Synthesis of biomimetic polyamines

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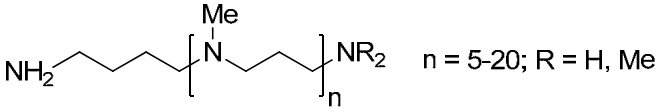
Abstract

Synthesis of methylated oligopropylamines by the stepwise repetition of reactions between methyl acrylate and amine, amidation and reduction of the resulting amide is reported. Long-chain oligomers (average 15 nitrogen atoms) were obtained via condensation reactions utilising 1,3-dibromopropane. Three new acrylic monomers were prepared by reaction of oligopropylamines with acryloyl chloride. The synthesized amines and monomers are promising as model compounds for biosilicification reactions, as biologically active substances and as building blocks in organic and polymer chemistry.

Keywords: Biogenic amines, methyl acrylate, amidation, reduction, dibromopropane, acrylic monomers

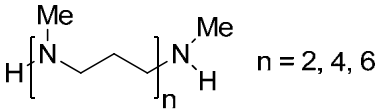
Introduction

Short-chain polyamines such as spermine, spermidine and putrescine are found in many types of organism.[1] They take part in a number of biochemical reactions, in particular these amines are necessary for cell division with an increase of their concentration being used as a cancer marker[1b] and their analogs being considered as potential anti-cancer drugs.[1c] Other, larger polyamines are found in biosilicifiying organisms – diatom algae[2] and, more recently sponges.[3] These compounds are relatively long-chain polypropylamines, usually with methylated nitrogens that often contain a putrescine group at one end of the molecule.



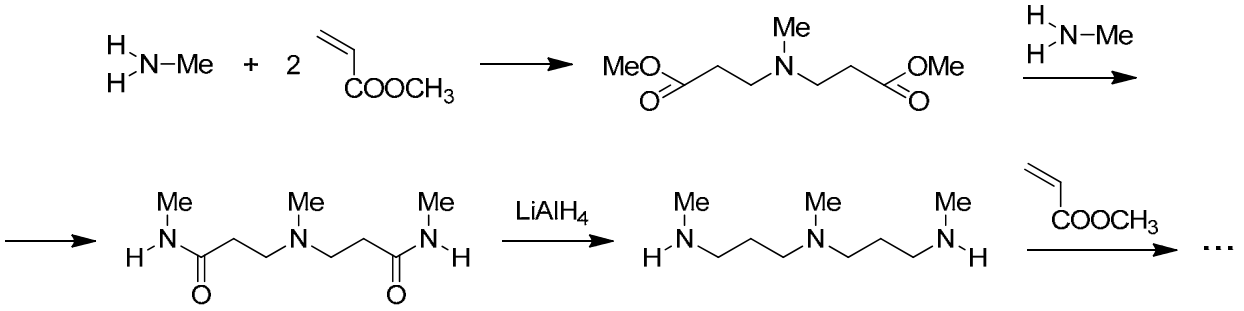
Methylated polypropylamines (MPPA) have been found in living organisms in the free state and as part of complex post-translationally modified proteins – silaffins.[2,3] The physiological function of these compounds is not clear though they are associated with biogenic silica and so are likely to be important for the formation of silica structures – exoskeletons (frustules) of diatoms and the spicules of sponges. Understanding the biochemical behaviour of MPPA is impossible without knowledge of their chemical and physico-chemical properties, especially their influence on the condensation of silicic acid or its precursors. Isolation of MPPA from natural sources is a relatively complex process and investigators have only been able to generate microgram quantities of these polyamines which seriously limits the *in vitro* experimentation possible. Additionally, MPPA are interesting molecules in their own right due to their potential physiological activity and also as building blocks for more sophisticated compounds, including polymers.

