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Regiospecific Alkylation of Histidine and Histamine at N-1 (τ)[1]

Rahul Jain and Louis A. Cohen*

Laboratory of Bioorganic Chemistry, NIDDK, National Institutes of Health, Bethesda, MD 20892

Abstract: *Series of 1-alkyl histidines and histamines have been synthesized by the alkylation of the corresponding 5,6,7,8-tetrahydro-5-oxoimidazo[1,5-c]pyrimidines with alkyl halides in aprotic solvents. The method of conversion of the intermediate quaternary salt to the amino acid or amine depends on the nature of the alkyl group.* Published by Elsevier Science Ltd

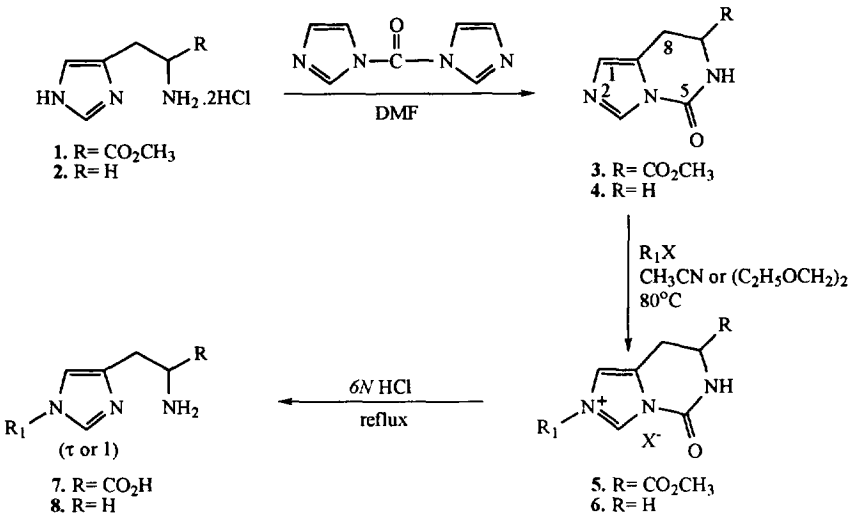
Our interest in histamine and histidine derivatives as novel antimalarials[2] and as polypeptide components[3] created a need for a general synthetic route to N(1)$^{\tau}$-alkyl bioimidazoles (***Scheme 1***)[4]. It is commonly known that direct ring alkylation of suitably protected histamine or histidine almost always results in a mixture of τ (1) and π (3) derivatives[5]. Although the desired τ derivative is often the major product, it is rarely exclusive; in addition, difficulty in separating the closely similar isomers, particularly on a preparative scale, renders the direct approach uninviting.

Only two classes of reagent, the halonitrobenzenes[6] and triarylmethyl halides[7] appear to give exclusively τ products. The common assumption that partial or total preference for the τ nitrogen is the result of steric accommodation may not be entirely valid, since ring systems as bulky as those of benzpyrene[8], riboflavin[9] and FAD[10] lead to mixtures containing substantial amounts of π isomer. Thus, the isomer ratio may be influenced more by subtleties in the mechanism of alkylation (or arylation) than by steric effect.

Clearly, specific alkylation at the τ nitrogen requires protection of the π nitrogen, in addition to that of the side-chain functions. Such an approach was used by Beyerman[11] for the syntheses of τ-methyl-L-histidine (**7a**) and τ-ethyl-L-histidine (**7b**) (***Scheme 1, Table I***). Reaction of L-histidine methyl ester with carbonyldiimidazole in DMF provided the cyclic urea **3**. Alkylation of **3** with methyl or ethyl iodide in refluxing DMF led to the quaternary salts **5a** and **5b**, which were deprotected in dilute mineral acid at reflux. The analogous approach has been used to prepare τ-methylhistamine (**8a**) via **4** and **6a**[12]. Thus, acylation at N-3 does not reduce the basicity or nucleophilicity of N-1 enough to impair S_N2 alkylation.

When we attempted to extend the same alkylation of **3** or **4** to higher alkyl halides, the products were complex mixtures from which the quaternary salts could not be isolated in satisfactory yield or purity. Much better results were obtained with acetonitrile or 1,2-diethoxyethane as solvent at 80 °C. A control experiment with **5d** [R_1= $CH(CH_3)_2$] showed that the quaternary salts are unstable in DMF, even at 80 °C, reverting to **3** and a variety of unidentified products. This instability appears to be due to the higher polarity of DMF, rather than to the higher reaction temperature. By use of less polar solvents, a variety of quaternary salts (**5,6** and

Table I) were obtained in yields of 70-95%. Although a crude salt was obtained with *tert*-butyl bromide (**5f**), no alkylation was observed with cyclohexyl halides[13].

