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SYNTHESIS OF 2-BROMO-3-(5-IMIDAZOLYL)PROPANOL, ITS N^{π}-METHYL ANALOGUE AND RELATED 2-BROMOHISTIDINE DERIVATIVES†

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Abstract—2-Bromo-3-(5-imidazolyl)propanol (3) and its N^{π}-Me derivative (8) were synthesized starting from histidine. The introduction of the Br atom in L-histidine, via diazotization, causes racemization. The correct position of the Me group on the imidazole nucleus in methyl 2-bromo-3-(1-methyl-5-imidazolyl)propionate (7) was proved in two ways.

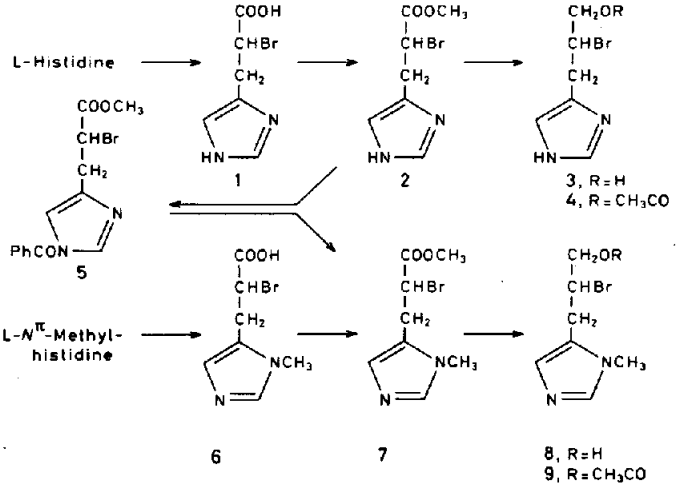
D,L-2-Bromo-3-(5-imidazolyl)propionic acid (1) has been used to modify cysteine residues in papain[1] and it is a potential affinity labelling reagent for the metalloenzymes liver and yeast alcohol dehydrogenases.[2,3] The possible applications of related compounds as affinity labels and as inhibitors of histidine decarboxylase in medicinal chemistry,[4] prompted us to report the synthesis of a number of hitherto unknown 2-bromohistidine derivatives.

RESULTS

The diazotization of D,L-histidine to 2 - bromo - 3 - (5 - imidazolyl) - propionic acid (1) has been described;[5] by improving the work-up procedure, we were able to increase the yield.[6] Selective reduction of the carboxyl group in 1, with preservation of the Br atom, was achieved by means of calcium tetrahydroborate reduction of the methyl ester 2. The bromoalcohol 3 was protected against formation of the epoxide by esterification with acetyl bromide to the acetate 4.

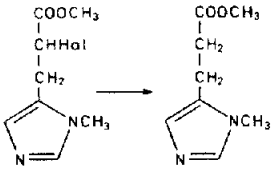
Methyl 2-bromo-3-(5-imidazolyl)propionate (2), after protection of the N^{τ}-atom with the benzoyl group (5), was methylated with trimethyloxonium fluoroborate, which gave the methyl ester of 2 - bromo - 3 - (1 - methyl - 5 - imidazolyl)propionic acid (7). To prove that the N^{π}-atom had been methylated selectively, the latter compound was also synthesized starting from L-N^{π}-methylhistidine[7] by successive diazotization to the 2-bromo analogue (6) and esterification of 6 with methanol to 7. The products 7, obtained in these two ways were identical. The methyl ester of 2 - bromo - 3 - (1 - methyl - 5 - imidazolyl)propionic acid (7) was reduced to the alcohol as described for the nor-Me compound. The bromoalcohol (8) was finally also converted into the acetate (9). Differences in the chemical shifts in the ^{1}H NMR and ^{13}C NMR spectra of the N^{π}-Me and the N^{τ}-Me group in the corresponding histidine derivatives of 2 are too small for identification purposes. Therefore, an additional proof of the position of the Me group was afforded.

†For the numbering of the imidazole nucleus we follow Ref. 7 and 12, where the pros-nitrogen (N^{π}) has position 1 and the tele-nitrogen (N^{τ}) position 3.



Scheme 1. Synthesis of 2-bromo-3-(5-imidazolyl)propanol (3) and of 2-bromo-3-(1-methyl-5-imidazolyl)propanol (8).

