Synthesis of N^1,N^1,N^3,N^3-tetrasubstituted diethylenetriamines

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Preparative procedures for the synthesis of N^1,N^1,N^3,N^3-tetrasubstituted diethylenetriamines *via* aminoalkylation of *N,N*-disubstituted ethylenediamines with *N,N*-disubstituted 2-chloroethylamines were developed. Aminoalkylation of *N,N*-dimethylethylenediamine under heating gave simultaneously secondary N^1,N^1,N^3,N^3-tetrasubstituted diethylenetriamines and quaternary ammonium salts, *N*-(2-aminoethyl)-*N*-(2-dialkylaminoethyl)-*N,N*-dimethylammonium chlorides. Structures of the synthesized compounds were established by IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, and electrospray ionization mass spectrometry.

Key words: synthesis, aminoalkylation, ethylenediamines, diethylenetriamines, quaternary ammonium salts.

Aliphatic polyamines and their derivatives have found wide applications in medicinal and organic chemistry.[1—4] Due to wide variety of their properties, aliphatic diethylenetriamines and their derivatives are used as ligands,[5—9] amphiphilic reagents,[10] and components of medications.[11] In contrast to well-studied symmetrical analogs, nonsymmetrical aliphatic diethylenetriamines are less explored.

The present work continues our studies on synthesis of N^1,N^1,N^3,N^3-tetrasubstituted diethylenetriamines bearing secondary and ternary amino groups that can be further transformed into different diamino amides with potential biological activities.[12]

N^1,N^1,N^3,N^3-Tetrasubstituted diethylenetriamines can be synthesized by several following pathways: basic hydrolysis of the corresponding *N*-lithio derivatives of diethylenetriamines,[13] reduction of the amide group of amine-substituted carboxamides,[11,14,15] hydrogenation of aminoacetonitriles,[16,17] and amination of bis(chloroethyl)amine with secondary amines.[5,18] The main drawbacks of these methods are instability of the starting compounds, the technical complexity of the synthetic procedure, and the lack of generality.

Aminoalkylation of diamine to synthesize bis(2-diethylaminoethyl)amine was also published.[19] Among the mentioned approaches, aminoalkylation of diamines is the most convenient and scalable procedure for the synthesis of diethylenetriamines bearing different substituents at the N(1) and N(3) atoms.

Results and Discussion

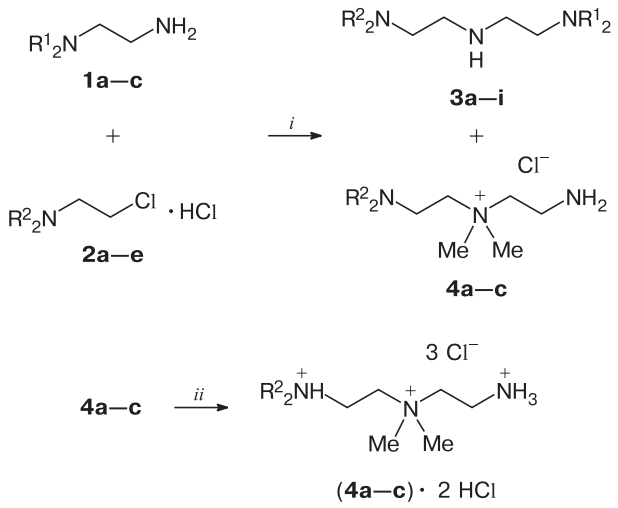
Aminoalkylation of *N,N*-disubstituted ethylenediamines **1a—c** with *N,N*-disubstituted 2-chloroethylamine hydrochlorides **2a—e** to give the target diethylenetriamines **3a—i** was carried out following two different experimental routes (Scheme 1). It is known that aminoalkylation with an excess of 2-chloroethylamines results in tetramines.[20] We prevented formation of tetramines by using limiting amount of 2-chloroethylamines. Thus, the ratios of ethylenediamine **1** to 2-chloroethylamine **2** were varied in the range from 1.5 : 1 to 2 : 1.

Molecules of *N,N*-disubstituted ethylenediamines **1a—c** comprise two nucleophilic centers, namely, the primary and ternary amino groups. Alkylation of these groups can result in two type of the products, *i.e.*, secondary amines and quaternary ammonium salts (the latter being the products of the Menshutkin reaction[21—24]). Optimization of the aminoalkylation reaction involved the following factors and reaction conditions: reaction temperature, the solvent nature, and the nature of haloamine used as an alkylating agent. Two experimental procedures were developed (methods ***A*** and ***B***).