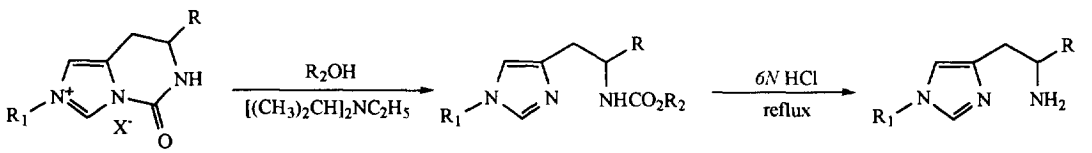


Scheme 1

Table I

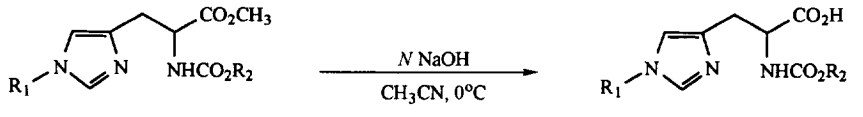
Identities of R_1 in Compounds **5-11**	
a) CH_3	g) $CH_2CO_2C_2H_5$
b) C_2H_5	h) CH_2CO_2H
c) $CH_2CH{=}CH_2$	i) $CH_2C_6H_5$
d) $CH(CH_3)_2$	j) $CH_2C_6H_4$-4-OCH_3
e) $CH(CH_3)(C_2H_5)$	k) $CH_2C_6H_4$-4-OH
f) $C(CH_3)_3$	l) $CH_2COC_6H_5$

In most cases, the τ-alkylhistidines (**7**) and τ-alkylhistamines (**8**) were obtained by the deprotection of **5** and **6** with refluxing *6N* HCl, followed by ion-exchange chromatography for the amino acids. In certain cases (**5d**, **5e**, **5j**), the quaternary halide proved difficult to purify or crystallize. The crude salt was then reacted with an alcohol,[13,14] in the presence of a tertiary amine at reflux for 2-5 days, to give the fully protected τ-alkyl derivatives (**9**, **10**) in good yield (***Scheme 2***). Acid hydrolysis of the latter compounds then provided **7** and **8**.



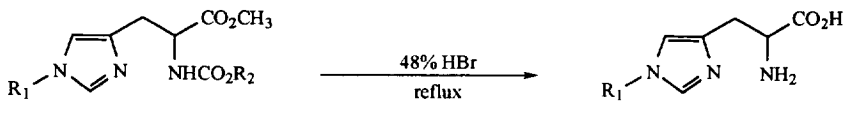
Scheme 2

Ring opening of **5** and **6** could be achieved not only with simple aliphatic alcohols but with *tert*-butyl alcohol or with benzyl alcohol (in acetonitrile), to provide **9** or **10** as the α-N-BOC or α-N-Z derivative, respectively. Selective hydrolysis of the methyl ester in **9** was achieved with *N* NaOH in acetonitrile (30 min at 0 °C) to provide **11**, derivatives suitable for use in peptide synthesis (***Scheme 3***).[15] In the case of **5f**, direct acid hydrolysis or attempted ring opening to **9** resulted in the loss of the *tert*-butyl group. Other approaches to **7f** and **8f** are in progress. Surprisingly, **5c** did not lose its allyl group on acid hydrolysis, but was dealkylated to **9** (R_1= H) on attempted ring opening to **9c**.



9 **11**

Scheme 3



9j **7k**

Scheme 4

Reaction of **9j** ($R_2 = CH_2C_6H_5$) with refluxing 48% HBr for 48 h resulted in full deprotection, including demethylation at R_1 to give **7k** (***Scheme 4***).

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Gemini 300 (300 MHz) spectrometer. Mass spectra were provided by the Instrumentation Section of the Laboratory of Analytical Chemistry, NIDDK. Elemental analysis were performed by Atlantic Microlab, Norcross, GA or by Galbraith Laboratories, Knoxville, TN. Melting points were recorded on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 MC Polarimeter. Chromatographic purification was performed with silica gel 60 (230-400 mesh). All TLC (silica gel) development was performed by use of 5% CH_3OH in $CHCl_3$. All reagents were obtained from commercial sources and were of analytical grade.

General procedure for the synthesis of (+)-(7S)-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo-[1,5-c] pyrimidine (3) and 5,6,7,8-tetrahydro-5-oxoimidazo[1,5-c]pyrimidine (4). A mixture of L-histidine methyl ester dihydrochloride (**1**, 24.2 g, 0.1 mol) or histamine dihydrochloride (**2**, 18.4 g, 0.1 mol)[16] and carbonyldiimidazole (16.2 g, 0.1 mol) in DMF (500 mL) was stirred at 60-70 °C for 5 h. At that point, TLC showed the absence of starting material. All DMF was removed *in vacuo*, yielding an oil which was dissolved in 1 liter of *N* $NaHCO_3$. The aqueous solution was extracted with dichloromethane (8 x 200 mL), the combined extracts were dried (Na_2SO_4) and evaporated. The residual solid was recrystallized from acetonitrile to give 80-95% of the product : **3**, mp 156-158 °C, $[\alpha]_D^{25}$ +60.2° (c=1.4, CH_3OH) (lit[11] mp 156-157 °C, $[\alpha[_D^{25}$ +59° (c=1.1, CH_3OH); **4**, mp 220-221 °C (lit[12] mp 219-220 °C).