Both the methyl esters of 2 - chloro - 3 - (1 - methyl - 5 - imidazolyl)propionic acid[8] (10) and of 2 - bromo - 3 - (1-methyl - 5 - imidazolyl)propionic acid (7) were converted into the methyl ester of 3 - (1 - methyl - 5 - imidazolyl)propionic acid (11); the two compounds were identical. Since the position of the Me group on the N^{π}-nitrogen in the 2-chloro derivative has been established,[8] this also proves the correctness of our conclusion.



Scheme 2.

DISCUSSION

Diazotization of α-amino acids is known to proceed with net retention of configuration,[9] via an α-lactone intermediate,[10] due to the neighbouring group participation of the carboxyl group. In agreement with this, the preparation of (*S*) - 2 - chloro - 3 - (5 - imidazolyl)propionic acid from L-histidine proceeds without racemization and with retention of configuration.[11,12] The same holds when the amino group of a number of optically active α-amino acids (e.g. L-alanine[13] and L-leucine[14]) is replaced by bromine. The diazotization of both L- and D-histidine, however, gave in all cases racemic 2 - bromo - 3 - (5 - imidazolyl)propionic acid.[5] The racemization is caused by the repetitive nucleophilic attack (S_N2) of the bromide anions. The desired product cannot be separated quickly from the reaction mixture (e.g. extraction in the case of L-alanine and L-leucine). That (*S*) - 2 - chloro - 3 - (5 - imidazolyl)propionic acid is isolated as an optically pure acid, can be explained by realizing that chloride is a less powerful nucleophile and a poor leaving group compared to bromide. L-N^{π}-methylhistidine presents the same picture. The introduction of the chloro substituent proceeds with retention of configuration,[8] and we have now found that here too, for the same reason as mentioned above, that introduction of the Br atom, via diazotization, causes racemization.

EXPERIMENTAL

Combustion analyses were performed by Mr. H. M. A. Buurmans. PMR spectra were obtained with a Varian T-60 spectrometer and the ^{13}CNMR were obtained with a Varian CFT-20 spectrometer. The mass spectra were measured by Mrs A. H. Knol-Kalkman, Dr B. van de Graaf and Dr P. J. W. Schuyl on a Varian Mat 311 A mass spectrometer. The rotations were measured with a Perkin–Elmer P-141 polarimeter. The IR spectra were recorded on a Hilger and Watts Infrascan spectrometer and a Beckman spectrophotometer IR 4210.

2 - *Bromo* - 3 - (5 - *imidazolyl)propionic acid* (1) *monohydrate.* A soln of $NaNO_2$ (40.0 g; 580 mmol) in 80 ml H_2O was added dropwise over 90 min, to a well-stirred suspension of L-histidine (30.4 g; 196 mmol) in 440 ml of 48% aqueous HBr at −5 to 0°. After the addition, the soln was stirred for 1 hr at 0° and 1 hr at room temp. The dark soln was concentrated *in vacuo* at 50°, leaving a yellow oil with a white ppt. This concentrate was extracted 4 times with 50 ml acetone and the acetone soln was evaporated *in vacuo.* To remove the excess of HBr, the residue was dissolved in 100 ml H_2O and evaporated *in vacuo.* This procedure was repeated once. The residue was dissolved in 160 ml H_2O and the pH was adjusted to 4.6 by addn of 2 N ammonia at 0°. The soln was decolorized with activated charcoal, filtered, and evaporated at 50°. The resulting oil was crystallized from hot H_2O, yielding 34.0 g (143 mmol; 73%) of 2 - bromo - 3 - (5 - imidazolyl)propionic acid monohydrate, m.p. 107–110° (Ref. 5: 46%; 108–111°).

Methyl 2 - *bromo* - 3 - (5 - *imidazolyl)propionate* (2). Dry HCl was bubbled through a stirred suspension of 2 - bromo - 3 - (5 - imidazolyl)propionic acid monohydrate (10.0 g; 42 mmol) in 150 ml of anhyd MeOH at 10°. After the reaction was complete (about 2hr), the soln was evaporated *in vacuo* at 50°, yielding an oil, which crystallized at room temp. This product was dissolved in 150 ml of 1 M $NaHCO_3$ of 0° and the aqueous soln was extracted 4 times with 100 ml $CHCl_3$. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*; a yellowish oil (3; 9.6 g; 41 mmol; 98%) was obtained. A sample was crystallized as the hydrochloride from a mixture of MeOH and ether, m.p. 133–134°. (Found: C, 31.3; H, 3.7; N, 10.2. Calc. for $C_7H_9BrN_2O_2 \cdot HCl$ (269.55): C, 31.19; H, 3.74; N, 10.39%). ^{1}H NMR of 2 ($CDCl_3$): δ 3.40 (dd, 2 H, $CH_2C_3H_3N_2$), 3.73 (s, 3 H, CH_3), 4.56 (t, 1 H, CHBr), 6.97 (s, 1 H, CCHN), 7.63 (s, 1 H, NCHN), 10.37 (s, 1 H, NH). MS: M^+ 232–234.

