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Regiospecific Alkylation of Histidine and Histamine at N-1 $(\tau)^1$

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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 antimalarials² and as polypeptide components³ 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) derivatives⁵. 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 halonitrobenzenes⁶ and triarylmethyl halides⁷ 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 benzpyrene⁸, riboflavin⁹ and FAD¹⁰ 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 Beyerman¹¹ 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 6a¹². Thus, acylation at N-3 does not reduce the basicity or nucleophilicity of N-1 enough to impair SN2 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	
Identities of \mathbf{R}_1 in Compounds 5-11	
a) CH ₃	g) CH ₂ CO ₂ C ₂ H ₅
b) C ₂ H ₅	h) CH ₂ CO ₂ H
c) CH ₂ CH=CH ₂	i) CH ₂ C ₆ H ₅
d) CH(CH ₃) ₂	j) CH ₂ C ₆ H ₄ -4-OCH ₃
e) CH(CH ₃)(C ₂ H ₅)	k) CH ₂ C ₆ H ₄ -4-OH
f) C(CH ₃) ₃	I) CH ₂ COC ₆ H 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.



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 (R₁= H) on attempted ring opening to 9c.



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 ¹³C 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% CH₃OH in CHCl₃. 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 NaHCO₃. The aqueous solution was extracted with dichloromethane (8 x 200 mL), the combined extracts were dried (Na₂SO₄) 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, CH₃OH) (lit¹¹ mp 156-157 °C, $[\alpha]_D^{25}$ +59° (c=1.1, CH₃OH); 4, mp 220-221 °C (lit¹² mp 219-220 °C).

General procedure for the synthesis of (+)-(7S)-2-alkyl-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5oxoimidazo[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 1,2diethoxyethane 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) [lit¹¹ mp 162 °C (dec)]; ¹H NMR (D₂O) δ 3.43 (d, 2H, CH₂, J= 5.6 Hz), 3.70 (s, 3H, OCH₃), 3.90 (s, 3H, N-CH₃), 4.68 (t, 1H, CH, J= 5.6 Hz), 7.35 (s, 1H, 4-H), 9.30 (s, 1H, 2-H); analysis for C₉H₁₂N₃O₃I (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; [α]_D²⁵ +45.2° (c=1.7, H₂O) [lit¹¹ + 46° (c= 0.7, H₂O)]; MS(CI-NH₃) m/z 210 (M+1-HI).

(S)-2-Ethyl-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo[1,5-c]pyrimidinium iodide (Sb). Yield: 97% [methanol-ether]; mp 146.5-147 °C (dec) [lit¹¹ mp 146 °C (dec)]; ¹H NMR (D₂O) δ 1.52 (t, 3H, CH₃, J= 7.4 Hz), 3.46 (d, 2H, CH₂, J= 5.8 Hz), 3.77 (s, 3H, OCH₃), 4.31 (q, 2H, N-CH₂, 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 C₁₀H₁₄N₃O₃I (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; [α]_D²⁵ +37.3° (c=1.66, H₂O) [lit¹¹ +35° (c = 2.3, H₂O)]; MS(CI-NH₃) 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); ¹H NMR (D₂O) δ 3.39 (m, 2H, CH₂), 3.68 (s, 3H, OCH₃), 4.64 (t, 1H, CH, J= 5.6 Hz), 4.78 (d, 2H, N-CH₂, 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 C₁₁H₁₄N₃O₃I (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, H₂O); MS(CI-NH₃) 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; ¹H NMR (D₂O) δ 3.33 (d, 2H, CH₂, J=5.7 Hz), 3.65 (s, 3H, OCH₃), 4.60 (t, 1H, CH, J= 5.7 Hz), 5.35 (s, 2H, N-CH₂), 7.35 (m, 6H, 4-H & aryl protons) 9.34 (s, 1H, 2-H); analysis for C₁₅H₁₆N₃O₃Br (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; [α]_D²⁵ +6.4° (c=2.22, H₂O); MS(CI-NH₃) m/z 286 (M+1-HBr).

