Synthesis of Certain *N*- and *C*-Alkyl Purine Analogs

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Dedicated to the memory of Professor Roland K. Robins

A number of *N*- and *C*-alkyl derivatives of selected guanine analogs have been synthesized as potential antiviral agents. *n*-Pentyl, *n*-hexyl and 6-hydroxyhexyl derivatives in the imidazo[1,2-*a*]-*s*-triazine, **9-11**, imidazo[1,2-*a*]pyrimidine, **13-17**, and thiazolo[4,5-*d*]pyrimidine, **19-21**, ring system have been prepared by the direct alkylation of the sodium salt of the appropriate aglycon with the respective alkylbromides. Dehydrative coupling of 3-amino-6-hydrazino-1,2,4-triazin-5(4*H*)-one (**22**) with either hexanoic acid or heptanoic acid, and further ring closure of the reaction products **24a** and **24b** provided the *n*-pentyl and *n*-hexyl derivatives of 6-amino-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one **25a** and **25b**, respectively. A similar condensation of 3-amino-6-aminomethyl-1,2,4-triazin-5(4*H*)-one (**23**) with heptanoic acid, followed by ring annulation, readily gave 2-amino-7-*n*-hexylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one (**25c**). Bromination of **25c** with *N*-bromosuccinimide afforded the corresponding 5-bromo derivative **26**. Alkylation of the *in situ* generated sodium salt of 4-methoxycarbonylmethyl-5-methoxycarbonyl-2-oxo-1*H*,3*H*-imidazole (**27**) with 1-bromohexane gave the N-1 alkylated product **31**. Manipulation of the functional groups in **31** and further hydrazine mediated ring annulation furnished 5,6-diamino-1-*n*-hexyl-3-methylimidazo[4,5-*c*]pyridine-2,4-dione (**39**). Catalytic hydrogenation of **39** gave 7-methyl-8-oxo-9-hexyl-3-deazaguanine (**40**), a congener of the immunostimulator 7-methyl-8-oxoguanosine.

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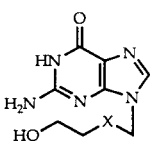
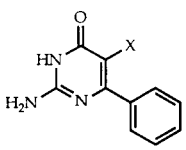
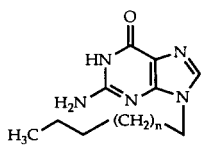
As a consequence of serendipitous studies [1-3] involving adenosine deaminase as a model enzyme for examining structural features required for antiviral activity, several acyclic purine nucleosides have emerged as potential antiviral agents. The forerunner in this array of compounds is the guanosine analog acyclovir [9-(2-hydroxyethoxymethyl)guanine, **1**] [4]. Acyclovir has proven to be active against herpes viruses [5], especially HSV-1 and HSV-2 (herpes simplex virus type 1 and 2) and remains the drug of choice for control of HSV infections. Acyclovir has also been shown to be efficacious when used systemically in the prophylaxis of HSV infections in immunosuppressed patients, *e.g.* bone marrow transplant recipients [6]. The corresponding carba analog HBG [9-(4-hydroxybutyl)guanine, **2**] has also shown good inhibition of HSV in cell culture [7] as well as in animals [8].



1, X = O
2, X = CH_2



3
X = Br, I



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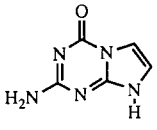
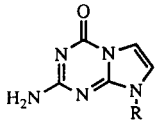
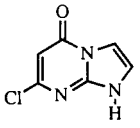
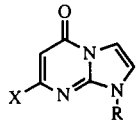
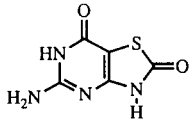
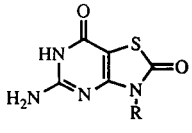
Both compounds **1** and **2** are believed to act by the same general mechanism [8-11]. These guanine derivatives are selectively converted to the monophosphates in herpes virus-infected cells by viral-induced thymidine kinase. The monophosphate is further phosphorylated by host cell guanosine monophosphate (GMP) kinase to the corresponding diphosphate, which in turn is phosphorylated to the triphosphate by unidentified cellular enzymes [9]. The triphosphate then inhibits HSV viral DNA polymerase but not cellular DNA polymerase, thus preventing viral replication [12].

These antiviral agents are largely virustatic and not viricidal in the host. The total control of the viral infection, however, is largely dependent on the modulation of the host immune response [13] to eliminate the virus. Failure of the immune system to rid the host of the virus is the primary cause of chronic or persistent viral infections. Modulation of the host immune system can be provided selectively by adenosine (by inhibition) and guanosine (by stimulation) analogs [13]. The immuno-stimulatory activity of a new group of compounds has recently been documented [14]. The biological profile of this group of agents, *viz.* 6-arylpyrimidinones (**3**) is very similar to that of the guanosine anaologs **1** and **2**. Moreover, a similarity between these two group of compounds, relative to their effects on B lymphocytes, has recently been demonstrated [15], suggesting that they interact with the same cellular components in the target cells [16]. This leads to the conclusion that a carbohydrate moiety, which is an integral

part of a nucleoside, has little or no effect on the observed immunostimulation. These findings and the observation that certain 9-alkylguanines **4** [17] exhibit potent antiviral activity [18] by virtue of immunopotentiation, stimulated the synthesis of a series of *N*- and *C*-alkyl substituted guanine analogs as potential antiviral agents. A part of these studies is the subject of this report.

Table 1

Condensation of the Sodium Salt of Various Purine Analogs with Alkylbromides

Purine Analog	Alkylbromide	Product
 **5**	6, $H_3C(CH_2)_3CH_2Br$ 7, $H_3C(CH_2)_4CH_2Br$ 8, $HOH_2C(CH_2)_4CH_2Br$	 9, R = $-(CH_2)_4CH_3$ 10, R = $-(CH_2)_5CH_3$ 11, R = $-(CH_2)_5CH_2OH$
 **12**	6 7 8	 13, X = Cl; R = $-(CH_2)_4CH_3$ 14, X = NH_2; R = $-(CH_2)_4CH_3$ 15, X = Cl; R = $-(CH_2)_5CH_3$ 16, X = NH_2; R = $-(CH_2)_5CH_3$ 17, X = Cl; R = $-(CH_2)_5CH_2OH$
 **18**	6 7 8	 19, R = $-(CH_2)_4CH_3$ 20, R = $-(CH_2)_5CH_3$ 21, R = $-(CH_2)_5CH_2OH$

The syntheses of certain *N*-alkyl derivatives of selected guanine analogs are shown in Table 1. In this study, direct alkylation of the sodium salt of the aglycons **5**, **12** and **18** with alkyl bromides was found to be very successful. The sodium salt of 2-aminoimidazo[1,2-*a*]-*s*-triazin-4(8*H*)-one (**5**) [19], generated *in situ* by the treatment with sodium hydride in *N,N*-dimethylformamide, was alkylated with 1-bromopentane at ambient temperature. A clean reaction mixture was obtained, and the desired product was purified by silica gel column chromatography to give 2-amino-8-*n*-pentylimidazo[1,2-*a*]-*s*-triazin-4-one (**9**) in a 60% yield.

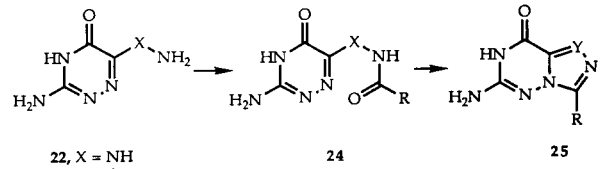
A similar treatment of **5** with 1-bromohexane in the presence of sodium hydride gave 2-amino-8-*n*-hexylimidazo-[1,2-*a*]-*s*-triazin-4-one (**10**). However, alkylation of the sodium salt of **5** with 6-bromo-1-hexanol in *N,N*-dimethylformamide at room temperature did not result in an appreciable amount of the desired 2-amino-8-(6-hydroxyhexyl)-imidazo[1,2-*a*]-*s*-triazin-4-one (**11**); heating (70-80°) of the reaction mixture was found to be necessary to obtain **11**.

