217. Synthesis of Reversible Inhibitors of Acetylcholinesterase (EC 3.1.1.7)

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Summary

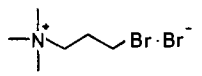
The synthesis and characterization of some reversible acetylcholinesterase inhibitors are described in detail. They are structurally related to the natural substrate acetylcholine. All of them bear a trimethylammonium moiety as 'cationic head'. Instead of an electrophilic ester group, the title compounds include a variety of functionalities, such as halide, ether, thioether, epoxide, amide, ketone and a double bond. The substances are thus suited as probes for the investigation of the esteratic subsite of the acetylcholinesterase active center.

Most of the synthesized compounds inhibit the enzyme in a competitive manner with inhibition constants in the range of 10^{-5} M to 10^{-3} M. With respect to acetylcholine ($K_D \leqslant 10^{-5}$ M and $K_m = (1.6 \pm 0.5)\ 10^{-4}$ M) their affinity to acetylcholinesterase is in the same order of magnitude.

The active site of acetylcholinesterase (EC 3.1.1.7) is generally described as consisting of two principal parts: an anionic subsite bearing at least 6–7 monovalent anionic groups (probably carboxylate groups [1]) and a serine-containing esteratic subsite [2–4]. The quaternary ammonium group of acetylcholine associates with the negatively charged cavity (in addition there may be a hydrophobic interaction) [3] [5] and the hydrolytic process is initiated by a nucleophilic attack of an enzymic serine OH-group on the ester carbonyl group [2] [6–9].

Much work has been done to elucidate the structure of the anionic subsite [1] [3] [5] [10–12] and the mechanism of enzyme action [1] [2] [6–9] [13] [14], but so far little is known about the esteratic subsite. To investigate the structure of this subsite we prepared some competitive inhibitors (acetylcholine congeners). All of them contain a trimethylammonium substituent but different functional groups instead of the ester group. The synthesis and characterization of these compounds is described here. A detailed account of the kinetic measurements (pH-statmethod) for the determination of the inhibition constants is in preparation.

The substances **1–5** were prepared from the corresponding halogenated hydrocarbons by nucleophilic substitution of one halogen atom with Me_3N [15]. To favor



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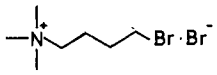

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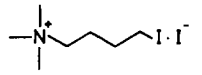

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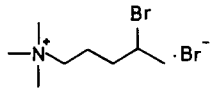

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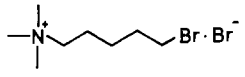

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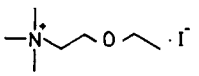
monosubstitution we used at least a five fold molar excess of the appropriate dihalide, with respect to the amine, in a non-polar solvent. In such a medium the products precipitated as salts and further reaction was impossible. A low reaction temperature prevented elimination. The decreased reaction rates were compensated by long reaction times. In addition the synthesis of compound **4** took advantage of the higher reactivity of the primary C-atom in 1,4-dibromopentane towards nucleophilic substitution.



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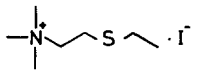

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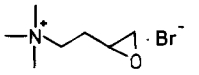

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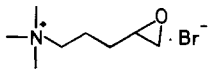

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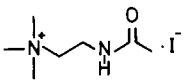
To obtain ether **6** we first treated 1-chloro-2-ethoxyethane with NaI in acetone according to *Finkel'štejn* [16]. Subsequently the iodine was exchanged with Me_3N affording **6** [15]. A different synthesis for **6** with 1-(dimethylamino)-2-ethoxyethane as intermediate is described in [17]. The iodide proved to be best suited to our purposes (not hygroscopic, easily crystallized). Reaction of 2-chloroethyltrimethylammonium chloride according to *Williamson* [18] was unsuccessful.

Acidic hydrolysis of acetylthiocholine iodide followed by alkylation with EtI yielded **7** [19], the thio-analogue of **6**.