Biogenic short-chain polyamines, their analogs and derivatives are studied for many years.[4] Unfortunately, MPPA were not in focus of these investigations. There are several works only describing synthesis of MPPA with 3-6 nitrogen atoms[5] but the procedures are not universal and complicated with formation of amine mixtures. On the other hand, in the synthesis of polyamidoamine dendrimers[6] an elegant scheme for increase of amidoamine chain is used. Taking into account these ideas, we had elaborated[7] a step-wise method for the synthesis of MPPA and obtained three amines with 3, 5 and 7 nitrogen atoms:



The procedure consisted of repetitions of reactions between methyl acrylate and an amine, followed by amidation and reduction of the resulting amide (Scheme 1). A study of the silicifying activity of these MPPA allowed us to hypothesize the biological role of such molecules.[8] Further development of the bio-modeling studies needed further MPPA molecules, including oligomeric samples closer in size to the natural polyamines as well as polymers with side polyamine chains that would mimic the silaffins.

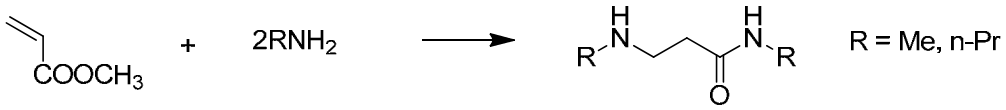
This study was devoted to elaboration of synthetic procedures that allowed us to obtain the required new polyamines and some known structures by more convenient approaches.



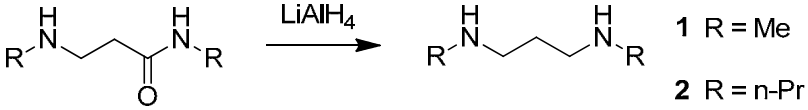
Scheme 1. Step-wise synthesis of the odd numbered MPPA molecules.

Result and Discussion

Synthesis of symmetrical MPPA with even numbers of nitrogens (Table, **1-4**) was started from the reaction of methyl acrylate with two equivalents of methylamine followed by reduction of the resulting amide:



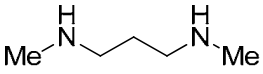
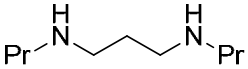
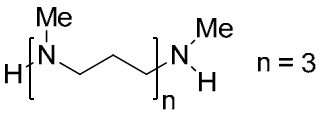
Method A

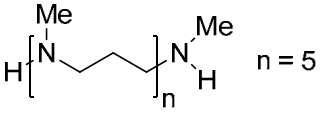
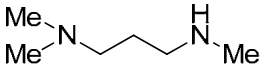
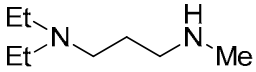
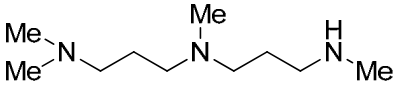
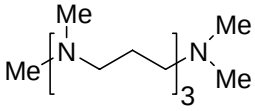
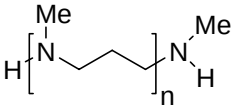
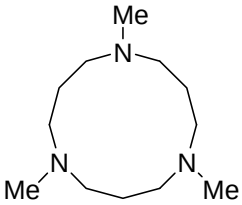
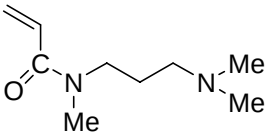
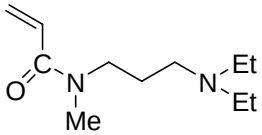
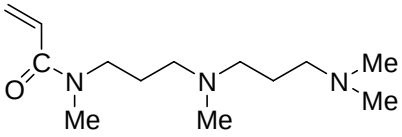


Method B

Scheme 2

Table. Chemical structures of synthesized amines

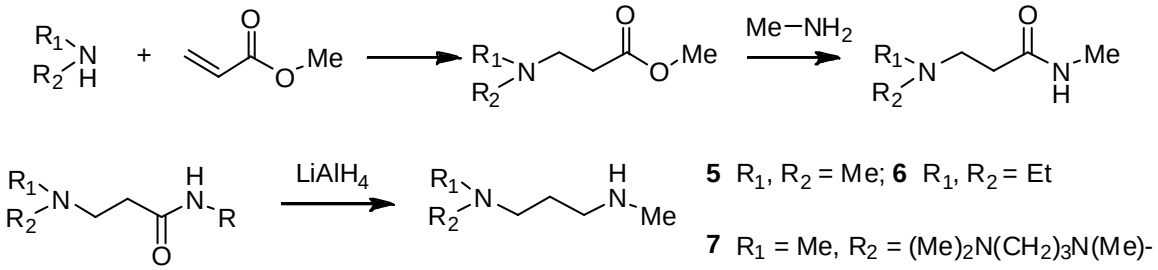
#	Chemical structure	Method	Yield, %
1		A	35
2		A	30
3		B	36