The preparation of the alkyl derivatives of the imidazo-[1,2-*a*]pyrimidine ring system is also outlined in Table 1. 7-Amino-1-*n*-pentylimidazo[1,2-*a*]pyrimidin-5-one (**14**) and the corresponding *n*-hexyl derivative **16** were prepared by ammonolysis of the respective 7-chloro-1-*n*-alkyl derivatives **13** and **15**. Compounds **13** and **15** were prepared by the treatment of the sodium salt of 7-chloroimidazo[1,2-*a*]-pyrimidin-5-one (**12**) [20] with either 1-bromopentane or 1-bromohexane. The reaction proceeded smoothly at room temperature. However, the alkylation of **12** with 6-bromo-1-hexanol was rather sluggish at room temperature. When the reaction mixture was heated at 135° for two days, 7-chloro-1-(6-hydroxyhexyl)imidazo[1,2-*a*]pyrimidin-5-one (**17**) was obtained in a 45% yield. Our attempts to convert **17** into the corresponding amino derivative with methanolic ammonia under a variety of experimental conditions were unsuccessful.

The alkyl derivatives of 5-aminothiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione (**18**) [21] were also obtained by the sodium salt mediated alkylation procedure. Thus, treatment of **18** with 1-bromopentane in the presence of sodium hydride in *N,N*-dimethylformamide at 80°, followed by extensive purification of the condensation product by silica gel column chromatography gave 5-amino-3-*n*-pentylthiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione (**19**). The isolated yield of **19** was only 34%, while alkylation of **18** with 1-bromohexane under similar reaction conditions furnished **20** in a 25% yield. The hydroxyhexyl derivative **21** was obtained in a 50% yield by the treatment of **18** with 6-bromo-1-hexanol in the presence of sodium hydride in *N,N*-dimethylformamide at 70-80°.

For every compound prepared by direct alkylation of a guanine analog, the site of alkylation was verified by comparison of the ultraviolet spectra with that of the corresponding ribonucleosides [12,20,22], which were found to be very similar. In each case the comparision unequivocally supported the site of alkylation as assigned.

Scheme 1

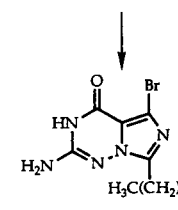


22, X = NH
23, X = CH_2

24

25

Series a, X = NH; Y = N; R = $-(CH_2)_4CH_3$
b, X = NH; Y = N; R = $-(CH_2)_5CH_3$
c, X = CH_2; Y = CH; R = $-(CH_2)_5CH_3$



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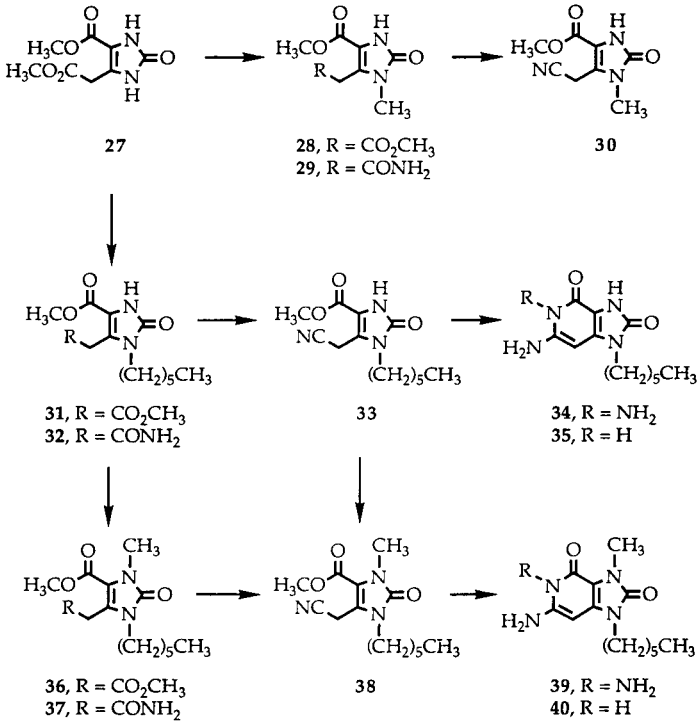
For the synthesis of the *C*-alkyl derivatives of selected bases, an alternative approach was used (Scheme 1). The

ring annulation strategy as described by Revankar and coworkers [23] for the synthesis of 6-amino-3-β-D-ribo-furanosyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one was found to be well-suited for the preparation of **25a** and **25b**. The appropriately functionalized 1,2,4-triazines **22** and **23**, required for the preparation of **25a** and **25b**, were prepared as reported [24,25]. Dehydrative coupling of **22** with hexanoic acid in the presence of 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole in anhydrous *N,N*-dimethylformamide at ambient temperature gave the viable intermediate **24a**, which on further heating in ethylene glycol at 200° ring closed [23] to furnish 6-amino-3-*n*-pentyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**25a**). A similar condensation of **23** with heptanoic acid gave the intermediate **24b**, which on ring annulation by heating in ethylene glycol gave 6-amino-3-*n*-hexyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**25b**). Hexanoic acid, (3-amino-4,5-dihydro-5-oxo-1,2,4-triazin-6-yl)methylamide (**24c**) was also prepared by dehydrative coupling of heptanoic acid and 3-amino-6-aminomethyl-1,2,4-triazin-5(4*H*)-one (**23**) [25] in the presence of EDC and 1-hydroxybenzotriazole. Subsequent cyclization of the condensation product **24c** by heating in ethylene glycol at 200° gave 2-amino-7-*n*-hexylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one (**25c**) in a 75% yield. Bromination of **25c** with *N*-bromosuccinimide in anhydrous *N,N*-dimethylformamide furnished the corresponding 5-bromo derivative (**26**) in >65% yield. The chemical structures of **25a,b,c** were confirmed by ir, uv, ^{1}H nmr and elemental analyses.

Scheme 2



The ultraviolet absorption spectra of these compounds were found to be very similar to that reported for the corresponding ribofuranosyl derivatives [23,25].

Certain 8-substituted-guanosine derivatives have shown the ability to activate B cells [26-28], natural killer cells, and macrophages [29]. A structurally related compound, 7-methyl-8-oxoguanosine, originally synthesized by Robins *et al.* [30], is also reported to be a B-cell activator [31] and to exhibit potent antiviral activity [22]. At optimal concentrations, the peak response evoked by 7-methyl-8-oxoguanosine is reported [31] to be about twice the magnitude of that exhibited by other 8-substituted guanosines (especially 8-bromo- and 8-mercaptoguanosines). On the basis of structure-activity relationship studies, it was concluded that the two structural features, the 7-methyl function and the 8-oxo group, are both necessary for the observed level of B-cell stimulatory activity. In view of these observations and the noted broad spectrum antiviral activity of 3-deazaguanosine [32], we initiated the total synthesis of 7-methyl-8-oxo-9-alkyl-3-deazaguanine (**40**).

It was envisaged that the synthesis of **40** might be realized from the cyclization of the appropriate alkyl derivative of a imidazole precursor (Scheme 2). The synthesis of such a substituted imidazole, 4-methoxycarbonylmethyl-5-methoxycarbonyl-2-oxo-1*H*,3*H*-imidazole (**27**) was accomplished as reported [33]. An attempted alkylation of **27** *via* the silylation procedure [34] proved to be unsuccessful. Treatment of the trimethylsilyl derivative of **27**, obtained by the treatment with hexamethyldisilazane and ammonium sulfate, with either iodomethane or 1-bromohexane in the presence or absence of trimethylsilyl trifluoromethanesulfonate or tin(IV) chloride resulted in no desired product. However, the alkylation of the sodium salt of **27** proceeded well to give the desired products. Treatment of the sodium salt of **27** (generated *in situ* by treatment with sodium hydride in *N,N*-dimethylformamide) with iodomethane at 55° for 24 hours, gave a mixture of two compounds. The compound having the higher R_f was obtained as a minor product (<5%) and is assumed to be the N1,N3-dimethylated derivative on the basis of ^{1}H nmr and elemental analyses. The major product (49%), with the lower R_f, was isolated and characterized (see experimental) as the N1 monomethylated derivative **28**. Subsequent treatment of **28** with methanolic ammonia (saturated at 0°) at ambient temperature afforded the mono-amide (**29**), which on dehydration with phosgene in anhydrous toluene gave methyl 5-cyanomethyl-1-methyl-2-oxo-1*H*,3*H*-imidazole-4-carboxylate (**30**) in 77% yield. The site of methylation in **30** was unequivocally established by single crystal X-ray diffraction studies, which will be published elsewhere.

