buffer, ammonium acetate (10 mM, pH 6), was chosen for preparative HPLC of the sulfated peptides.

The selective sulfation of *p*-aminophenylalanine or serine in a peptide also containing tyrosine was made possible by tyrosine's lower reactivity toward complexed sulfur trioxide. *p*-Aminophenylalanine and serine were completely sulfated by SO_3·pyridine in anhydrous DMF and pyridine under argon within 1 h while sulfation of tyrosine in similar peptides required up to 24 h to complete. For example the sulfation of *p*-aminophenylalanine in 11 (pyridine–DMF solution 20 mM in peptide, 300 mM in SO_3·pyridine at room temperature for 1.0 h) gave 91% 12 and only 9% disulfated material by HPLC. Similarly HPLC of the sulfation of the four serines in 18 (pyridine–DMF solution 14 mM in peptide, 660 mM in SO_3·pyridine at room temperature for 1.0 h) showed 58% 19, 19% sulfated tyrosine, and 23% incomplete sulfation of serine (combined areas of four peaks).

The sulfated peptides were purified by preparative HPLC on a Rainin (21.4 × 250 mm) C_{18} column at 40 mL/min with a CH_3CN gradient in 10 mM ammonium acetate buffer at pH 6.0. The major peak was collected and lyophilized and then twice dissolved in deionized water and relyophilized to remove ammonium acetate.

Identity and purity for the sulfated peptides and precursors were assayed by analytic HPLC, FAB-MS on a VG Analytical ZAB2-SE instrument, and amino acid analysis (Table II and Table III). Sulfation at the *p*-aminophenylalanine residue rather than the tyrosine in 12 and 17 was confirmed by comparing their ^1H NMR and UV spectra with those of 3–7.

Hydrolysis. Since loss of sulfate can be a potential problem in the purification and storage of peptides containing sulfotyrosine, the rates of acid hydrolysis of purified sulfotyrosine in 14 and *p*-sulfoaminophenylalanine in 17 were compared. Samples of each peptide were dissolved in 10 mM TFA, pH 2.0, to make 250 μM solutions. The disappearance of sulfated peptide and appearance of desulfated material at room temperature were measured by HPLC (Vydac 218TP54 4.6 × 250 mm C18 column, gradient 5–30% CH_3CN/25 min in 0.1% TFA aqueous buffer at 2.0 mL/min) over 125 days. A fit of the data to the equation $C = C_0 \exp(-kt)$, where C is the concentration of sulfated peptide determined by HPLC at time t, C_0 the concentration at time 0, and k the rate constant for hydrolysis at pH 2, gives $k = 4.8 \times 10^{-8}$ s^{-1} for 14 and 9.5×10^{-8} s^{-1} for 17. This corresponds to less than 1% loss of sulfate after 24 h and $t_{1/2}$ of 167 and 84 days, respectively.

Anticoagulant Assay. Inhibition of fibrin clot formation was determined as previously described.[1] In brief, 50 μL (0.2 pmol) of bovine thrombin (Sigma) was added to the wells of a microtiter plate (Falcon) containing 50 μL of a solution of the synthetic peptide to be tested (0–25 nmol). After a 1-min agitation and an additional incubation for 10 min at 24 °C, 100 μL of diluted human plasma (1:10) in 0.1% EDTA was added and vortexed for 20 s. The turbidity of the solution was monitored by an autoreader (EL 309, Bio-Tek Instruments) at 405 nm at 5-min intervals. All of the above reagents were diluted in an assay buffer containing 0.12 M sodium chloride, 0.01 M sodium phosphate, 0.01% sodium azide, and 0.1% bovine serum albumin, pH 7.4.

Registry No. 3, 129521-72-8; 4, 131791-94-1; 5, 131791-95-2; 6, 131791-96-3; 7, 131831-88-4; 8, 131791-97-4; 9, 131791-98-5; 10, 131831-77-1; 11, 131791-99-6; 12, 131831-89-5; 13, 131831-78-2; 14, 131792-00-2; 15, 131792-01-3; 16, 131792-02-4; 17, 131792-03-5; 18, 131792-04-6; 19, 131792-05-7.

Adenosine Deaminase Inhibitors: Synthesis and Structure–Activity Relationships of Imidazole Analogues of *erythro*-9-(2-Hydroxy-3-nonyl)adenine

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A series of *erythro*-1-(2-hydroxy-3-nonyl)imidazole derivatives have been synthesized and evaluated for adenosine deaminase (ADA) inhibitory activity, in order to introduce simplifications in the ADA inhibitors *erythro*-9-(2-hydroxy-3-nonyl)adenine (EHNA, 1a) and 3-deaza-EHNA (1c). Opening the pyrimidine or pyridine ring of EHNA or 3-deaza-EHNA respectively led to compounds which are still ADA inhibitors. The most potent compound was *erythro*-1-(2-hydroxy-3-nonyl)imidazole-4-carboxamide (5, $K_i = 3.53 \times 10^{-8}$ M), which provided potential donor and acceptor sites for hydrogen bonding. Lack of one of this sites could account for the order of potency of all compounds examined in this series. Opening the same ring in adenosine and in 3-deazaadenosine led to fully inactive compounds. These results support the hypothesis of the existence, at or near the enzyme active site, of a hydrophobic region able to bind the *erythro*-nonyl moiety.

Deamination of adenosine and 2′-deoxyadenosine to form inosine and 2′-deoxyinosine is catalyzed by adenosine deaminase (ADA). In the last decade, inhibitors of adenosine deaminase have aroused interest as potential codrugs for use in combination with certain anticancer or antiviral agents which are adenosine analogues.[1] Inherited deficiency of ADA results in a block in development of the lymphoid system, causing severe combined immunodeficiency disease (SCID).[2] ADA inhibitors may be used to mimic the effect of the genetic deficiency of the enzyme and also in the chemotherapy of lymphoproliferative disorders and in the immunosuppressive therapy (i.e. in graft rejection).