(S)-2-Ethoxycarbonylmethyl-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo-[1,5-c]pyrimidinium bromide (Sg). Yield: 75%, [acetone]; mp 160-165 °C; ¹H NMR (D₂O) δ 1.17 (t, 3H, CH₃, J= 7.1 Hz), 3.40 (d, 2H, CH₂, J= 5.8 Hz), 3.67 (s, 3H, CO₂CH₃), 4.19 (q, 2H, CO₂CH₂, J= 7.0 Hz), 4.64 (m, 1H, CH), 5.13 (s, 2H, N-CH₂), 7.40 (s, 1H, 4-H), 9.39 (s, 1H, 2-H); analysis for C₁₂H₁₆N₃O₅Br (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-NH₃) 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 [lit¹³ mp 223-224 °C]; ¹H NMR (DMSO-d₆) δ 3.45 (m, 2H, CH₂), 3.69 (s, 3H, OCH₃), 4.70 (m, 1H, CH), 6.09 (s, 2H, N-CH₂), 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 C₁₆H₁₆N₃O₄Br (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; $[\alpha]_D^{2^5}$ +32.9° (c=2.24, H₂O); MS(CI-NH₃) 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; ¹H NMR (D₂O) δ 3.01 (t, 2H, CH₂, J= 6 Hz), 3.53 (t, 2H, CH₂, J= 6.6 Hz), 4.78 (d, 2H, N-CH₂, 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 C₉H₁₂N₃OI (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-NH₃) 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, ¹H NMR (DMSO-d₆) δ 0.48 (d, 6H, 2 x CH₃, J= 6.7 Hz), 3.0 (t, 2H, CH₂, J= 6.3 Hz), 3.31 (s, 3H, OCH₃), 3.46 (m, 2H, CH₂), 4.70 (m, 1H, N-CH), 7.80 (s, 1H, 4-H), 9.01 (bs, 1H, NH), 9.75 (s, 1H, 2-H);

2-Ethoxycarbonylmethyl-5,6,7,8-tetrahydro-5-oxoimidazo[1,5-c]pyrimidinium bromide (6g). Yield: 77% [acetone]; mp 177-178 °C; ¹H NMR (D₂O) 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 C₁₀H₁₄N₃O₃Br+0.3 H₂O (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-NH₃): 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; ¹H NMR (CDCl₃) δ 3.02 (m, 2H, CH₂), 3.60 (s, 3H, CH₃), 3.65 (s, 3H, CH₃), 3.69 (s, 3H, CH₃), 4.55 (m, 1H, CH), 6.22 (bd, 1H, NH), 6.62 (s, 1H, 4H), 7.31 (s, 1H, 2H); MS(CI-NH₃) m/z 242 (M+1); exact mass : calcd 241.1062, found 241.1065; analysis for C₁₀H₁₅N₃O₄ (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, $R_2 = C_2H_3$). Yield: 72%, oil; ¹H NMR (CDCl₃) δ 1.21 (t, 3H, CH₃, J= 6.2 Hz), 1.39 (t, 3H, CH₃, J= 7.32 Hz), 3.02 (m, 2H, CH₂), 3.68 (s, 3H, OCH₃), 3.89 (q, 2H, OCH₂, J= 15.3 Hz), 4.08 (q, 2H, N-CH₂, 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); ¹³C NMR (CDCl₃) 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-NH₃) m/z 270 (M+1); exact mass : calcd 269.1375, found 269.1373.