General procedure for the synthesis of (+)-(7S)-2-alkyl-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo[1,5-c]pyrimidinium salts (5) and 2-alkyl-5,6,7,8-tetrahydro-5-oxoimidazo-[1,5-c]pyrimidinium salts (6). To a suspension of **3** (1.0 g, 5.12 mmol) or **4** (1.0 g, 7.29 mmol) in 15 mL of acetonitrile or 1,2-diethoxyethane was added 3 equivalents of alkyl bromide or iodide. The reaction mixture was heated at reflux

for 24 h, at which point TLC showed the absence of **3** or **4**. The solution was cooled, evaporated to dryness *in vacuo* and the residual solid was recrystallized from the appropriate solvent.

(S)-5,6,7,8-Tetrahydro-7-(methoxycarbonyl)-2-methyl-5-oxoimidazo[1,5-c]pyrimidinium iodide (5a). Yield: 98% [methanol-ether]; mp 164 °C(dec) [lit[11] mp 162 °C (dec)]; ^{1}H NMR (D_2O) δ 3.43 (d, 2H, CH_2, J= 5.6 Hz), 3.70 (s, 3H, OCH_3), 3.90 (s, 3H, N-CH_3), 4.68 (t, 1H, CH, J= 5.6 Hz), 7.35 (s, 1H, 4-H), 9.30 (s, 1H, 2-H); analysis for $C_9H_{12}N_3O_3I$ (337.12), calcd., C, 32.07; H, 3.59; N, 12.46; I, 37.64; found, C, 32.14; H, 3.62; N, 12.39; I, 37.74 ; $[\alpha]_D^{25}$ +45.2° (c=1.7, H_2O) [lit[11] + 46° (c= 0.7, H_2O)]; MS(CI-NH_3) m/z 210 (M+1-HI).

(S)-2-Ethyl-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo[1,5-c]pyrimidinium iodide (5b). Yield: 97% [methanol-ether]; mp 146.5-147 °C (dec) [lit[11] mp 146 °C (dec)]; ^{1}H NMR (D_2O) δ 1.52 (t, 3H, CH_3, J= 7.4 Hz), 3.46 (d, 2H, CH_2, J= 5.8 Hz), 3.77 (s, 3H, OCH_3), 4.31 (q, 2H, N-CH_2, J= 7.4 Hz), 4.72 (t, 1H, CH, J= 5.8 Hz), 7.50 (s, 1H, 4-H), 9.40 (s, 1H, 2-H); analysis for $C_{10}H_{14}N_3O_3I$ (351.14), calcd., C, 34.21; H, 4.02; N, 11.97; I, 36.14; found, C, 34.17; H, 4.00; N, 11.90; I, 36.20; $[\alpha]_D^{25}$ +37.3° (c=1.66, H_2O) [lit[11] +35° (c = 2.3, H_2O)]; MS(CI-NH_3) m/z 224 (M+1-HI).

(S)-2-Allyl-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxo-imidazo[1,5-c]pyrimidinium iodide (5c). Yield: 67% [acetone]; mp 167-168 °C (dec); ^{1}H NMR (D_2O) δ 3.39 (m, 2H, CH_2), 3.68 (s, 3H, OCH_3), 4.64 (t, 1H, CH, J= 5.6 Hz), 4.78 (d, 2H, N-CH_2, J= 5.82 Hz), 5.38 (m, 2H, vinyl protons), 5.96 (m, 1H, vinyl protons), 7.36 (s, 1H, 4-H), 9.32 (s, 1H, 2-H); analysis for $C_{11}H_{14}N_3O_3I$ (363.16), calcd., C, 36.38; H, 3.89; N, 11.57; ,I 34.94; found, C, 36.49; H, 3.95; N, 11.50; I, 34.84 ; $[\alpha]_D^{25}$ +29° (c=1.72, H_2O); MS(CI-NH_3) m/z 236 (M+1-HI).

(S)-2-Benzyl-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo[1,5-c]pyrimidinium bromide (5i). Yield: 74% [acetone-ether]; mp 199-203 °C; ^{1}H NMR (D_2O) δ 3.33 (d, 2H, CH_2, J=5.7 Hz), 3.65 (s, 3H, OCH_3), 4.60 (t, 1H, CH, J= 5.7 Hz), 5.35 (s, 2H, N-CH_2), 7.35 (m, 6H, 4-H & aryl protons) 9.34 (s, 1H, 2-H); analysis for $C_{15}H_{16}N_3O_3Br$ (366.22), calcd., C, 49.2; H, 4.4; N, 11.47; Br, 21.82; found, C, 49.1; H, 4.35; N, 11.5; Br, 21.50; $[\alpha]_D^{25}$ +6.4° (c=2.22, H_2O); MS(CI-NH_3) m/z 286 (M+1-HBr).

(S)-2-Ethoxycarbonylmethyl-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo-[1,5-c]pyrimidinium bromide (5g). Yield: 75%, [acetone]; mp 160-165 °C; ^{1}H NMR (D_2O) δ 1.17 (t, 3H, CH_3, J= 7.1 Hz), 3.40 (d, 2H, CH_2, J= 5.8 Hz), 3.67 (s, 3H, CO_2CH_3), 4.19 (q, 2H, CO_2CH_2, J= 7.0 Hz), 4.64 (m, 1H, CH), 5.13 (s, 2H, N-CH_2), 7.40 (s, 1H, 4-H), 9.39 (s, 1H, 2-H); analysis for $C_{12}H_{16}N_3O_5Br$ (362.18) : calcd., C, 39.8; H, 4.45; N, 11.6; Br, 22.06, found, C, 39.64; H, 4.49; N, 11.51; Br, 21.94; MS(CI-NH_3) m/z 282 (M+1-HBr).