In method ***A***, the reaction was carried out in 10% aqueous NaOH. Aminoalkylation of *N,N*-dimethylenediamine (**1a**) with *N*-(2-chloroethyl)pyrrolidine (**2c**) at room temperature for 24 h gives selectively quaternary ammonium salt **4b** in 75% yield without any formation of the target triamine **3b**. An increase in the reaction temperature results in the appearance of the target products in the reaction mixture. When the reaction is carried out at 60—70 °C, secondary ethylenediamines **3a—c** are formed in the yield of 18—28%. The nature of the starting diamine significantly affects the yields of the target products **3**. Thus, the reactions of *N,N*-diethylethylenediamine (**1b**) and *N*-(2-aminoethyl)piperidine (**1c**) with 2-chloroethylamines **2b—e** at 65—70 °C for 15—18 h result mainly in secondary triamines **3d—i** not contaminated with quaternary ammonium salts. Products were extracted from the

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 0840—0843, May, 2018.

Scheme 1



Product	NR^1_2	NR^2_2	Starting compounds
3a	NMe_2	NMe_2	**1a**, **2a**
3b	NMe_2	NC_4H_8	**1a**, **2c**
3c	NMe_2	NC_5H_{10}	**1a**, **2d**
3d	NEt_2	NEt_2	**1b**, **2b**
3e	NEt_2	NC_4H_8	**1b**, **2c**
3f	NEt_2	NC_5H_{10}	**1b**, **2d**
3g	NEt_2	NC_4H_8O	**1b**, **2e**
3h	NC_5H_{10}	NC_4H_8	**1c**, **2c**
3i	NC_5H_{10}	NC_4H_8O	**1c**, **2e**

Note. NC_4H_8 is pyrrolidin-1-yl, NC_5H_{10} is piperidin-1-yl, NC_4H_8O is morpholin-4-yl.

Reaction and conditions: *i*. Method ***A***: NaOH, H_2O, 60—70 °C or method ***B***: K_2CO_3, KI, MeCN, reflux; *ii*. HCl, dioxane, Pr^iOH.

aqueous reaction mixtures with ethyl acetate and purified by vacuum distillation. Method ***A*** gives compounds **3d**—**i** in 38—56% yields.

To increase the yields of diethylenetriamines **3a**—**c**, we elaborated another method of their synthesis *via* generated *in situ* ternary iodoethylamines (method ***B***). The reactions were carried out at a 2 : 1 molar ratio of *N,N*-dimethylethylenediamine (**1a**) to *N*-(2-chloroethyl)amine **2a**,**c**,**d** in the presence of K_2CO_3 and KI in refluxing MeCN for 16—18 h. Under these reaction conditions, the formed inorganic salts were almost insoluble in MeCN and precipitated out. After completion of the reaction, the inorganic precipitate was filtered off, and the filtrate was concentrated. The target secondary diethylenetriamines **3a**—**c** were isolated by extraction of the residue with diethyl ether and subsequent vacuum distillation. Method ***B*** gives compounds **3a**—**c** in 26—38% yields. Poorly soluble in diethyl ether quaternary ammonium salts **4a**—**c** were isolated in the yields of 52—54% and converted into the corresponding dihydrohlorides (**4a**—**c**) · 2HCl in 56—72% yields.

A comparison of both methods revealed that method ***B*** gives higher yields of the target products. The apparent reasons are the intermediate formation of reactive *N*-(2-iodoethyl)amines and lower stabilization of the quaternary ammonium salts in aprotic polar MeCN by the I^- counter ion than that of Cl^-. An increase in the size of the substituent at the nitrogen atom of halo-substituted aminoalkylating agent **2** (Et_2N (**2b**) and $(CH_2)_5N$ (**2d**) *vs.* Me_2N (**2a**)) also does not favor the stabilization of the quaternary ammonium salts and, therefore, these salts are almost not formed. In turn, the reagents with the bulkier *N*-substituents give the higher yields of the corresponding products **3d**—**i** than that of **3a**—**c**.

Purity of the synthesized compounds was confirmed by TLC, their structures were established by IR and NMR spectroscopy and mass spectrometry.

