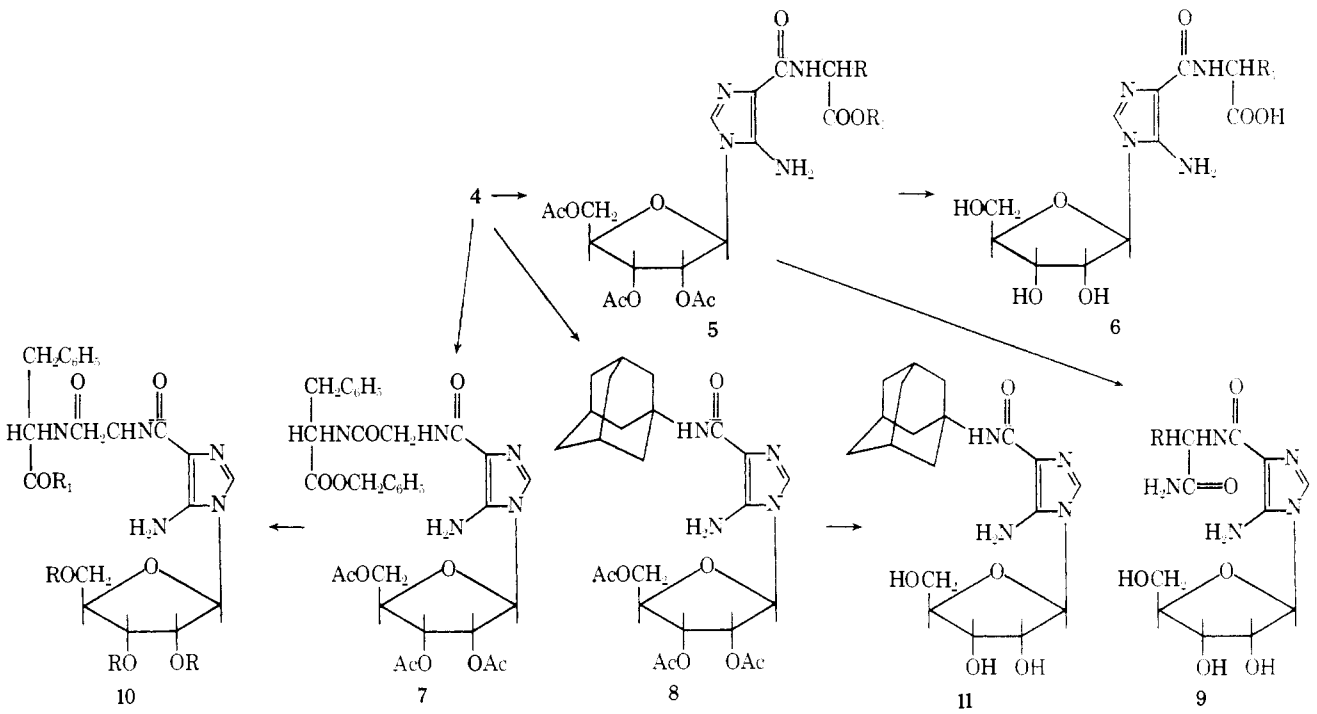



1 2 3 4

†For a recent review of the subject of imidazole nucleosides and nucleotides, see ref 3.

‡Purchased from ICN Nutritional Biochemicals Corp., Cleveland, Ohio 44128.

Scheme II



a, R = H; $R_1$ = $CH_3$
b, R = $CH_3$; $R_1$ = $CH_2C_6H_5$
c, R = $CH_2C_6H_5$; $R_1$ = $CH_2C_6H_5$
d, R = $CH_2COOCH_2C_6H_5$; $R_1$ = $CH_2C_6H_5$
e, R = $(CH_2)_4NHCBz$; $R_1$ = $CH_3$
f, $R_1$ = H
g, $R_1$ = $CH_3$
h, $R_1$ = $CH_2C_6H_5$
i, $R_1$ = $CH_2COOH$
j, $R_1$ = $(CH_2)_4NH_2$
k, R = H
l, R = $CH_3$
m, R = $COCH_3$; $R_1$ = OH
n, R = H; $R_1$ = OH
o, R = H; $R_1$ = $NH_2$