The synthesis of the epoxides **8** and **9** was accomplished by the following sequence of two steps. As starting materials we used the unsaturated bromides 1-bromo-3-butene for **8** and 1-bromo-4-pentene for **9**. In the first step the double bond was oxidized with *m*-chloroperbenzoic acid [20]. We only obtained satisfying results by refluxing in $CHCl_3$. Substitution of the bromide by Me_3N in a non-polar medium supplied the desired quaternary ammonium salts [15]. Although we carried out the reaction with

only one equivalent of Me_3N under mild conditions, the precipitation of the product was important in order to prevent the opening of the oxirane ring. An attempt to reverse the reaction sequence failed because the ammonium salts were insoluble in organic solvents.



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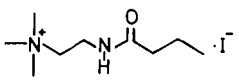

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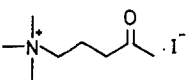

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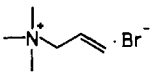
As amidase activity has been reported for acetylcholinesterase (EC 3.1.1.7) [21], especially for **10** as substrate, we reinvestigated this phenomenon. The synthesis of the amides **10** and **11** has been achieved by acylating 2-(dimethylamino)ethylamine with a suitable activated acid derivative (Ac_2O in the case of **10** and butyryl chloride for **11**) followed by methylation with MeI [15] [22].

Discrepancies in the literature [7] with respect to the physical properties, purity and inhibition constant of **12** prompted us to reexamine this inhibitor. Difficulties encountered in the preparation of the ketone **12** by direct reaction of 1-chloro-4-pentanone with trimethylamine as described in [17] [23]. The reaction gave rise to a complex, intractable mixture (probably polymers). Protection of the ketone as an acetal followed by exchange of chlorine with iodide according to *Finkel'štejn* [16], replacement of iodide [15] and deprotection yielded the desired product.



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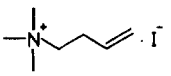

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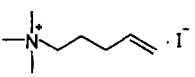

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The unsaturated inhibitors **13**–**15** were easily obtained by a substitution reaction, after halogen exchange in the case of **14** and **15**.

All products (except the epoxides **8** and **9**) were crystalline compounds. All analytical data, including IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra (except for **9**) and elemental analyses were consistent with the assigned structures.

The ^{1}H-decoupled ^{13}C-NMR spectra of all compounds showed a splitting into a triplet or at least a broadening for the signals of the C-atoms adjacent to the N-atom. Compounds **1**–**5**, **8**, **9**, **12** and **15** exhibited the same pattern for further signals. In our opinion this might be due to heteronuclear coupling between ^{13}C and ^{14}N ($^1J(^{14}N, ^{13}C)$).

The electron-impact mass spectra were composed of the spectra of at least two uncharged species. This was not astonishing in the case of quaternary ammonium salts, since they have a very low volatility. Hence their evaporation is only possible after

thermolysis, generating neutral alkyl halides and tertiary amines. With all substances we registered *m/z* 58 as base peak (except **13**; *m/z* 41 as base peak) originating from a dimethylalkylamine.

This work was supported by a grant of the *Swiss National Science Foundation*. We wish to thank the following persons for their help: Dr. *R. Hollenstein* (NMR), Dr. *H. Mändli* (MS) and Mr. *Frohofer* (elemental analyses). We are also indebted to Drs. *H. Mändli, M.C. Schaub, W.H. Hopff* and *A. Hofmann* for critically reading the manuscript.

Experimental Part

General. Solvents, reagents and chemicals were purchased either from *Fluka AG*, Buchs (Switzerland) or from *E. Merck AG*, Darmstadt (F.R.G.) in the highest commercially available purity (except 1,4-diiodobutane and 2-pentanone-ethylene acetal from *Ega Chemie*, Steinheim (F.R.G.)). They were used without further purification. Removal of solvents was carried out in a rotatory evaporator at reduced pressure (about 10 Torr) and at low temp. ($\leq 40°$). For recrystallization the substance was dissolved in the first stated solvent (cold or hot), filtered and the second solvent was added until turbidity occurred. After a few hours at r.t., another portion of the second solvent was added and crystallization was completed at 4°. The solid product was collected by suction filtration, washed with the second solvent and dried for one day at reduced pressure (about 8 Torr) and *50–60°*. Melting points (m.p.) were determined on a *Kofler-Mikroheiztisch (Reichert)* and are uncorrected. IR spectra were recorded on an *AccuLab (Beckman)*, ν_{max} are given in cm^{-1}. Only characteristic bands above 1500 cm^{-1} are indicated (st: stretching vibration). ^{1}H-NMR spectra were registered either on a *Varian XL-100* at 100 MHz or on a *Varian XL-200* spectrometer at 200 MHz with D_2O as solvent. HOD or 3-trimethylsilyltetradeuteropropanoic acid (TSP) was used as internal standard or TMS as external standard. ^{13}C-NMR spectra were obtained on a *Varian XL-100* spectrometer at 25.2 MHz with D_2O as solvent and dioxane as internal reference. ^{13}C-NMR assignments were deduced from comparison with calculated values according to [24]. Mass spectra (MS) were taken on a LKB-2091 spectrometer. Characteristic peaks are indicated, omitting intensities.