In summary, the developed procedures enable synthesis of biologically active non-symmetric N^1,N^1,N^3,N^3-tetra-substituted diethylenetriamines and their derivatives.

Experimental

N,N-Dimethylethylenediamine (**1a**), *N,N*-diethylethylenediamine (**1b**), *N,N*-dimethyl-2-chloroethanamine hydrochloride (**2a**), *N,N*-diethyl-2-chloroethanamine hydrochloride (**2b**), *N*-(2-chloroethyl)pyrrolidine hydrochloride (**2c**), *N*-(2-chloroethyl)piperidine hydrochloride (**2d**), *N*-(2-chloroethyl)morpholine hydrochloride (**2e**) were purchased from Sigma-Aldrich. *N*-(2-Aminoethyl)piperidine (**1c**) was synthesized from 2-chloroethylamine and piperidine following the known procedure.[25]

Solvents were purified and dried by the standard procedures. Thin layer chromatography was performed with Kavalier Silufol UV-254 plates (elution with MeOH, spots were visualized with the iodine vapors). Melting points were measured using a Büchi MP-520 apparatus. IR spectra were recorded for pure compounds with a Bruker Alpha instrument operating in a single-pass attenuated total reflection mode. NMR spectra were run on a Bruker DPX-300 instrument (working frequencies of 300.13 MHz (^{1}H) and 75 MHz (^{13}C)) in $CDCl_3$, D_2O, and DMSO-d_6 relative to Me_4Si as an internal standard. Electrospray ionization mass spectrometry was performed with a LC/MSD Trap SL mass spectrometer. Samples were injected as solutions in methanol. High-resolution electrospray ionization mass spectra were recorded on a LTQ OrbitrapXL^{TM} mass spectrometer.

Synthesis of diethylenetriamines 3a—i (method *A*). To a stirred mixture of ethylenediamine **1a**—**c** (1.5—2 equiv.) and NaOH (2 equiv.) in water (9 mL per 1 g of NaOH), 2-chloroethanamine hydrochloride **2a**—**e** (1 equiv.) was added portionwise. The mixture was magnetically stirred at 65—70 °C for 16—18 h (TLC monitoring, methanol as an eluent). Products **3a—i** were extracted five times with equal volumes of ethyl acetate, the combined organic layers were dried with Na_2SO_4, and concentrated *in vacuo*. Vacuum distillation of the residues afforded diethylenetriamines **3a**—**i** as colorless liquids.

***N,N*-Bis(2-dimethylaminoethyl)amine (3a)** was synthesized from *N,N*-dimethylethylenediamine (**1a**) (3.67 g, 0.042 mol), NaOH (1.67 g, 0.042 mol), and *N,N*-dimethyl-2-chloroethanamine hydrochloride (**2a**) (3.0 g, 0.021 mol). Yield 0.59 g (18%). B.p. 112—115 °C (30 Torr). IR, ν/cm^{-1}: 3312 (NH). ^{1}H NMR ($CDCl_3$), δ: 1.98 (t, 4 H, 2 CH_2N, J = 6.3 Hz); 2.16 (s, 12 H, 4 CH_3N); 2.65 (t, 4 H, $C\underline{H}_2NHC\underline{H}_2$, J = 6.3 Hz).[13]

***N,N*-Dimethyl-*N′*-(2-pyrrolidinoethyl)ethylenediamine (3b)** was synthesized from *N,N*-dimethylethylenediamine (**1a**) (2.3 g, 0.0276 mol), NaOH (1.41 g, 0.036 mol), and *N*-(2-chloroethyl)-pyrrolidine hydrochloride (**2c**) (3.0 g, 0.018 mol). Yield 0.8 g (24%). B.p. 104—106 °C (12 Torr), n_D^{20} 1.4625, R_f 0.36. IR, ν/cm^{-1}: 3309 (NH). ^{1}H NMR ($CDCl_3$), δ: 1.73 (m, 4 H, β-H, NC_4H_8); 2.18 (s, 7 H, 2 CH_3N + NH); 2.38 (t, 2 H, CH_2N, J = 6.3 Hz); 2.46 (m, 4 H, α-H, NC_4H_8); 2.56 (t, 2 H, CH_2N, J = 6.6 Hz); 2.65—2.74 (m, 4 H, C<u>H</u>$_2$NHC<u>H</u>$_2$). ^{13}C NMR ($CDCl_3$), δ: 23.32 (2 β-C, NC_4H_8); 45.50 (2 CH_3N); 47.50 (CH_2NH); 48.76 (CH_2NH); 54.18 (2 α-C, NC_4H_8); 55.99 (CH_2N); 59.11 (CH_2N). MS, m/z: 186.0 $[M + H]^+$.