#	Chemical structure	Method	Yield, %
4*		B	31
5		C	47
6		C	44
7*		C	41
8		D	27
9*	 n = 8, 11, 14, 17,...	D	33
10		D	4.2
11*		E	81
12*		E	76
13*		E	70

*New compounds

Amine **1** can be synthesized by various routes, but the method proposed here seems to be an universal one opening the way to diamines with various substituents by changing the starting alkylamine, e.g. using propylamine we obtained **2**. The amine **2** and similar propylamines had been synthesized previously starting from 1,3-dibromopropane and primary amines but with low yields (<10%) and the reaction was complicated by various side-reactions[9] which were reduced by using toluenesulphonamide protective groups.[10] Increase of the chain length (amines **3** and **4**) is possible according to Scheme 1 by consecutive reaction with methyl acrylate, methyl amine and $LiAlH_4$ (**Method B**). Amine **3** had also been obtained by condensation of BOC-protected **1** with 1,3-dibromopropane[11].

Unsymmetrical MPPA containing one N-H moiety only (compounds **5-7**) are interesting as monofunctional building blocks for the design of more complex compounds. These polyamines were prepared with an approach similar to that depicted in Scheme 1 starting from the corresponding dialkylamines:

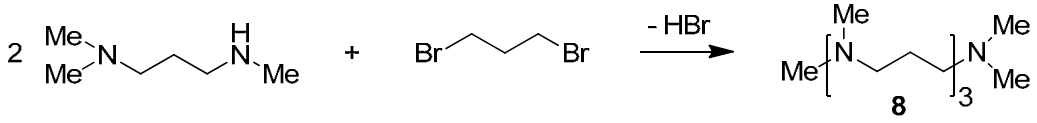


Method C

Scheme 3

Diamines **5** and **6** have also been synthesized by others by the reduction of *N*-(3-dimethylamino-propyl)-formamide[12] and *N*-(3-diethylamino-propyl)-formamide[13a] or cleavage of 3-diethylamino-1-methylanilino-propane with $NaNO_2/HCl$[13b] respectively.

Reaction of unsymmetrical MPPA with 1,3-dibromopropane opens the way to the doubling of the chain length of MPPA in a single stage:

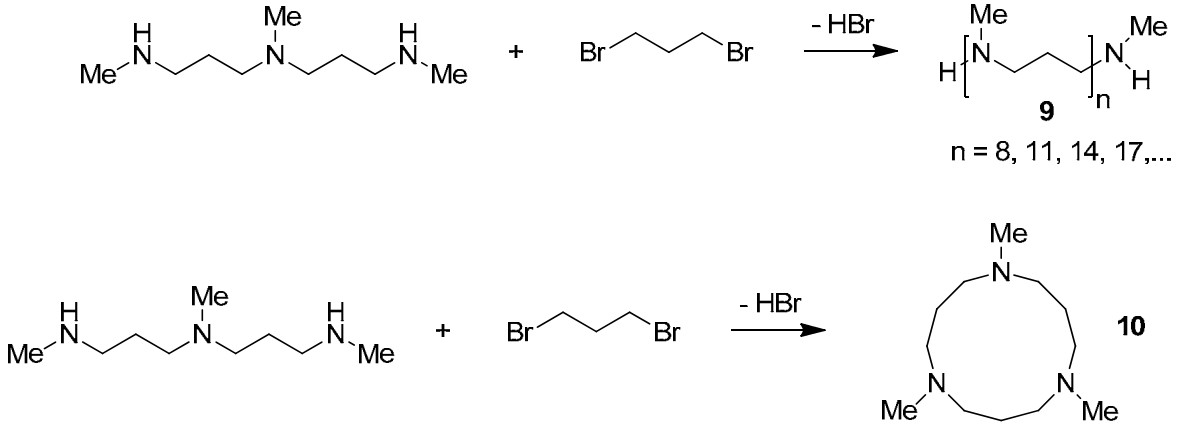


Method D

Scheme 4

This approach was used to obtain tetra-amine **8** which had previously been prepared by reduction of (*N*,*N*-dimethyl-β-ala)-(*N*-methyl-β-ala)-*N*-methyl-β-ala-dimethylamide.[14] In the case