General Procedure for the Preparation of **1–5**. Me_3N (2 ml, 33% in EtOH, 8 mmol) was added dropwise to a stirred and ice-cold solution of the corresponding dihalide (40 mmol) in dry Et_2O (100 ml). After 1 h at 0° the mixture was warmed to r.t. and kept for 3 days in the dark. The precipitation of the product began after about 2 h. The product was filtered off by suction, washed with dry Et_2O and recrystallized three times from EtOH/Et_2O.

(3-Bromopropyl)trimethylammonium bromide (**1**). White crystals (74% yield); m.p. 209–212°. ^{1}H-NMR (200 MHz, TSP): 3.55–3.45 (*m*, 4 H, 2 H–C(1) and 2 H–C(3)); 3.15 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 2.35–2.30 (*m*, 2 H, 2 H–C(2)). ^{13}C-NMR: 66.2 (*t*, C(1)); 54.3 (*q*, $\overset{+}{N}(CH_3)_3$); 30.55 and 26.6 (2*t*, C(2) and C(3)). MS: 167/165 ($C_5H_{12}BrN$), 122/120 (C_3H_5Br), 96/94 (CH_3Br), 58 (C_3H_8N).

$C_6H_{15}Br_2N$ (261.0)	Calc.	C 27.61	H 5.79	Br 61.23	N 5.37%
	Found	C 27.62	H 5.88	Br 61.79	N 5.17%

(4-Bromobutyl)trimethylammonium bromide (**2**). White powder (85% yield); m.p. 132–133°. ^{1}H-NMR (100 MHz, TMS): 4.05 (*t*, $J = 7$, 2 H, 2 H–C(4)); 4.0–3.75 (*m*, 2 H, 2 H–C(1)); 3.6 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 2.45 (*quint.*, $J = 4$, 4 H, 2 H–C(2) and 2 H–C(3)). ^{13}C-NMR: 66.5 (*t*, C(1)); 54.1 (*q*, $\overset{+}{N}(CH_3)_3$); 34.8 (*t*, C4)); 29.7 and 22.4 (2*t*, C(2) and C(3)). MS: 136/134 (C_4H_7Br), 96/94 (CH_3Br), 58 (C_3H_8N).

$C_7H_{17}Br_2N$ (275.0)	Calc.	C 30.57	H 6.23	Br 58.11	N 5.09%
	Found	C 30.90	H 6.17	Br 58.71	N 5.38%

(4-Iodobutyl)trimethylammonium iodide (**3**). Pale yellow needles (80% yield); m.p. 163–164°. ^{1}H-NMR (100 MHz, TMS): 3.9–3.7 (*m*, 4 H, 2 H–C(1) and 2 H–C(4)); 3.55 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 2.45–2.2 (*m*, 4 H, 2 H–C(2) and 2 H–C(3)). ^{13}C-NMR: 64.2 (*t*, C(1)); 54.1 (*q*, $\overset{+}{N}(CH_3)_3$); 28.6 and 21.5 (2*t*, C(2) and C(3)); 8.7 (*t*, C(4)). MS: 182 (C_4H_7I), 142 (CH_3I), 58 (C_3H_8N).

