The Regiospecific Alkylation of Histidine Side Chains

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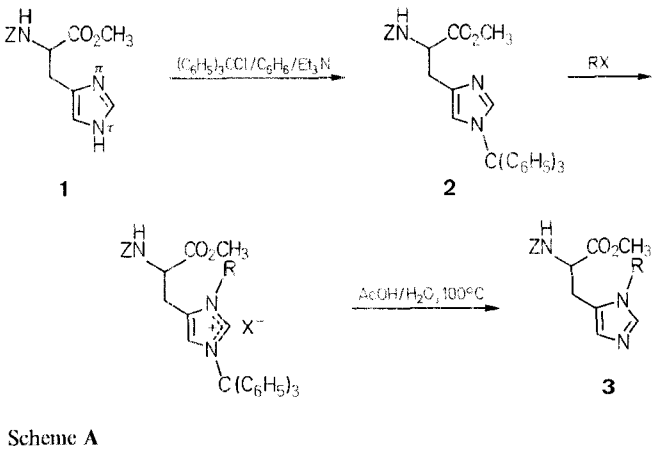
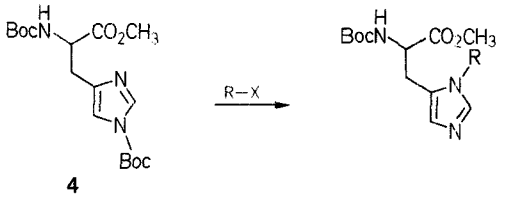
Further work on the regiospecific alkylation of histidine and imidazole derivatives is reported, including convenient preparations of $N(\alpha)$-benzyloxycarbonyl-$N(\pi)$-benzyl-L-histidine and $N(\alpha)$-benzyloxycarbonyl-$N(\pi)$-benzyloxymethyl-L-histidine, and a sequence of reactions enabling controlled exclusive alkylation of the least hindered *im*-nitrogen (tritylation, phenacylation, detritylation, alkylation, and finally dephenacylation with zinc/acetic acid) in 4(5)-alkylimidazoles.

A recent paper[1] on the regiospecific $N(\pi)$-alkylation[2] of histidine derivatives prompts us to report some elaborations of our own work[3,4] in this area. The procedures we have so far described follow Schemes **A** or **B**. Although it is the case, as recently pointed out,[1] that Scheme **A** has only been illustrated by a limited number of special cases employing rather reactive alkylating agents (such as chloromethyl ethers and phenacyl bromides), the implication that it lacks generality is misleading. More extended reaction times, and/or large excesses of alkylating agents are required with less powerful reagents, but the approach still works well and provides, for example, a convenient route to $N(\alpha)$-benzyloxycarbonyl-$N(\pi)$-benzyl-L-histidine.



Scheme **A**

The method of Scheme **B** is very convenient with $N(\alpha)$-*tert*-butoxycarbonyl protection because of the ease with which $N(\alpha)$, $N(\tau)$-bis-*tert*-butoxycarbonyl-L-histidine methyl ester **(4)** can be prepared and purified;[4] the demonstration[1] that triflates can be used in this strategy is a valuable extension.