Following the same synthetic strategy, the *N*1-hexyl derivative **31** of **27** was prepared. The yield of analytically pure **31** was 56%. When the diester **31** was allowed to

stand in methanolic ammonia (saturated at 0°) at ambient temperature for 24 hours, 1-*n*-hexyl-4-methoxycarbonyl-2-oxo-1*H*,3*H*-imidazole-5-acetamide (**32**) was formed. Phosgene mediated dehydration of **32** gave a 77% yield of methyl 5-cyanomethyl-1-*n*-hexyl-2-oxo-1*H*,3*H*-imidazole-4-carboxylate (**33**). The similarity of uv spectrum of **30** and **33** established the site of alkylation as N1 in **33**. Annulation of **33** by the treatment with hydrazine hydrate in ethanol [34] at reflux temperature gave an excellent yield of 5,6-diamino-1-*n*-hexyl-2,3,4,5-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-2,4-dione (**34**). A plausible mechanism for this ring closure, **33** to **34** may be visualized simply as occurring by the direct attack of hydrazine on the ester carbonyl carbon [35], which then cyclizes immediately to form **34**.

Subsequent hydrogenation of **34** in the presence of Raney nickel (W-4) catalyst provided 6-amino-1-*n*-hexyl-1*H*-imidazo[4,5-*c*]pyridine-2,4(3*H*,5*H*)-dione (**35**) in a 47% yield. Our attempted methylation of **35** with iodomethane under a variety of experimental conditions was unsuccessful. A complex reaction mixture always resulted, from which the desired product **40** could not be isolated in appreciable amount. Therefore, the following alternate route to **40** was investigated.

Methylation of **31** with iodomethane, as described for the preparation of **28** from **27**, afforded 1-*n*-hexyl-4-methoxycarbonyl-5-methoxycarbonylmethyl-3-methyl-2-oxo-Δ^4-imidazoline (**36**) in a 72% yield. Further treatment of **36** with methanolic ammonia (saturated at 0°) at ambient temperature gave an intractable reaction mixture consisting of mono- and bisamides, along with several other products, as judged by tlc analysis. No attempt was made to separate these products. However, when the ammonolysis was carried out under stringent conditions (0 to −5°), a mixture consisting of one major reaction product (along with a few minor products) was obtained. The major product was isolated in a 53% yield by extensive silica gel column chromatography and identified as 1-*n*-hexyl-4-methoxycarbonyl-3-methyl-2-oxo-Δ^4-imidazoline-5-acetamide (**37**). Dehydration of **37** with phosgene in anhydrous toluene gave the corresponding 5-cyanomethyl derivative **38**. Compound **38** was also readily obtained by methylation of **33** with iodomethane and found to be identical with **38** derived from **37**. The yield of **38** by both of the methods was >78%. Annulation of **38** with hydrazine hydrate in ethanol at reflux temperature gave 5,6-diamino-1-*n*-hexyl-3-methyl-2,3,4,5-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-2,4-dione (**39**) in a moderate yield. Raney nickel catalyzed hydrogenation of **39** under similar reaction conditions as described for the preparation of **35** from **34**, gave the desired 6-amino-1-*n*-hexyl-3-methyl-2,3,4,5-1*H*-imidazo[4,5-*c*]pyridine-2,4-dione (7-methyl-8-oxo-9-hexyl-3-deazaguanine, **40**) in a 39% yield.

The single crystal X-ray diffration analysis of **30**, and the detailed biological evaluation data of all the *N*- and *C*-alkyl derivatives of the purine analogs synthesized during this study will be published elsewhere.

EXPERIMENTAL

Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting-point apparatus. Elemental analyses were performed by Robertson Laboratory, Madison, NJ and Quantitative Technologies Inc., Whitehouse, NJ. The presence of water as indicated by elemental analysis was verified by ^{1}H nmr spectroscopy. Thin layer chromatography (tlc) was performed on aluminum plates coated (0.2 mm) with silica gel $60F_{254}$ (EM Science) and the components were visualized by uv absorbance. EM Science silica gel (230-400 mesh, 60 Å) was used for flash column chromatography. All solvents and chemicals used were reagent grade, and were not further dried/purified unless otherwise noted. Evaporations were carried out at a temperature ≤30° and under diminished pressure for solvents with bp <80° or under high vacuum for higher boiling solvents. Infrared (ir) spectra were recorded in potassium bromide or nujol with a Perkin-Elmer 1420 ir spectrophotometer and ultraviolet spectra (uv) were recorded with a Beckman DU-50 spectrophotometer or Hewlett-Packard 8452 diode array spectrophotometer. Nuclear magnetic resonance (^{1}H nmr) spectra were recorded at 300 MHz with an IBM NR/300 spectrometer or at 400 MHz with a Brüker AM400 wide bore nmr sepctrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard (key: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad).

2-Amino-8-*n*-pentylimidazo[1,2-*a*]-*s*-triazin-4-one (**9**).

To a suspension of 2-aminoimidazo[1,2-*a*]-*s*-triazin-4(8*H*)-one [19] (**5**, 0.5 g, 3.36 mmoles) in anhydrous *N*,*N*-dimethylformamide (45 ml) was added sodium hydride (60% dispersion in mineral oil, 0.112 g, 4.69 mmoles). The mixture was protected from moisture and stirred at ambient temperature for 30 minutes. To this suspension, 1-bromopentane (**6**, 0.685 g, 4.53 mmoles) was added and the stirring was continued at ambient temperature for 16 hours. The reaction mixture was evaporated in vacuum and the residue was coevaporated with methanol (2 x 20 ml). A solution of the residue in methanol (15 ml) was adsorbed onto silica gel (15 g) and placed on the top of a dry silica gel column (2.5 x 25 cm). The column was eluted with dichloromethane:methanol (9:1, v/v). The appropriate homogeneous fractions were collected and evaporated to give a colorless solid, which was crystallized from a mixture of dichloromethane and hexane to afford 0.435 g (60%) of **9**, mp 210-211°; ir: ν 1690 (C=O) cm^{-1}; uv (*p*H 1): λ max 262 nm (ε 16,400); (*p*H 7): λ max 256 nm (ε 16,200); (*p*H 11): λ max 256 nm (ε 16,600); ^{1}H nmr (DMSO-d_6): δ 0.86 (t, 3 H, CH_3), 1.29 (br s, 4 H, 2CH_2), 1.72 (t, 2 H, CH_2), 3.88 (t, 2 H, NCH_2), 6.88 (br s, 2 H, NH_2), 7.23 (d, J = 2.52 Hz, 1 H, C$_6H$), 7.29 (d, J = 2.7 Hz, 1 H, C$_7H$).

Anal. Calcd. for $C_{10}H_{15}N_5O$ (221.26): C, 54.28; H, 6.83; N, 31.65. Found: C, 54.19; H, 6.74; N, 31.37.

2-Amino-8-*n*-hexylimidazo[1,2-*a*]-*s*-triazin-4-one (**10**).