***N,N*-Dimethyl-*N′*-(2-piperidinoethyl)ethylenediamine (3c)[11]** was synthesized from *N,N*-dimethylethylenediamine (**1a**) (5.7 g, 0.066 mol), NaOH (2.64 g, 0.066 mol), and *N*-(2-chloroethyl) piperidine hydrochloride (**2d**) (6.0 g, 0.033 mol). Yield 1.8 g (28%). B.p. 118—122 °C (14 Torr), n_D^{20} 1.4675, R_f 0.25. IR, ν/cm^{-1}: 3311 (NH). ^{1}H NMR ($CDCl_3$), δ: 1.39 (m, 2 H, γ-H, NC_5H_{10}); 1.53 (m, 4 H, β-H, NC_5H_{10}); 2.19 (s, 6 H, 2 CH_3N); 2.32—2.44 (m, 9 H, 4 CH_2N + NH); 2.64—2.71 (m, 4 H, C<u>H</u>$_2$NHC<u>H</u>$_2$). ^{13}C NMR ($CDCl_3$), δ: 24.36 (γ-C, NC_5H_{10}); 25.88 (2 β-C, NC_5H_{10}; 45.46 (2 CH_3N); 46.83 (CH_2NH); 47.43 (CH_2NH); 54.70 (2 α-C, NC_5H_{10}); 58.66 (CH_2N); 59.11 (CH_2N). Found: m/z 200.2121 $[M + H]^+$, 222.1942 $[M + Na]^+$. $C_{11}H_{26}N_3$. Calculated: M + H = 200.2127, M + Na = 222.1946.

***N,N*-Bis(2-diethylaminoethyl)amine (3d)** was synthesized from *N,N*-diethylethylenediamine (**1b**) (6.08 g, 0.052 mol), NaOH (2.8 g, 0.07 mol), and *N,N*-diethyl-2-chloroethanamine hydrochloride (**2b**) (6 g, 0.035 mol). Yield 3.15 g (42%). B.p. 116—120 °C (7 Torr), n_D^{20} 1.4500, R_f 0.43. IR, ν/cm^{-1}: 3308 (NH). ^{1}H NMR ($CDCl_3$), δ: 1.01 (t, 12 H, 4 CH_3, J = 7.1 Hz); 2.04 (br.s, 1 H, NH); 2.48—2.57 (m, 12 H, 6 CH_2N); 2.66—2.70 (m, 4 H, C<u>H</u>$_2$NHC<u>H</u>$_2$).[14,15]

***N,N*-Diethyl-*N′*-(2-pyrrolidinoethyl)ethylenediamine (3e)** was synthesized from *N,N*-diethylethylenediamine (**1b**) (6.2 g, 0.053 mol), NaOH (2.8 g, 0.07 mol), and *N*-(2-chloroethyl)-pyrrolidine hydrochloride (**2c**) (6.0 g, 0.035 mol). Yield 3.2 g (43%). B.p. 142—144 °C (14 Torr), n_D^{20} 1.4659, R_f 0.52. IR, ν/cm^{-1}: 3310 (NH). ^{1}H NMR ($CDCl_3$), δ: 0.96 (t, 6 H, 2 CH_3, J = 7.1 Hz); 1.71 (m, 4 H, β-H, NC_4H_8); 2.17 (br.s, 1 H, NH); 2.43—2.57 (m, 12 H, 6 CH_2N); 2.62—2.73 (m, 4 H, C<u>H</u>$_2$NHC<u>H</u>$_2$). ^{13}C NMR ($CDCl_3$), δ: 11.27 (2 CH_3); 22.91 (2 β-C, NC_4H_8); 46.55 (2 CH_2N, NEt_2); 47.28 (CH_2NH); 48.32 (CH_2NH); 52.20 (CH_2N); 53.73 (2 α-C, NC_4H_8); 55.54 (CH_2N). Found: m/z 214.2269 $[M + H]^+$, 236.2087 $[M + Na]^+$. $C_{12}H_{28}N_3$. Calculated: M + H = 214.2283, M + Na = 236.2103.