(S)-5,6,7,8-Tetrahydro-7-(methoxycarbonyl)-2-(2′-oxo-2′-phenylethyl)-5-oxoimidazo-[1,5-c]pyrimidinium bromide (5l). Yield: 95% [methanol]; mp 222-223 °C [lit[13] mp 223-224 °C]; ^{1}H NMR (DMSO-d_6) δ 3.45 (m, 2H, CH_2), 3.69 (s, 3H, OCH_3), 4.70 (m, 1H, CH), 6.09 (s, 2H, N-CH_2), 7.64 (m, 3H, 4-H, phenyl protons), 7.77 (m, 1H, phenyl proton), 8.04 (m, 2H, phenyl protons), 9.62 (d, 1H, NH, J= 4.2 Hz), 9.73 (s, 1H, 2-H); analysis for $C_{16}H_{16}N_3O_4Br$ (394.23), calcd., C, 48.75; H, 4.09; N, 10.66; Br, 20.27; found, C, 48.61; H, 4.01; N, 10.64; Br, 20.19; $[\alpha]_D^{25}$ +32.9° (c=2.24, H_2O); MS(CI-NH_3) m/z 314 (M+1-HBr).

2-Allyl-5,6,7,8-tetrahydro-5-oxoimidazo[1,5-c]pyrimidinium iodide (6c). Yield: 56% [acetone]; mp 180 °C; ^{1}H NMR (D_2O) δ 3.01 (t, 2H, CH_2, J= 6 Hz), 3.53 (t, 2H, CH_2, J= 6.6 Hz), 4.78 (d, 2H, N-CH_2, J= 7.2 Hz), 5.37 (m, 2H, vinyl H), 5.97 (m, 1H, vinyl H), 7.3 (s, 1H, 2-H), 9.34 (s, 1H, 4-H); analysis for $C_9H_{12}N_3OI$ (305.11) calcd., C, 35.43; H, 3.96; N, 13.77; I, 41.59; found, C, 35.55; H, 3.92; N, 13.79; I, 41.48; MS(CI-NH_3) m/z 178 (M+1-HI).

2-Isopropyl-5,6,7,8-tetrahydro-5-oxoimidazo[1,5-c]pyrimidinium iodide (6d). Yield: 77% [acetone]; mp 225-227 °C; ^{1}H NMR (DMSO-d_6) δ 0.48 (d, 6H, 2 x CH_3, J= 6.7 Hz), 3.0 (t, 2H, CH_2, J= 6.3 Hz), 3.31 (s, 3H, OCH_3), 3.46 (m, 2H, CH_2), 4.70 (m, 1H, N-CH), 7.80 (s, 1H, 4-H), 9.01 (bs, 1H, NH), 9.75 (s, 1H, 2-H);

analysis for $C_9H_{14}N_3OI$ (307.14) calcd., C, 35.2; H, 4.59; N, 13.68; I 41.32; found, C, 35.07; H, 4.71; N, 13.61; I, 43.26; MS(CI-NH_3) m/z 180 (M+1-HI).

2-Ethoxycarbonylmethyl-5,6,7,8-tetrahydro-5-oxoimidazo[1,5-c]pyrimidinium bromide (6g). Yield: 77% [acetone]; mp 177-178 °C; ^{1}H NMR (D_2O) δ 1.17 (t, 3H, J= 7.1 Hz), 3.02 (t, 2H, J= 6.3 Hz), 3.53 (t, 2H, J= 6.6 Hz), 4.19 (q, 2H, J= 7.3 Hz), 5.11 (s, 2H), 7.33 (s, 1H), 9.28 (s, 1H); analysis for $C_{10}H_{14}N_3O_3Br$+0.3 H_2O (309.55) calcd, C, 38.8; H, 4.74; N, 13.51; Br, 25.81; found, C, 38.68; H, 4.78; N, 13.55; Br, 25.72; MS(CI-NH_3): m/z 224 (M+1-HBr).

General method for the synthesis of 9 or 10. To a solution of **5** or **6** (1 mmol) in the appropriate alcohol (10 mL) was added diisopropylethylamine (2 mmol) and the solution was heated at reflux for 48-120 h under argon. The solvent was removed *in vacuo* and the residue dissolved in methylene chloride. The solution was washed with water (2 x 15 mL) , dried over Na_2SO_4 and concentrated *in vacuo* to afford an oil which was purified by column chromatography on silica gel.

N-α-(Methoxycarbonyl)-1-methyl-L-histidine methyl ester (9a, R_2 = CH_3). Yield: 80%; mp 75-76 °C; ^{1}H NMR ($CDCl_3$) δ 3.02 (m, 2H, CH_2), 3.60 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 4.55 (m, 1H, CH), 6.22 (bd, 1H, NH), 6.62 (s, 1H, 4H), 7.31 (s, 1H, 2H); MS(CI-NH_3) m/z 242 (M+1); exact mass : calcd 241.1062, found 241.1065; analysis for $C_{10}H_{15}N_3O_4$ (241.24), calcd., C, 49.79; H, 6.27; N, 17.42; found , C, 49.68; H, 6.31; N, 17.51.