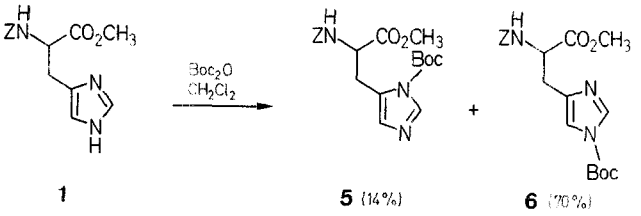


4

R = alkyl

Scheme **B**

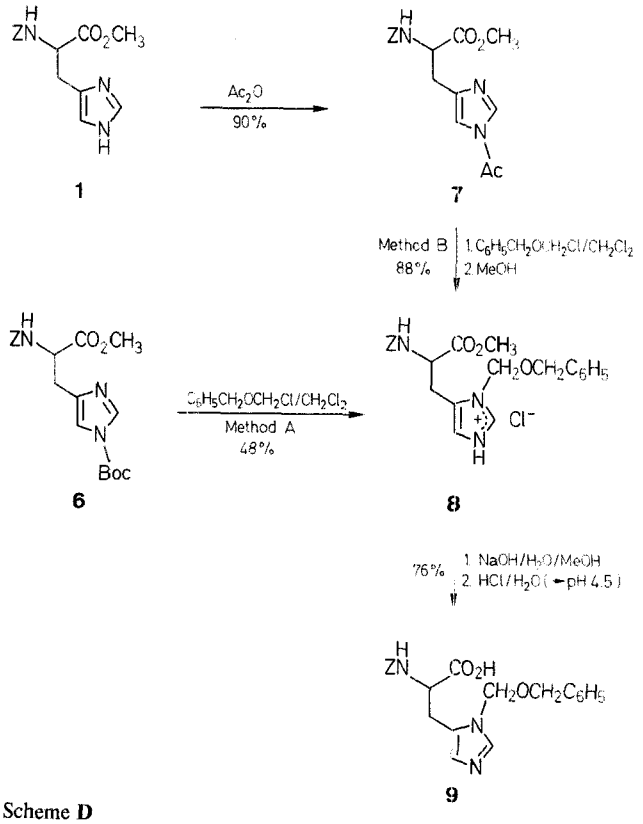
With $N(\alpha)$-benzyloxycarbonyl protection, on the other hand, the corresponding $N(\tau)$-*tert*-butoxycarbonyl derivative **6** is not so easily obtained pure: during its preparation using di-*tert*-butyl dicarbonate, the isomer **5** is also formed (Scheme **C**).[5]



1 **5** (14%) **6** (70%)

Scheme C

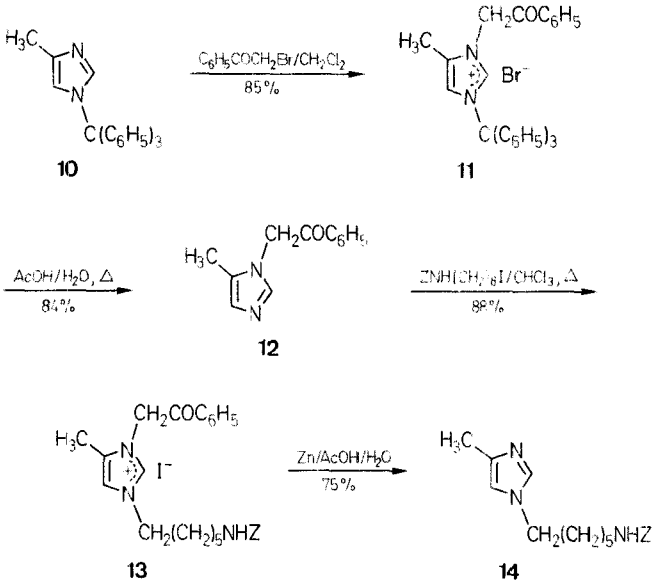
Methyl carbonochloridate, piperidine-1-carbonyl chloride, and mesitoyl chloride also give π-τ mixtures.[6] More reactive acid chlorides, in contrast, give single isomers.[6] Acetic anhydride behaves in the same way, giving a very high yield of the $N(\tau)$-derivative.[7] This is probably a matter of thermodynamic control: at any rate, all our efforts[6] to prepare the $N(\pi)$-acetyl isomer by roundabout means gave only the $N(\tau)$-derivative.[7] This compound reacts smoothly with benzyl chloromethyl ether and allows simple access to $N(\alpha)$-benzyloxycarbonyl-$N(\pi)$-benzyloxymethyl-L-histidine **(9)** as shown in Scheme **D**.[8]



1 **7** **6** **8** **9**

Scheme **D**

We are aware of only one example of regiospecific preparation of an $N(\tau)$-alkylhistidine derivative, via the cyclic urea with a link between $N(\alpha)$ and $N(\pi)$,[9] an approach which is not appropriate when an $N(\alpha)$-alkoxycarbonyl group is required to be in place. For many simple cases, the random alkylation of unmodified side chains is adequate, because the $N(\tau)$-alkylation product always predominates. But the necessary separations are sometimes difficult, and the uncontrolled approach is quite inappropriate for complicated cases. Various strategies for imposing control can be envisaged: we have recently established one by the model conversions shown in Scheme **E**. Preliminary results show that these tactics, although circuitous, are nevertheless superior to haphazard alkylation for the introduction of protected aminoalkyl groups at histidine $N(\tau)$-positions.