Treatment of 1 with sodium hydroxide caused evolution of ammonia. The optimum conditions for product formation were found to be treatment of 1 with 6 equiv of 6 *N* sodium hydroxide in refluxing solution for 4 hr. The product, sodium 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (2), was formed in 92.5% yield. Formation of 2 was accompanied by a change in the ultraviolet spectrum from 266 to 250 nm in pH 11 solution. The structure of 2 was confirmed by disappearance of the carbonyl stretching signal at 1635 $cm^{-1}$ (amide) and appearance of a carbonyl stretching signal at 1600 $cm^{-1}$ (carboxylate ion).[7] Final corroboration was obtained by satisfactory elemental analysis. Attempts to obtain the free carboxylic acid by lowering the pH caused rapid evolution of carbon dioxide presumably to 5-amino-1-(β-D-ribofuranosyl)imidazole[8] followed by decomposition to a dark intractable mixture.

The free carboxylic acid was obtained by treatment of 2 with acetic anhydride and pyridine at 10°. The resulting blocked amino acid nucleoside, 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid (3), was then isolated in 57% yield. The related amino acid imidazole, 5-amino-1-cyclohexylimidazole-4-carboxylic acid, has been proposed to possess a zwitterionic structure in solution.[9] Inspection of the infrared spectra of 3 revealed that there was no strong signal in the range 1700–1680 $cm^{-1}$ (aryl carboxylic acid stretching) but there were signals at 1560 and 1380 $cm^{-1}$ (carboxylate anion stretching) indicating the possibility of the zwitterionic nature of 3 in the solid state.

Synthesis of the amino acid nucleoside, *N*-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]-L-aspartic acid (6i), was previously reported by Shaw and Wilson.[10] To achieve peptide bond formation these workers utilized dimethyl L-aspartate and dicyclohexylcarbodiimide (DCC) with the isopropylidene blocked pyridine salt of 2. The physical characteristics of this compound were not reported, probably due to the limited quantities of starting material available. The direct condensation of blocked amino acids with 2 and DCC under a variety of conditions was unsuccessful. The active ester method of Bodanszky[11] utilizing *p*-nitrophenyl esters for peptide bond formation has recently been used with good success for the synthesis of various nucleoside peptide compounds.[4,5,12] The use of *N*-hydroxysuccinimide esters of acylamino acids has also been reported for peptide synthesis.[13] This method appeared to be more advantageous for the present study as the *N*-hydroxysuccinimide esters are reported to be crystalline solids and the by-product of coupling an activated ester with an amino ester is water-soluble *N*-hydroxysuccinimide. The *N*-hydroxysuccinimidyl ester 4 was therefore prepared by the action of DCC and *N*-hydroxysuccinimide on 3. It was found unnecessary to block the 5-amino moiety of 3 since under these reaction conditions there was no indication of inter- or intramolecular attack of the 5-amino function on the 4-carbonyl group. This active ester compound was found to be stable for more than 6 months when stored at room temperature; however, facile displacement of the *N*-hydroxysuccinimidyl moiety was accomplished when 4 was treated with methanolic ammonium hydroxide. Deacetylation accompanied this displacement and afforded 1. When 4 was treated with the bulky amine adamantamine, the product, 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-*N*-(1-adamantyl)carboxamide (8), was obtained in 89% yield

(Scheme II). Removal of the acetyl-blocking groups was accomplished by the action of methanolic ammonium hydroxide and gave the free nucleoside 11 in excellent yield.

The *N*-hydroxysuccinimidyl group of 4 was also readily displaced by appropriately protected amino acids. When the glycine methyl ester, L-alanine benzyl ester, or L-phenylalanine benzyl ester was treated with a methylene chloride solution of 4, the blocked amino acid nucleoside **5a**, **5b**, or **5c** was obtained in yields of 80, 88, and 84%, respectively. Similarly, the action of the L-aspartic acid dibenzyl ester or *N*-carbobenzyloxy-L-lysine methyl ester on 4 afforded compounds **5d** and **5e** in yields of 85 and 77%, respectively (Table I).

The blocked dipeptide nucleoside **7** was obtained in 86% yield when 4 was treated with glycyl-L-phenylalanine benzyl ester.