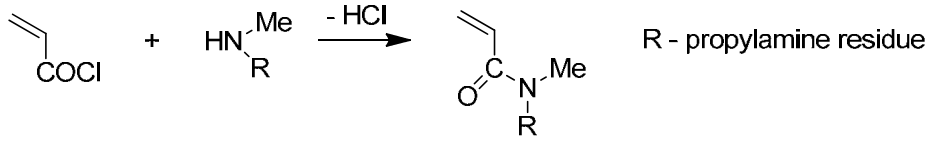
of MPPA having two NH moieties competing reactions of oligomerization and cyclization were observed:



Scheme 5

The oligomerization reaction results in an oligomeric mixture **9** very similar to the polyamines found in diatom algae.[2] The average chain length corresponds to 15 nitrogens according to NMR data. Mass-spectra show (Figure 1) the presence of oligomers containing up to 18 nitrogens with minor amounts of higher fractions with up to 27 nitrogens. The cyclic compound **10** has been synthesized previously by reductive methylation of 1,5,9-tiazacyclododecane[15] but the approach presented here may be more usable as it is one-stage synthesis from commercial compounds.

Three new acrylic monomers **11-13** were synthesized with good yields by interaction of acryloyl chloride with the corresponding amines **5-7**:



Method E

Scheme 6

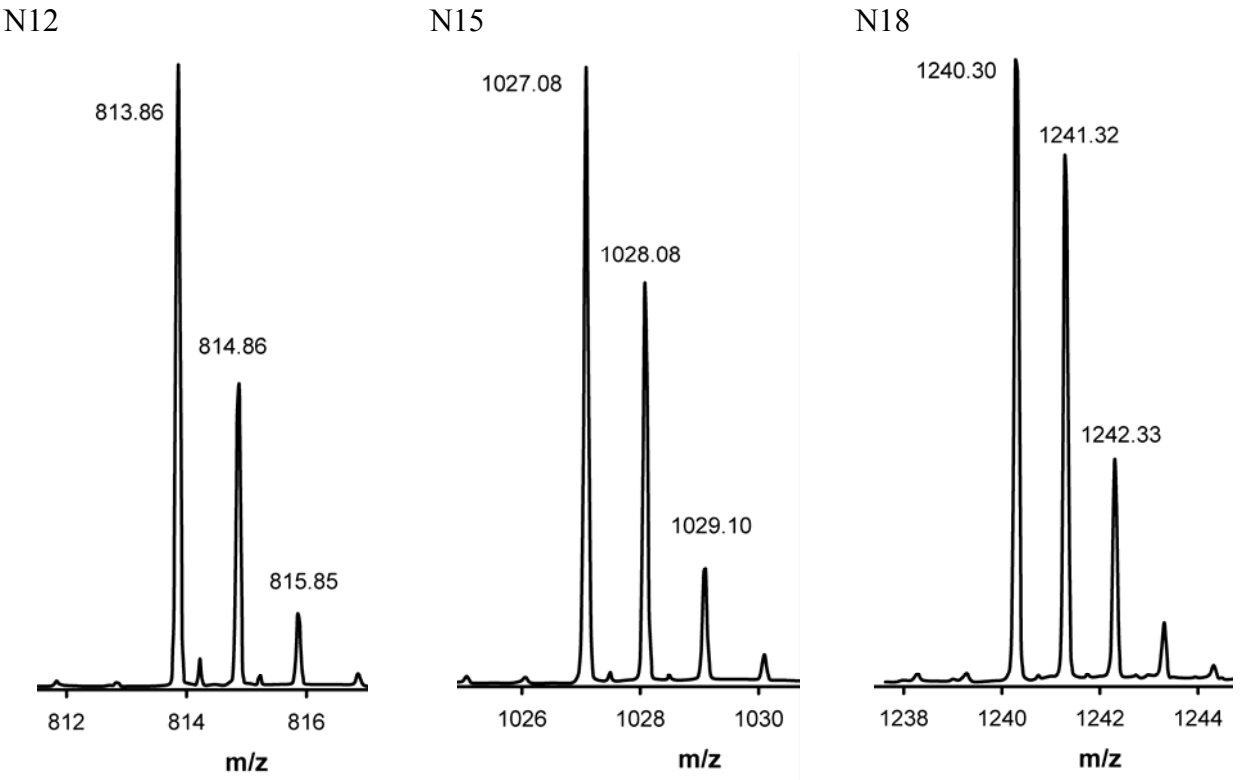


Figure 1. Fragments of mass-spectrum of oligomer **9**. Captions above the traces correspond to the number of nitrogens in the oligomer fractions.

Conclusions

In our study of methods to generate MPPAs we have obtained 3 new polyamines and 3 amine-containing acrylic monomers. The developed procedures are relatively universal and allow the synthesis of a number of new substances by simple changes of substituents in the starting materials. The absence of expensive protective groups and solid-phase supports is attractive for large-scale production. These new polyamines and amino-containing monomers are promising not only as model compounds for studies of biosilicification but also in following areas:

- as starting materials in organic synthesis;
- catalysts in synthesis of ordered silica and other inorganic structures, e.g. we have shown formation of submicron hollow silica spheres using MPPA as template[8];
- design of new polymers, especially smart, "intelligent" systems capable of intensive reply to small change of the environment. Acrylamide monomers **11-13** are interesting as representatives of the very small class of amino-containing monomers. Preliminary experiments show their high activity in radical polymerization and the obtained polymers demonstrate thermosensitivity similar to poly(N-isopropylacrylamide)[16] due to the