$C_7H_{17}I_2N$ (369.0)	Calc.	C 22.78	H 4.64	I 68.78	N 3.80%
	Found	C 23.00	H 4.79	I 68.23	N 3.60%

(±)-*(4-Bromopentyl)trimethylammonium bromide* (**4**). White cubes (88% yield); m.p. 131–134°. ^{1}H-NMR (100 MHz, TMS): 4.85 (*qt*, J_q = 7, J_t = 7, 1 H, H–C(4)); 3.95–3.7 (*m*, 2 H, 2 H–C(1)); 3.6 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 2.6–2.3 (*m*, 4 H, 2 H–C(2) and 2 H–C(3)); 2.2 (*d*, J = 7, 3 H, 3 H–C(5)). ^{13}C-NMR: 66.7 (*t*, C(1)); 54.3 (*q*, $\overset{+}{N}(CH_3)_3$); 53.4 (*d*, C(4)); 37.8 (br. *t*, C(3)); 27.3 (*q*, C(5)); 22.3 (*t*, C(2)). MS: 150/148 (C_5H_9Br), 96/94 (CH_3Br), 58 (C_3H_8N).

$C_8H_{19}Br_2N$ (289.1)	Calc.	C 33.24	H 6.63	Br 55.29	N 4.85%
	Found	C 33.56	H 6.46	Br 54.54	N 4.94%

(5-Bromopentyl)trimethylammonium bromide (**5**). White powder (86% yield); m.p. 141–142°. ^{1}H-NMR (100 MHz, TMS): 4.05 (*t*, J = 7, 2 H, 2 H–C(5)); 3.95–3.75 (*m*, 2 H, 2 H–C(1)); 3.6 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 2.6–2.2 (*m*, 4 H, 2 H–C(2) and 2 H–C(4)); 2.2–1.9 (*m*, 2 H, 2 H–C(3)). ^{13}C-NMR: 67.1 (*t*, C(1)); 54.1 (*q*, $\overset{+}{N}(CH_3)_3$); 36.0 and 32.6 (2*t*, C(4) and C(5)); 25.3 and 22.7 (2*t*, C(2) and C(3)). MS: 150/148 (C_5H_9Br), 96/94 (CH_3Br), 58 (C_3H_8N).

$C_8H_{19}Br_2N$ (289.1)	Calc.	C 33.24	H 6.63	Br 55.29	N 4.85%
	Found	C 33.78	H 6.73	Br 54.70	N 5.27%

(3-Oxapentyl)trimethylammonium iodide (**6**). 1-Chloro-2-ethoxyethane (8.7 g, 80 mmol) was added to a 1 M solution (100 ml) of NaI in dry acetone. Precipitation of NaCl began immediately. After 4 days at r.t. in the dark the solid was separated by filtration and washed with cold, dry Et_2O. The combined filtrates and 100 ml dry Et_2O were stored at −20° for one day to complete the precipitation of NaCl and excess NaI. The solvent was partially removed. The remaining 100 ml were treated with Me_3N (25 ml, 33% in EtOH, 100 mmol) at 0°. The mixture was kept at r.t. for 3 days in the dark. The solid precipitate was collected by filtration, washed with dry Et_2O and recrystallized from EtOH/Et_2O giving pale brown needles (yield 8 g, 40%); m.p. 165–167°. ^{1}H-NMR (200 MHz, HDO): 4.05–3.95 (*m*, 2 H, 2 H–C(2)); 3.7 (*q*, J = 7, 2 H, 2 H–C(4)); 3.65 (*t*, J = 3.5, 2 H, 2 H–C(1)); 3.25 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 1.25 (*t*, J = 7, 3 H, 3 H–C(5)). ^{13}C-NMR: 67.55 and 64.55 (2*t*, C(2) and C(4)); 66.1 (*t*, C(1)); 54.85 (*q*, $\overset{+}{N}(CH_3)_3$); 15.0 (*q*, C(5)). MS: 142 (CH_3I) 117 ($C_6H_{15}NO$), 73 (C_4H_9O), 58 (C_3H_8N).