The title compounds were obtained by removal of the blocking groups. *N*-[5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]glycine (**6f**) was prepared by treating **5a** with sodium methoxide in methanol followed by sodium hydroxide solution. The benzyl-blocking groups of **5b**, **5c**, and **5d**, as well as the carbobenzyloxy group of **5e**, were removed by catalytic hydrogenolysis with palladium on carbon. The remainder of the protecting groups were cleaved by alkaline hydrolysis. The resulting respective amino acid nucleosides, *N*-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]-L-alanine (**6g**), *N*-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]-L-phenylalanine (**6h**), *N*-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]-L-aspartic acid (**6i**), and *N*-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]-L-lysine (**6j**), were produced in good yields (Table I).

Following a similar procedure the blocked dipeptide nucleoside **7** on catalytic hydrogenation was converted into *N*-[5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonyl]glycyl-L-phenylalanine (**10m**) which on alkaline hydrolysis gave the corresponding deblocked dipeptide nucleoside *N*-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]glycyl-L-phenylalanine (**10n**).

Compounds **5a**, **5b**, **7**, and 8 could be converted to their respective deblocked carboxamide derivatives **9k**, **9l**, **10o**, and 11 by the action of methanolic ammonium hydroxide.

The amino acid conjugates of 1-(β-D-ribofuranosyl)imidazole-4-carboxylic acid described here did not show significant antiviral activity (virus rating[14] of 0.4 or less) when tested for inhibition of type 3 adeno, type 1 herpes simplex, type 3 parainfluenza, and type 13 rhino viruses in concentrations ranging in 0.5 log dilutions from 1000 to 1 μg/ml using human carcinoma of the nasopharynx (KB) cells. These compounds were also tested against certain organisms at concentrations of 0.4 μmol/ml or less by broth dilution in defined medium and the *in vitro* antimicrobial activity against *Proteus mirabilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans*, and *Trichophyton mentagrophytes* was not detected.

## Experimental Section

The ir spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer (KBr). Nmr spectra were determined on a Hitachi Perkin-Elmer Model R-20A spectrometer using DSS as an internal standard. Where indicated by elemental analyses, hydration was confirmed by nmr spectroscopy in absolute DMSO-$d_6$ by exchange with $D_2O$ and reintegration. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The uv spectra were recorded on a Cary 15 ultraviolet spectrometer. The optical rotations were obtained with a Perkin-Elmer Model 141 automatic digital read-out polarimeter.

The homogeneity of the compounds was checked by thin-layer chromatography using precoated (250-μ) Brinkman tlc plates (silica gel F-254). Shortwave ultraviolet light (mineralite UVS 11) was used to detect the spots and the chromatographic solvent systems used were: A, chloroform–methanol, 4:1 (v/v); B, chloroform–methanol, 1:4 (v/v); C, ethyl acetate–chloroform–acetone, 5:3:2 (v/v); D, methanol–dichloromethane–ammonium hydroxide, 2:2:1 (v/v).

**Sodium 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (2).** A solution of AICA ribonucleoside (25.8 g, 0.1 mol) and 6 *N* NaOH (100 ml) in a 500-ml round-bottom flask was fitted with a reflux condenser and protected from atmospheric $CO_2$ with a sodalime tube. The reaction mixture was heated at gentle reflux for 4 hr and chilled in ice, then ethanol (200 ml) was added, and the mixture was vigorously stirred. The syrup which formed was separated from the supernatent and triturated with 50-ml portions of ethanol (three times) and then 25-ml portions of ethanol (three times), and the supernatent was decanted each time. Finally the syrup was placed in a vacuum desiccator for 24 hr and the crystalline solid (or thick syrup) was triturated with methanol (~50 ml); the solid thus formed was collected and dried (NaOH) in a vacuum desiccator giving 26 g (92.5%) of **2** which could be used for further reaction. A portion of this crude product was crystallized from ethanol–water to give an analytical crystalline sample of **2**: mp 244–245° dec; $[\alpha]^{25}D$ 57.1° (*c* 1, $H_2O$); $\lambda_{max}$ (pH 1) 248 nm (sh) (ε 8992) and 265 (11,015); $\lambda_{max}$ ($H_2O$) 249 nm (ε 10,003); $\lambda_{max}$ (pH 11) 250 nm (ε 11,055); ir 1592 and 1300–1320 $cm^{-1}$ ($COO^-$); nmr ($D_2O$) δ 7.43 (s, 1, $C_2H$), 5.65 (d, 1, *J* = 6 Hz, $C_1'H$), and 3.7–4.6 ppm ($C_5'H_2$, $C_4'H$, $C_3'H$, and $C_2'H$). *Anal.* Calcd for $C_9H_{12}N_3NaO_6$: C, 38.44; H, 4.30; N, 14.94. Found: C, 38.31; H, 4.15; N, 15.10.