This compound was obtained (80.5%) from **5** (0.50 g, 3.7 mmoles) and 1-bromohexane (**7**, 0.55 g, 3.33 mmoles) by the procedure as described for **9**. Compound **10** was crystallized from a mixture of dichloromethane and hexane, mp 185°; ir: ν 1695

(C=O) cm^{-1}; uv (*p*H 1): λ max 263 nm (ε 25,600); (*p*H 7 and 11): λ max 256 nm (ε 25,200); ^{1}H nmr (DMSO-d_6): δ 0.86 (t, 3 H, CH_3), 1.26 (br s, 6 H, 3CH_2), 1.72 (t, 2 H, CH_2), 3.88 (t, 2 H, NCH_2), 6.81 (br s, 2 H, NH_2), 7.30 (d, J = 2.68 Hz, 1 H, C$_6H$), 7.32 (d, J = 2.56 Hz, 1 H, C$_7H$).

Anal. Calcd. for $C_{11}H_{17}N_5O$ (235.29): C, 56.15; H, 7.28; N, 29.76. Found: C, 55.96; H, 7.09; N, 29.69.

2-Amino-8-(6-hydroxyhexyl)imidazo[1,2-*a*]-*s*-triazin-4-one (**11**).

A mixture of **5** (0.5 g, 3.33 mmoles), sodium hydride (80% dispersion in mineral oil, 0.10 g, 3.33 mmoles) and anhydrous *N,N*-dimethylformamide (10 ml) was protected from moisture and stirred at ambient temperature for 1.5 hours. 6-Bromo-1-hexanol (**8**, 95%, 0.5 ml, 3.63 mmoles) was added and the mixture was stirred and heated at 70-80° (oil bath) for 4 hours. The mixture was evaporated under vacuum and then water (10 ml) was added. The *p*H was adjusted to 6 with acetic acid and the mixture was refrigerated for 16 hours. The solid was removed by filtration and the filtrate was evaporated in vacuum. The residue was dissolved in methanol (25 ml) and silica gel (5 g) was added. The mixture was evaporated and the dry powder was placed on top of a silica gel column (3.5 x 29 cm). The column was progressively flash eluted with increasing concentrations of methanol in dichloromethane (% methanol, volume in 1): (0, 0.5), (2, 0.5), (4, 0.5), (6, 1), (8, 1), and (10, 1). Eluate containing the homogeneous product was evaporated and the residue was dried in vacuum at 64° for 2 days, 91 mg, mp 126-128°; ir: ν 1710 (C=O), 3160-3360 (NH) cm^{-1}; uv (*p*H 1): λ max 264 nm (ε 14,400); (methanol): λ max 258 nm (ε 13,600); (*p*H 11): λ max 258 nm (ε 13,000); ^{1}H nmr (DMSO-d_6): δ 1.27 (m, 4 H, 2CH_2), 1.37 (m, 2 H, CH_2), 1.70 (m, 2 H, CH_2), 3.36 (t, 2 H, CH_2OH), 3.86 (t, 2 H, NCH_2), 4.35 (br s, 1 H, O*H*), 6.05 (s, 2 H, NH_2), 7.31 (2d, 2 H, C$_6H$ and C$_7$H).

Anal. Calcd. for $C_{11}H_{17}N_5O_2 \cdot 0.25H_2O$ (255.80): C, 51.65; H, 6.90; N, 27.38. Found: C, 51.62; H, 6.87; N, 26.93.

7-Chloro-1-*n*-pentylimidazo[1,2-*a*]pyrimidin-5-one (**13**).

This compound was obtained (71%) from 7-chloroimidazo[1,2-*a*]pyrimidin-5-one [20] (**12**, 1.0 g, 7.4 mmoles) and **6** by the procedure as described for **9**. Compound **13** was crystallized from a mixture of dichloromethane and methanol, mp 72-73°; ir: ν 1670 (C=O) cm^{-1}; uv (*p*H 1, 7 and 11): λ max 298 nm (ε 11,500); ^{1}H nmr (DMSO-d_6): δ 0.86 (t, 3 H, CH_3), 1.27 (m, 4 H, 2CH_2), 1.81 (t, 2 H, CH_2), 4.07 (t, 2 H, NCH_2), 5.91 (s, 1 H, C$_6H$), 7.70 (d, J = 2.67 Hz, 1 H, C$_3H$), 7.73 (d, J = 2.7 Hz, 1 H, C$_2H$).

Anal. Calcd. for $C_{11}H_{14}ClN_3O$ (239.69): C, 55.12; H, 5.89; N, 17.53; Cl, 14.79. Found: C, 55.11; H, 5.76; N, 17.38; Cl, 14.89.

7-Amino-1-*n*-pentylimidazo[1,2-*a*]pyrimidin-5-one (**14**).

A mixture of **13** (0.275 g, 1.14 mmoles) and methanolic ammonia (saturated at 0°, 25 ml) was heated in a stainless steel pressure reaction vessel at 105° for 7 days. The vessel was cooled to −15° and opened carefully. The solvent was evaporated and the residue was dissolved in dichloromethane (2 ml). The solution was applied to a silica gel column (2.5 x 20 cm) and the column was flash eluted with dichloromethane:methanol (8:2, v/v). Eluate containing the homogeneous product was evaporated and the residue was crystallized from a mixture of dichloromethane and methanol to afford 0.19 g (75%) of **14**, mp 174-176°; ir: ν 1675 (C=O) cm^{-1}; uv (*p*H 1): λ max 275 nm (ε 10,500); (*p*H 7): λ max 270 nm (ε 10,300); (*p*H 11): λ max 269 nm (ε 11,000); ^{1}H nmr (DMSO-d_6): δ 0.87 (t, 3 H, CH_3), 1.33 (br s, 4 H, 2CH_2), 1.76 (m, 2 H, CH_2), 3.94 (t, 2 H, NCH_2), 4.61 (s, 1 H, C$_6H$), 6.51 (br s, 2 H, NH_2), 7.37 (d, J = 2.64 Hz, 1 H, C$_3H$), 7.40 (d, J = 2.52 Hz, 1 H, C$_2H$).

Anal. Calcd. for $C_{11}H_{16}N_4O$ (220.24): C, 59.97; H, 7.32; N, 25.43. Found: C, 59.86; H, 7.24; N, 25.31.

7-Chloro-1-*n*-hexylimidazo[1,2-*a*]pyrimidin-5-one (**15**).

This compound was obtained (40%) from **12** (0.50 g, 3.7 mmoles) and **7** (0.63 g, 3.8 mmoles) by the procedure as described for **9**. Compound **15** was crystallized from methanol, mp 65-67°; ir: ν 1670 (C=O) cm^{-1}; uv (*p*H 1, 7 and 11): λ max 298 nm (ε 12,000); ^{1}H nmr (DMSO-d_6): δ 0.81 (t, 3 H, CH_3), 1.27 (m, 6 H, 3CH_2), 1.80 (t, 2 H, CH_2), 4.08 (t, 2 H, NCH_2), 5.93 (s, 1 H, C$_6H$), 7.71 (d, J = 2.60 Hz, 1 H, C$_3H$), 7.73 (d, J = 2.56 Hz, 1 H, C$_2H$).

Anal. Calcd. for $C_{12}H_{16}ClN_3O$ (253.72): C, 56.80; H, 6.35; N, 16.56; Cl, 13.97. Found: C, 56.62; H, 6.26; N, 16.71; Cl, 13.91.

7-Amino-1-*n*-hexylimidazo[1,2-*a*]pyrimidin-5-one (**16**).

This compound was obtained (60%) by amination of **15** (0.50 g, 2.13 mmoles) following the procedure as described for **14**. Compound **16** was crystallized from methanol, mp 101-103°; ir: ν 1670 (C=O) cm^{-1}; uv (*p*H 1, 7 and 11): λ max 270 nm (ε 12,600); ^{1}H nmr (DMSO-d_6): δ 0.87 (t, 3 H, CH_3), 1.25 (br s, 6 H, 3CH_2), 1.72 (t, 2 H, CH_2), 3.91 (t, 2 H, NCH_2), 4.82 (s, 1 H, C$_6H$), 6.24 (br s, 2 H, NH_2), 7.29 (d, 1 H, C$_3H$), 7.32 (d, 1 H, C$_2H$).