2 - *Bromo* - 3 - (5 - *imidazolyl)propanol* (3). Compound 2 (2.8 g; 12 mmol) was dissolved in 50 ml anhyd 2-propanol at 0°. While stirring, anhyd $CaBr_2$ (7.2 g; 36 mmol) was added and subsequently, over 3 hr sodium tetrahydroborate (0.9 g; 24 mmol) was added to this suspension. Stirring was continued for about 2 days at 0-4°. The mixture was carefully treated at 0° with 2 N HBraq until pH 1. The clear soln was evaporated *in vacuo* and the residue dissolved in 100 ml H_2O. The pH was adjusted to 8 by addn of $NaHCO_3$. The soln was filtered and the filtrate extracted continuously with CH_2Cl_2, yielding 1.8 g (9 mmol; 75%) of the oily product 3. ^{1}H NMR (CD_3OD): δ 3.13 (dd, 2 H, $CH_2C_3H_3N_2$), 3.77 (d, 2 H, CH_2OH), 4.16 (m, 1 H, CHBr), 5.72 (s, 2 H, OH and NH), 6.90 (s, 1 H, CCHN), 7.60 (s, 1 H, NCHN). MS: M^+ 204–206.

2 - *Bromo* - 3 - (5 - *imidazolyl)propyl acetate* (4). Acetyl bromide (1.8 g; 15 mmol) was added to a suspension of 2 - bromo - 3 - (5 - imidazolyl)propanol (1.0 g; 5 mmol) in 50 ml CH_2Cl_2. The mixture was stirred for 30 min and then evaporated *in vacuo.* The oily residue was dissolved in 40 ml H_2O and extracted 3 times with 30 ml ether. The pH was adjusted to 8 with $NaHCO_3$ and the aqueous soln was extracted 4 times with 20 ml $CHCl_3$. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*, to yield 1.2 g (5 mmol; 100%) of 4. An analytical sample was crystallized as its hydrochloric acid salt from a mixture of EtOH and ether, m.p. 126–127°. (Found: C, 34.2; H, 4.3; N, 9.8. Calc. for $C_8H_{11}BrN_2O_2 \cdot HCl$ (283.57): C, 33.89; H, 4.27; N, 9.88%). ^{1}H NMR of 4 ($CDCl_3$) δ 2.10 (s, 3 H, CH_3), 3.17 (d, 2 H, $CH_2C_3H_3N_2$), 4.33 (m, CHBr and CH_2O), 6.89 (s, 1 H, CCHN), 7.66 (s, 1 H NCHN), 10.21 (s, 1 H, NH). MS: M^+ 246–248.

Methyl 2 - *bromo* - 3 - (3 - *benzoyl* - 5 - *imidazolyl)propionate* (5). A soln of dicyclohexylamine (7.6 g; 42 mmol) in 30 ml THF and a soln of benzoyl chloride (5.9 g; 42 mmol) in 30 ml THF were added dropwise, simultaneously, in 90 min to a well-stirred soln of methyl 2 - bromo - 3 - (5 - imidazolyl)propionate (9.6 g; 41 mmol) in 300 ml anhyd THF. The mixture was stirred for 1 addnl hr. The precipitated dicyclohexylammonium chloride was filtered off and washed with 30 ml THF. The combined solns were evaporated *in vacuo* at 50°, yielding a yellow oil, which was crystallized by addn of 200 ml of anhyd hot n-hexane, followed by stirring until crystallization took place. The yield was 13.1 g (30 mmol; 95%) of 5, m.p. 71–72°. ^{1}H NMR (CD_3OD): δ 3.34 (m, 2 H, CH_2CHBr), 3.72 (s, 3 H, CH_3), 4.66 (t, 1 H, CHBr), 7.4–7.9 (m, 6 H, C_6H_5 and CCHN), 8.07 (s, 1 H, NCHN). MS: M^+ 336–338.