**5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic Acid (3).** Acetic anhydride (270 ml) was added dropwise over a period of 50 min to a stirred suspension of **2** (28.1 g, 0.1 *M*) in dry pyridine (530 ml) at 0° under anhydrous conditions. After complete addition of acetic anhydride the reaction mixture was stirred for additional 5–6 hr at a temperature of 10 ± 5°. Celite analytical filteraid (*ca.* 15 g) was then added to the reaction mixture, stirred for 10–15 min, and filtered through a Celite pad. The clear filtrate was concentrated (*ca.* 15 ml) *in vacuo* (temperature ≤20°) and then water (50 ml) was added and removed under vacuum. This process was repeated four times. On final addition of water a crystalline residue separated which was filtered, washed with cold water and cold acetone, and dried immediately to give 22 g (57%) of crude **3** as a white crystalline compound: mp 145° dec. This was recrystallized from acetone to give mp 145–146° dec: $[\alpha]^{25}D$ −28.2° (*c* 1, MeOH); $\lambda_{max}$ (pH 1) 265 nm (ε 11,803) and 248 (sh) (10,200); $\lambda_{max}$ ($H_2O$) 250 nm (ε 10,175); $\lambda_{max}$ (pH 11) 248.5 nm (ε 11,803); ir 1380, 1370 (sh), and 1562 $cm^{-1}$ ($COO^-$); nmr (DMSO-$d_6$) δ 7.47 (s, 1, $C_2H$), 6.17 [s (br), 2, $NH_2$], 5.98 (d, 1, *J* = 6 Hz, $C_1'H$), 5.7–5.3 (m, 2, $C_2'H$, $C_3'H$), 4.35 (s, 3, $C_5'H_2$, $C_4'H$), and 2.13 ppm [s, 9, 2′,3′,5′-tri-*O*-$C(=O)CH_3$]. It was necessary to store this compound in a dessiccator to avoid decomposition. *Anal.* Calcd for $C_{15}H_{19}N_3O_9$: C, 46.75; H, 4.97; N, 10.91. Found: C, 46.91; H, 5.18; N, 10.74.

***N*-Succinimidyl-5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate (4).** DCC (2.266 g, 11 mmol) was added to a mixture of **3** (3.85 g, 10 mmol) and *N*-hydroxysuccinimide (1.151 g, 10 mmol) in dry DMF (25 ml). The reaction mixture was stirred for 48 hr at room temperature. Acetic acid (300 mg) was added and the reaction mixture was stirred for an additional 1 hr to decompose the excess of DCC. The crystalline dicyclohexylurea was filtered and washed with ethyl acetate (25 ml) and the filtrate was evaporated to dryness (temperature 40–50°). The residue thus obtained was dissolved in ethyl acetate (100 ml), washed with water (2 × 40 ml), and dried ($MgSO_4$). Removal of solvent *in vacuo* gave a residue which was crystallized from benzene to yield 3.8 g (80%) of **4** as shining white crystals: mp softens at 85° and slowly melts above 110°; $[\alpha]^{25}D$ −26.96° (*c* 1, $CH_3OH$); $\lambda_{max}$ (pH 1) 276 nm (ε 16,527) and 242 (sh) (6227); $\lambda_{max}$ (MeOH) 275 nm (ε 16,527) and 240 (sh) (6227); $\lambda_{max}$ (pH 11), 270 nm (ε 15,569) and 240 (sh) (8670); nmr (DMSO-$d_6$) δ 6.8 (s, 2, $NH_2$) and 2.87 ppm (s, 4, $CH_2CH_2$-succinimidyl). *Anal.* Calcd for $C_{19}H_{22}N_4O_{11}$: C, 47.30; H, 4.59; N, 11.61. Found: C, 47.62; H, 4.73; N, 11.41.