Anal. Calcd. for $C_{12}H_{18}N_4O$ (234.29): C, 61.51; H, 7.76; N, 23.91. Found: C, 61.55; H, 7.82; N, 23.78.

7-Chloro-1-(6-hydroxyhexyl)imidazo[1,2-*a*]pyrimidin-5-one (**17**).

A mixture of **12** (1.0 g, 7.4 mmoles), potassium carbonate (1.05 g, 7.6 mmoles) and 6-bromo-1-hexanol (1.33 g, 7.4 mmoles) in anhydrous *N,N*-dimethylformamide (50 ml) was heated at 135° for 2 days. The reaction mixture was cooled to room temperature, filtered and the filtrate was evaporated to dryness. The residue was dissolved in methanol (25 ml), adsorbed onto silica gel (10 g) and placed on the top of a dry silica gel column (2.5 x 25 cm). The column was eluted with dichloromethane:methanol (9:1, v/v). The appropriate homogeneous fractions were collected and evaporated to give a light yellow syrup, which on standing solidified. The solid was crystallized from methanol to give 0.8 g (45%) of **17**, mp 118-120°; ^{1}H nmr (DMSO-d_6): δ 1.22 (m, 4 H, 2CH_2), 1.76 (m, 6 H, 3CH_2), 4.30 (m, 2 H, NCH_2), 4.35 (br s, 1 H, O*H*), 5.74 (s, 1 H, C$_6H$), 7.33 (d, 1 H, C$_3H$), 7.45 (d, 1 H, C$_2H$).

Anal. Calcd. for $C_{12}H_{16}ClN_3O_2$ (269.72): C, 53.43; H, 5.98; N, 15.57. Found: C, 53.62; H, 5.75; N, 15.35.

5-Amino-3-*n*-pentylthiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione (**19**).

A mixture of 5-aminothiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione [21] (**18**, 0.30 g, 1.63 mmoles) and anhydrous *N,N*-dimethylformamide (15 ml) was sonicated to obtain a fine suspension. The mixture was protected from moisture and sodium hydride (80% dispersion in mineral oil, 0.05 g, 1.67 mmoles) was added. The mixture was stirred at ambient temperature for 1 hour. 1-Bromopentane (**6**, 0.25 ml, 2.02 mmoles) was added, the mixture was heated at 70-80° (oil bath temperature), and stirring was continued for 4 hours. The solvent was removed in vacuum and then water (20 ml) was added to the residue. The aqueous mixture was stirred and carefully acidified (*p*H 3) with dilute hydrochloric acid. The solid that separated was collected by filtration, dissolved in methanol (25 ml) and adsorbed onto silica gel (10 g).

The dry powder was placed on top of a silica gel column (3.5 x 24 cm) and the column was flash eluted with progressively increasing concentrations of methanol in dichloromethane (% methanol, volume in 1): (0, 0.5), (1, 0.5), (2, 0.5), and (5, 1). Eluate containing the homogeneous product was evaporated to furnish 0.14 g (34%) of **19**, mp 253-255°; ir: ν 1710 (C=O), 3225 (NH), 3325 (NH), 3425 (NH) cm^{-1}; uv (*p*H 1): λ max 302 nm (ϵ 9,600), 250 (8,200), 222 (30,100); (methanol): λ max 302 nm (ϵ 9,100), 250 (8,500), 222 (29,800); (*p*H 11): λ max 292 nm (ϵ 7,700), 250 (7,500), 224 (11,500); ^{1}H nmr (DMSO-d_6): δ 0.85 (t, 3 H, CH_3), 1.26 (m, 4 H, $2CH_2$), 1.62 (m, 2 H, CH_2), 3.75 (t, 2 H, NCH_2), 6.84 (br s, 2 H, NH_2), 11.01 (br s, 1 H, NH).

Anal. Calcd. for $C_{10}H_{14}N_4O_2S$ (254.31): C, 47.23; H, 5.55; N, 22.03. Found: C, 47.46; H, 5.48; N, 21.63.

5-Amino-3-*n*-hexylthiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione (**20**).

To a sonicated mixture of **18** (0.92 g, 5 mmoles) in anhydrous *N,N*-dimethylformamide (10 ml) was added sodium hydride (80% dispersion in mineral oil, 0.175 g, 5.8 mmoles). The mixture was protected from moisture and stirred at ambient temperature for 3 hours. 1-Bromohexane (**7**, 0.77 ml, 5.5 mmoles) was added and the stirring was continued at ambient temperature for 16 hours. The mixture was heated at 50° (oil bath) for 3 hours, cooled to room temperature, and then filtered. The filtrate was evaporated in vacuum and water (50 ml) was added to the residue. The mixture was allowed to stand at room temperature for 16 hours and the solid that deposited was collected by filtration. The solid was crystallized from aqueous methanol to give 0.34 g (25%) of **20**, mp 255-256°; ir: ν 1710 (C=O), 3350 (NH), 3440 (NH) cm^{-1}; uv (*p*H 1): λ max 302 nm (ϵ 10,000), 250 (8,600), 222 (31,400); (methanol): λ max 302 nm (ϵ 9,500), 250 (9,000), 222 (31,300); (*p*H 11): λ max 292 nm (ϵ 8,100), 250 (7,900), 224 (11,900); ^{1}H nmr (DMSO-d_6): δ 0.853 (t, 3 H, CH_3), 1.27 (m, 6 H, $3CH_2$), 1.62 (m, 2 H, CH_2), 3.76 (t, 2 H, NCH_2), 6.82 (br s, 2 H, NH_2), 10.97 (br s, 1 H, NH).

Anal. Calcd. for $C_{11}H_{16}N_4O_2S$ (268.34): C, 49.24; H, 6.01; N, 20.88. Found: C, 49.31; H, 6.02; N, 20.85.

5-Amino-3-(6-hydroxyhexyl)thiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione (**21**).

A mixture of **18** (0.27 g, 1.47 mmoles), anhydrous *N,N*-dimethylformamide (10 ml), and sodium hydride (80% dispersion in mineral oil, 0.047 g, 1.57 mmoles) was protected from moisture and stirred at ambient temperature for 1 hour. 6-Bromo-1-hexanol (**8**, 95%, 0.25 ml, 1.81 mmoles) was added and the mixture was heated at 70-80° (oil bath) for 4.5 hours. The mixture was evaporated in vacuum and then water (20 ml) was added to the syrupy residue. The mixture was allowed to stand at 5° for 16 hours and then the solid was collected by filtration. The solid was dissolved in methanol, silica gel (5 g) was added, and the mixture was evaporated to dryness. The dry powder was placed on top of a silica gel column (3.5 x 22 cm) and the column was flash eluted with progressively increasing concentrations of methanol in dichloromethane (% methanol, volume in 1): (0, 0.5), (1, 0.5), (2, 0.5), (5, 2), and (10, 1). Eluate containing the homogeneous product was evaporated and the residue was dried in vacuum at 95° for 2 days to give 0.21 g (50%) of **21**, mp 227-229°; ir: ν 1705 (C=O), 3340 (NH), 3415 (NH) cm^{-1}; uv: (*p*H 1): λ max 302 nm (ϵ 9,700), 250 (8,400), 222 (30,300); (methanol): λ max 302 nm (ϵ 9,200), 250 (8,600), 222 (30,100); (*p*H 11): λ max 292 nm (ϵ 7,700), 248 (7,500), 224 (11,900); ^{1}H nmr (DMSO-d_6): δ 1.27 (m, 4 H, $2CH_2$), 1.37 (m, 2 H, CH_2), 1.60 (t, 2 H, CH_2), 3.36 (m, 2 H, CH_2OH), 3.74 (t, 2 H, NCH_2), 4.34 (t, 1 H, OH), 6.92 (br s, 2 H, NH_2), 11.10 (br s, 1 H, NH).