***N,N*-Diethyl-*N′*-(2-piperidinoethyl)ethylenediamine (3f)** was synthesized from *N,N*-diethylethylenediamine (**1b**) (6.3 g, 0.054 mol), NaOH (2.16 g, 0.054 mol), and *N*-(2-chloroethyl)piperidine hydrochloride (**2d**) (5.0 g, 0.027 mol). Yield 3.4 g (56%). B.p. 152—156 °C (14 Torr), n_D^{20} 1.4720, R_f 0.35. IR, ν/cm^{-1}: 3307 (NH). ^{1}H NMR ($CDCl_3$), δ: 0.96 (t, 6 H, 2 CH_3, J = 7.1 Hz); 1.39 (m, 2 H, γ-H, NC_5H_{10}); 1.51 (m, 4 H, β–H, NC_5H_{10}); 2.32—2.52 (m, 13 H, 6 CH_2N + NH); 2.61—2.69 (m, 4 H, C<u>H</u>$_2$NHC<u>H</u>$_2$). ^{13}C NMR ($CDCl_3$), δ: 11.27 (2 CH_3); 23.92 (γ-C, NC_5H_{10}); 25.47 (2 β-C, NC_5H_{10}); 46.34 (CH_2NH); 46.52 (2 CH_2N, NEt_2); 47.17 (CH_2NH); 52.15 (CH_2N); 54.23 (2 α-C, NC_5H_{10}); 58.13 (CH_2N). MS, m/z: 228.1 $[M + H]^+$.

***N,N*-Diethyl-*N′*-(2-morpholinoethyl)ethylenediamine (3g)** was synthesized from *N,N*-diethylethylenediamine (**1b**) (5.6 g, 0.048 mol) and NaOH (2.56 g, 0.064 mol) in water (23 mL) and *N*-(2-chloroethyl)morpholine hydrochloride (**2e**) (6.0 g, 0.032 mol). Yield 2.8 g (38%). B.p. 166—168 °C (22 Torr), n_D^{20} 1.4698, R_f 0.42. IR, ν/cm^{-1}: 3310 (NH). ^{1}H NMR ($CDCl_3$), δ: 0.99 (t, 6 H, 2 CH_3, J = 7.1 Hz); 2.41—2.57 (m, 12 H, 6 CH_2N); 2.66—2.74 (m, 4 H, C<u>H</u>$_2$NHC<u>H</u>$_2$); 3.07 (s, 1 H, NH); 3.68 (t, 4 H, 2 CH_2O, J = 4.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 11.30 (2 CH_3); 45.46 (CH_2NH); 46.48 (2 CH_2N, NEt_2); 46.86 (CH_2NH); 51.89 (CH_2N); 53.18 (2 CH_2N, NC_4H_8O); 57.44 (CH_2N); 66.49 (2 CH_2O). Found: m/z 230.2220 $[M + H]^+$, 252.2039 $[M + Na]^+$. $C_{12}H_{28}N_3O$. Calculated: M + H = 230.2232, M + Na = 252.2052.

***N*-[2-(2-Pyrrolidinoethylamino)ethyl]piperidine (3h)** was synthesized from *N*-(2-amonoethyl)piperidine (**1c**) (3.39 g, 0.0264 mol), NaOH (1.41 g, 0.0352 mol), and *N*-(2-chloroethyl) pyrrolidine hydrochloride (**2c**) (3.0 g, 0.0176 mol). Yield 2.1 g (52%). B.p. 168—174 °C (21 Torr), n_D^{20} 1.4868, R_f 0.35. IR, ν/cm^{-1}: 3311 (NH). ^{1}H NMR ($CDCl_3$), δ: 1.40 (m, 2 H, γ-H, NC_5H_{10}); 1.54 (m, 4 H, β-H, NC_5H_{10}); 1.74 (m, 4 H, β-H, NC_4H_8); 1.95 (br.s, 1 H, NH); 2.33—2.37 (m, 4 H, 2 CH_2N); 2.42 (t, 2 H, CH_2N, J = 6.3 Hz); 2.48 (m, 4 H, 2 CH_2N); 2.57 (t, 2 H, CH_2N, J = 6.3 Hz); 2.68—2.74 (m, 4 H, C<u>H</u>$_2$NHC<u>H</u>$_2$). ^{13}C NMR ($CDCl_3$), δ: 23.48 (2 β-C, NC_4H_8); 24.49 (γ-C, NC_5H_{10}); 26.04 (2 β-C, NC_5H_{10}); 46.94 (CH_2NH); 48.78 (CH_2NH); 54.15 (2 α-C, NC_4H_8); 54.72 (2 α-C, NC_5H_{10}); 56.01(CH_2N); 58.66 (CH_2N).