Among the ADA inhibitors, *erythro*-9-(2-hydroxy-3-nonyl)adenine (EHNA, 1a), a semi-tight-binding inhibitor ($K_i = 1.6 \times 10^{-9}$ M), is advocated as a possible inhibitor of choice for use with such nucleosides and was preferred to coformycin and deoxycoformycin, two extremely potent naturally occurring inhibitors ($K_i = 10^{-11}$–10^{-12} M).[3] In order to investigate which structural parameters in the purine moiety of EHNA were critical for inhibitory activity, we synthesized and tested the deaza analogues of EHNA, 1b–e (Table I).[4–6]

We demonstrated that isosteric monosubstitution of the pyrimidine nitrogens by carbons can be tolerated at the enzymatic binding site. In fact, 3-deaza-EHNA (1c) was found to have an inhibitory activity comparable to that

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Scheme I

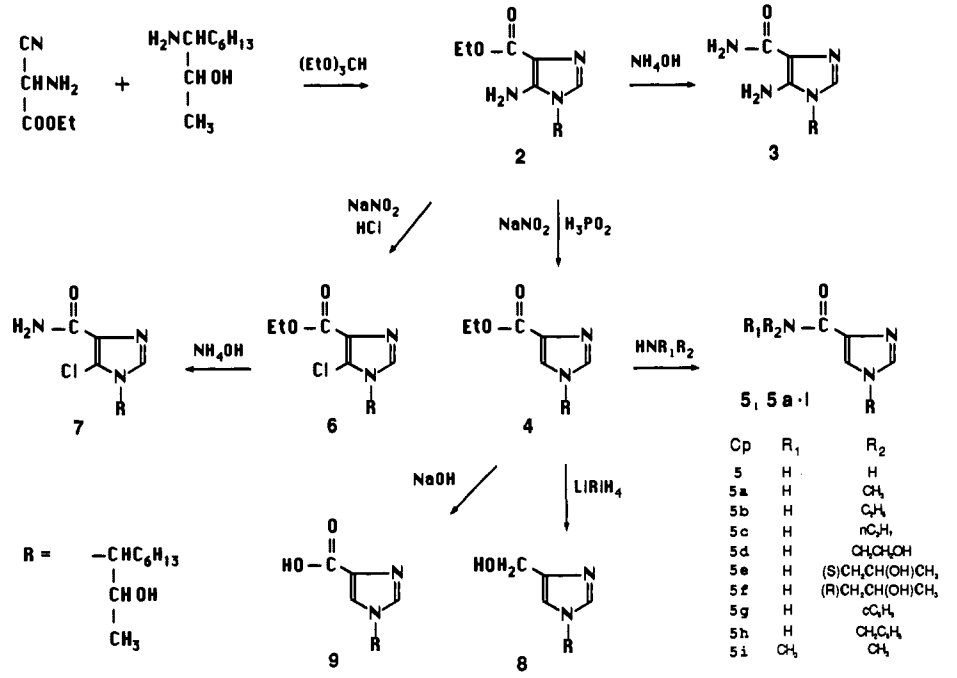
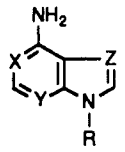
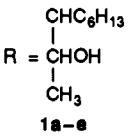
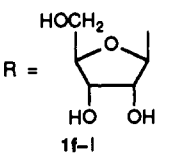


Table I. Inhibition Constants of Calf Intestinal Adenosine Deaminase[5]







no.	X	Y	Z	K_i, M
1a[a]	N	N	N	0.7×10^{-8}
1b[a]	CH	N	N	1.6×10^{-7}
1c[a]	N	CH	N	1.0×10^{-8}
1d[a]	N	N	CH	4.0×10^{-4}
1e[a]	CH	CH	N	7.1×10^{-5}
1f	CH	N	N	6.6×10^{-7}
1g	N	CH	N	3.6×10^{-4}
1h	N	N	CH	not active
1i	CH	CH	N	1.1×10^{-4}
1l	CH	N	CH	not active

[a] Mixture of two isomers: 2′*S*,3′*R* and 2′*R*,3′*S*.

of EHNA itself, and 1-deaza-EHNA (**1b**), though less potent, is a good inhibitor. On the contrary, substitution of a methine group for the nitrogen atom in the 7-position of the purine moiety of EHNA produces a dramatic drop in the inhibitory activity (**1d**). Also the contemporary substitution of pyrimidine nitrogens by carbons brings about a considerable reduction of activity (**1e**). In order to introduce additional simplifications to the EHNA chemical structure, a series of *erythro*-1-(2-hydroxy-3-nonyl)imidazole derivatives have been synthesized.

Chemistry

Condensation of ethyl 2-amino-2-cyanoacetate[7] with *erythro*-3-amino-2-nonanol[8] in the presence of triethyl orthoformate gave ethyl *erythro*-5-amino-1-(2-hydroxy-3-nonyl)imidazole-4-carboxylate (**2**) (Scheme I). Ammonolysis of **2** in a sealed tube at 110 °C for 3 days afforded *erythro*-5-amino-1-(2-hydroxy-3-nonyl)imidazole-4-carboxamide (**3**).

Treatment of the same compound (**2**) with sodium nitrite at −20 °C in the presence of 50% hypophosphorous acid gave ethyl *erythro*-1-(2-hydroxy-3-nonyl)imidazole-4-carboxylate (**4**), which was converted by methanolic ammonia at 110 °C to *erythro*-1-(2-hydroxy-3-nonyl)-imidazole-4-carboxamide (**5**). Treatment of ethyl ester **4** with the appropriate amine provided *N*-substituted amides **5a–i**. Nitrosation of compound **2** at −25 °C in the presence of 6 N hydrochloric acid and cuprous chloride afforded ethyl *erythro*-5-chloro-1-(2-hydroxy-3-nonyl)imidazole-4-carboxylate (**6**) which was converted by 30% ammonium hydroxide at 110 °C to *erythro*-5-chloro-1-(2-hydroxy-3-nonyl)imidazole-4-carboxamide (**7**). Reduction of **4** with $LiAlH_4$ in THF provided *erythro*-1-(2-hydroxy-3-nonyl)-4-(hydroxymethyl)imidazole (**8**).

Basic hydrolysis of the same ester **4** gave *erythro*-1-(2-hydroxy-3-nonyl)imidazole-4-carboxylic acid (**9**) in 66% yield. Condensation of aminomalonitrile with *erythro*-3-amino-2-nonanol[8] in the presence of triethyl orthoformate gave *erythro*-5-amino-1-(2-hydroxy-3-nonyl)imidazole-4-carbonitrile (**10**). Compound **10** was diazotized with isopentyl nitrite in tetrahydrofuran (THF) at reflux to give 50% *erythro*-1-(2-hydroxy-3-nonyl)imidazole-4-carbonitrile (**13**).