N-α-(Ethoxycarbonyl)-1-ethyl-L-histidine methyl ester (9b, R_2 = C_2H_5). Yield: 72%, oil; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3H, CH_3, J= 6.2 Hz), 1.39 (t, 3H, CH_3, J= 7.32 Hz), 3.02 (m, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.89 (q, 2H, OCH_2, J= 15.3 Hz), 4.08 (q, 2H, N-CH_2, J= 12 Hz), 4.55 (m, 1H, CH), 6.15 (bd, 1H, NH), 6.66 (s, 1H, 4-H), 7.38 (s, 1H, 2-H); ^{13}C NMR ($CDCl_3$) δ 14.5, 16.14, 30.0, 41.65, 52.02, 53.81, 60.76, 115.8, 136.06, 137.15, 156.06, 172.05; MS(CI-NH_3) m/z 270 (M+1); exact mass : calcd 269.1375, found 269.1373.

N-α-(Ethoxycarbonyl)-1-isopropyl-L-histidine methyl ester (9d, R_2 = C_2H_5). Yield: 90%, oil; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, CH_3, J= 7.1 Hz), 1.39 (d, 6H, 2 x CH_3, J= 6.8 Hz), 3.00 (m, 2H, CH_2), 3.64 (s, 3H, OCH_3), 4.05 (q, 2H, OCH_2, J= 7.1 Hz), 4.21 (m, 1H, N-CH), 4.52 (m, 1H, CH), 6.19 (bd, 1H, NH), 6.67 (s, 1H, 4-H), 7.38 (s, 1H, 2-H); ^{13}C NMR ($CDCl_3$) δ 14.55, 23.61, 30.13, 49.05, 52.03, 53.91, 60.79, 114.09, 134.73, 137.03, 156.11, 172.12; MS(CI-NH_3) m/z 284 (M+1); exact mass, calcd 283.1532, found 283.1536.

N-α -(tert-Butoxycarbonyl)-1-(sec-butyl)-L-histidine methyl ester (9e, R_2 = $C(CH_3)_3$). Yield: 43%, oil; ^{1}H NMR ($CDCl_3$) δ 0.75 (m, 5H, CH_2 & CH_3), 1.40 (s, 9H, *tert*-butyl), 1.66 (m, 2H, CH_2), 2.98 (m, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.92 (m, 1H, N-CH), 4.50 (m, 1H, CH), 5.93 (m, 1H, NH), 6.63 (s, 1H, 4-H), 7.34 (s, 1H, 2-H); ^{13}C NMR ($CDCl_3$) δ 10.5, 21.0, 24.08, 25.03, 25.08, 51.91, 53.59, 55.1, 79.34, 114.16, 135.49, 137.5, 160.18, 174.05; MS(CI-NH_3) m/z 326(M+1); exact mass, calcd 325.2001, found 325.1990.

N-α -(Methoxycarbonyl)-1-benzyl-L-histidine methyl ester (9i, R_2 = CH_3). Yield: 78%; mp: 97-98 °C; ^{1}H NMR ($CDCl_3$) δ 3.05 (m, 2H, CH_2), 3.64 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 4.60 (m, 1H, CH), 5.05 (s, 2H, N-CH_2), 6.30 (bd, 1H, NH), 6.65 (s, 1H, 4-H), 7.11 (m, 2H, aryl protons), 7.33 (m, 3H, aryl protons), 7.50 (s, 1H, 2-H); MS(CI-NH_3) m/z 318 (M+1); analysis for $C_{16}H_{19}N_3O_4$ (317.34) , calcd., C, 60.56; H, 6.03; N, 13.24; found, C, 60.57; H, 6.10; N, 13.18.

N-α -(Benzyloxycarbonyl)-1-(4-methoxybenzyl)-L-histidine methyl ester (9j, R_2 = $CH_2C_6H_5$). Yield: 61%; mp 72-73 °C; ^{1}H NMR ($CDCl_3$) δ 2.94 (m, 2H, CH_2), 3.55 (s, 3H, OCH_3), 3.68 (s, 3H, CO_2CH_3), 4.48 (m, 1H, CH), 4.75 (s, 2H, CH_2), 5.00 (s, 2H, CH_2), 6.1 (d, 1H, NH, J=12 Hz), 6.52 (s, 1H, 4-H), 6.78 (m, 2H, aromatic protons), 6.95 (m, 2H, aromatic protons), 7.25 (m, 5H, aromatic protons), 7.32 (s, 1H, 2-H); analysis for $C_{23}H_{25}N_3O_5$ (423.47), calcd., C, 65.24; H, 5.9; N, 9.92; found, C, 65.31; H, 5.95; N, 9.94; MS(CI-NH_3) m/z 424(M+1).