2 - *Bromo* - 3 - (1 - *methyl* - 5 - *imidazolyl)propionic acid* (6). A soln of $NaNO_2$ (14.4 g; 209 mmol) in 30 ml H_2O was added dropwise to a vigorously stirred soln of L-N^{π}-methylhistidine (11.8 g; 70 mmol) in 160 ml of 48% HBraq at −5–0°. After the addition was complete (60 min), the soln was stirred for 1 addnl hr at room temp. The dark-coloured soln was concentrated *in vacuo* at 50°; this resulted in a yellow oil with a white ppt, which was extracted 4 times with 20 ml acetone. The acetone soln was

evaporated *in vacuo* to an oil, which was dissolved in 100 ml H_2O, followed by evaporation *in vacuo* at 50°. The brown oil was dissolved in 80 ml H_2O and the pH was adjusted to 4.8 with 2 N ammonia at 0°; subsequently the soln was decolorized with charcoal and evaporated *in vacuo* to dryness at 50°. The residue was crystallized from hot H_2O, to afford the desired product (13.1 g; 56 mmol; 80%). An analytical sample was crystallized as the hydrobromide from H_2O, m.p. 187–188°. (Found: C, 27.0; H, 3.1; N, 9.1. Calc. for $C_7H_9BrN_2O_2 \cdot HBr$ (314.00): C, 26.77; H, 3.21; N, 8.92%) ^1H NMR (D_2O): δ 3.53 (d, 2 H, $CH_2C_4H_5N_2$), 3.93 (s, 3H, CH_3), 4.73 (m, 3 H, CHBr, COOH and HBr). 7.44 (s, 1 H, CCHN), 8.25 (s, 1 H, NCHN). MS: M^+ 232–234.

Methyl 2 - *bromo* - 3 - (1 - *methyl* - 5 - *imidazolyl)propionate* (7) *from* 5. A soln of trimethyloxonium fluoroborate (7.5 g; 51 mmol) in 30 ml anhyd nitromethane was added dropwise, in 15 min, under N_2 to a vigorously stirred soln of methyl 2 - bromo - 3 - (3 - benzoyl - 5 - imidazolyl)propionate (12.5 g; 37 mmol) in 60 ml anhyd nitromethane at 0°. After the stirring had been continued for 4 hr, the soln was evaporated *in vacuo*; this resulted in a yellow oil, which was dissolved with vigorous stirring, in 200 ml warm H_2O. After cooling to room temp, the acidic soln was extracted 3 times with 100 ml ether. The pH was adjusted to 8–9 by addn of $NaHCO_3$ and the aqueous soln was extracted 4 times with 100 ml $CHCl_3$. The $CHCl_3$ soln was dried over $MgSO_4$. After filtration, the soln was evaporated *in vacuo*, yielding a light yellow oil (8.9 g; 36 mmol; 97%), which was crystallized as the hydrobromide from a mixture of MeOH and ether, m.p. 153–154°. (Found: C, 29.5; H, 3.8; N, 8.7. Calc. for $C_8H_{11}BrN_2O_2 \cdot HBr$ (328.03): C, 29.29; H, 3.69; N, 8.54%) ^1H NMR of 7 ($CDCl_3$): δ 3.33 (dd, 2 H, $CH_2C_4H_5N_2$), 3.63 (s, 3 H, OCH_3), 3.72 (s, 3 H, NCH_3), 4.46 (t, 1 H, CHBr), 6.90 (s, H, CCHN), 7.44 (s, 1 H, NCHN). MS: M^+ 246–248.

Methyl 2 - *bromo* - 3 - (1 - *methyl* - 5 - *imidazolyl)propionate* (7) *from* 6. A stream of dry HCl was passed through a stirred suspension of 2 - bromo - 3 - (1 - methyl - 5 - imidazolyl)propionic acid (3.3 g; 14 mmol) in 50 ml anhyd MeOH at 10°. After complete conversion (1 hr) the soln was evaporated *in vacuo*, yielding an oil, which crystallized at room temp. The solid crude hydrochloride of 7 was dissolved in 50 ml of 1 M $NaHCO_3$ and extracted 4 times with 50 ml $CHCl_3$. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*; this resulted in an oily product (3.2 g; 13 mmol; 93%). The oil was crystallized as the hydrobromide from a mixture of MeOH and ether and was identical (m.p.; mixed m.p. and IR) with the product obtained from 5.