Anal. Calcd. for $C_{11}H_{16}N_4O_3S$ (284.34): C, 46.47; H, 5.67; N, 19.70. Found: C, 46.10; H, 5.52; N, 19.47.

Hexanoic Acid, 2-(3-Amino-4,5-dihydro-5-oxo-1,2,4-triazin-6-yl)hydrazide (**24a**).

A mixture of 3-amino-6-hydrazino-1,2,4-triazin-5(4*H*)-one [24] (**22**, 1.0 g, 7.04 mmoles), hexanoic acid (0.88 ml, 7.04 mmoles), 1-hydroxybenzotriazole (0.95 g, 7.04 mmoles), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC, 1.35 g, 7.04 mmoles) and anhydrous *N,N*-dimethylformamide (100 ml) was stirred at ambient temperature for 20 hours, with the exclusion of moisture. The insoluble material was removed by filtration and the filtrate was concentrated to a small volume (~ 10 ml) and allowed to stand at room temperature overnight. The crystalline product that separated was collected, washed with ether (5 x 15 ml) and dried at 80° to yield 0.95 g (56%) of **24a**, mp >275°; ^{1}H nmr (DMSO-d_6): δ 0.87 (t, 3 H, CH_3), 1.27 (m, 4 H, $2CH_2$), 1.50 (m, 2 H, CH_2), 2.08 (t, 2 H, CH_2-CO), 6.44 (br s, 2 H, NH_2), 7.85 (s, 1 H, NH), 9.53 (s, 1 H, NH), 11.21 (s, 1 H, NH).

Anal. Calcd. for $C_9H_{16}N_6O_2$ (240.27): C, 44.99; H, 6.71; N, 34.98. Found: C, 44.89; N, 6.66; N, 34.81.

6-Amino-3-*n*-pentyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**25a**).

A solution of **24a** (0.30 g, 1.25 mmoles) in anhydrous ethylene glycol (15 ml) was heated at 200° for 2 hours. The reaction mixture was allowed to cool to room temperature and then poured into water (100 ml). The product that precipitated was collected by filtration and washed several times with acetone (5 x 10 ml). After drying at 80° under vacuum, 0.15 g (54%) of **25a** was obtained, mp >275°; ir: ν 1720 (C=O), 3100-3300 (NH, NH_2) cm^{-1}; uv (*p*H 1): λ max 280 nm (ϵ 2,200), 248 (5,800); (*p*H 7): λ max 282 nm (ϵ 2,600), 248 (4,100); *p*H (11): λ max 286 nm (ϵ 2,900), 254 (4,800); ^{1}H nmr (DMSO-d_6): δ 0.87 (t, 3 H, CH_3), 1.31 (m, 4 H, $2CH_2$), 1.72 (m, 2 H, CH_2), 2.83 (t, 2 H, CH_2), 6.38 (s, 2 H, NH_2), 11.47 (s, 1 H, NH).

Anal. Calcd. for $C_9H_{14}N_6O \cdot 0.1H_2O$ (224.05): C, 48.24; H, 6.39; N, 37.51. Found: C, 48.46; H, 6.39; N, 37.36.

Heptanoic Acid, 2-(3-Amino-4,5-dihydro-5-oxo-1,2,4-triazin-6-yl)-hydrazide (**24b**).

This compound was obtained (42%) from **22** (1.0 g, 7.04 mmoles) and heptanoic acid (1 ml, 7.04 mmoles) by the procedure as described for **24a**, mp 246-248°; ^{1}H nmr (DMSO-d_6): δ 0.91 (t, 3 H, CH_3), 1.31 (m, 6 H, $3CH_2$), 1.55 (m, 2 H, CH_2), 2.14 (t, 2 H, CH_2CO), 6.52 (s, 2 H, NH_2), 7.93 (s, 1 H, NH), 9.60 (s, 1 H, NH), 11.26 (s, 1 H, NH).

Anal. Calcd. for $C_{10}H_{18}N_6O_2 \cdot 0.25H_2O$ (258.79): C, 46.41; H, 7.20; N, 32.47. Found: C, 46.60; H, 6.99; N, 32.69.

6-Amino-3-*n*-hexyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**25b**).

This compound was obtained (63%) from **24b** (0.28 g, 1.12 mmoles) by the procedure as described for **25a**, mp >275°; ir: ν 1720 (C=O), 3200-3350 (NH, NH_2) cm^{-1}; uv (*p*H 1): λ max 280 nm (ϵ 1,900); (*p*H 7): λ max 282 nm (ϵ 2,800); (*p*H 11): λ max 286 nm (ϵ 3,200); ^{1}H nmr (DMSO-d_6): δ 0.86 (t, 3 H, CH_3), 1.29 (m, 6 H, $3CH_2$), 1.71 (m, 2 H, CH_2), 2.83 (t, 2 H, CH_2), 6.38 (s, 2 H, NH_2),

11.46 (s, 1 H, N*H*).

Anal. Calcd. for $C_{10}H_{16}N_6O \cdot 0.2H_2O$ (239.88): C, 50.07; H, 6.89; N, 35.03. Found: C, 50.37; H, 6.74; N, 34.77.

Hexanoic Acid, (3-Amino-4,5-dihydro-5-oxo-1,2,4-triazin-6-yl)-methylamide (**24c**).

This compound was obtained (45%) from 3-amino-6-aminomethyl-1,2,4-triazin-5(4*H*)-one [25] (**23**) (1.5 g, 10.8 mmoles) and heptanoic acid by the procedure as described for **24a**. Compound **24c** was crystallized from aqueous ethanol, mp 237-240°; ^{1}H nmr (DMSO-d_6): δ 0.87 (t, 3 H, CH_3), 1.31 (m, 6 H, 3CH_2), 1.58 (m, 2 H, CH_2), 2.24 (t, 2 H, CH_2CO), 4.28 (d, 2 H, CH_2NH), 6.62 (br s, 2 H, NH_2), 7.94 (t, 1 H, N*H*), 11.55 (br s, 1 H, N*H*).

Anal. Calcd. for $C_{11}H_{19}N_5O_2$ (253.30): C, 52.16; H, 7.56; N, 27.65. Found: C, 52.40; H, 7.84; N, 27.72.

2-Amino-7-*n*-hexylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one (**25c**).

This compound was obtained (75%) from **24c** (0.50 g, 2.07 mmoles) by the procedure as described for **25a** and crystallized from aqueous ethanol, mp 212-214°; ^{1}H nmr (DMSO-d_6): δ 0.85 (t, 3 H, CH_3), 1.29 (m, 6 H, 3CH_2), 1.72 (m, 2 H, CH_2), 2.86 (t, 2 H, CH_2), 6.64 (br s, 2 H, NH_2), 7.95 (s, 1 H, C$_5H$), 11.58 (br s, 1 H, N*H*).

Anal. Calcd. for $C_{11}H_{17}N_5O$ (235.29): C, 56.15; H, 7.28; N, 29.76. Found: C, 56.25; H, 7.31; N, 29.61.

2-Amino-5-bromo-7-*n*-hexylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one (**26**).

To a solution of **25c** (1.5 g, 6.38 mmoles) in anhydrous *N,N*-dimethylformamide (40 ml) was added *N*-bromosuccinimide (2.04 g, 11.46 mmoles) and the mixture was stirred at ambient temperature for 16 hours. The solvent was evaporated and the residue was dissolved in dichloromethane (25 ml). The solution was applied to a silica gel column (2.5 x 25 cm) and the column was flash eluted with dichloromethane:methanol (9:1, v/v). Eluate containing the homogeneous product was evaporated and the residue was crystallized from aqueous ethanol to yield 1.35 g (66%) of **26**, mp 220-222°; ^{1}H nmr (DMSO-d_6): δ 0.87 (t, 3 H, CH_3), 1.27 (m, 6 H, 3CH_2), 1.66 (m, 2 H, CH_2), 2.75 (t, 2 H, CH_2), 6.18 (s, 2 H, NH_2), 10.85 (s, 1 H, N*H*).