N- α -(*Ethoxycarbonyl*)-1-isopropyl-L-histidine methyl ester (9d, $R_2 = C_2H_3$). Yield: 90%, oil; ¹H NMR (CDCl₃) δ 1.28 (t, 3H, CH₃, J= 7.1 Hz), 1.39 (d, 6H, 2 x CH₃, J= 6.8 Hz), 3.00 (m, 2H, CH₂), 3.64 (s, 3H, OCH₃), 4.05 (q, 2H, OCH₂, 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); ¹³C NMR (CDCl₃) 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-NH₃) 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; ¹H NMR (CDCl₃) δ 0.75 (m, 5H, CH₂ & CH₃), 1.40 (s, 9H, tert-butyl), 1.66 (m, 2H, CH₂), 2.98 (m, 2H, CH₂), 3.66 (s, 3H, OCH₃), 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); ¹³C NMR (CDCl₃) 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-NH₃) 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; ¹H NMR (CDCl₃) δ 3.05 (m, 2H, CH₂), 3.64 (s, 3H, CH₃), 3.66 (s, 3H, CH₃), 4.60 (m, 1H, CH), 5.05 (s, 2H, N-CH₂), 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-NH₃) m/z 318 (M+1); analysis for C₁₆H₁₉N₃O₄ (317.34), calcd., C, 60.56; H, 6.03; N, 13.24; found, C, 60.57; H, 6.10; N, 13.18.

 $N-\alpha$ -(Benzyloxycarbonyl)-1-(4-methoxybenzyl)-L-histidine methyl ester (9j, $R_2 = CH_2C_6H_5$). Yield: 61%; mp 72-73 °C; ¹H NMR (CDCl₃) δ 2.94 (m, 2H, CH₂), 3.55 (s, 3H, OCH₃), 3.68 (s, 3H, CO₂CH₃), 4.48 (m, 1H, CH), 4.75 (s, 2H, CH₂), 5.00 (s, 2H, CH₂), 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 C₂₃H₂₅N₃O₅ (423.47), calcd., C, 65.24; H, 5.9; N, 9.92; found, C, 65.31; H, 5.95; N, 9.94; MS(CI-NH₃) m/z 424(M+1).

*N-\alpha -(Methoxycarbonyl)-1-methylhistamine (10a, R₂ = CH₃)*¹⁷. Yield: 92%; mp 101-102 °C; ¹H NMR (CDCl₃) δ 2.73 (t, 2H, CH₂, J= 6.4 Hz), 3.46 (m, 2H, CH₂), 3.63 (s, 3H, CH₃), 3.65 (s, 3H, CH₃), 6.65 (s, 1H, 4-H), 7.34 (s, 1H, 2-H); MS(CI-NH₃) m/z 184(M+1); analysis for C₈H₁₃N₃O₂ (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, $R_2 = C_2H_3$)¹⁷. Yield: 55%; mp 97-98 °C; ¹H NMR (CDCl₃) δ 1.23 (t, 3H, CH₃, J= 7.05 Hz), 2.73 (t, 2H, CH₂, J= 6.3 Hz), 3.46 (m, 2H, CH₂), 3.63 (s, 3H, CH₃), 4.10 (q, 2H, CH₂, J= 7.05, 14.2 Hz), 6.66 (s, 1H, 4-H), 7.34 (s, 1H, 2-H); MS (CI-NH₃) m/z 198 (M+1); analysis for C₉H₁₅N₃O₂ (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% NH₄OH. 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) [lit¹¹ mp 246-248 °C (dec)]; ¹H NMR (D₂O) δ 2.98 (m, 2H, CH₂), 3.54 (s, 3H, N-CH₃), 3.80 (m, 1H, α -CH), 6.83 (s, 1H, 4-H), 7.44 (s, 1H, 2-H); analysis for C₇H₁₁N₃O₂+0.3H₂O (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, H₂O) [lit¹¹ $[\alpha]_D^{25}$ -24.7° (c= 2.0, H₂O)].

1-Ethyl-L-histidine (7b). Yield: 90%; mp 210-212 °C (dec); ¹H NMR (D₂O) δ 1.27 (t, 3H, CH₃, J= 7.56 Hz), 3.00 (m, 2H, CH₂), 3.87 (m, 3H, α -CH and N-CH₂), 6.93 (s, 1H, 4-H), 7.54 (s, 1H, 2-H); analysis for C₈H₁₃N₃O₂+0.25 H₂O (186.81), calcd., C, 51.43; H, 7.22; N, 22.49; found, C, 51.4;, H, 7.25; N, 22.39; [α]_D²⁵ -17.8° (c=1.65, H₂O).