Amidine **12** was prepared from **10** in two steps: treatment of nitrile **10** with dry hydrogen chloride in methanol at 0 °C provided 83% methyl *erythro*-5-amino-1-(2-hydroxy-3-nonyl)imidazole-4-carboximidate hydrochloride (**11**) (Scheme II). The latter compound was further converted into *erythro*-5-amino-1-(2-hydroxy-3-nonyl)-imidazole-4-carboxamidine hydrochloride (**12**) when treated with methanolic ammonia at 80 °C for 4 h. The same reactions did not work well in the case of nitrile **13**. The alternative route includes synthesis of amidoxime **14** by treatment of **13** with hydroxylamine, followed by reduction with hydrogen and Raney Ni catalyst at 45 psi for 6 h to give *erythro*-1-(2-hydroxy-3-nonyl)imidazole-4-carboxamidine hydrochloride (**15**). Treatment of **13** with hydrogen sulfide in dry pyridine and triethylamine at room temperature gave *erythro*-1-(2-hydroxy-3-nonyl)-imidazole-4-thiocarboxamide (**16**). Hydrogenation of the same carbonitrile **13** in the presence of 5% Pd/C tri-

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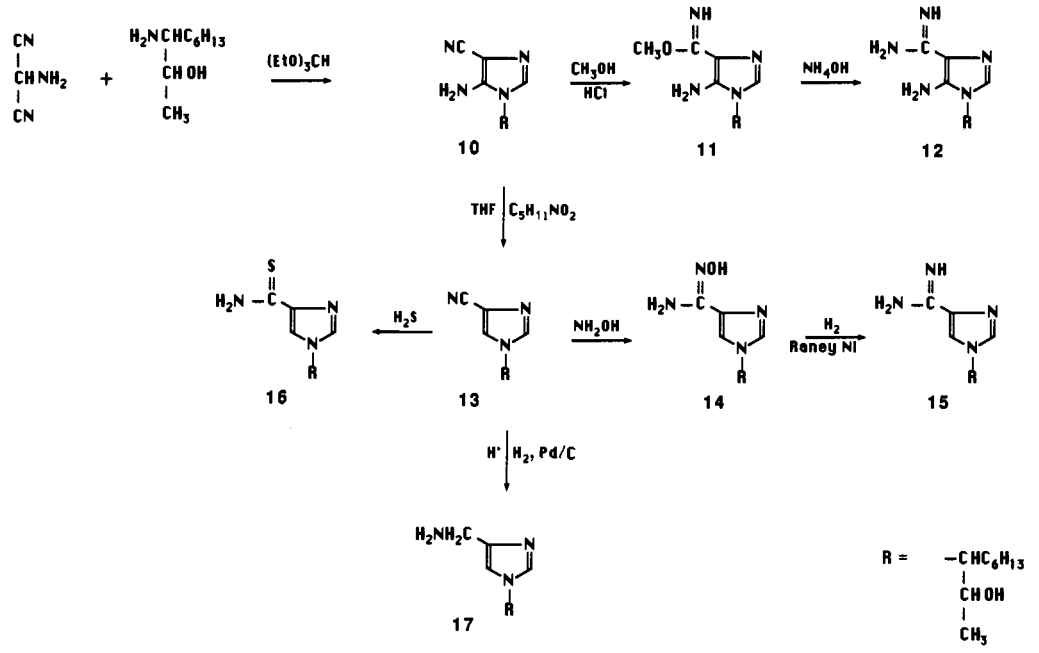
Scheme II



fluoroacetic acid at 40 psi provided *erythro*-1-(2-hydroxy-3-nonyl)-4-(aminomethyl)imidazole (**17**).

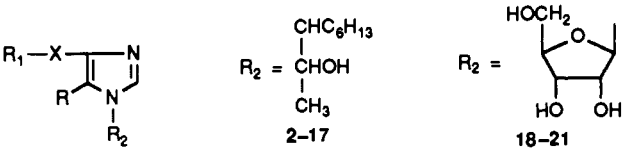
Biological Evaluation and Discussion

The synthesized esters **2** and **4**, amides **3** and **5**, carboxylic acid **9**, and amidines **12** and **15** were tested as inhibitors of adenosine deaminase from calf intestine, and the results are reported in Table II. As shown by the results, all of them proved to be active at different concentration, esters and amidines being weaker inhibitors than amides in the series. The presence of an amino group in the 5-position produced a drop in the inhibitory activity. So the most active compound was *erythro*-1-(2-hydroxy-3-nonyl)imidazole-4-carboxamide (**5**) with K_i of 3.8×10^{-8} M. Also, the introduction of a chlorine atom in 5-position of compound **5** to give *erythro*-5-chloro-1-(2-hydroxy-3-nonyl)imidazole-4-carboxamide (**7**) resulted in a weaker inhibitor with $K_i = 1.26 \times 10^{-7}$. To obtain additional structure–activity relationships the corresponding amides and amidines of 1-β-D-ribofuranosylimidazole, 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (**18**) (AICA riboside, SIGMA), 1-β-D-ribofuranosylimidazole-4-carboxamide (**19**),[9] 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamidine (**20**),[10] and 1-β-D-ribofuranosylimidazole-4-carboxamidine (**21**)[9] were tested as inhibitors of ADA from calf intestine. As reported in Table II, all the ribofuranosyl derivatives were inactive.

To evaluate the effect of substituents on amide **5**, the *erythro*-1-(2-hydroxy-3-nonyl)imidazole-4-*N*-substituted-carboxamides **5a–i** were prepared and tested. The results showed that the introduction of any substituent brought about a decrease in the inhibitory activity of amide **5**. Increasing chain length, and therefore lipophilicity and steric interactions, gave a corresponding decrease in activity. In fact methylamide **5a** is 1 order of magnitude less active than the parent compound **5** ($K_i = 3.68 \times 10^{-7}$ M vs 3.53×10^{-8} M) and it is 100-fold more active than the more lipophilic ethylamide **5b** and propylamide **5c**. The presence of a hydroxy group resulted in increased activity mostly in the case of the hydroxyethylamide **5d** when compared to ethylamide **5b** ($K_i = 0.93 \times 10^{-6}$ M vs 1.79×10^{-5} M). The diastereomeric hydroxypropyl derivatives **5e** and **5f** showed a 5-fold difference in activity ($K_i = 6.90 \times 10^{-6}$ M vs 3.21×10^{-5} M), indicating a different interaction with the enzyme.

Cyclopentylamide **5g** and benzylamide **5h**, which presented the most lipophilic and bulky groups, were also the

Table II. Inhibition Constants of Calf Intestinal Adenosine Deaminase



no.	R	X	R_1	K_i, M
2[a]	NH_2	C=O	OEt	3.47×10^{-4}
3[a]	NH_2	C=O	NH_2	1.04×10^{-6}
4[a]	H	C=O	OEt	6.60×10^{-5}
5[a]	H	C=O	NH_2	3.53×10^{-8}
5a[a]	H	C=O	$NHCH_3$	3.68×10^{-7}
5b[a]	H	C=O	$NHCH_2CH_3$	1.79×10^{-5}
5c[a]	H	C=O	$NHCH_2CH_2CH_3$	1.60×10^{-5}
5d[a]	H	C=O	$NHCH_2CH_2OH$	9.30×10^{-7}
5e[a]	H	C=O	(*S*)-$NHCH_2CHOHCH_3$	6.90×10^{-6}
5f[a]	H	C=O	(*R*)-$NHCH_2CHOHCH_3$	3.21×10^{-5}
5g[a]	H	C=O	$NHcC_5H_9$	4.11×10^{-5}
5h[a]	H	C=O	$NHCH_2C_6H_5$	8.60×10^{-5}
5i[a]	H	C=O	$N(CH_3)_2$	3.63×10^{-5}
7[a]	Cl	C=O	NH_2	1.26×10^{-7}
8[a]	H	CH_2	OH	2.52×10^{-6}
9[a]	H	C=O	OH	3.90×10^{-5}
12[a]	NH_2	C=NH	NH_2	1.06×10^{-5}
15[a]	H	C=NH	NH_2	2.56×10^{-6}
16[a]	H	CS	NH_2	4.71×10^{-8}
17[a]	H	CH_2	NH_2	4.02×10^{-6}
18	NH_2	C=O	NH_2	not active
19	H	C=O	NH_2	not active
20	NH_2	C=NH	NH_2	not active
21	H	C=NH	NH_2	not active
1a (EHNA)				0.70×10^{-8}
1c (3-deaza-EHNA)				1.00×10^{-8}

[a] Mixture of two isomers: 2′*S*,3′*R* and 2′*R*,3′*S*.