presence of hydrophobic methylene, methyl or ethyl groups. This effect is also pH-responsive which is useful in drug-delivery systems

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-500S (500 MHz) spectrometer in deuterochloroform ($CDCl_3$). Infrared spectra were recorded on an Infralum FT-801 spectrophotometer.
Purity of the prepared compounds was ascertained with an HP-4890 gas-liquid chromatograph equipped with a flame ionization detector and capillary column (15 m long, 15% polyphenylsiloxane as the stationary liquid phase). During the analyses the temperature was programmed to rise from 100 ° up to 250 °C over five minutes.

Conditions of mass spectrometric analysis. The apparatus used was an Agilent 6210 TOF LC/MS System. Samples were dissolved in water containing 0.1% formic acid at concentrations of 25 mg/l. The flow rate of the mobile phase was set at 0.1 ml/min, the injection volume of sample solution was 20 µl, and the stop time was set at 2 min. The usual conditions for TOF MS were as follows: mass range was m/z 150-2000 and scan time was 1 s with interscan delay of 0.1 s; mass spectra were recorded under ES+, V mode, centroid, normal dynamic range, and cone voltage using tune page; tune parameters were capillary voltage (3500 V), sample cone voltage (100 V), desolvation temp (325 °C), source temp (100 °C), cone gas flow (50 l/min), desolvation gas flow (300 l/min). Under these conditions, major peaks of the poly(N-methylpropylamines) appeared as proton-bound ions.

General procedure for amide reduction
To a 0.385 M solution of an amide in diethyl ether (for diamides dilution doubled) was portionwise added powdered lithium aluminum hydride (1.36 mole of $LiAlH_4$ per amide group) within about five hours. At that the mixture was stirred with a magnetic bar under a reflux condenser. The resulted suspension was gently refluxed for a day, cooled with an ice bath, carefully quenched with water (71 mL per a mole of $LiAlH_4$), then mixed with a 50% (w/w) solution of potassium hydroxide in water (107 g. of the solution per a mole of $LiAlH_4$). The precipitate was filtered with a Buchner funnel and washed with ether (2 x 600 mL per a mole of initial amide). The combined filtrate was dried with potassium hydroxide pellets, evaporated, and the residue distilled under reduced pressure to give the target amine.