1-Allyl-L-histidine (7c). Yield: 74%; mp 238-240 °C (dec); ¹H NMR (D₂O) δ 2.97 (m, 2H, CH₂), 3.82 (m, 1H, α -CH), 4.47 (d, 2H, N-CH₂, 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 C₉H₁₃N₃O₂+0.9H₂O (211.44), calcd., C, 51.12; H, 7.05; N, 19.87; found : C, 51.11; H, 6.74; N, 19.61; [α]_D²⁵ -17.9° (c=1.2, H₂O).

1-Isopropyl-L-histidine (7d). Yield: 94%; mp 200-202 °C (dec); ¹H NMR (D₂O) δ 1.31 (d, 6H, 2 x CH₃, J= 6.84), 3.00 (m, 2H, CH₂), 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 C₉H₁₅N₃O₂+1.3 H₂O (220.66), calcd, C, 48.98; H, 8.04; N, 19.04; found, C, 49.21; H, 7.84; N, 18.74; [α]_D²⁵ -27.7° (c=1.1, H₂O).

1-sec-Butyl-L-histidine (7e). Yield: 70%; mp 190-193 °C (dec); ¹H NMR (D₂O) δ .63 (t, 3H, CH₃, J= 7.26 Hz), 1.31 (d, 3H, CH₃, J= 6.84 Hz), 1.62 (m, 2H, CH₂), 2.95 (m, 2H, CH₂), 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 C₁₀H₁₇N₃O₂+1.2 H₂O (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, H₂O).

1-Carboxymethyl-L-histidine (7h). Yield: 93%; mp 185-189 °C; ¹H NMR (D₂O) δ 2.89 (m, 1H, CH), 3.12 (m, 1H, CH), 3.84 (m, 1H, CH), 4.51 (s, 2H, N-CH₂), 6.91 (s, 1H, 4-H), 7.60 (s, 1H, 2-H); analysis for C₈H₁₁N₃O₄+1.3 H₂O (236.62), calcd., C, 40.61; H, 5.79; N, 17.75; found, C, 40.61; H, 6.07; N17.92; $[\alpha]_D^{25} - 32^\circ$ (c=1.7, H₂O).

1-Benzyl-L-Histidine (7i). Yield: 83%; mp 230-232 °C (dec); ¹H NMR (D₂O) δ 3.00 (m, 2H, CH₂), 3.82 (m, 1H, α -CH), 5.08 (s, 2H, N-CH₂), 6.95 (s, 1H, 4-H), 7.28 (m, 5H, aryl protons), 7.65 (s, 1H, 2-H); analysis for C₁₃H₁₅N₃O₂+1.2 H₂O (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); ¹H NMR (DMSO-d₆) δ 2.90 (m, 2H, CH₂), 3.76 (m, 1H, α -CH),3.73 (s, 3H, OCH₃), 5.04 (s, 2H, N-CH₂), 6.98 (m, 3H, 4-H and aromatic protons), 7.08 (d, 2H, aromatic protons), 7.69 (s, 1H, 2-H), analysis for C₁₄H₁₇N₃O₃+1.8 H₂O (307.74), calcd., C, 54.64; H, 6.74; N, 13.65; found, C, 54.42; H, 6.74; N, 13.54; [α]_D²⁵ +13.75° (c=1.6, *N* HCl).

1-(2-Oxo-2-phenylethyl)-L-histidine (7l). Yield: 87%; mp 205 °C (dec); ¹H NMR (DMSO-d₆) δ 2.70 (m,1H), 3.07 (m, 1H), 3.37 (m, 1H, α -CH), 5.70 (s, 2H, N-CH₂), 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 C₁₄H₁₅N₃O₃+H₂O (291.31), calcd., C, 57.72; H, 5.88; N, 14.42; found, C, 57.79; H, 5.88; N, 14.37; [α]_D²⁵ -1.1° (c=1.2, *N* HCl).