$C_7H_{18}INO$ (259.1)	Calc.	C 32.45	H 7.00	I 48.97	N 5.41%
	Found	C 32.38	H 7.09	I 48.33	N 5.08%

(3-Thiapentyl)trimethylammonium iodide (**7**). A solution of acetylthiocholine iodide (3.5 g, 12.1 mmol) in EtOH (100 ml) and 37% HCl (25 ml) was refluxed for 7 h. The solvents were removed and excess HCl evaporated by adding and distilling off some EtOH (3×, 10–20 ml each). The dry, colourless residue was recrystallized from H_2O/i-PrOH/Et_2O affording 2.4 g (79%) pure thiocholine iodide. White needles; m.p. 161°. IR (KBr): S–H (st) not detectable, 1680 absent (thioester C=O, st). MS: 142 (CH_3I), 105 ($C_4H_{11}NS$), 58 (C_3H_8N).

NaOH (200 mg, 5 mmol) in H_2O (5 ml) and EtI (630 mg, 4.1 mmol) were added consecutively to thiocholine iodide (1 g, 4.1 mmol) dissolved in EtOH/H_2O (30 ml, 2:1). After boiling the mixture for 6 h the solvents were removed and the solid residue was triturated thrice with dry EtOH to extract the thioether **7**. The combined extracts were stored for 1 day at 4°. The solution was freed from the precipitate by filtration and EtOH was removed *i.v.* The residue was recrystallized from EtOH/Et_2O to give 750 mg (67%) pure **7** as a white powder; m.p. 134–137° (decomposition). ^{1}H-NMR (200 MHz, HOD): 3.65–3.5 (*m*, 2 H, 2 H–C(1)); 3.2 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 3.05–2.95 (*m*, 2 H, 2 H–C(2)); 2.55 (*q*, J = 7.5, 2 H, 2 H–C(4)); 1.25 (*t*, J = 7.5, 3 H, 3 H–C(5)). ^{13}C-NMR: 66.35 (*t*, 1 CH_2, C(1)); 53.85 (*q*, $\overset{+}{N}(CH_3)_3$); 26.3 and 24.1 (2*t*, C(2) and C(4)); 14.85 (*q*, C(5)). MS: 216 (C_4H_9IS), 142 (CH_3I), 133 ($C_6H_{15}NS$), 89 (C_4H_9S), 75 (C_3H_7S), 61 (C_2H_5S), 58 (C_3H_8N).

$C_7H_{18}INS$ (275.2)	Calc.	C 30.55	H 6.59	I 46.11	N 5.09 S 11.65%
	Found	C 30.91	H 6.61	I 45.26	N 5.14 S 12.86%

General Procedure for the Synthesis of the Epoxides **8** *and* **9**. A solution of *m*-chloroperbenzoic acid (5.7 g, 33 mmol) in dry $CHCl_3$ (50 ml) was added dropwise to an ice-cold, stirred solution of the corresponding 1-bromoalkene (1-bromo-3-butene for **8** and 1-bromo-4-pentene for **9**) in $CHCl_3$ (50 ml). After 1 h at 0° the mixture was refluxed for 7 h. To assure complete epoxidation a further portion of *m*-chloroperbenzoic acid (2 g, 11.6 mmol) was added and the mixture was kept overnight at r.t. The solution was diluted with $CHCl_3$ (150 ml). This org. phase was washed consecutively with cold 10% NaOH (3 × 100 ml), with brine (3 × 100 ml), dried over $MgSO_4$ and filtered. The solvent was gently removed. 1-Bromo-3,4-epoxybutane and 1-bromo-4,5-epoxypentane were obtained as colourless liquids. IR (liquid): C=C between 1650 and 1635 cm^{-1} was absent. The two bromocpoxides were not further purified and characterized but used immediately in the next step.

A stirred solution of 1-bromo-3,4-epoxybutane or 1-bromo-4,5-epoxypentane in dry Et_2O (100 ml) was cooled to 0° and treated with one equivalent of Me_3N (33% in EtOH). The mixture was kept at r.t. in the dark for one week. In both cases an oily phase containing some crystals separated. The solvent was evaporated. From both epoxides oily residues were obtained which failed to crystallize. The products were therefore precipitated thrice from EtOH with Et_2O.