10 **11** **12** **13** **14**

Scheme **E**

Organic extracts were dried with commercially dried $MgSO_4$ and evaporated under reduced pressure below 40 °C. Melting points were determined on a Kofler hot-stage apparatus. Optical rotations were determined on a Perkin-Elmer 241 automatic polarimeter in a 1 dm cell. Mass spectra were measured on a V.G. micromass ZAB 1F mass spectrometer. ^{1}H-NMR spectra were recorded on a Bruker WH 300 spectrometer operating at 300 MHz. Nuclear Overhauser enhancements (NOE's) were obtained as described[10] previously.

All compounds discussed in this paper were obtained in a chromatographically homogeneous state.

$N(\alpha)$-Benzyloxycarbonyl-$N(\pi)$-benzyl-L-histidine Methyl Ester (3: R = $C_6H_5CH_2$):

Benzyl bromide (6 mL, 50.5 mmol) is added to $N(\alpha)$-benzyloxycarbonyl-$N(\tau)$-triphenylmethyl-L-histidine methyl ester[3] (**2**; 2.10 g, 3.85 mmol). Chloroform (3 mL) is added to make the solution homogeneous. The solution is set aside for 3 days at room temperature. The $CHCl_3$ is evaporated and the residue dissolved in 50% AcOH (40 mL). This solution is stirred for 15 min at 100 °C, cooled, washed with Et_2O (50 mL), and extracted with $CHCl_3$ (4 × 30 mL). The combined $CHCl_3$ extracts are evaporated and subjected to flash chromatography, eluting with 4% MeOH in $CHCl_3$. The appropriate fractions are combined, dried, and evaporated to give the title compound as a white glassy powder; yield: 1.04 g (69%).

MS(CI): m/e = 394 (M + 1).

^{1}H-NMR ($CDCl_3$): δ = 3.0 (m, 2H, $CHCH_2$); 3.72 (s, 3H, OCH_3); 4.53 (m, 1H, $CHCH_2$); 4.95–5.15 (complex, 4H, $C_6H_5CH_2O$ + $C_6H_5CH_2N$); 5.53 (br. d, 1H, NH); 6.8 (s, 1H, 4^{im}-H); 7.0–7.4 (complex, 10H), $C_6H_5CH_2O$ + $C_6H_5CH_2N$); 7.45 (s, 1H, 2^{im}-H).

N(α)-Benzyloxycarbonyl-N(π)-benzyl-L-histidine:

N(α)-Benzyloxycarbonyl-N(π)-benzyl-L-histidine methyl ester (0.95 g, 2.42 mmol) is dissolved in MeOH (10 mL), 1 molar NaOH solution (10 mL, 10 mmol) is added, and the mixture is stirred at room temperature for 1 h. The mixture is then diluted with H_2O (10 mL) and the MeOH evaporated. The aqueous phase is washed with $CHCl_3$ (2 × 20 mL), acidified to pH 4 (dilute HCl/H_2O), and extracted with $CHCl_3$ (5 × 30 mL). The combined $CHCl_3$ extracts are dried and evaporated to a white solid. Precipitation from $CHCl_3$ with light petroleum gives the title compound as a colourless crystalline solid; yield: 0.67 g (73%). Recrystallisation from $CHCl_3$/light petroleum gives material of m.p. 138–141 °C; $[\alpha]_D^{20}$ +4.86° (*c* = 0.5, MeOH).

$C_{21}H_{21}N_3O_4$	calc.	C 66.5	H 5.5	N 11.1
(379.4)	found	66.2	5.6	10.9

MS (FAB): *m/e* = 380 (M + 1).

^{1}H-NMR (DMSO-d_6): δ = 2.8 (dd + dd, 2H, CH_2CH); 4.15 (m, 1H, CH_2CH); 5.03 (s, 2H, $PhCH_2N$); 6.77 (s, 1H, 4^{im}-H); 7.1–7.7 (m, 10H, $C_6H_5CH_2O$ + $C_6H_5CH_2N$); 7.72 (s, 1H, 2^{im}-H).

Irradiation of the 2^{im}-H (δ = 7.72) gives a 1.5% NOE at $PhCH_2N$ (δ = 5.20). Irradiation of the 4^{im}-H (δ = 6.77) gives an NOE only at the α-CH. Irradiation of $PhCH_2N$ (δ = 5.20) gives a 10.9% NOE at 2^{im}-H, but no enhancement at 4^{im}-H.