N-α -(Methoxycarbonyl)-1-methylhistamine (10a, R_2 = CH_3)[17]. Yield: 92%; mp 101-102 °C; ^{1}H NMR ($CDCl_3$) δ 2.73 (t, 2H, CH_2, J= 6.4 Hz), 3.46 (m, 2H, CH_2), 3.63 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 6.65 (s, 1H, 4-H), 7.34 (s, 1H, 2-H); MS(CI-NH_3) m/z 184(M+1); analysis for $C_8H_{13}N_3O_2$ (183.21), calcd., C, 52.45; H, 7.15; N, 22.9; found, C, 52.3; H, 7.13; N, 22.76.

N-α -(Ethoxycarbonyl)-1-methylhistamine (10a, R_2 = C_2H_5)[17]. Yield: 55%; mp 97-98 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3, J= 7.05 Hz), 2.73 (t, 2H, CH_2, J= 6.3 Hz), 3.46 (m, 2H, CH_2), 3.63 (s, 3H, CH_3), 4.10 (q, 2H, CH_2, J= 7.05, 14.2 Hz), 6.66 (s, 1H, 4-H), 7.34 (s, 1H, 2-H); MS (CI-NH_3) m/z 198 (M+1); analysis for $C_9H_{15}N_3O_2$ (197.23), calcd., C, 54.81; H, 7.67; N, 21.3; found, C, 54.82; H, 7.62; N, 21.21.

General method for the synthesis of 1-alkyl-L-histidines (7) and 1-alkylhistamines (8). A solution of **5** or **6** in *6N* HCl was refluxed for 12-24 h. The solvent was evaporated *in vacuo* to afford the dihydrochloride of the 1-alkylhistamine or monohydrochloride salt of the 1-alkyl-L-histidine. A solution of the 1-alkyl-L-histidine hydrochloride in water was applied to an ion-exchange column (Dowex 50 X 2-200, H^+ form). The column was eluted with water until the eluant was neutral to pH paper. The amino acid was then eluted with 10% NH_4OH. Evaporation of solvent gave the free crystalline amino acid.[18] The dihydrochloride salts of the 1-alkylhistamines were obtained directly by evaporation of the acid hydrolysis solutions.

1-Methyl-L-histidine (7a). Yield: 99%; mp 248-250 °C (dec) [lit[11] mp 246-248 °C (dec)]; ^{1}H NMR (D_2O) δ 2.98 (m, 2H, CH_2), 3.54 (s, 3H, N-CH_3), 3.80 (m, 1H, α-CH), 6.83 (s, 1H, 4-H), 7.44 (s, 1H, 2-H); analysis for $C_7H_{11}N_3O_2$+0.3H_2O (174.59), calcd., C, 48.15; H, 6.69; N, 24.06; found : C, 7.99; H, 6.67; N, 24.27; FABMS : 170 (M+1); exact mass : calcd. 169.1846, found, 169.0854; $[\alpha]_D^{25}$ -27.4° (c= 2.8, H_2O) [lit[11] $[\alpha]_D^{25}$ -24.7° (c= 2.0, H_2O)].

1-Ethyl-L-histidine (7b). Yield: 90%; mp 210-212 °C (dec); ^{1}H NMR (D_2O) δ 1.27 (t, 3H, CH_3, J= 7.56 Hz), 3.00 (m, 2H, CH_2), 3.87 (m, 3H, α-CH and N-CH_2), 6.93 (s, 1H, 4-H), 7.54 (s, 1H, 2-H); analysis for $C_8H_{13}N_3O_2$+0.25 H_2O (186.81), calcd., C, 51.43; H, 7.22; N, 22.49; found, C, 51.4;, H, 7.25; N, 22.39; $[\alpha]_D^{25}$ -17.8° (c=1.65, H_2O).

1-Allyl-L-histidine (7c). Yield: 74%; mp 238-240 °C (dec); ^{1}H NMR (D_2O) δ 2.97 (m, 2H, CH_2), 3.82 (m, 1H, α-CH), 4.47 (d, 2H, N-CH_2, J= 4.9 Hz), 5.10 (m, 2H, allyl protons), 5.99 (m, 1H, allyl proton), 6.89 (s, 1H, 4-H), 7.51 (s, 1H, 2-H); analysis for $C_9H_{13}N_3O_2$+0.9H_2O (211.44), calcd., C, 51.12; H, 7.05; N, 19.87; found : C, 51.11; H, 6.74; N, 19.61; $[\alpha]_D^{25}$ -17.9° (c=1.2, H_2O).

1-Isopropyl-L-histidine (7d). Yield: 94%; mp 200-202 °C (dec); ^{1}H NMR (D_2O) δ 1.31 (d, 6H, 2 x CH_3, J= 6.84), 3.00 (m, 2H, CH_2), 3.82 (m, 1H, α-CH), 4.27 (M, 1H, CH), 6.98 (S, 1H, 4-H), 7.59 (S, 1H, 2-H); analysis for $C_9H_{15}N_3O_2$+1.3 H_2O (220.66), calcd, C, 48.98; H, 8.04; N, 19.04; found, C, 49.21; H, 7.84; N, 18.74; $[\alpha]_D^{25}$ -27.7° (c=1.1, H_2O).