(9) Srivastava, P. C.; Ivanovics, G. A.; Rousseau, R. J.; Robins, R. K. *J. Org. Chem.* **1975**, *40*, 2920.

(10) Fujii, T.; Itaya, T.; Saito, T.; Kawanishi, M. *Chem. Pharm. Bull.* **1978**, *26*, 1929.

less active in the series. The disubstituted dimethylamide **5i** was 1000-fold less active than unsubstituted amide **5** and 100-fold less active than methylamide **5a** (K_i = 3.63 × 10^{-5} M vs 3.68 × 10^{-7} M).

Hydrolysis of ester **4** gave carboxylic acid **9**, which proved to be 2-fold more active than the parent ester (K_i = 3.90 × 10^{-5} M vs 6.6 × 10^{-5} M) but 1000-fold less active than amide **5**.

Substitution of the oxygen with a sulfur atom gave thioamide **16**, whose activity was equivalent to that of amide **5** (K_i = 3.53 × 10^{-8} M vs 4.71 × 10^{-8} M). In the case of substitution of the carbonyl with a methylene group to give 4-(aminomethyl) derivative **17**, a 400-fold decrease in activity was observed (K_i = 3.53 × 10^{-8} M vs 1.41 × 10^{-5} M). In conclusion, opening the pyrimidine or pyridine ring of EHNA or 3-deaza-EHNA respectively led to compounds which are still ADA inhibitors. The amido group at C-4 of the most potent compound **5** (K_i = 3.53 × 10^{-8} M) provided potential donor and acceptor sites for hydrogen bonding. Lack of one of this sites could account for the order of potency of all compounds examined in this series. In fact, a substantial reduction in activity was observed when the carbonyl group is replaced (**8**, **15**, **17**) and an even more dramatic drop in inhibitory potency was found when only the acceptor group of the hydrogen bond is present in the molecule (**4**, **5i**, **9**). Substitution of a hydrogen atom of the amido group of **5** brought about a decrease in activity, probably related to the increased lipophilicity and steric hindrance of the side chain. The presence of an amino group or a chlorine atom at C-5 (**2**, **3**, **7**, **12**), which might be involved in intramolecular hydrogen bonding with the substituents at C-4, lowered the inhibitory activity.

Opening the same rings in adenosine and in 3-deazaadenosine led to fully inactive compounds (i.e. **5** vs **19**).

These results support the hypothesis of the existence, at or near the enzyme active site, of a hydrophobic region able to bind the *erythro*-nonyl moiety. Such a region could restrict the area of the site normally occupied by the ribosidic moiety of the substrate.[5]

Experimental Section

Chemistry. Melting points were determined with a Büchi apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Varian VX 300 MHz. IR spectra were recorded on a Perkin-Elmer Model 297 spectrophotometer. TLC were carried out on precoated TLC plates with silica gel 60 F-254 (Merck). For column chromatography, silica gel 60 (Merck) was used. Microanalytical results are indicated by atomic symbols and are within ±0.4% of the theoretical values.

Ethyl *erythro*-5-Amino-1-(2-hydroxy-3-nonyl)imidazole-4-carboxylate (2). A mixture of 9 g (65.1 mmol) of ethyl 2-amino-2-cyanoacetate[7] and 11.4 g (77 mmol) of triethyl orthoformate in 230 mL of nitromethane was heated under reflux for 45 min. To the cooled mixture was added 9 g (56.7 mmol) of *erythro*-3-amino-2-nonanol[8] and the solution was stirred at room temperature overnight. The solvent was evaporated and the residue was chromatographed on a silica gel column. Elution with EtOAc–MeOH (97:3) yielded 11.2 g (40%) of **2** as a chromatographically pure solid: mp 111–114 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.96 (d, 3 H, CH_3-1), 1.19 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.24 (t, 3 H, CH_2CH_3), 1.82 (m, 2 H, CH_2-4), 3.82 (m, 2 H, CH-2 and CH-3), 4.15 (1, 2 H, CH_2CH_3), 5.16 (d, 1 H, OH), 5.97 (s, 2 H, NH_2-5), 7.26 (s, 1 H, H-2). Anal. ($C_{15}H_{27}N_3O_3$) C, H, N.

***erythro*-5-Amino-1-(2-hydroxy-3-nonyl)imidazole-4-carboxamide (3).** A solution of 400 mg (1.34 mmol) of **2** in 15 mL of 30% NH_4OH was heated at 110 °C for 48 h in a sealed tube. The mixture was cooled and extracted with chloroform. The combined extracts were washed with H_2O, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed on a silica gel column eluting with $CHCl_3$–MeOH (95:5) to give 240 mg (67%) of **3** as a chromatographically pure solid: mp 137–140 °C; ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3 H, CH_3-9), 0.96 (d, 3 H, CH_3-1), 1.20 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.82 (m, 2 H, CH_2-4), 3.80 (m, 2 H, CH-2 and CH-3), 5.11 (d, 1 H, OH), 5.70 (s, 2 H, NH_2-5), 6.65 (br d, 2 H, $CONH_2$), 7.11 (s, 1 H, H-2). Anal. ($C_{13}H_{24}N_4O_2$) C, H, N.