***N*-[2-(2-Piperidinoethylamino)ethyl]morpholine (3i)** was synthesized from *N*-(2-amonoethyl)piperidine (**1c**) (3.1 g, 0.024 mol), NaOH (1.3 g, 0.032 mol), and *N*-(2-chloroethyl)morpholine hydrochloride (**2d**) (3.0 g, 0.016 mol). Yield 1.9 g (49%). B.p. 187—194 °C (21 Torr), n_D^{20} 1.4884, R_f 0.35. IR, ν/cm^{-1}: 3308 (NH). ^{1}H NMR ($CDCl_3$), δ: 1.40 (m, 2 H, H(γ), NC_5H_{10}); 1.54 (m, 4 H, β-H, NC_5H_{10}); 1.98 (br.s, 1 H, NH); 2.33—2.49 (m, 12 H, 6 CH_2N); 2.67—2.71 (m, 4 H, C<u>H</u>$_2$NHC<u>H</u>$_2$); 3.68 (t, 4 H, 2 CH_2O, J = 4.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 24.47 (γ-C, NC_5H_{10}); 26.08 (2 β-C, NC_5H_{10}); 46.20 (CH_2NH); 46.79 (CH_2NH); 53.71 (2 α-C, NC_5H_{10}); 54.68 (2 CH_2N, NC_4H_8O); 58.28 (CH_2N); 58.54 (CH_2N); 67.01 (2 CH_2O).

Synthesis of diethylenetriamines 3a—c and quaternary ammonium salt hydrochlorides (4a—c)· 2 HCl (method *B*). To a stirred mixture of *N,N*-dimethylethylenediamine (**1a**) (2 equiv.), K_2CO_3 (4 equiv.), and KI (0.1 equiv.) in MeCN (12 mL per 1 g of compound **1a**), 2-chloroethylamine hydrochloride **2a**,**c**,**d** (1 equiv.) was added portionwise at 50 °C. The mixture was magnetically stirred under reflux for 16 h (TLC monitoring, methanol as an eluent). The mixture was cooled to room temperature, inorganic precipitate was filtered off. The volatiles (solvent and unreacted starting compound **1a**) were removed *in vacuo*. Triamines **3a—c** and ammonium salts **4a—c** were separated by extraction of the residue with diethyl ether. Ether-soluble compounds **3a—c** were isolated from the organic extracts by removal of the solvent *in vacuo* and subsequent vacuum distillation of the residues. Physicochemical properties of compounds **3a—c** synthesized by methods ***A*** and ***B*** are identical.

The insoluble materials remained after diethyl ether extraction were vacuum dried over $CaCl_2$ to give salts **4a—c**. Quaternary ammonium salt hydrochlorides (**4a—c**)· 2HCl were prepared by treatment of the solutions of salts **4a—c** in propan-2-ol with a solution of HCl in dioxane. The products were washed with anhydrous acetone, dried *in vacuo* over P_2O_5, and recrystallized from anhydrous methanol—anhydrous acetone.

***N,N*-Bis(2-dimethylaminoethyl)amine (3a)[13]** was synthesized from *N,N*-dimehylethylenediamine (**1a**) (6.12 g, 0.07 mol), K_2CO_3 (19.3 g, 0.14 mol), and KI (0.58 g, 0.0035 mol) in MeCN (70 mL) and 2-chloroethyldimethylamine hydrochloride (**2a**) (5.0 g, 0.035 mol). Yield 1.5 g (26%).