1-sec-Butyl-L-histidine (7e). Yield: 70%; mp 190-193 °C (dec); ^{1}H NMR (D_2O) δ .63 (t, 3H, CH_3, J= 7.26 Hz), 1.31 (d, 3H, CH_3, J= 6.84 Hz), 1.62 (m, 2H, CH_2), 2.95 (m, 2H, CH_2), 3.77 (m, 1H, α-CH), 4.01 (m, 1H, N-CH), 6.95 (s, 1H, 4-H), 7.56 (s, 1H, 2-H); analysis for $C_{10}H_{17}N_3O_2$+1.2 H_2O (247.30), calcd., C, 50.75; H, 8.64; N, 16.99; found : C, 50.61; H, 7.63; N, 16.67; $[\alpha]_D^{25}$ -30° (c=1.2, H_2O).

1-Carboxymethyl-L-histidine (7h). Yield: 93%; mp 185-189 °C; ^{1}H NMR (D_2O) δ 2.89 (m, 1H, CH), 3.12 (m, 1H, CH), 3.84 (m, 1H, CH), 4.51 (s, 2H, N-CH_2), 6.91 (s, 1H, 4-H), 7.60 (s, 1H, 2-H); analysis for $C_8H_{11}N_3O_4$+1.3 H_2O (236.62), calcd., C, 40.61; H, 5.79; N, 17.75; found, C, 40.61; H, 6.07; N17.92; $[\alpha]_D^{25}$ -32° (c=1.7, H_2O).

1-Benzyl-L-Histidine (7i). Yield: 83%; mp 230-232 °C (dec); ^{1}H NMR (D_2O) δ 3.00 (m, 2H, CH_2), 3.82 (m, 1H, α-CH), 5.08 (s, 2H, N-CH_2), 6.95 (s, 1H, 4-H), 7.28 (m, 5H, aryl protons), 7.65 (s, 1H, 2-H); analysis for $C_{13}H_{15}N_3O_2$+1.2 H_2O (266.90), calcd., C, 58.5; H, 6.57; N, 15.70; found, C, 58.34; H, 6.4; N, 15.7; $[\alpha]_D^{25}$ +14.03° (c=1.3, *N* HCl).

1-(4-Methoxybenzyl)-L-histidine (7j). Yield: 90%; mp 220-224 °C (dec); ^{1}H NMR (DMSO-d_6) δ 2.90 (m, 2H, CH_2), 3.76 (m, 1H, α-CH),3.73 (s, 3H, OCH_3), 5.04 (s, 2H, N-CH_2), 6.98 (m, 3H, 4-H and aromatic protons), 7.08 (d, 2H, aromatic protons), 7.69 (s, 1H, 2-H); analysis for $C_{14}H_{17}N_3O_3$+1.8 H_2O (307.74), calcd., C, 54.64; H, 6.74; N, 13.65; found, C, 54.42; H, 6.74; N, 13.54; $[\alpha]_D^{25}$ +13.75° (c=1.6, *N* HCl).

1-(2-Oxo-2-phenylethyl)-L-histidine (7l). Yield: 87%; mp 205 °C (dec); ^{1}H NMR (DMSO-d_6) δ 2.70 (m,1H), 3.07 (m, 1H), 3.37 (m, 1H, α-CH), 5.70 (s, 2H, N-CH_2), 6.95 (s, 1H, 4-H), 7.59 (m, 3H, 2-H and Ar-H), 7.72 (m, 1H, Ar-H), 8.03 (m, 2H, Ar-H); analysis for $C_{14}H_{15}N_3O_3$+H_2O (291.31), calcd., C, 57.72; H, 5.88; N, 14.42; found, C, 57.79; H, 5.88; N, 14.37; $[\alpha]_D^{25}$ -1.1° (c=1.2, *N* HCl).

1-Allyl histamine.2HCl (8c). Yield: 88%; mp 185-189 °C; ^{1}H NMR (D_2O) δ 3.02 (t, 2H, CH_2, J= 7.4 Hz), 3.22 (t, 2H, CH_2, J= 7.6 Hz), 4.69 (d, 2H, N-CH_2, J= 6.93 Hz), 5.30 (m, 2H, allyl protons), 5.94 (m, 1H, allyl protons), 7.31 (s, 1H, 4-H), 8.59 (s, 1H, 2-H); ^{13}C NMR (CD_3OD) δ 24.94, 39.79, 51.70, 120.29, 120.67, 133.36, 134.09, 137.52; analysis for $C_8H_{13}N_3$.2HCl+H_2O (242.15), calcd., C, 39.68; H, 7.08; N, 17.35; Cl, 29.28; found, C, 39.40; H, 6.94; N, 17.30; Cl, 29.08; MS(CI-NH_3) m/z 152 (M+1).

1-Isopropyl histamine.2HCl (8d). Yield: 83%; mp 205-207 °C; ^{1}H NMR (D_2O) δ 1.41 (d, 6H, 2 x CH_3, J= 6.63 Hz), 3.01 (t, 2H, CH_2, J= 7.5 Hz), 3.21 (t, 2H, CH_2, J= 7.4 Hz), 4.51 (m, 1H, CH), 7.40 (s, 1H, 4-H), 8.61 (s, 1H, 2-H); ^{13}C NMR (CD_3OD) δ 23.11, 24.12, 39.27, 53.96, 119.43, 131.68, 135.36; analysis for $C_8H_{15}N_3$.2HCl+H_2O (244.17), calcd, C, 39.35; H, 7.84; N, 17.21; Cl, 29.04; found, C, 39.55; H, 7.98; N, 17.30; Cl, 29.20; MS(CI-NH_3) m/z 154 (M+1).