1-Allyl histamine.2HCl (8c). Yield: 88%; mp 185-189 °C; ¹H NMR (D₂O) δ 3.02 (t, 2H, CH₂, J= 7.4 Hz), 3.22 (t, 2H, CH₂, J= 7.6 Hz), 4.69 (d, 2H, N-CH₂, 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); ¹³C NMR (CD₃OD) δ 24.94, 39.79, 51.70, 120.29, 120.67, 133.36, 134.09, 137.52; analysis for C₈H₁₃N₃.2HCl+H₂O (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-NH₃) m/z 152 (M+1).

1-Isopropyl histamine.2HCl (8d). Yield: 83%; mp 205-207 °C; ¹H NMR (D₂O) δ 1.41 (d, 6H, 2 x CH₃, J= 6.63 Hz), 3.01 (t, 2H, CH₂, J= 7.5 Hz), 3.21 (t, 2H, CH₂, J= 7.4 Hz), 4.51 (m, 1H, CH), 7.40 (s, 1H, 4-H), 8.61 (s, 1H, 2-H); ¹³C NMR (CD₃OD) δ 23.11, 24.12, 39.27, 53.96, 119.43, 131.68, 135.36; analysis for C₈H₁₅N_{3.2}HCl+H₂O (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-NH₃) m/z 154 (M+1).

1-Carboxymethyl histamine. 2HCl (8h). Yield: 98%; mp 176-180 °C; ¹H-NMR (D₂O) δ 3.03 (t, 2H,CH₂, J= 7.05 Hz), 3.23 (t, 2H, CH₂, J= 7.26 Hz), 4.90 (s, 2H, CH₂), 7.32 (s, 1H, 4-H), 8.64 (s, 1H, 2-H); analysis for C₇H₁₃N₃O₂.2HCl+2.3 H₂O (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-NH₃) m/z 170 (M+1).

General synthesis of N- α -Carboalkoxy-1-alkyl-L-histidines (11). A stirred solution of fully protected 1alkyl-L-histidine 9 (0.07 mmol) in CH₃CN (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% NH₄OH.

N-\alpha-Carbomethoxy-1-methyl-L-histidine (11a, R₂ = CH₃). Yield: 98%; mp 140-142 °C (dec), ¹H NMR (D₂O) δ 2.79 (m, 1H, CH), 2.96 (m, 1H, CH), 3.48 (s, 3H, CH₃), 3.60 (s, 3H, CH₃), 4.07 (m, 1H, CH), 6.89 (s, 1H, 4-H), 7.82 (s, 1H, 2-H); analysis for C₉H₁₃N₃O₄+0.8 H₂O (241.63), calcd., C, 44.81; H, 6.10; N, 17.39; found, C, 44.81; H, 6.45; N, 17.16; [α]_D²⁵ +31.2° (c=4.3, CH₃OH).

N-α-Carbomethoxy-1-benzyl-L-histidine (11i, $R_2 = CH_3$). Yield: 97%; mp 214-216 °C; ¹H NMR (D₂O) δ 2.76 (m, 1H, CH), 2.99 (m, 1H, CH), 3.41 (s, 3H, CO₂CH₃), 4.06 (m, 1H, CH), 5.14 (s, 2H, N-CH₂), 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 C₁₅H₁₇N₃O₄ (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, H₂O).

N-α-Carbobenzyloxy-1-(4-methoxybenzyl)-L-histidine (11j, $R_2 = CH_2C_6H_3$). Yield: 95%; mp 209-210 °C; ¹H NMR (DMSO-d₆) δ 2.80 (m, 2H, CH₂), 3.71 (s, 3H, OCH₃), 4.21 (m, 1H, CH), 4.98 (bd, 2H, CH₂), 5.03 (s, 2H, N-CH₂), 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 C₂₂H₂₃N₃O₅ (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% NH₄OH; the solvent was removed *in vacuo* to afford 7k. Yield: 89%; mp 214-216 °C (dec); ¹H NMR (DMSO-d₆) δ 2.64 (m, 1H, CH), 2.99 (m, 1H, CH), 3.33 (m, 1H, α -CH), 4.97 (s, 1H, N-CH₂), 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 C₁₃H₁₅N₃O₂+2H₂O (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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