(±)-*(3,4-Epoxybutyl)trimethylammonium bromide* (**8**). White powder (precipitate) (yield 55%); m.p. *ca.* 171° (decomposition). ^{1}H-NMR (200 MHz, TSP): 3.55–3.45 (*m*, 2 H, 2 H–C(1)); 3.2 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 2.8 (*m*, 1 H, H–C(3)); 2.55 (*m*, 2 H, 2 H–C(4)); 2.15–1.95 (*m*, 2 H, 2 H–C(2)). ^{13}C-NMR: 70.85 (br. *t*, C(1)); 64.35 (*d*, C(3)); 55.3 (br. *t*, C(4)); 54.15 (*q*, $\overset{+}{N}(CH_3)_3$); 29.4 (*t*, C(2)). MS: 115 ($C_6H_{13}NO$), 96/94 (CH_3Br), 58 (C_3H_8N).

$C_7H_{16}BrNO$ (210.1)	Calc.	C 40.01	H 7.68	Br 38.03	N 6.67%
	Found	C 40.18	H 7.81	Br 35.09	N 6.44%

(±)-*(4,5-Epoxypentyl)trimethylammonium bromide* (**9**). Colourless oil (yield 42%). ^{1}H-NMR (200 MHz, TSP): 3.5–3.4 (*m*, 2 H, 2 H–C(1)); 3.25 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 2.8 (*m*, 1 H, H–C(4)); 2.55 (*m*, 2 H, 2 H–C(5)); 2.2–2.0 (*m*, 4 H, 2 H–C(2) and 2 H–C(3)). ^{13}C-NMR: 72.65 (br. *t*, C(1)); 64.05 (*d*, C(4)); 59.5 (*t*, C(5)); 57.0 (*q*, 3 CH_3, $\overset{+}{N}(CH_3)_3$); 34.6 (*t*, C(3)); 21.8 (*t*, C(2)).

$C_8H_{18}BrNO$ (224.1)	Calc.	C 43.06	H 8.13	Br 35.81	N 6.28%
	Found	C 42.56	H 8.58	Br 34.90	N 6.67%

General Procedure for Amides **10** *and* **11**. 2-(Dimethylamino)ethylamine (8.8 g, 100 mmol) was dissolved in dry pyridine (100 ml) and a suitable activated acid derivative (150 mmol) (Ac_2O for **10** and butyryl chloride for **11**) was added slowly after cooling to 0°. The mixture was kept at r.t. for one week in the dark and evaporated to dryness. The oily residue was redissolved in 10% H_2SO_4 (until pH 2–3, about 50 ml) and washed thrice with Et_2O. The org. phase was discarded. The pH of the H_2O-phase was adjusted to 10 by carefully adding solid NaOH under cooling and vigorous stirring. An oil separated, *N*-[2-(dimethylamino)ethyl]acetamide or *N*-[2-(dimethylamino)ethyl]butyramide. Because of the different solubilities of the two products, different solvents were needed for their extraction. The acetamide was extracted with $CHCl_3$ (3 × 200 ml) and the butyramide with Et_2O (3 × 200 ml). In both cases the combined org. phases were dried ($CHCl_3$ with $MgSO_4$ and Et_2O with Na_2SO_4), filtered and evaporated to a pale yellow oil (yield about 90%). The products were used directly in the next step without further purification.

N-[2-(Dimethylamino)ethyl]acetamide. IR (liquid): 3310 (N–H, st), 1660 (C=O, st; amide I), 1560 and 1545 (N–C=O, st; amide II).

N-[2-(Dimethylamino)ethyl]butyramide. IR (liquid): 3310 (N–H, st), 1650 (C=O, st; amide I), 1555 and 1545 (N–C=O, st; amide II).

For conversion of the above mentioned amines to **10** and **11** MeI (2.5 ml) was added in small portions to a stirred and cooled solution of the amine (20 mmol) in dry CH_2Cl_2 (10 ml). The mixture was refluxed for 7 h, evaporated to give a solid residue. Pure product was obtained by recrystallization (3×) from EtOH/Et_2O.