1-Carboxymethyl histamine. 2HCl (8h). Yield: 98%; mp 176-180 °C; ^{1}H-NMR (D_2O) δ 3.03 (t, 2H,CH_2, J= 7.05 Hz), 3.23 (t, 2H, CH_2, J= 7.26 Hz), 4.90 (s, 2H, CH_2), 7.32 (s, 1H, 4-H), 8.64 (s, 1H, 2-H); analysis for $C_7H_{13}N_3O_2$.2HCl+2.3 H_2O (285.56), calcd., C, 29.44; H, 6.91; N, 14.71; Cl, 24.83; found, C, 29.23; H, 4.53; N, 14.63; Cl, 24.46; MS(CI-NH_3) m/z 170 (M+1).

General synthesis of N-α-Carboalkoxy-1-alkyl-L-histidines (11). A stirred solution of fully protected 1-alkyl-L-histidine **9** (0.07 mmol) in CH_3CN (5 mL) was cooled to 0 °C, *N* NaOH (1 mL) was added and stirring was continued for 30 minutes. Solvent was removed and the residue was applied to an ion-exchange column (Dowex 50 X 2-200, H^+ form). The column was eluted with water until neutral to pH paper. The product was eluted with 15% NH_4OH.

N-α-Carbomethoxy-1-methyl-L-histidine (11a, $R_2 = CH_3$). Yield: 98%; mp 140-142 °C (dec), ^{1}H NMR (D_2O) δ 2.79 (m, 1H, CH), 2.96 (m, 1H, CH), 3.48 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 4.07 (m, 1H, CH), 6.89 (s, 1H, 4-H), 7.82 (s, 1H, 2-H); analysis for $C_9H_{13}N_3O_4$+0.8 H_2O (241.63), calcd., C, 44.81; H, 6.10; N, 17.39; found, C, 44.81; H, 6.45; N, 17.16; $[\alpha]_D^{25}$ +31.2° (c=4.3, CH_3OH).

N-α-Carbomethoxy-1-benzyl-L-histidine (11i, $R_2 = CH_3$). Yield: 97%; mp 214-216 °C; ^{1}H NMR (D_2O) δ 2.76 (m, 1H, CH), 2.99 (m, 1H, CH), 3.41 (s, 3H, CO_2CH_3), 4.06 (m, 1H, CH), 5.14 (s, 2H, N-CH_2), 7.0 (s, 1H, 4-H), 7.21 (m, 2H, aromatic protons), 7.30 (m, 3H, aromatic protons), 8.14 (s, 1H, 2-H); analysis for $C_{15}H_{17}N_3O_4$ (303.32), calcd., C, 59.4; H, 5.65; N, 13.85; found, C, 59.57; H, 5.54; N, 13.97; $[\alpha]_D^{25}$ +15.5° (c=1.2, H_2O).

***N*-α-Carbobenzyloxy-1-(4-methoxybenzyl)-L-histidine (11j, $R_2 = CH_2C_6H_5$).** Yield: 95%; mp 209-210 °C; ^{1}H NMR (DMSO-d_6) δ 2.80 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 4.21 (m, 1H, CH), 4.98 (bd, 2H, CH_2), 5.03 (s, 2H, N-CH_2), 6.88 (m, 2H, 4-H & aromatic proton), 7.18 (d, 2H, aromatic proton, J= 8.46 Hz), 7.33 (m, 5H, aromatic proton), 7.49 (d, 1H, J= 8 Hz, aromatic proton), 7.65 (s, 1H, 2-H); analysis for $C_{22}H_{23}N_3O_5$ (409.44), calcd., C, 64.54; H, 5.66; N, 10.26; found, C, 64.38; H, 5.71; N, 10.22; $[\alpha]_D^{25}$ -16.4° (c=0.5, *N* HCl).

Synthesis of 1-(4-Hydroxybenzyl)-L-histidine (7k). A solution of **9i** (1 mmol) in 48% HBr (15 mL) was refluxed for 48 h. All solvent was removed and the residue was applied to an ion-exchange column (Dowex 50 x 2-200, H^+ form). The column was eluted with water until neutral to pH paper. The amino acid was eluted with 10% NH_4OH; the solvent was removed *in vacuo* to afford **7k**. Yield: 89%; mp 214-216 °C (dec); ^{1}H NMR (DMSO-d_6) δ 2.64 (m, 1H, CH), 2.99 (m, 1H, CH), 3.33 (m, 1H, α-CH), 4.97 (s, 1H, N-CH_2), 6.72 (d, 2H, aromatic protons), 6.94 (s, 1H, 4-H), 7.10 (d, 2H, aromatic protons), 7.66 (s, 1H, 2-H); analysis for $C_{13}H_{15}N_3O_2$+2H_2O (264.88), calcd., C, 58.94; H, 5.86; N, 15.86; found, C, 58.7; H, 5.83; N, 15.76; $[\alpha]_D^{25}$ +10.36° (c=1.25, *N* HCl).

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