Anal. Calcd. for $C_{11}H_{16}BrN_5O$ (314.19): C, 42.04; H, 5.13; N, 22.29; Br, 25.43. Found: C, 42.24; H, 5.29; N, 22.19; Br, 25.63.

5-Methoxycarbonylmethyl-4-methoxycarbonyl-1-methyl-2-oxo-1*H*,3*H*-imidazole (**28**).

To a suspension of 4-methoxycarbonylmethyl-5-methoxycarbonyl-2-oxo-1*H*,3*H*-imidazole [32] (**27**, 4.8 g, 22.4 mmoles) in anhydrous *N,N*-dimethylformamide (150 ml) was added sodium hydride (60% in mineral oil, 1.14 g, 28.5 mmoles), and the mixture was stirred at ambient temperature under argon for 1 hour. Iodomethane (1.54 ml, 25.2 mmoles) was added to the reaction mixture over a period of 15 minutes and the mixture was stirred at 55° (bath temperature) for 24 hours. The solvent was evaporated in vacuum and the residue was dissolved in hot ethyl acetate (50 ml). After cooling (0-5°, overnight), the solid that deposited was collected by filtration and the filtrate was evaporated to dryness. The residue was dissolved in dichloromethane (20 ml), adsorbed onto silica gel (10 g), and placed on the top of a silica gel column (2.5 x 35 cm). The column was eluted with dichloromethane:methanol (95:5, v/v). The appropriate homogeneous fractions were collected and evaporated to give additional solid. The combined solid was crystallized from ethanol to yield 2.50 g (49%) of **28**, mp 184°; uv (*p*H 1 and 7): λ max 272 nm (ε 14,500); (*p*H 11): λ max 282 nm (ε 10,600); ^{1}H nmr (DMSO-d_6): δ 3.08 (s, 3 H, NCH_3), 3.65 (s, 3 H, COOCH_3), 3.70 (s, 3 H, COOCH_3), 4.02 (s, 2 H, CH_2), 10.78 (br s, 1 H, N*H*).

Anal. Calcd. for $C_9H_{12}N_2O_5$ (228.21): C, 47.36; H, 5.30; N, 12.27. Found: C, 47.32; H, 5.40; N, 12.25.

4-Methoxycarbonyl-1-methyl-2-oxo-Δ^4-imidazoline-5-acetamide (**29**).

A mixture of **28** (0.30 g, 1.31 mmoles) and methanolic ammonia (saturated at 0°, 10 ml) was stirred at ambient temperature in a pressure bottle for 14 hours. The solvent was evaporated to furnish a pink residue, which on crystallization from ethanol gave 0.22 g (78%) of **29**, mp 262°; uv (*p*H 1 and 7): λ max 272 nm (ε 19,500); (*p*H 11): λ max 281 nm (ε 14,200); ^{1}H nmr (DMSO-d_6): δ 3.06 (s, 3 H, NCH_3), 3.70 (s, 3 H, OCH_3), 3.75 (s, 2 H, CH_2), 7.09 and 7.52 (2 br s, 2 H, CONH_2), 10.63 (br s, 1 H, N*H*).

Anal. Calcd. for $C_8H_{11}N_3O_4$ (213.19): C, 45.06; H, 5.20; N, 19.71. Found: C, 45.28; H, 5.11; N, 19.54.

Methyl 5-Cyanomethyl-1-methyl-2-oxo-1*H*,3*H*-imidazole-4-carboxylate (**30**).

To an ice-cold solution of **29** (2.5 g, 11.7 mmoles) in dichloromethane (100 ml) and pyridine (1.76 ml, 22 mmoles) was added, dropwise with stirring, a solution of phosgene (12%) in toluene (18 ml, 22 mmoles) over a period of 20 minutes. The mixture was stirred at 0° for 2 hours and allowed to warm to room temperature slowly. The resulting homogeneous solution was quenched with ice (5 g) and stirred for 30 minutes. The solvent was evaporated and the residue was dissolved in dichloromethane (25 ml), adsorbed onto silica gel (15 g), and placed on the top of a silica gel column (3 x 35 cm). The column was eluted with dichloromethane:methanol (6:1, v/v). The homogeneous fractions were collected, evaporated to dryness and the residue was crystallized from ethanol to yield 1.77 g (77%) of **30**, mp 215°; uv (*p*H 1 and 7): λ max 271 nm (ε 27,000); (*p*H 11): λ max 287 nm (ε 21,300); ^{1}H nmr (DMSO-d_6): δ 3.20 (s, 3 H, NCH_3), 3.76 (s, 3 H, OCH_3), 4.28 (s, 2 H, CH_2CN), 10.95 (br s, 1 H, N*H*).

Anal. Calcd. for $C_8H_9N_3O_3$ (195.17): C, 49.22; H, 4.64; N, 21.52. Found: C, 49.26; H, 4.49; N, 21.23.

1-*n*-Hexyl-5-methoxycarbonylmethyl-4-methoxycarbonyl-2-oxo-1*H*,3*H*-imidazole (**31**).

This compound was obtained (56%) from **27** (10 g, 46.7 mmoles) and **7** (6.58 ml, 46.7 mmoles) by the procedure as described for **28**. Compound **31** was crystallized from a mixture of ethanol:ether (7:3, v/v), mp 96°; uv: (*p*H 1 and 7): λ max 274 nm (ε 15,700); (*p*H 11): λ max 281 nm (ε 11,000); ^{1}H nmr (deuteriochloroform): δ 0.81 (t, 3 H, CH_3), 1.23 (br s, 6 H, 3CH_2), 1.54 (m, 2 H, CH_2), 3.58 (t, 2 H, CH_2), 3.67 and 3.77 (2s, 6 H, 2OCH_3), 3.89 (s, 2 H, CH_2), 10.07 (br s, 1 H, N*H*).

Anal. Calcd. for $C_{14}H_{22}N_2O_5$ (298.34): C, 56.35; H, 7.43; N, 9.39. Found: C, 56.37; H, 7.69; N, 9.36.

1-*n*-Hexyl-4-methoxycarbonyl-2-oxo-1*H*,3*H*-imidazole-5-acetamide (**32**).

This compound was obtained (81%) from **31** (4.5 g, 15.1 mmoles) by the procedure as described for **29** and crystallized from ethanol, mp 196°; uv (*p*H 1 and 7): λ max 274 nm (ε 16,000); (*p*H 11): λ max 281 nm (ε 12,200); ^{1}H nmr (DMSO-d_6): δ 0.84 (t, 3 H, CH_3), 1.22 (br s, 6 H, 3CH_2), 1.50 (m, 2 H, CH_2), 3.46 (t, 2 H, CH_2), 3.69 (s, 3 H, OCH_3), 3.71 (s, 2 H, CH_2CO), 7.10 and 7.50 (2

br s, 2 H, CONH_2), 10.63 (br s, 1 H, NH).

Anal. Calcd. for $C_{13}H_{21}N_3O_4$ (283.32): C, 55.10; H, 7.47; N, 14.83. Found: C, 55.00; H, 7.38; N, 15.00.

Methyl 5-Cyanomethyl-1-*n*-hexyl-2-oxo-1*H*,3*H*-imidazole-4-carboxylate (**33**).

This compound was obtained (77%) from **32** (1.13 g, 4 mmoles) by the procedure as described for **30** and crystallized from ethanol containing hexanes, mp 107°; uv (*p*H 1 and 7): λ max 272 nm (ε 15,500); (*p*H 11): λ max 288 nm (ε 11,500); ^{1}H nmr (deuteriochloroform): δ 0.89 (t, 3 H, CH_3), 1.32 (m, 6 H, 3CH_2), 1.74 (m, 2 H, CH_2), 3.77 (t, 2 H, NCH_2), 3.89 (s, 3 H, OCH_3), 4.08 (s, 2 H, CH_2CN), 9.79 (br s, 1 H, NH).