Method A. Methylacrylate was added dropwise to a stirred cooled (t < 10 ºC) 8-25 M solution of a primary amine ($R\text{-}NH_2$) in ethanol (5.6 mole of methylacrylate per a mole of amine). The reaction mixture was kept at ambient temperature in the case of methyl amine or refluxed in the case of n-propyl amine until FTIR spectroscopy showed no ester C=O (1740 cm^{-1}). Then the

volatiles were evaporated with a water pump and the residue distilled in vacuum to give the corresponding *N*-Alkyl-3-(alkylamino)-propanamide. Reduction of the amide according to the general procedure gave the target N^1,N^3-dialkyl-1,3-propanediamine.

Method B. To a cooled (t < 10 ºC) stirred 15% solution of amine **1** or **3** in ethanol was added dropwise a three-fold molar excess of methylacrylate. The resulted mixture was refluxed for about 24 hours in whole. Then the volatiles were evaporated with a water pump and the residue kept at 80 °C on a water bath in vacuum of an oil pump for 90 minutes. After cooling to RT the obtained oily diester was mixed up with a four-fold molar excess of 8 M solution of methylamine in ethanol. The mixture was kept at RT until FTIR spectroscopy showed no ester C=O (1740 cm^{-1}). Then the volatiles were removed in the above manner leaving the corresponding crude diamide. Its reduction according to the general procedure gave the target amine.

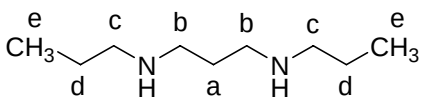
Method C. Methylacrylate was added dropwise to an equimolar amount of a stirred and cooled (t < 10 ºC) 5.5-5.6 M solution of a secondary amine (R-NH-R) in ethanol. The reaction mixture was kept for two days at ambient temperature; the solvent was evaporated with a water pump. The residue was distilled under reduced pressure to give the corresponding methyl 3-(dialkylamino)propanoate. Following ammonolysis (control over the 1740 cm^{-1} band) with a double molar excess of 8 M solution of methylamine in ethanol gave the amide which was in turn converted to the target amine through the general reduction procedure.

Method D. N^1,N^3-dimethyl-N^1-[3-(methylamino)propyl]-1,3-propanediamine[4] was condensed with 1,3-dibromopropane in ethanol at 70 ˚C. The manner, the rate of mixing of the reagents and the isolation way were tuned up depending on what linear or cyclic target product is preferable.

Method E. A solution of amine **5** or **6** or **7** (0.120 mol) in 45 mL of methylene chloride was dropped in to a cooled, stirred solution of the equimolar amount of acryloyl chloride (10.86 g, 0.120 mol) in 250 mL of methylene chloride keeping the reaction mixture at about -10 ºC. When the addition was finished, stirring was continued at room temperature for 20 minutes. Then the mixture was quenched with 34 g. of a potassium carbonate water solution (50% w/w) followed by the addition of anhydrous potassium carbonate to thicken the water phase. The methylene chloride solution was poured off, dried with potassium carbonate, evaporated at a water pump pressure and distilled in vacuo to yield the corresponding acrylamide.

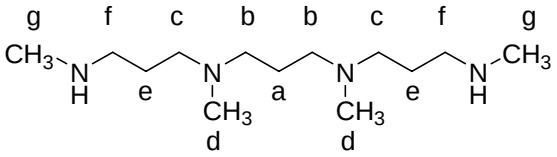
N^1,N^3-Dimethyl-1,3-propanediamine, 1. The **method A** was followed using methylacrylate (40.5 mL, 0.45 mol), 8 M solution of methylamine in ethanol (2.5 mol, 312 mL) to obtain *N*-Methyl-3-(methylamino)-propanamide **1b** as a colorless oily liquid (35.0 g, 67%, b.p. 94°C/0.5 Hgmm); purity 98% (by GC). Then **1b** (30 g, 0.258 mol) was reduced to **1** (14.0 g of a colorless liquid, 53%, b.p. 36ºC/10 Hgmm; purity 97% by GC). FTIR (film, cm^{-1}): 3282, 2932, 2879, 2845, 2791, 1474, 1448, 1370, 1273, 1146, 1124, 1053, 811, 758.