Reaction of N(α)-Benzyloxycarbonyl-L-histidine Methyl Ester with Di-*tert*-butyl Dicarbonate:

N(α)-Benzyloxycarbonyl-L-histidine methyl ester[3] (1; 1.32 g, 4.36 mmol) and di-*tert*-butyl dicarbonate (0.98 g, 4.5 mmol) are dissolved in CH_2Cl_2 (10 mL) and this solution is left overnight at room temperature. The solvent is evaporated, and the residue is flash-chromatographed on a silica column (15 cm × 6 cm), using 1.5% MeOH in Et_2O as eluant.

The less polar product is *N(α)-benzyloxycarbonyl*-N(τ)-tert-*butyloxycarbonyl-L-histidine methyl ester* (**6**), obtained as an oil; yield: 0.91 g (70%).

MS (CI): *m/e* = 404 (M + 1).

^{1}H-NMR ($CDCl_3$): δ = 1.61 (s, 9H, t-C_4H_9); 3.02–3.20 (dd + dd, 2H CH_2CH); 3.75 (s, 3H, OCH_3); 4.64–4.73 (m, 1H, $CHCH_2$); 5.13 (s, 2H, $C_6H_5CH_2O$); 6.12 (br. d, 1H, *J* = 8 Hz, NH); 7.12 (s, 1H, 5^{im}-H); 7.31–7.39 (m, 5H, C_6H_5); 7.97 (s, 1H, 2^{im}-H).

The more polar component, *N(α)-benzyloxycarbonyl*-N(π)-tert-*butoxycarbonyl-L-histidine methyl ester* (**5**), is also obtained as an oil; yield: 0.18 g (14%).

MS (CI): *m/e* = 404 (M + 1).

^{1}H-NMR ($CDCl_3$): δ = 1.66 (s, 9H, t-C_4H_9); 3.17–3.25, 3.44–3.51 (dd + dd, 2H, CH_2CH); 3.76 (s, 3H, OCH_3); 4.69–4.80 (m, 1H, $CHCH_2$); 5.05 (s, 2H, $C_6H_5CH_2O$); 5.40 (br. d, 1H, *J* = 8 Hz, NH); 6.80 (s, 1H, 4^{im}-H); 7.27–7.39 (m, 5H, C_6H_5); 8.03 (s, 1H, 2^{im}-H).

A further 0.11 g of the mixed isomers **5** and **6** remains after chromatography. No interconversion of the isomers occurs, as judged by TLC and NMR, when 87 mmolar solutions of the pure isomers are heated in $CDCl_3$ at 60 °C for 2 days. The addition of 4-(dimethylamino)pyridine (10 mmolar) does not effect isomerisation under these conditions.

N(α)-Benzyloxycarbonyl-N(τ)-acetyl-L-histidine Methyl Ester (7):

N(α)-Benzyloxycarbonyl-L-histidine methyl ester (**1**; 1.46 g, 4.23 mmol) is dissolved in Ac_2O (5 mL). After 5 min, the solvent is evaporated and dry Et_2O (8 mL) is added to give crystalline product **7**; yield: 1.49 g (90%); m.p. 97–102 °C; $[\alpha]_D^{20}$ +31.0° (*c* = 0.98, $CHCl_3$); after 3 recrystallisations from $CHCl_3$/hexane: m.p. 97–100.5 °C; $[\alpha]_D^{20}$ +35.5 °C (*c* = 1.08, $CHCl_3$).

$C_{17}H_{19}N_3O_5$	calc.	C 59.1	H 5.5	N 12.2
(345.4)	found	59.1	5.5	11.9

^{1}H-NMR ($CDCl_3$): δ = 2.58 (s, 3H, $COCH_3$); 3.0–3.2 (m, 2H, CH_2CH); 3.79 (s, 3H, OCH_3); 4.66–4.76 (m, 1H, $CHCH_2$); 5.10 (s, 2H, $C_6H_5CH_2O$); 6.05 (d, 1H, *J* = 9 Hz, NH); 7.24 (s, 1H, 5^{im}-H); 7.24–7.46 (m, 5H, $C_6H_5CH_2$); 8.02 (d, 1H, *J* < 2 Hz, 2^{im}-H).