Anal. Calcd. for $C_{13}H_{19}N_3O_3$ (265.30): C, 58.85; H, 7.21; N, 15.83. Found: C, 58.87; H, 7.23; N, 15.86.

5,6-Diamino-1-*n*-hexyl-2,3,4,5-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-2,4-dione (**34**).

A mixture of **33** (0.53 g, 2 mmoles) and hydrazine hydrate (1 ml, 20 mmoles) in ethanol (10 ml) was heated under reflux. Within 5 minutes a clear solution was obtained. Refluxing was continued for 16 hours. On cooling to room temperature, the product crystallized as fine needles. The crystalline product was collected by filtration, washed with cold ethanol (2 x 5 ml) and dried (80°) to furnish 0.42 g (79%) of **34**, mp 225°; uv (*p*H 1): λ max 312 nm (ε 6,700), 259 (7,000), 228 (35,800); (*p*H 7): λ max 310 nm (ε 10,400), 259 (8,000), 224 (47,700); (*p*H 11): λ max 312 nm (ε 10,800), 261 (8,800), 226 (46,900); ^{1}H nmr (DMSO-d_6): δ 0.83 (t, 3 H, CH_3), 1.25 (br s, 6 H, 3CH_2), 1.53 (m, 2 H, CH_2), 3.55 (t, 2 H, CH_2), 5.33 (br s, 2 H, N-NH_2), 5.37 (s, 1 H, C$_7H$), 6.19 (s, 2 H, NH_2), 10.0-11.0 (br s, 1 H, NH).

Anal. Calcd. for $C_{12}H_{19}N_5O_2 \cdot 0.25H_2O$ (269.81): C, 53.41; H, 7.28; N, 25.95. Found: C, 53.38; H, 7.26; N, 25.85.

6-Amino-1-*n*-hexyl-1*H*-imidazo[4,5-*c*]pyridine-2,4(3*H*,5*H*)-dione (**35**).

To a solution of **34** (0.38 g, 1.43 mmoles) in boiling water (60 ml) was added freshly prepared Raney nickle catalyst (W-4, wet weight ~1 g), and the mixture was heated under reflux for 12 hours. The mixture was filtered hot through a Celite pad to remove the catalyst, which was washed well with boiling water (3 x 10 ml). The combined filtrate and washings was evaporated to furnish a straw colored solid, which was crystallized from hot water to yield 0.17 g (47%) of **35**, mp 190° dec; ^{1}H nmr (DMSO-d_6): δ 0.83 (t, 3 H, CH_3), 1.24 (br s, 6 H, 3CH_2), 1.55 (m, 2 H, CH_2), 3.55 (t, 2 H, CH_2), 5.26 (s, 1 H, C$_7H$), 5.86 (br s, 2 H, NH_2), 10.5-11.0 (br s, 2 H, 2NH).

Anal. Calcd. for $C_{12}H_{18}N_4O_2$ (250.29): C, 57.58; H, 7.24; N, 22.38. Found: C, 57.24; H, 7.10; N, 22.25.

1-*n*-Hexyl-4-methoxycarbonyl-5-methoxycarbonylmethyl-3-methyl-2-oxo-Δ^4-imidazoline (**36**).

This compound was obtained (72%) as an oil from **31** (1.98 g, 6.64 mmoles) and iodomethane (0.61 ml, 10 mmoles) by the procedure as described for **28**; ^{1}H nmr (deuteriochloroform): δ 0.87 (t, 3 H, CH_3), 1.28 (br s, 6 H, 3CH_2), 1.59 (m, 4 H, 2CH_2), 3.49 (s, 3 H, NCH_3), 3.73 (s, 3 H, COOCH_3), 3.82 (s, 3 H, COOCH_3), 3.91 (s, 2 H, CH_2).

Anal. Calcd. for $C_{15}H_{24}N_2O_5$ (312.36): C, 57.67; H, 7.74; N, 8.97. Found: C, 57.46; H, 7.72; N, 8.81.

1-*n*-Hexyl-4-methoxycarbonyl-3-methyl-2-oxo-Δ^4-imidazoline-5-acetamide (**37**).

This compound was obtained (53%) from **36** (1.5 g, 4.8 mmoles) and methanolic ammonia (saturated at 0°, 25 ml) by the method as described for **29**. However, the reaction was carried out at 0 to −5° for 10 hours, mp 138°; uv (*p*H 1 and 7): λ max 276 nm (ε 17,900); (*p*H 11): λ max 275 nm (ε 15,500); ^{1}H nmr (DMSO-d_6): δ 0.84 (t, 3 H, CH_3), 1.23 (br s, 6 H, 3CH_2), 1.50 (m, 2 H, CH_2), 3.27 (s, 3 H, NCH_3), 3.52 (t, 2 H, CH_2), 3.72 (s, 5 H, OCH_3 and CH_2CO), 7.11 and 7.50 (2 br s, 2 H, NH_2).

Anal. Calcd. for $C_{14}H_{23}N_3O_4$ (297.35): C, 56.54; H, 7.79; N, 14.13. Found: C, 56.68; H, 7.78; N, 14.02.

5-Cyanomethyl-1-*n*-hexyl-4-methoxycarbonyl-3-methyl-2-oxo-Δ^4-imidazoline (**38**).

Method A.

This compound was obtained (85%) as an oil from **37** (0.70 g, 2.35 mmoles) and 12% phosgene in toluene (4.9 ml, 6 mmoles) by the method as described for **30**; uv (*p*H 1 and 7): λ max 275 nm (ε 15,000); (*p*H 11): λ max 274 nm (ε 15,400); ^{1}H nmr (deuteriochloroform): δ 0.85 (t, 3 H, CH_3), 1.29 (br s, 6 H, 3CH_2), 1.67 (m, 2 H, CH_2), 3.46 (s, 3 H, NCH_3) 3.73 (t, 2 H, CH_2), 3.87 (s, 3 H, OCH_3), 4.02 (s, 2 H, CH_2CN).

Anal. Calcd. for $C_{14}H_{21}N_3O_3$ (279.34): C, 60.19; H, 7.57; N, 15.04. Found: C, 59.95; H, 7.62; N, 15.04.

Method B.

This compound was also obtained (78%) by methylation of **33** by the procedure as described for **36**. This material was found to be identical in all respects (tlc, uv and ^{1}H nmr) to that obtained by Method A.

5,6-Diamino-1-*n*-hexyl-3-methyl-2,3,4,5-tetrahydro-1*H*-imidazo-[4,5-*c*]-2,4-dione (**39**).

This compound was obtained (68%) from **38** (0.52 g, 1.82 mmoles) and hydrazine hydrate (1 ml) by the procedure as described for the synthesis of **34**. Compound **39** was found to decompose on prolonged storage; ^{1}H nmr (DMSO-d_6): δ 0.83 (t, 3 H, CH_3), 1.23 (br s, 6 H, 3CH_2), 1.53 (m, 2 H, CH_2), 3.37 (s, 3 H, NCH_3), 3.58 (t, 2 H, CH_2), 5.39 (s, 1 H, C$_7H$), 6.27 (s, 2 H, NH_2).

6-Amino-1-*n*-hexyl-3-methyl-2,3,4,5-1*H*-imidazo[4,5-*c*]pyridine-2,4-dione (**40**).

This compound was obtained (39%) from **39** (0.15 g, 0.53 mmole) and Raney nickel (~1.0 g) by the procedure as described for the preparation of **35**. Compound **40** was crystallized from acetone, mp 180° dec; ^{1}H nmr (DMSO-d_6): δ 0.83 (t, 3 H, CH_3), 1.23 (br s, 6 H, 3CH_2), 1.54 (m, 2 H, CH_2), 3.36 (s, 3 H, NCH_3), 3.55 (t, 2 H, CH_2), 5.27 (s, 1 H, C$_7H$), 5.78 (br s, 2 H, NH_2).

Anal. Calcd. for $C_{13}H_{20}N_4O_2$ (264.32): C, 59.07; H, 7.62; N, 21.19. Found: C, 59.31; H, 7.66; N, 20.95.

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