2 - *Bromo* - 3 - (1 - *methyl* - 5 - *imidazolyl)propanol* (8). Small portions of sodium tetrahydroborate (0.9 g; 24 mmol) were added to a stirred suspension of methyl 2 - bromo - 3 - (1 - methyl - 5 - imidazolyl)propionate (3.0 g; 12 mmol) and anhyd $CaBr_2$ (4.9 g; 24 mmol) in 50 ml anhyd 2-propanol over 2 hr at 2–4°. After 2 days stirring, the mixture was treated carefully at 0° with 2 N HBraq until pH 1. The soln was evaporated *in vacuo*, the residue dissolved in 50 ml H_2O, and the pH was adjusted to 8–9 with $NaHCO_3$. After filtration the soln was extracted continuously with CH_2Cl_2, to afford 2.0 g (9 mmol; 75%) of the oily product 8. ^1H NMR (CD_3OD): δ 3.20 (m, 2 H, $CH_2C_4H_5N_2$). 3.63 (s, 3 H, CH_3), 3.87 (d, 2 H, CH_2OH), 4.18 (m, 1 H, CHBr), 4.85 (s, 1 H, OH), 6.88 (s, 1 H, CCHN), 7.50 (s, 1 H, NCHN). MS: M^+ 218–220.

2 - *Bromo* - 3 - (1 - *methyl* - 5 - *imidazolyl)propyl acetate* (9). Acetyl bromide (2.6 g; 21 mmol) was added to a suspension of 2 - bromo - 3 - (1 - methyl - 5 - imidazolyl)propanol (1.5 g; 7 mmol) in 50 ml of CH_2Cl_2. The mixture was stirred for 45 min and then evaporated *in vacuo*. The oily residue was dissolved in 50 ml H_2O and extracted 3 times with 50 ml ether. The pH was adjusted to 8 with $NaHCO_3$ and the aqueous soln was extracted 4 times with 25 ml $CHCl_3$. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*, which resulted in product 9 (1.8 g; 7 mmol; 100%). An analytical sample was crystallized as its hydrobromide from a mixture of EtOH and ether, m.p. 120–121°. (Found: C, 31.6; H, 4.0; N, 8.3. Calc. for $C_9H_{13}BrN_2O_2 \cdot HBr$ (342.05): c, 31.60; H, 4.13; N, 8.19%). ^1H NMR of 9 ($CDCl_3$): δ 2.09 (s, 3 H, OCH_3), 3.17 (d, 2 H, $CH_2C_4H_5N_2$), 3.60 (s, 3 H, NCH_3), 4.31 (m, 3 H, CHBr and CH_2O), 6.81 (s, 1 H, CCHN), 6.37 (s, 1 H, NCHN). MS: M^+ 260–262.

Methyl 3 - (1 - *methyl* - 5 - *imidazolyl)propionate* (11) *from* 7. A suspension of methyl 2 - bromo - 3 - (1 - methyl - 5 - imidazolyl)propionate hydrobromide (0.33 g; 1 mmol) and 3 g of Raney Ni in MeOH was stirred at room temp. After 30 min stirring, the Raney Ni was filtered off and the filtrate evaporated *in vacuo*. The residue was dissolved in 20 ml 1 M $NaHCO_3$ and extracted 4 times with 20 ml $CHCl_3$. After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo*, upon which the oily product 11 (0.17 g; 1 mmol; 100%) was obtained quantitatively. A sample was crystallized as the hydrobromide from EtOH, m.p. 191–192°. (Found: C, 38.6; H, 5.3; N, 11.0. Calc. for $C_8H_{12}N_2O_2 \cdot HBr$ (249.12): C, 38.57: H, 5.26: N, 11.25%) ^1H NMR of 11 ($CDCl_3$): δ 2.5–3.0 (m, 4 H, CH_2CH_2), 3.60 (s, 3 H, OCH_3), 3.71 (s, 3 H, NCH_3), 6.78 (s, 1 H, CCHN), 7.36 (s, 1 H, NCHN). MS: M^+ 168.

Methyl 3 - (1 - *methyl* - 5 - *imidazolyl)propionate* (11) *from* 10. The procedure as described for the debromination of 7 to 11 was repeated with 1 mmol (0.20 g) of methyl 2 - chloro - 3 - (1 - methyl - 5 - imidazolyl)propionate. After the reaction was complete, the product was isolated and crystallized as the hydrobromic acid salt. It was identical (m.p.; mixed m.p. and IR) with the product obtained from 7.

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