Ethyl *erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-carboxylate (4). To a stirred solution of 80 mL (293 mmol) of 50% hypophosphorous acid at −25 °C was added 2 g (6.72 mmol) of **2** in 15 mL of CH_3CN. A solution of 1.15 g of sodium nitrite in 15 mL of H_2O was added dropwise and the reaction mixture was stirred at −20 °C for 3 h and then at room temperature overnight. The mixture was neutralized with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layers were dried (Na_2SO_4), filtered, and concentrated to a residue which was flash chromatographed on a silica gel column. Elution with EtOAc–*n*-C_6H_{14} (80:20) gave 1.32 g (70%) of **4** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.87 (d, 3 H, CH_3-1), 1.19 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.27 (t, 3 H, CH_2CH_3), 1.83 (m, 2 H, CH_2-4), 3.77 (m, 1 H, CH-3), 3.94 (m, 1 H, CH-2), 4.22 (q, 2 H, CH_2CH_3), 5.06 (br s, 1 H, OH), 7.80 (s, 1 H, H-5), 7.91 (s, 1 H, H-2). Anal. ($C_{15}H_{26}N_2O_3$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-carboxamide (5).** A solution of 300 mg (1.06 mmol) of **4** in 12 mL of 30% NH_4OH was heated at 110 °C for 48 h in a sealed tube. The mixture was cooled and extracted with chloroform. The combined extracts were washed with H_2O, dried (Na_2SO_4), filtered, and concentrated in vacuo to give 219 mg (73%) of **5** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3 H, CH_3-9), 0.87 (d, 3 H, CH_3-1), 1.19 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.82 (m, 2 H, CH_2-4), 3.77 (m, 1 H, CH-3), 3.89 (m, 1 H, CH-2), 5.05 (d, 1 H, OH), 7.03 and 7.25 (s, 1 H each, $CONH_2$), 7.61 (s, 1 H, H-5), 7.66 (s, 1 H, H-2). Anal. ($C_{13}H_{23}N_3O_2$) C, H, N.

The product was converted to the oxalate salt by mixing equimolar amounts of **5** and oxalic acid in *i*-PrOH. The solution was left overnight at 0 °C, and the solid that precipitated was recrystallized from *i*-PrOH containing 1% oxalic acid to give the analytically pure sample, mp 157–158 °C. Anal. ($C_{13}H_{23}N_3O_2 \cdot C_2H_2O_4$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-*N*-methylcarboxamide (5a).** To 300 mg (1.06 mmol) of **4** in 10 mL of methanol was added 5 mL of methylamine and the mixture was stirred at room temperature for 48 h. The solvent was removed and the residue was chromatographed on a silica gel column eluting with $CHCl_3$–MeOH (97:3) to give 269 mg (86%) of **5a** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.87 (d, 3 H, CH_3-1), 1.19 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.84 (m, 2 H, CH_2-4), 2.72 (d, 3 H, NCH_3), 3.78 (m, 1 H, CH-3), 3.88 (m, 1 H, CH-2), 5.07 (d, 1 H, OH), 7.66 (s, 1 H, H-5), 7.70 (s, 1 H, H-2), 7.90 (q, 1 H, NH). Anal. ($C_{14}H_{25}N_3O_2$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-*N*-ethylcarboxamide (5b).** A solution of 300 mg (1.06 mmol) of **4** in 15 mL of ethylamine was heated at 120 °C for 20 h in a sealed tube. The solvent was removed and the residue was chromatographed on a silica gel column eluting with $CHCl_3$–MeOH (96:4) to give 230 mg (75%) of **5b** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.87 (d, 3 H, CH_3-1), 1.07 (t, 3 H, CH_2CH_3), 1.18 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.82 (m, 2 H, CH_2-4), 3.23 (m, 2 H, CH_2CH_3), 3.78 (m, 1 H, CH-3), 3.88 (m, 1 H, CH-2), 5.04 (d, 1 H, OH), 7.64 (s, 1 H, H-5), 7.69 (s, 1 H, H-2), 7.90 (t, 1 H, NH). Anal. ($C_{15}H_{27}N_3O_2$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-*N*-propylcarboxamide (5c).** A solution of 300 mg (1.06 mmol) of **4** in 15 mL of propylamine was heated at 120 °C for 20 h in a sealed tube. The solvent was removed and the residue was chromatographed on a silica gel column eluting with $CHCl_3$–MeOH (95:5) to give 235 mg (75%) of **5c** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.86 (m, 6 H, CH_3-1, $CH_2CH_2CH_3$), 1.19 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.48 (m, 2 H, $CH_2CH_2CH_3$), 1.83 (m, 2 H, CH_2-4), 3.15 (q, 2 H, $CH_2CH_2CH_3$), 3.78 (m, 1 H, CH-3), 3.88 (m, 1 H, CH-2), 5.05 (d, 1 H, OH), 7.64 (s, 1 H, H-5), 7.69 (s, 1 H, H-2), 7.89 (t, 1 H, NH). Anal. ($C_{16}H_{29}N_3O_2$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-*N*-(2-hydroxyethyl)carboxamide (5d).** A solution of 300 mg (1.06

mmol) of **4** in 15 mL of ethanolamine was heated at 120 °C for 20 h in a sealed tube. The solvent was removed and the residue was flash chromatographed on a silica gel column eluting with C_6H_6–AcOEt–MeOH (50:45:5) to give a 245 mg (80%) of **5d** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.81 (t, 3 H, CH_3-9), 0.86 (d, 3 H, CH_3-1), 1.18 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.83 (m, 2 H, CH_2-4), 3.27 (t, 3 H, NCH_2CH_2OH), 3.46 (m, 2 H, NCH_2CH_2OH), 3.77 (m, 1 H, CH-3), 3.89 (m, 1 H, CH-2), 4.70 (t, 1 H, OH), 5.05 (d, 1 H, OH), 7.65 (s, 1 H, H-5), 7.68 (s, 1 H, H-2), 7.79 (t, 1 H, NH). Anal. ($C_{15}H_{27}N_3O_3$) C, H, N.

(*S*)-*erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-*N*-(2-hydroxypropyl)carboxamide (5e). A solution of 300 mg (1.06 mmol) of **4** in 15 mL of (*S*)-(+)-1-amine-2-propanol was heated at 130 °C for 20 h in a sealed tube. The solvent was removed and the residue was chromatographed on a silica gel column eluting with $CHCl_3$–MeOH (95:5) to give 250 mg (75%) of **5e** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3 H, CH_3-9), 0.87 (d, 3 H, CH_3-1), 1.04 (d, 3 H, $CH_2CHOHCH_3$), 1.19 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.84 (m, 2 H, CH_2-4), 3.07 and 3.24 (m, 1 H each, $CH_2CHOHCH_3$), 3.76 (m, 2 H, CH-3 and $CH_2CHOHCH_3$), 3.89 (m, 1 H, CH-2), 4.80 (d, 1 H, $CH_2CHOHCH_3$), 5.04 (d, 1 H, OH), 7.68 (s, 1 H, H-5), 7.70 (s, 1 H, H-2), 7.72 (t, 1 H, NH). Anal. ($C_{16}H_{29}N_3O_3$) C, H, N.