***N*-[5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonyl]glycine Methyl Ester (5a).** To a cold solution of glycine methyl ester hydrochloride[15] (630 mg, 5 mmol) in methylene chloride (25 ml) was added dry triethylamine (0.7 ml, 5 mmol) and the mixture was stirred at 0° for 20 min. The triethylamine hydrochloride which separated was removed by filtration. To the clear filtrate was added 4 (2.17 g, 4.5 mmol) and the reaction mixture was stirred at room temperature for 16 hr. At the

**Table I**

| Compd | Mp, °C | $[\alpha]^{25}D$, deg | Yield, % | Ultraviolet spectral data: $\lambda_{max}$ (pH 1), nm ($\epsilon \times 10^{-3}$) | Ultraviolet spectral data: $\lambda_{max}$ (pH 11), nm ($\epsilon \times 10^{-3}$) | Formula | Calcd, % C | Calcd, % H | Calcd, % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5b** | 70–72 | −43.7 (*c* 1, MeOH) | 88 | 245 (9.53) (sh), 268 (11.07) | 265 (12.88) | $C_{25}H_{30}N_4O_{10}$ | 54.94 | 5.53 | 10.25 | 54.84 | 5.40 | 10.19 |
| **5c** | 87 (softens) | −12.6 (*c* 1, $CHCl_3$) | 84 | 250 (10.07) (sh), 269 (12.20) | 267 (14.65) | $C_{31}H_{34}N_4O_{10}$ | 59.80 | 5.50 | 9.00 | 59.64 | 5.54 | 8.79 |
| **5d** | Glass | Darkly colored | 85 | 247 (10.56) (sh), 268 (12.50) | 265 (15.28) | Analyzed after deblocking step | | | | | | |
| **5e** | 88–90 | −21 (*c* 1, $CHCl_3$) | 77 | 248 (10.14) (sh), 269 (13.83) | 267 (15.63) | $C_{30}H_{39}N_5O_{12}$ | 54.45 | 5.94 | 10.58 | 54.19 | 5.87 | 10.38 |
| **6g** | Glass | Darkly colored | 51 | 245 (6.44) (sh), 268 (7.15) | 265 (8.62) | $C_{12}H_{18}N_4O_7 \cdot 1.5H_2O$ | 40.34 | 5.92 | 15.68 | 40.25 | 5.80 | 15.54 |
| **6h** | 86 | −4.7 (*c* 1, $H_2O$) | 86 | 248 (8.84) (sh), 268 (10.65) | 266 (13.06) | $C_{18}H_{22}N_4O_7$ | 53.20 | 5.46 | 13.79 | 52.94 | 5.48 | 13.49 |
| **6i** | Sticky solid | Darkly colored | 42 | 248 (6.54) (sh), 268 (7.34) | 265 (8.87) | $C_{13}H_{18}N_4O_9 \cdot H_2O$ | 39.80 | 5.14 | 14.28 | 40.05 | 5.48 | 14.75 |
| **6j** | 90 (softens) | Darkly colored | 51 | 245 (9.60) (sh), 268.5 (11.66) | 265 (13.90) | $C_{15}H_{25}N_5O_7 \cdot H_2O$ | 44.44 | 6.71 | 17.28 | 44.68 | 6.70 | 17.23 |
| **9k** | 180–181 | −56.22 (*c* 1, $H_2O$) | 80 | 250 (10.13) (sh), 268.5 (12.50) | 267 (15.16) | $C_{11}H_{17}N_5O_6$ | 41.90 | 5.43 | 22.21 | 41.72 | 5.31 | 21.99 |
| **9l** | 184 | −41.53 (*c* 1, $H_2O$) | 78 | 247 (10.34) (sh), 269 (12.93) | 265 (15.03) | $C_{12}H_{19}N_5O_6$ | 43.76 | 5.82 | 21.27 | 44.00 | 5.96 | 21.08 |
| **10o** | 215–216 | −28.75 (*c* 1, $H_2O$) | 70 | 250 (10.40) (sh), 269 (12.58) | 268 (14.52) | $C_{20}H_{26}N_6O_7 \cdot H_2O$ | 49.99 | 5.88 | 17.49 | 50.20 | 5.71 | 17.59 |
| **11** | 93 dec | −45.0 (*c* 1, MeOH) | 90 | 245 (12.67) (sh), 269 (13.48) | 267 (16.61) | $C_{19}H_{28}N_9O_5$ | 58.14 | 7.19 | 14.27 | 57.96 | 7.29 | 14.10 |