[2-(Acetylamino)ethyl]trimethylammonium iodide (**10**). White powder (yield 52%); m.p. 123°. IR (KBr): 3460 and 3260 (N–H, st), 3060, 3020, 2970 and 2820 (C–H, st), 1625 (C=O, st; amide I), 1540 (N–C=O, st; amide II). ^{1}H-NMR (200 MHz, TSP): 3.7 (br. *t*, J = 7, 2 H) and 3.5 (*t*, J = 7, 2 H) (2 H–C(1) and 2 H–C(2)); 3.2 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 2.05 (*s*, 3 H, CH_3–CO). ^{13}C-NMR: 175.25 (*s*, CO); 65.25 (*t*, C(1)); 54.75 (*q*, $\overset{+}{N}(CH_3)_3$); 34.7 (*t*, C(2)); 23.4 (*q*, CH_3–CO). MS: 142 (CH_3I), 130 ($C_6H_{14}N_2O$), 86 (C_4H_8NO), 58 (C_3H_8N).

$C_7H_{17}IN_2O$ (272.1)	Calc.	C 30.90	H 6.30	I 46.63	N 10.29%
	Found	C 31.26	H 6.39	I 46.30	N 10.00%

[2-(Butyrylamino)ethyl]trimethylammonium iodide (**11**). Pale brownish leaflets (yield 62%); m.p. 81–82°. IR (KBr): 3450 and 3270 (N–H, st), 3010, 2960 and 2870 (C–H, st), 1650 (C=O, st; amide I), 1525 (N–C=O, st; amide II). ^{1}H-NMR (200 MHz, TSP): 3.7 (br. *t*, J = 7, 2 H) and 3.55 (*t*, J = 7, 2 H) (2 H–C(1) and 2 H–C(2)); 3.2 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 2.25 (*t*, J = 7, 2 H, CH_2CO); 1.6 (*sext.*, J = 7, 2 H, CH_2CH_2CO); 0.9 (*t*, J = 7, 3 H, CH_3)). ^{13}C-NMR: 178.05 (*s*, CO); 65.3 (*t*, C(1)); 54.8 (*q*, $\overset{+}{N}(CH_3)_3$); 38.75 and 34.55 (2*t*, C(2) and CH_2–CO); 19.85 (*t*, CH_2CH_2CO); 14.25 (*q*, CH_3). MS: 158 ($C_8H_{18}N_2O$), 142 (CH_3I), 114 ($C_6H_{12}NO$), 58 (C_3H_8N).

$C_9H_{21}IN_2O$ (300.2)	Calc.	C 36.01	H 7.05	I 42.28	N 9.33%
	Found	C 36.76	H 7.19	I 41.22	N 9.16%

(4-Oxopentyl)trimethylammonium iodide (**12**). 5-Chloro-2-pentanoneethylene acetal (3 g, 18.2 mmol) was treated with a 1 M solution (30 ml) of NaI in dry acetone as described for **6**. The final volume was adjusted to

100 ml with dry Et_2O. This solution was treated with Me_3N (10 ml, 33% in EtOH, about 40 mmol) for one week in the dark. The solvent was removed, the residue was dissolved in water (20 ml) and washed with Et_2O (3 × 100 ml). Deprotection of the carbonyl group was achieved by adding dil. HCl (conc. HCl/H_2O 1:10) and distilling off the solvent. The dry residue was recrystallized thrice from EtOH/Et_2O to give **12** as a white powder (yield 81%); m.p. 97–99°. IR (KBr): 3050, 2950 and 2910 (C–H, st), 1710 (C=O, st). ^{1}H-NMR (100 MHz, TMS): 3.75 (br. *t*, J = 5, 2 H, 2 H–C(1)); 3.55 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 3.15 (*t*, J = 7, 2 H, 2 H–C(3)); 2.65 (*s*, 3 H, 3 H–C(5)); 2.6–2.3 (*m*, 2 H, 2 H–C(2)). ^{13}C-NMR: 213.85 (*s*, C(4)); 66.45 (*t*, C(1)); 54.15 (*q*, $\overset{+}{N}(CH_3)_3$); 40.2 (*t*, C(3)); 30.75 (*q*, C(5)); 17.5 (*t*, C(2)). MS: 142 (CH_3I), 129 ($C_7H_{15}NO$), 85 (C_5H_9O), 58 (C_3H_8N).