(*R*)-*erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-*N*-(2-hydroxypropyl)carboxamide (5f). A solution of 300 mg (1.06 mmol) of **4** in 15 mL of (*R*)-(−)-1-amino-2-propanol was heated at 130 °C for 20 h in a sealed tube. The solvent was removed and the residue was chromatographed on a silica gel column eluting with $CHCl_3$–MeOH (93:7) to give 305 mg (92%) of **5f** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.87 (d, 3 H, CH_3-1), 1.04 (d, 3 H, $CH_2CHOHCH_3$), 1.20 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.83 (m, 2 H, CH_2-4), 3.08 and 3.25 (m, 1 H each, $CH_2CHOHCH_3$), 3.75 (m, 2 H, CH-3 and $CH_2CHOHCH_3$), 3.90 (m, 1 H, CH-2), 4.80 (d, 1 H, $CH_2CHOHCH_3$), 5.05 (d, 1 H, OH), 7.67 (s, 1 H, H-5), 7.70 (s, 1 H, H-2), 7.73 (t, 1 H, NH). Anal. ($C_{16}H_{29}N_3O_3$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-*N*-cyclopentylcarboxamide (5g).** A solution of 300 mg (1.06 mmol) of **4** in 15 mL of cyclopentylamine was heated at 120 °C for 30 h in a sealed tube. The solvent was removed and the residue was chromatographed on a silica gel column eluting with C_6H_6–AcOEt–MeOH (50:45:5) to give 180 mg (60%) of **5g** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.87 (d, 3 H, CH_3-1), 1.19 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.41–1.96 (br m, 10 H, CH_2-4 and H cyclopentyl), 3.77 (m, 1 H, CH-3), 3.88 (m, 1 H, CH-2), 4.17 (m, 1 H, H-1 cyclopentyl), 5.06 (d, 1 H, OH), 7.63 (t, 1 H, NH), 7.66 (s, 1 H, H-5), 7.69 (s, 1 H, H-2). Anal. ($C_{18}H_{31}N_3O_2$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-*N*-benzylcarboxamide (5h).** A solution of 300 mg (1.06 mmol) of **4** in 15 mL of methanol and 2.26 g (21 mmol) of benzylamine was heated at 140 °C for 48 h in a sealed tube. The solvent was removed and the residue was chromatographed on a silica gel column eluting with C_6H_6–AcOEt–MeOH (50:45:5) to give 250 mg (73%) of **5h** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.89 (d, 3 H, CH_3-1), 1.85 (m, 2 H, CH_2-4), 3.78 (m, 1 H, CH-3), 3.90 (m, 1 H, CH-2), 4.40 (d, 1 H, $CH_2C_6H_5$), 5.06 (d, 1 H, OH), 7.30 (m, 5 H, $CH_2C_6H_5$), 7.70 (s, 1 H, H-5), 7.72 (s, 1 H, H-2), 8.45 (t, 1 H, NH). Anal. ($C_{20}H_{29}N_3O_2$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-*N*,*N*-dimethylcarboxamide (5i).** A solution of 300 mg (1.06 mmol) of **4** in 20 mL of dimethylamine was heated at 130 °C for 20 h in a sealed tube. The solvent was removed and the residue was chromatographed on a silica gel column eluting with $CHCl_3$–MeOH (95:5) to give 225 mg (75%) of **5i** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.88 (d, 3 H, CH_3-1), 1.21 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.85 (m, 2 H, CH_2-4), 2.91 (br s, 3 H, NCH_3), 3.41 (br s, 3 H, NCH_3), 3.78 (m, 1 H, CH-3), 3.89 (m, 1 H, CH-2), 5.07 (d, 1 H, OH), 7.65 (s, 1 H, H-5), 7.69 (s, 1 H, H-2). Anal. ($C_{15}H_{27}N_3O_2$) C, H, N.

Ethyl *erythro*-5-Chloro-1-(2-hydroxy-3-nonyl)imidazole-4-carboxylate (6). To a stirred solution of 20 mL of 6 N hydrochloric acid at −25 °C was added 0.5 g (1.68 mmol) of **2** in 15 mL of CH_3CN. A solution of 0.58 g of sodium nitrite in 2 mL of H_2O and, after 5 min, a solution of 0.85 g of CuCl in 2 mL of H_2O were added dropwise. The reaction mixture was stirred at −25 °C for 1.5 h and then the mixture was neutralized with saturated $NaHCO_3$ solution and extracted with chloroform. The combined extracts were washed with H_2O, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed on a silica gel column eluting with $CHCl_3$–MeOH (97:3) to give 215 mg (40%) of **6** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3 H, CH_3-9), 0.92 (d, 3 H, CH_3-1), 1.22 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.28 (t, 3 H, CH_2CH_3), 1.92 (m, 2 H, CH_2-4), 3.84 (m, 1 H, CH-3), 4.00 (m, 1 H, CH-2), 4.25 (q, 2 H, CH_2CH_3), 5.21 (br s, 1 H, OH), 8.01 (s, 1 H, H-2). Anal. ($C_{15}H_{25}ClN_2O_3$) C, H, N.

***erythro*-5-Chloro-1-(2-hydroxy-3-nonyl)imidazole-4-carboxamide (7).** A solution of 500 mg (1.58 mmol) of **6** in 12 mL of 30% NH_4OH was heated at 110 °C for 3 days in a sealed tube. The mixture was cooled and extracted with chloroform. The combined extract was washed with H_2O, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed on a silica gel column eluting with c-C_6H_{12}–AcOEt–MeOH (50:40:10) to give 225 mg (50%) of **7** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.92 (d, 3 H, CH_3-1), 1.20 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.95 (m, 2 H, CH_2-4), 3.84 (m, 1 H, CH-3), 3.97 (m, 1 H, CH-2), 5.19 (d, 1 H, OH), 7.93 (2, 1 H, H-2). Anal. ($C_{13}H_{22}ClN_3O_2$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)-4-(hydroxymethyl)imidazole (8).** A suspension of 35 mg (0.92 mmol) of $LiAlH_4$ in 10 mL of a mixture of dry Et_2O–THF was heated at reflux under an atmosphere of N_2 for 40 min. To the cooled mixture was added 200 mg (0.71 mmol) of **4** in 10 mL of THF and the mixture was stirred at room temperature for 4 h. After the solid was removed by filtration through Celite, the filtrate was concentrated to a residue which was chromatographed on a silica gel column. Elution with $CHCl_3$–MeOH (95:5) gave 130 mg (76%) of **8** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.84 (m, 6 H, CH_3-9 and CH_3-1), 1.12 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.77 (m, 2 H, CH_2-4), 3.71 and 3.79 (m, 1 H each, CH-2 and CH-3), 4.30 (d, 1 H, CH_2OH), 4.76 (t, 1 H, CH_2OH), 4.95 (d, 1 H, OH), 6.96 (s, 1 H, H-5), 7.48 (s, 1 H, H-2). Anal. ($C_{13}H_{24}N_2O_2$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-carboxylic Acid (9).** A solution of 1 g (3.54 mmol) of **4** in 10 mL of ethanol containing 180 mg (4.5 mmol) of sodium hydroxide in 1 mL of water was stirred at room temperature for 48 h. The reaction mixture was diluted with 20 mL of water, concentrated to remove ethanol, acidified to pH 3 with 10% hydrochloric acid and then extracted with ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was recrystallized from methanol to give 590 mg (66%) of **9** as a light yellow solid: mp 145–147 °C (dec); ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3 H, CH_3-9), 0.87 (d, 3 H, CH_3-1), 1.19 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.82 (m, 2 H, CH_2-4), 3.77 (m, 1 H, CH-3), 3.89 (m, 1 H, CH-2), 7.68 (s, 1 H, H-5), 7.75 (s, 1 H, H-2). Anal. ($C_{13}H_{22}N_2O_3$) C, H, N.