Examination of the Et_2O liquors by TLC and ^{1}H-NMR shows only the N(τ)-acetyl compound **7**, together with AcOH and Ac_2O.

N(α)-Benzyloxycarbonyl-N(π)-benzyloxymethyl-L-histidine Methyl Ester Hydrochloride (8):

Method A, from the N(τ)-*tert*-Butoxycarbonyl Compound **6**: A solution of N(α)-benzyloxycarbonyl-N(τ)-*tert*-butoxycarbonyl-L-histidine methyl ester (**6**; 0.33 g, 0.82 mmol) in CH_2Cl_2 (4 mL) is treated with benzyl chloromethyl ether (180 µL, 1.31 mmol) and left to stand overnight. Prolonged evaporation gives a solid, which is triturated with Et_2O (25 mL) and recrystallised from MeOH/Et_2O to give product **8** as colourless needles; yield: 0.18 g (48%); m.p. 137–145 °C; after a second recrystallisation: m.p. 142–145 °C; $[\alpha]_D^{20}$: −27.8° (*c* = 0.82, MeOH).

$C_{23}H_{26}ClN_3O_5$	calc.	C 60.1	H 5.7	N 9.1
(459.9)	found	60.2	5.7	9.2

^{1}H-NMR ($CDCl_3$): δ = 3.14–3.41 (dd + dd, 2H, CH_2CH); 3.75 (s, 3H, OCH_3); 4.58–4.71 (m, 3H, $CHCH_2$ and $C_6H_5CH_2OCH_2$); 5.07 (s, 2H, $C_6H_5CH_2OCO$); 5.68 (br. s, 2H, NCH_2O); 5.85 (br. d, 1H, *J* = 6 Hz, NH); 7.15 (s, 1H, 4^{im}-H); 7.25–7.42 (m, 10H, $C_6H_5CH_2OCH_2$ and $C_6H_5CH_2OCO$); 9.32 (s, 1H, 2^{im}-H).

Method B, from the N(τ)-Acetyl Compound **7**: A solution of N(α)-benzyloxycarbonyl-N(τ)-acetyl-L-histidine methyl ester (**7**; 5.00 g, 15.5 mmol) in CH_2Cl_2 (20 mL) is treated with benzyl chloromethyl ether (2.82 mL, 20.3 mmol). After 4.5 h, the solvent is removed, leaving a hygroscopic foam which is triturated with dry Et_2O (120 mL) and dissolved in MeOH (40 mL). After 2 h, the MeOH is evaporated to leave an oil, which crystallises on addition of Et_2O; yield of **8**: 5.86 g (88%); m.p. 139–145 °C; $[\alpha]_D^{20}$: −28.7° (*c* = 0.68, MeOH). The product is identical by 300 MHz NMR to that from Method A.

N(α)-Benzyloxycarbonyl-N(π)-benzyloxymethyl-L-histidine Methyl Ester:

Distribution of hydrochloride **8** between $CHCl_3$ and aqueous $NaHCO_3$, washing with H_2O, drying, and evaporation of the solvent gives N(α)-benzyloxycarbonyl-N(π)-benzyloxymethyl-L-histidine methyl ester as a colourless, viscous oil; yield: ~100%.

MS (CI): *m/e* = 424 (M + 1).

^{1}H-NMR ($CDCl_3$): δ = 3.11–3.29 (dd + dd, 2H, CH_2CH); 3.72 (s, 3H, OCH_3); 4.42 (complex, 2H, $C_6H_5CH_2OCH_2$); 4.64–4.71 (m, 1H, $CHCH_2$); 5.09 (s, 2H, $C_6H_5CH_2OCO$); 5.24 (virtual s, 2H, NCH_2O); 5.55 (br. d, 1H, *J* = 7 Hz, NH); 6.87 (s, 1H, 4^{im}-H); 7.27–7.40 (m, $10H_{arom}$); 7.47 (s, 1H, 2^{im}-H).

Irradiation of the 4^{im}-H (δ = 6.87) gives a 1.2% NOE at the β-CH_2 and a 1.7% NOE at the α-CH. Irradiation of the 2^{im}-H (δ = 7.47) gives NOE's of 1.6% at both CH_2 of the benzyloxymethyl group.