***N*-(2-Aminoethyl)-*N,N*-dimethyl-*N*-(2-dimethylaminoethyl)-ammonium chloride (4a).** Yield 3.7 g (54%), heavy oil. IR, ν/cm^{-1}: 3342, 3267 (NH_2). ^{1}H NMR ($CDCl_3$), δ: 2.28 (s, 6 H, 2 CH_3N); 2.51 (br.s, 2 H, NH_2); 2.77 (t, 2 H, CH_2N, J = 4.8 Hz); 3.27 (t, 2 H, C$\underline{H}_2NH_2$, J = 6.5 Hz); 3.44 (s, 6 H, 2 CH_3N^+); 3.74—3.81 (m, 4 H, 2 CH_2N^+).

***N*-(2-Aminoethyl)-*N,N*-dimethyl-*N*-(2-dimethylaminoethyl)-ammonium chloride dihydrochloride (4a · 2 HCl).** Yield 2.8 g (56%). M.p. 169—172 °C. IR, ν/cm^{-1}: 2470—2666 (HN^+). ^{1}H NMR (DMSO-d_6), δ: 2.84 (s, 6 H, 2 C$\underline{H}_3NH^+$); 3.24 (s, 6 H, 2 CH_3N^+); 3.40 (m, 2 H, CH_2NH^+, partially overlaps with the solvent signal); 3.70 (m, 4 H, C$\underline{H}_2NH_3^+$ + C$\underline{H}_2N^+$); 3.73—3.90 (m, 2 H, CH_2N^+); 8.61 (s, 3 H, H_3N^+); 11.24 (s, 1 H, HN^+). ^{13}C NMR (DMSO-d_6), δ: 32.16 ($CH_2NH_3^+$); 42.50 (2 CH_3NH^+); 48.33 (CH_2NH^+); 51.41 (2 CH_3N^+); 56.42 (CH_2N^+); 59.55 (CH_2N^+).

***N,N*-Dimethyl-*N′*-(2-pyrrolidinoethyl)ethylenediamine (3b)** was synthesized from *N,N*-dimethylethylenediamine (**1a**) (5.3 g, 0.06 mol), K_2CO_3 (16.2 g, 0.12 mol), KI (0.5 g, 0.003 mol), and *N*-(2-chloroethyl)pyrrolidine hydrochloride (**2c**) (5 g, 0.03 mol). Yield 2.05 g (37%).

***N*-(2-Aminoethyl)-*N,N*-dimethyl-*N*-(2-pyrrolidinoethyl)ammonium chloride (4b).** Yield 3.4 g (52%), heavy oil. IR, ν/cm^{-1}: 3348 (br., NH_2). ^{1}H NMR (D_2O), δ: 1.74 (m, 2 H, β-H, NC_4H_8); 2.59 (m, 4 H, α-H, NC_4H_8); 2.97 (m, 2 H, CH_2N); 3.13 (s, 6 H, 2 CH_3N^+); 3.33—3.51 (m, 6 H, C$\underline{H}_2NH_2$ + 2 C$\underline{H}_2N^+$). ^{13}C NMR (D_2O), δ: 21.76 (2 β-C, NC_4H_8); 34.50 (CH_2NH_2); 46.66 (CH_2N); 50.48 (2 CH_3N^+); 52.57 (2 α-C, NC_4H_8); 60.97 (CH_2N^+); 62.64 (CH_2N^+).

***N*-(2-Aminoethyl)-*N,N*-dimethyl-*N*-(2-pyrrolidinoethyl)ammonium chloride dihydrochloride (4b · 2 HCl).** Yield 2.9 g (64%). M.p. 188—190 °C. R_f 0.19. IR, ν/cm^{-1}: 2455—2671 (HN^+). ^{1}H NMR (DMSO-d_6—D_2O), δ: 1.95 (m, 4 H, β-H, NC_4H_8); 3.14—3.47 (m, 12 H, C$\underline{H}_2NH^+$ + 2 CH_3N^+ + 4 α-H of NC_4H_8); 3.67 (m, 2 H, C$\underline{H}_2NH_3^+$); 3.73—3.86 (m, 4 H, 2 CH_2N^+). ^{1}H NMR (DMSO-d_6), δ: 1.98 (m, 4 H, β-H, NC_4H_8); 3.13 (br.s, 2 H, C$\underline{H}_2NH^+$); 3.28 (s, 6 H, 2 CH_3N^+); 3.36—3.52 (m, 4 H, α-H, NC_4H_8, partially overlaps with the solvent signal); 3.73—3.98 (m, 6 H, C$\underline{H}_2NH_3^+$ + 2 C$\underline{H}_2N^+$); 8.92 (s, 3 H, H_3N^+); 11.69 (s, 1 H, HN^+). ^{13}C NMR (DMSO-d_6), δ: 22.76 (2 β-C), NC_4H_8); 32.14 ($CH_2NH_3^+$); 45.78 (CH_2NH^+); 51.56 (2 CH_3N^+); 53.15 (2 α-C, NC_4H_8); 57.05 (CH_2N^+); 59.38 (CH_2N^+).