***erythro*-5-Amino-1-(2-hydroxy-3-nonyl)imidazole-4-carbonitrile (10).** Dry ammonia was bubbled for 30 min through a stirred suspension of 4.5 g (17.7 mmol) of aminomalonitrile *p*-toluenesulfonate in 200 mL of dry acetonitrile. After the solid that separated was filtered, the liquid was concentrated to 100 mL and then added to 2.65 g (2.97 mL, 17.7 mmol) of triethyl orthoformate. The solution was heated under reflux for 15 min. To the cooled mixture was added 2.81 g (17.7 mmol) of *erythro*-3-amino-2-nonanol[8] and the solution was stirred at room temperature overnight. The solvent was evaporated and the residue was flash chromatographed on a silica gel column. Elution with $CHCl_3$–MeOH (96:4) provided 2.0 g (45%) of **10** as a chromatographically pure solid: mp 99–103 °C; IR ν_{max} 2212 (C≡N); ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.94 (d, 3 H, CH_3-1), 1.20 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.78 (m, 2 H, CH_2-4), 3.79 (m, 2 H, CH-2 and CH-3), 5.14 (br s, 1 H, OH), 6.06 (s, 2 H, NH_2-5), 7.24 (s, 1 H, H-2). Anal. ($C_{13}H_{22}N_4O$) C, H, N.

Methyl *erythro*-5-Amino-1-(2-hydroxy-3-nonyl)imidazole-4-carboximidate Hydrochloride (11). A cooled solution (ice bath) of 2 g (7.99 mmol) of **10** in 30 mL of methanol was saturated with dry hydrochloric acid and then Et_2O was added, whereupon a cloudiness formed. The suspension was left

at 0 °C for 24 h and the resulting white precipitate was collected and dried to give 2.12 g (83%) of **11** as a chromatographically homogeneous solid: mp 119–122 °C. ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 1.05 (d, 3 H, CH_3-1), 1.22 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.86 (m, 2 H, CH_2-4), 3.82 (m, 1 H, CH-2), 3.97 (m, 1 H, CH-3), 5.30 (d, 1 H, OH), 6.64 (s, 1 H, C=NH), 7.61 (s, 2 H, NH_2-5), 8.68 (s, 1 H, H-2). Anal. ($C_{14}H_{26}N_4O_2$·HCl) C, H, N.

***erythro*-5-Amino-1-(2-hydroxy-3-nonyl)imidazole-4-carboxamidine Hydrochloride (12).** A solution of 1 g (3.13 mmol) of **11** in 50 mL of methanolic ammonia was sealed in a glass tube and heated at 80 °C for 4 h. The solvent was evaporated and the residue was chromatographed on a silica gel column eluting with $CHCl_3$–MeOH–NH_3 (70:29:1) to give 540 mg of nearly pure **12**. Recrystallization from water gave 410 mg (43%) of **12** as a viscous, pure solid: ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3 H, CH_3-9), 0.98 (d, 3 H, CH_3-1), 1.19 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.82 (m, 2 H, CH_2-4), 3.80 (m, 1 H, CH-2), 3.97 (m, 1 H, CH-3), 5.27 (d, 1 H, OH), 6.65 (s, 1 H, C(=N*H*)NH_2), 7.24 (br d, 2 H, C(=NH)N*H*$_2$), 7.50 (s, 1 H, H-2), 8.06 (s, 3 H, NH_2·HCl-5). Anal. ($C_{13}H_{25}N_5O$·HCl) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-carbonitrile (13).** To a boiling mixture of isopentyl nitrite in THF was added dropwise over 1 h a solution of 1 g (4.4 mmol) of **10** in 20 mL of THF. After the addition was over, the mixture was refluxed for 3 h and then cooled and concentrated in vacuo. The residue was flash chromatographed, eluting with c-C_6H_{12}–$CHCl_3$–MeOH (55:40:5) to give 460 mg (50%) of **13** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.84 (t, 3 H, CH_3-9), 0.87 (d, 3 H, CH_3-1), 1.20 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.83 (m, 2 H, CH_2-4), 3.77 (m, 1 H, CH-3), 4.00 (m, 1 H, CH-2), 5.11 (d, 1 H, OH), 7.91 (2, 1 H, H-5), 8.17 (s, 1 H, H-2). Anal. ($C_{13}H_{21}N_3O$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-carboxamide Oxime (14).** A mixture of 470 mg (2 mmol) of **13** and 660 mg (20 mmol) of NH_2OH in 10 mL of ethanol was refluxed for 3 h. After concentration in vacuo, the residue was flash chromatographed on a silica gel column. Elution with $CHCl_3$–MeOH (93:7) provided 440 mg (82%) of **14** as a chromatographically pure solid: mp 107–110 °C; ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3 H, CH_3-9), 0.87 (d, 3 H, CH_3-1), 1.19 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.72 and 1.90 (m, 2 H, CH_2-4), 3.80 (m, 2 H, CH-2 and CH-3), 5.02 (d, 1 H, OH), 5.48 (br s, 2 H, C(=NOH)N*H*$_2$), 7.34 (s, 1 H, H-5), 7.64 (s, 1 H, H-2), 9.08 (s, 1 H, C(=NOH)NH_2). Anal. ($C_{13}H_{24}N_4O_2$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-carboxamidine Hydrochloride (15).** To a solution of 380 mg (1.41 mmol) of **14** in 25 mL of 50% ethanol was added 78 mg of NH_4Cl and 800 mg of Raney nickel catalyst, and the mixture was shaken under hydrogen pressure at 45 psi for 6 h. After the catalyst was removed by filtration, the filtrate was concentrated to a residue which was flash chromatographed on a silica gel column. Elution with $CHCl_3$–MeOH (90:10) gave 220 mg (54%) of **15** as a viscous pure solid: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, 3 H, CH_3-9), 0.94 (d, 3 H, CH_3-1), 1.21 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.82 (m, 2 H, CH_2-4), 3.79 (m, 1 H, CH-2), 4.05 (m, 1 H, CH-3), 5.18 (d, 1 H, OH), 7.97 (s, 1 H, H-5), 8.03 (2, 1 H, H-2), 8.80 (br s, 6 H, C(=NH)N*H*$_2$, C(=N*H*)NH_2, NH_2·HCl-5). Anal. ($C_{13}H_{24}N_4O$·HCl) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)imidazole-4-thiocarboxamide (16).** Hydrogen sulfide was bubbled for 3 h at room temperature through a stirred solution of 300 mg (1.11 mmol) of **13** in 50 mL of dry pyridine and 5 mL of triethylamine. The stirring was continued for another 12 h and then nitrogen was bubbled into the flask until the remaining hydrogen sulfide was removed. The solution was concentrated in vacuo and the residue chromatographed on a silica gel column. Elution with $CHCl_3$–MeOH (95:5) provided 230 mg (67%) of **16** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.84 (t, 3 H, CH_3-9), 0.91 (d, 3 H, CH_3-1), 1.21 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.74 (m, 2 H, CH_2-4), 3.81 (m, 1 H, CH-3), 3.95 (m, 1 H, CH-2), 5.08 (d, 1 H, OH), 7.76 (s, 1 H, H-5), 7.83 (s, 1 H, H-2), 8.97, 9.31 (s, 1 H each, CSN*H*$_2$). Anal. ($C_{13}H_{23}N_3OS$) C, H, N.