N(α)-Benzyloxycarbonyl-N(π)-benzyloxymethyl-L-histidine (9):

A solution of N(α)-benzyloxycarbonyl-N(π)-benzyloxymethyl-L-histidine methyl ester hydrochloride (**8**; 2.51 g, 5.46 mmol) in MeOH (16 mL) is stirred with 1 molar aqueous NaOH (11.5 mL) for 15 min. Excess MeOH is then removed at 20 °C/20 mbar (15 min), H_2O (90 mL) is added, and 2 molar HCl/H_2O is added to pH 9. The mixture is washed with $CHCl_3$ (2 × 30 mL), then further acidified to pH 4.5, and the product is extracted into $CHCl_3$ (5 × 30 mL). Drying and evaporation gives a white foam which crystallises as prisms from MeOH/Et_2O; yield: 1.69 g (76%); m.p. 156–160 °C; $[\alpha]_D^{22}$ −16.6° (*c* = 2.0, DMF).

$C_{22}H_{23}N_3O_5$	calc.	C 64.5	H 5.7	N 10.3
(409.4)	found	64.7	5.8	10.1

^{1}H-NMR (DMSO-d_6): δ = 2.89–2.99, 3.08–3.18 (dd + dd, 2H, CH_2CH); 4.18–4.27 (m, 1H, $CHCH_2$); 4.40 (s, 2H, $C_6H_5CH_2OCH_2$); 5.00 (s, 2H, $C_6H_5CH_2OCO$); 5.36, 5.40, 5.43, 5.46 (complex, 2H, NCH_2O); 6.73 (s, 1H, 4^{im}-H); 7.25–7.45 (m, 10H, $C_6H_5CH_2OCO$ and $C_6H_5CH_2OCH_2$); 7.50 (br. d, 1H, *J* = 8 Hz, NH); 7.72 (s, 1H, 2^{im}-H).

4-Methyl-3-phenacyl-1-triphenylmethylimidazolium Bromide (11):

4-Methyl-1-triphenylmethylimidazole[11] (**10**; 5.15 g, 15.9 mmol) is dissolved in dry CH_2Cl_2 (300 mL). Phenacyl bromide (3.18 g, 16 mmol) in Et_2O (100 mL) is added, and the solution is kept at room temperature for 2 days. Ether (500 mL) is added and the mixture is cooled to 4 °C. The crystalline *imidazolium salt* is filtered off and washed with Et_2O; yield: 7.11 g (85%); m.p. 203–208 °C.

$C_{31}H_{27}BrN_2O$	calc.	C 71.1	H 5.2	N 5.4
(523.5)	found	71.0	5.3	5.8

5-Methyl-1-phenacylimidazole (12):

4-Methyl-3-phenacyl-1-triphenylmethylimidazolium bromide (**11**; 4.22 g, 8.1 mmol) is refluxed in 50% aqueous acetic acid (75 mL) for 15 min. The mixture is left to cool overnight, filtered to remove triphenylmethanol, and evaporated to dryness. The residue is taken up in

$CHCl_3$ (200 mL), washed first with 10% aqueous Na_2CO_3 (100 mL) and then with H_2O (100 mL), dried, and evaporated. Recrystallisation from benzene/cyclohexane (1:3) gives product **12** as buff needles; yield: 1.35 g (84%); m.p. 121–126 °C.

$C_{12}H_{12}N_2O$	calc.	C 72.0	H 6.0	N 14.0
(200.2)	found	71.8	6.2	14.0

MS (EI): $m/e = 200$ (M^+).

IR ($CHCl_3$): $\nu = 1705\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$): $\delta = 2.12$ (d, 3H, $J = 0.9$ Hz, CH_3); 5.30 (s, 2H, CH_2CO); 6.87 (s, 1H, 4^{im}-H); 7.43 (s, 1H, 2^{im}-H); 7.53–7.71 (m, 3H, 3-, 4-, 5-H_{arom}); 8.01 (dd, 2H, $J = 5$ Hz, 1.7 Hz, 2-, 6-H_{arom}).