$C_8H_{18}INO$ (271.1)	Calc.	C 35.44	H 6.69	I 46.80	N 5.17%
	Found	C 35.02	H 6.69	I 46.51	N 5.13%

Allyltrimethylammonium bromide (**13**) was prepared from allyl bromide (3.6 g, 30 mmol) as stated above for **12** (EtOH as solvent), without halide exchange. **13** (4 g, 74%) was obtained as a white, hygroscopic solid; m.p. 170°. IR (KBr): 3015 and 2970 (C–H, st), 1620 (C=C, st). ^{1}H-NMR (100 MHz, TMS): 6.75–6.4 (*m*, 1 H, CH_2–C*H*=CH_2); 5.8–5.5 (*m*, 2 H, CH_2–CH=C*H*$_2$); 4.35 (*m*, 2 H, CH_2); 3.2 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$). ^{13}C-NMR: 131.5 (*d*, CH_2–*C*H=CH_2); 119.4 (*t*, CH_2–CH=*C*H$_2$); 73.5 (*t*, CH_2); 55.0 (*q*, $\overset{+}{N}(CH_3)_3$). MS: 122/120 (C_3H_5Br), 96/94 (CH_3Br), 85 ($C_5H_{11}N$), 58 (C_3H_8N), 41 (C_3H_5).

$C_6H_{14}BrN$ (180.1)	Calc.	C 40.01	H 7.84	Br 44.37	N 7.78%
	Found	C 39.62	H 7.63	Br 43.77	N 8.11%

(3-Butenyl)trimethylammonium iodide (**14**). Halide exchange of 1-bromo-3-butene (3 g, 2.2 mmol) was achieved as described for **6**. Substitution of iodide with Me_3N was carried out as stated for **12**. This gave 4.1 g (77%) **14** as a white powder; m.p. about 250°. IR (KBr): 3080 (=C–H, st), 3010, 2980, 2960 (C–H, st), 1645 (C=C, st). ^{1}H-NMR (100 MHz, TMS): 6.5–6.0 (*m*, 1 H, H–C(3)); 5.8–5.5 (*m*, 2 H, 2 H–C(4)); 3.95–3.7 (*m*, 2 H, 2 H–C(1)); 3.55 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 3.2–2.8 (*m*, 2 H, 2 H–C(2)). ^{13}C-NMR: 133.45 (*d*, C(3)); 120.4 (*t*, C(4)); 66.5 (*t*, C(1)); 54.75 (*q*, $\overset{+}{N}(CH_3)_3$); 28.3 (*t*, C(2)). MS: 182 (C_4H_7I), 142 (CH_3I), 99 ($C_6H_{13}N$), 58 (C_4H_8N), 55 (C_4H_7).

$C_7H_{16}IN$ (241.1)	Calc.	C 34.87	H 6.69	I 52.63	N 5.81%
	Found	C 34.20	H 6.24	I 52.38	N 6.50%

(4-Pentenyl)trimethylammonium iodide (**15**). Using the same procedure as in the preparation of **14** 1-bromo-4-pentene (3 g, 20.1 mmol) was converted to **15**, obtained as white leaflets (yield 79%); m.p. 228–230°. IR (KBr): 3090 (=C–H, st), 3030, 2970, 2890, 2840 and 2800 (C–H, st), 1650 (C=C, st). ^{1}H-NMR (100 MHz), TMS): 6.5–6.1 (*m*, 1 H, H–C(4)); 5.7–5.4 (*m*, 2 H, 2 H–C(5)), 3.75–3.6 (*m*, 2 H, 2 H–C(1)); 3.55 (*s*, 9 H, $\overset{+}{N}(CH_3)_3$); 2.8–2.2 (*m*, 4 H, 2 H–C(2) and 2 H–C(3)). ^{13}C-NMR: 138.1 (*d*, C(4)); 117.75 (*t*, C(5)); 67.2 (br. *t*, C(1)); 54.55 (*q*, $\overset{+}{N}(CH_3)_3$); 30.7 (*t*, C(3)); 22.8 (*t*, C(2)). MS: 196 (C_5H_9I), 142 (CH_3I), 113 ($C_7H_{15}N$), 69 (C_5H_9), 58 (C_3H_8N).

$C_8H_{18}IN$ (255.1)	Calc.	C 37.66	H 7.11	I 49.74	N 5.49%
	Found	C 37.04	H 6.76	I 49.44	N 5.49%

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