end of this time, methylene chloride (25 ml) was added and the whole mixture was washed successively with water (30 ml), 5% citric acid (25 ml), 5% $Na_2CO_3$ (20 ml), and water (2 × 30 ml) and dried ($MgSO_4$). Evaporation of the solvent gave 1.6 g (80%) of **5a**. This was recrystallized from 2-propanol to give an analytical sample: mp *ca.* 130° (sinters at *ca.* 80°); $[\alpha]^{25}D$ −30.2° (*c* 1, DMF); $\lambda_{max}$ (pH 1) 267.5 nm (ε 12,609) and 247 (sh) (10,832); $\lambda_{max}$ (pH 11) 265 nm (ε 14,732). *Anal.* Calcd for $C_{18}H_{24}N_4O_{10}\cdot 0.5H_2O$: C, 46.41; H, 5.39; N, 12.02. Found: C, 46.31; H, 5.34; N, 11.85.

**General Procedure A (Table I) for the Preparation of 5b–e.** *N*-Succinimidyl-5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate (1.929 g, 4 mmol) was added to a solution of the appropriate blocked amino acid [L-alanine benzyl ester[16] (990 mg, 5 mmol) for **5b**; L-phenylalanine benzyl ester[17] (1.275 g, 5 mmol) for **5c**; L-aspartic acid dibenzyl ester[17] (1.565 g, 5 mmol) for **5d**; $N^{\epsilon}$-carbobenzyloxy-L-lysine methyl ester[18] (1.47 g, 5 mmol) for **5e**] in $CH_2Cl_2$ (25 ml) and the reaction mixture was stirred at room temperature for 24 hr. Methylene chloride (25 ml) was added and the whole mixture was washed successively with water (25 ml), 5% acetic acid (20 ml), 5% $Na_2CO_3$ (20 ml), and water (2 × 25 ml) and dried ($MgSO_4$).

Analytical samples were obtained (in each case) by removing the solvent and treating the residue thus obtained with benzene and petroleum ether to give an amorphous solid (dried over $P_2O_5$ for 5 hr *in vacuo* at room temperature).

***N*-[5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]glycine (6f).** Sodium methoxide (108 mg, 2 mmol) was dissolved in methanol (15 ml), **5a** (hemihydrate, 932 mg, 2 mmol) was added, and the mixture was refluxed for 1 hr. The solvent was removed *in vacuo* and the residue was dissolved in water (5 ml). The solution was kept 30 min at room temperature. Dowex 50 ([$H^+$] form, 100–200 mesh, 5 ml) was added and the solution was stirred for 30 min. The resin was filtered and washed with water (2 × 10 ml). Filtrate and washings were mixed and lyophilized and then dried over $P_2O_5$ *in vacuo* at 56° to yield 348 mg (55%) of **6f**: mp 104° (slow decomposition above 104°, sinters at *ca.* 70°); $[\alpha]^{25}D$ −29.9° (*c* 1, $H_2O$). *Anal.* Calcd for $C_{11}H_{16}N_4O_7$: C, 41.77; H, 5.10; N, 17.72. Found: C, 41.51; H, 4.98; N, 17.57.

**General Procedure B (Table I) for the Removal of Benzyl-Blocking Groups by Catalytic Hydrogenation Followed by Deacetylation with Sodium Methoxide. Preparation of Compounds 6g–j.** Catalyst Pd on C (10%, 200 mg) was added to a cooled solution of the respective benzyl ester compound (**5b–e**, 2 mmol) in methanol (20 ml) under nitrogen atmosphere. The reaction mixture was hydrogenated at room temperature on a Parr apparatus at 45 psi for 5 hr. The catalyst was removed by filtration (Celite pad) and washed with methanol. The filtrate and washings were mixed and evaporated to dryness. The dry residue was dissolved in methanol (15 ml) containing NaOMe (108 mg) and the mixture refluxed for 1 hr. The residue obtained after evaporating the solvent *in vacuo* was dissolved in water (5 ml). The solution§ was stirred with Dowex 50 ([$H^+$] form, 100–200 mesh, 5 ml) for 1 hr. The product was isolated in the same way as described for **6f**.