1-[6-Benzyloxycarbonylamino)hexyl]-4-methyl-3-phenacylimidazolium Iodide (13):

5-Methyl-1-phenacylimidazole (**12**; 0.67 g, 3.35 mmol) and 1-(benzyloxycarbonylamino)-6-iodohexane[12] (1.27 g, 3.51 mmol) are refluxed together in $CHCl_3$ (8 mL) for 28 h. The solvent is evaporated and the residue is triturated with Et_2O (25 mL) to give a pale yellow powder. Recrystallisation from $CHCl_3/Et_2O$ gives the quaternary salt **13**; yield: 1.66 g (88%); m.p. 124–129 °C. Further recrystallisation gives material of m.p. 130–131 °C.

$C_{26}H_{32}IN_3O_3$	calc.	C 55.6	H 5.7	N 7.5
(561.4)	found	55.5	5.7	7.4

^{1}H-NMR ($CDCl_3$): $\delta = 1.3–2.0$ [m, 8H, $C(CH_2)_4C$]; 2.20 (s, 3H, CH_3); 3.18 (q, 2H, $J = 7$ Hz, $NHCH_2$); 4.18 (t, 2H, $J = 7$ Hz, 1^{im}-CH_2); 5.07 (br. s, 3H, $C_6H_5CH_2O$ and NH); 6.22 (s, 2H, $COCH_2$); 7.09 (s, 1H, 5^{im}-H); 7.28–7.35 (m, 5H, $C_6H_5CH_2O$); 7.52–7.70 (m, 3H, 3-, 4-, 5-H_{arom}); 8.10 (d, 2H, $J = 6$ Hz, 2-, 6-H_{arom}); 9.85 (s, 1H, 2^{im}-H).

1-[6-(Benzyloxycarbonylamino)hexyl]-4-methylimidazole (14):

The imidazolium salt **13** (320 mg, 0.569 mmol) in 80% AcOH (12 mL) is treated with zinc dust (740 mg, 11.4 mmol) in portions over 30 min. After a further 10 min, the mixture is filtered through celite, evaporated, and extracted with $CHCl_3$ (40 mL). The extract is washed with aqueous $NaHCO_3$ (40 mL). The washings are extracted with $CHCl_3$ (20 mL), and the combined organic layers are dried and concentrated. Flash chromatography (10% MeOH in $CHCl_3$) on silica gel removes traces of acetophenone. The eluate is evaporated and the residue triturated with Et_2O/petroleum ether (1:3; ~4 mL) to give product **14** as a white powder; yield: 158 mg (88%); m.p. 62–66 °C. Recrystallization from Et_2O/hexane affords product **14** as needles; yield: 134 mg (75%); m.p. 66–68 °C.

$C_{18}H_{25}N_3O_2$	calc.	C 68.5	H 8.0	N 13.3
(315.4)	found	68.8	8.1	13.3

MS (CI): $m/e = 316$ (M + 1).

^{1}H-NMR ($CDCl_3$): $\delta = 1.3–1.8$ [m, 8H, $C(CH_2)_4C$]; 2.22 (s, 3H, CH_3); 3.18 (q, 2H, $J = 7$ Hz, $NHCH_2$); 3.83 (t, 2H, $J = 7$ Hz, 1^{im}-CH_2); 4.73 (br. s, 1H, NH); 5.1 (s, 2H, $C_6H_5CH_2O$); 6.58 (s, 1H, 5^{im}-H); 7.2–7.4 (m, 6H, C_6H_5 and 2^{im}-H).

Irradiation of the methyl group gives 6.7% NOE at 5^{im}-H and no enhancement elsewhere. Irradiation of 5^{im}-H gives 12.0% enhancement at the CH_3 group, and enhancements at all CH_2 groups of the $(CH_2)_6$ chain.

We are grateful to Pfizer Central Research for a Studentship (held by P.B.W.).

Received: 30 March 1987; revised: 11 June 1987

(1) Hodges, J.C. *Synthesis* **1987**, 20.
(2) The positional designations used for *im*-substituted histidines in this paper are as recommended by the IUPAC-IUB Joint Commission on Biochemical Nomenclature: *Nomenclature and Symbolism for Amino Acids and Peptides. Recommendations 1983*, in: *Eur. J. Biochem.* **1984**, *138*, 9 (see Sect. 2.2.4.). Reference to positions in histidine derivatives by numbers has led to manifold confusion in the past, and expressions like "3-Substituted L-Histidines", as in the title of Ref. 1, are ambiguous.
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