***erythro*-1-(2-Hydroxy-3-nonyl)-4-(aminomethyl)imidazole (17).** To a solution of 300 mg (1.11 mmol) of **13** in 20 mL of methanol was added 1 mL of trifluoroacetic acid and 150 mg of 5% Pd/C, and the mixture was shaken under hydrogen pressure at 40 psi for 6 h. After the catalyst was removed by filtration, the filtrate was neutralized with 6 N NaOH and extracted several times with EtOAc. The organic layers were dried (Na_2SO_4), filtered, and concentrated to a residue which was flash chromatographed on a silica gel column. Elution with $CHCl_3$–MeOH–NH_3 (95:4:1) gave 240 mg (79%) of **17** as a chromatographically pure oil: ^{1}H NMR (DMSO-d_6) δ 0.84 (m, 6 H, CH_3-9 and CH_3-1), 1.21 (m, 8 H, CH_2-5, CH_2-6, CH_2-7, CH_2-8), 1.78 (m, 2 H, CH_2-4), 3.28 (br s, 2 H, NH_2), 3.53 and 3.70 (m, 1 H each, C*H*$_2$$NH_2$), 3.73 (m, 2 H, CH-2 and CH-3), 5.14 (br s, 1 H, OH), 6.91 (s, 1 H, H-5), 7.49 (s, 1 H, H-2). Anal. ($C_{13}H_{25}N_3O$) C, H, N.

Biological Studies. Enzyme Assay. The method used for the determination of activity against adenosine deaminase has been described in a preceding paper.[4]

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Registry No. (2′*S*,3′*R*)-**2**, 130694-09-6; (2′*R*,3′*S*)-**2**, 130694-16-5; (2′*S*,3′*R*)-**3**, 130694-10-9; (2′*R*,3′*S*)-**3**, 130694-17-6; (2′*S*,3′*R*)-**4**, 130573-53-4; (2′*R*,3′*S*)-**4**, 130573-80-7; (2′*S*,3′*R*)-**5** (free base), 130573-54-5; (2′*S*,3′*R*)-**5**·oxalate, 130573-92-1; (2′*R*,3′*S*)-**5** (free base), 130573-81-8; (2′*R*,3′*S*)-**5**·oxalate, 130573-93-2; (2′*S*,3′*R*)-**5a**, 130573-65-8; (2′*R*,3′*S*)-**5a**, 130573-73-8; (2′*S*,3′*R*)-**5b**, 130573-66-9; (2′*R*,3′*S*)-**5b**, 130573-74-9; (2′*S*,3′*R*)-**5c**, 130573-67-0; (2′*R*,3′*S*)-**5c**, 130573-75-0; (2′*S*,3′*R*)-**5d**, 130573-68-1; (2′*R*,3′*S*)-**5d**, 130573-76-1; (2′*S*,3′*R*)-**5e**, 130573-69-2; (2′*R*,3′*S*)-**5e**, 130694-14-3; (2′*S*,3′*R*)-**5f**, 130694-13-2; (2′*R*,3′*S*)-**5f**, 130694-15-4; (2′*S*,3′*R*)-**5g**, 130573-70-5; (2′*R*,3′*S*)-**5g**, 130573-77-2; (2′*S*,3′*R*)-**5h**, 130573-71-6; (2′*R*,3′*S*)-**5h**, 130573-78-3; (2′*S*,3′*R*)-**5i**, 130573-72-7; (2′*R*,3′*S*)-**5i**, 130573-79-4; (2′*S*,3′*R*)-**6**, 130573-55-6; (2′*R*,3′*S*)-**6**, 130573-82-9; (2′*S*,3′*R*)-**7**, 130573-56-7; (2′*R*,3′*S*)-**7**, 130573-83-0; (2′*S*,3′*R*)-**8**, 130573-57-8; (2′*R*,3′*S*)-**8**, 130573-84-1; (2′*S*,3′*R*)-**9**, 130573-58-9; (2′*R*,3′*S*)-**9**, 130573-85-2; (2′*S*,3′*R*)-**10**, 130694-11-0; (2′*R*,3′*S*)-**10**, 130694-18-7; (2′*S*,3′*R*)-**11**, 130573-59-0; (2′*R*,3′*S*)-**11**, 130573-86-3; (2′*S*,3′*R*)-**12** (free base), 130694-20-1; (2′*S*,3′*R*)-**12**·HCl, 130694-12-1; (2′*R*,3′*S*)-**12** (free base), 130694-21-2; (2′*R*,3′*S*)-**12**·HCl, 130694-19-8; (2′*S*,3′*R*)-**13**, 130573-60-3; (2′*R*,3′*S*)-**13**, 130573-87-4; (2′*S*,3′*R*)-**14**, 130573-61-4; (2′*R*,3′*S*)-**14**, 130573-88-5; (2′*S*,3′*R*)-**15** (free base), 130573-94-3; (2′*S*,3′*R*)-**15**·HCl, 130573-62-5; (2′*R*,3′*S*)-**15** (free base), 130573-95-4; (2′*R*,3′*S*)-**15**·HCl, 130573-89-6; (2′*S*,3′*R*)-**16**, 130573-63-6; (2′*R*,3′*S*)-**16**, 130573-90-9; (2′*S*,3′*R*)-**17**, 130611-10-8; (2′*R*,3′*S*)-**17**, 130573-91-0; **18**, 2627-69-2; **19**, 5624-04-4; **20**, 24808-47-7; **21**, 130573-64-7; ADA, 9026-93-1; (2′*S*,3′*R*)-3-amino-2-nonanol, 79854-85-6; (2′*R*,3′*S*)-3-amino-2-nonanol, 79854-86-7; ethyl 2-amino-2-cyanoacetate, 32683-02-6; aminomalonitrile *p*-toluenesulfonate, 5098-14-6.