**5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-*N*-(1-adamantyl)carboxamide (8).** A mixture of admantanamine (166 mg, 1.1 mmol) and **4** (482 mg, 1 mmol) in methylene chloride (10 ml) was stirred for 10 hr at room temperature. The separated *N*-hydroxysuccinimide was removed by filtration. Methylene chloride (20 ml) was added to the filtrate and the whole mixture was washed with 5% HCl (10 ml), 10% $NaHCO_3$ (15 ml), and water (2 × 15 ml), respectively. The methylene chloride portion was dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was crystallized from benzene–petroleum ether to give 500 mg (89%) of **8** in the form of white crystalline solid: mp 133° (softens at 80°); $[\alpha]^{25}D$ −30° (*c* 1, $CHCl_3$); $\lambda_{max}$ (pH 1) 268 nm (ε 13,619) and 245 (17,074); $\lambda_{max}$ (pH 11) 265 nm (ε 16,616). *Anal.* Calcd for $C_{25}H_{34}N_4O_8\cdot H_2O$: C, 55.96; H, 6.76; N, 10.44. Found: C, 56.05; H, 6.65; N, 10.31.

***N*-[5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonyl]glycyl-L-phenylalanine Benzyl Ester (7).** Glycyl-L-phenylalanine benzyl ester *p*-toluenesulfonate salt[19] (1.48 g, 3.05 mmol) was added to a solution of $Na_2CO_3$ (400 mg) in water (20 ml) and the solution was extracted with methylene chloride (2 × 20 ml), washed in turn with water, dried ($MgSO_4$), and concentrated *in vacuo* to *ca.* 20 ml. To this was added **4** (1.205 g, 2.5 mmol), the reaction carried out, and the product isolated exactly in the same way as described for general procedure A to give 1.46 g (86%) of **7**: $[\alpha]^{25}D$ −23.1° (*c* 1, DMF); $\lambda_{max}$ (pH 1) 268 nm (ε 11,273) and 250 (sh) (9774); $\lambda_{max}$ (pH 11) 268 nm (ε 12,707). *Anal.* Calcd for $C_{33}H_{37}N_5O_{11}$: C, 58.31; H, 5.48; N, 10.30. Found: C, 58.34; H, 5.70; N, 10.07.

***N*-[5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonyl]glycyl-L-phenylalanine (10m).** Compound **7** (800 mg, 1.176 mmol) was dissolved in methanol, the solution was cooled, and catalyst [Pd/C (10%, 500 mg)] was added to it under nitrogen atmosphere. The mixture was hydrogenated at room temperature on a Parr apparatus at 40 psi for 3 hr. The catalyst was removed by filtration (Celite pad) and washed with methanol. The combined filtrate was evaporated to dryness *in vacuo* and the residue was purified by precipitation from methanol–acetone to give an amorphous solid (dried over $P_2O_5$ *in vacuo* at room temperature for 24 hr). *Anal.* Calcd for $C_{26}H_{31}N_5O_{11}\cdot H_2O$: C, 51.40; H, 5.47; N, 11.52. Found: C, 51.61; H, 5.39; N, 10.97.

***N*-[5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carbonyl]glycyl-L-phenylalanine (10n).** Compound **10m** (608 mg, 1 mmol) was dissolved in methanol (10 ml), sodium methoxide (100 mg) was added, and the reaction mixture refluxed for 1 hr. The solvents were removed *in vacuo* and the residue was taken in water (10 ml) and stirred with Dowex 50 ([$H^+$] form 100–200 mesh, 5 ml) for 1 hr. The resin was filtered. The clear filtrate was lyophilized to give 230 mg (50%) of **10n**: mp 151–152° (softens at 75° and resolidifies at 99°); $[\alpha]^{25}D$ +10.03° (*c* 0.5, $H_2O$). *Anal.* Calcd for $C_{20}H_{25}N_5O_8\cdot 2H_2O$: C, 48.09; H, 5.85; N, 14.02. Found: C, 47.99; H, 5.31; N, 14.41.

**General Procedure C (Table I) for the Preparation of Compounds 9k,l, 10o, and 11.** To a cooled solution of the respective compound (**5a,b**, **7**, and **8**), 1 mmol in methanol (10 ml), was added $NH_4OH$ (10 ml) and the mixture stirred at room temperature for 3 hr. This was concentrated to dryness, and methanol (5 × 10 ml) was added and removed *in vacuo*. The solid thus obtained was crystallized from methanol–water.

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§In the case of **6i**, the solution was kept for 30 min at room temperature before being treated with resin.