***N,N*-Dimethyl-*N′*-(2-piperidinoethyl)ethylenediamine (3c)[11]** was synthesized from *N,N*-dimethylethylenediamine (**1a**) (4.79 g, 0.054 mol), K_2CO_3 (14.9 g, 0.108 mol), KI (0.45 g, 0.0027 mol), and *N*-(2-chloroethyl)piperidine hydrochloride (**2d**) (5 g, 0.027 mol). Yield 2.06 g (38%).

***N*-(2-Aminoethyl)-*N,N*-dimethyl-*N*-(2-piperidinoethyl)ammonium chloride (4c).** Yield 3.3 g (53%), white deliquescent powder. IR, ν/cm^{-1}: 3321, 3267 (NH_2). ^{1}H NMR ($CDCl_3$), δ: 1.40 (m, 2 H, H(γ), NC_5H_{10}); 1.52 (m, 4 H, β-H, NC_5H_{10}); 2.40—2.50 (m, 6 H, NH_2 + 4 α-H, NC_5H_{10}); 2.76 (t, 2 H, CH_2N, J = 5.5 Hz); 3.24 (t, 2 H, C$\underline{H}_2NH_2$, J = 6.1 Hz); 3.43 (s, 6 H, 2 CH_3N^+); 3.71—3.78 (m, 4 H, 2 CH_2N^+).

***N*-(2-Aminoethyl)-*N,N*-dimethyl-*N*-(2-piperidinoethyl)ammonium chloride dihydrochloride (4c · 2 HCl).** Yield 3.1 g (72%). M.p. 182—184 °C. R_f 0.22. IR, ν/cm^{-1}: 2376—2662 (HN^+). ^{1}H NMR (D_2O), δ: 1.41 (m, 1 H, γ-H, NC_5H_{10}); 1.69 (m, 3 H, 2 β-H + γ-H, NC_5H_{10}); 1.85 (m, 2 H, β-H, NC_5H_{10}); 3.01 (m, 2 H, α-H of NC_5H_{10}); 3.22 (s, 6 H, 2 CH_3N^+); 3.48—3.54 (m, 4 H, 2 α-H of NC_5H_{10} + C$\underline{H}_2NH^+$); 3.63—3.75 (m, 4 H, C$\underline{H}_2NH_3^+$ + C$\underline{H}_2N^+$); 3.85—3.91 (m, 2 H, CH_2N^+). ^{1}H NMR (DMSO-d_6), δ: 1.45 (br.s, 1 H, γ-H, NC_5H_{10}); 1.61 (br.s, 1 H, γ-H, NC_5H_{10}); 1.80 (br.s, 4 H, β-H, NC_5H_{10}); 3.01 (br.s, 2 H, α-H, NC_5H_{10}); 3.26 (s, 6 H, 2 CH_3N^+), 3.37—3.48 (m, 4 H, 2 α-H of NC_5H_{10} + C$\underline{H}_2NH^+$, partially overlaps with the solvent signal); 3.73 (m, 4 H, C$\underline{H}_2NH_3^+$ + C$\underline{H}_2N^+$); 4.03 (m, 2 H, CH_2N^+); 8.87 (s, 3 H, H_3N^+); 11.35 (s, 1 H, HN^+). ^{13}C NMR (DMSO-d_6), δ: 21.13 (γ-C, NC_5H_{10}); 22.18 (2 β-C, NC_5H_{10}); 32.09 ($CH_2NH_3^+$); 47.53 (CH_2NH^+); 51.33 (2 CH_3N^+); 52.35 (2 α-C, NC_5H_{10}); 56.21 (CH_2N^+); 59.48 (CH_2N^+).

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Received November 8, 2017;
in revised form January 23, 2018;
accepted February 26, 2018