N^1,N^3-Dipropyl-1,3-propanediamine, 2



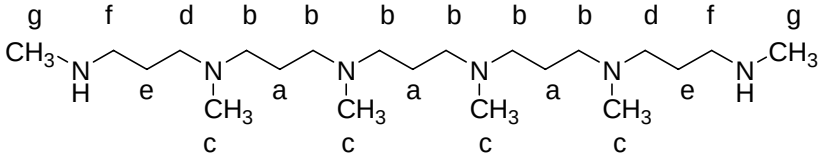
The **method A** was followed using n-propylamine (148 g, 2.5 mol in 100 mL of ethanol) to obtain *N*-n-Propyl-3-(n-propylamino)-propanamide **2b** as a colorless liquid (48.1 g, 62%, b.p. 125-130°C/1 Hgmm); purity 97% (by GC). The reduction of **2b** (5.0 g, 0.0290 mol) gave **2** as a colorless liquid (2.2 g, 48%, b.p. 47-50ºC/13 Hgmm); purity 95% (by GC). FTIR (film, cm^{-1}): 3287, 2957, 2930, 2873, 2807, 1459, 1377, 1339, 1296, 1131, 1067, 890, 778, 733. ^{13}C NMR (CCl_4): 11.79 ($2C_e$), 23.19 ($2C_d$), 30.3 (C_a), 48.61 ($2C_b$), 51.88 ($2C_c$). ^1H NMR (CCl_4): 0.9 ($6H_e$), 1.43 ($4H_d$), 1.55 ($2H_a$), 2.48 ($4H_b$), 2.58 ($4H_c$). MS (*m/z*): 159 $[M+H]^+$.

N^1,N^3-Dimethyl-N^1,N^3-bis[3-(methylamino)propyl]-1,3-propanediamine 3



The **method B** was followed using **1** (3.83 g, 0.0375 mol) to obtain **3** as a colorless liquid (3.3 g, 36%, 108ºC/0.5 Hgmm). FTIR (film, cm^{-1}): 3290, 2941, 2883, 2838, 2785, 1464, 1373, 1312, 1271, 1243, 1209, 1147, 1120, 1068, 1051, 820, 738. ^{13}C NMR (CCl_4): 25.22 ($2C_e$), 27.36 (C_a), 36.5 ($2C_g$), 42.13 ($2C_d$), 50.6 ($2C_f$), 55.76 ($2C_c$), 56.1 ($2C_b$). ^1H NMR (CCl_4): 1.56-1.66 ($6H_{2e,a}$), 2.20 ($6H_d$), 2.31-2.39 ($8H_{c,b}$), 2.40 ($6H_g$), 2.58 ($4H_f$). MS (*m/z*): 245 $[M+H]^+$.

N^1,N^{19},4,8,12,16-Hexamethyl-4,8,12,16-tetraazanonadecane-1,19-diamine 4

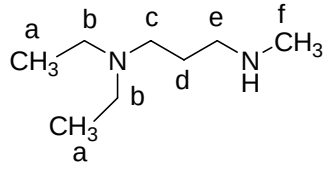


The **method B** was followed using **3** (4,2 g, 0.0172 mol) to obtain **4** as a colorless liquid (2.06 g, 31%, 160-170ºC/0.5 Hgmm). FTIR (film, cm-1): 3294, 2945, 2883, 2837, 2785, 1460, 1370, 1311, 1240, 1213, 1150, 1122, 1060, 972, 833, 739. ^1H NMR: 1.56-1.65 ($10H_{a,e}$), 2.20 (28Hd, b, c), 2.40 (6Hg), 2.58 (4Hf). ^{13}C NMR: 25.23 ($2C_e$), 27.38 ($3C_a$), 36.46 ($2C_g$), 42.11 ($4C_c$), 50.57 ($2C_f$), 55.67 ($2C_d$), 56.08 ($6C_b$). MS (m/z): 387 [M+H]+.

N^1,N^1-Dimethyl-N^3-methyl-1,3-propanediamine 5. The **method C** was followed using 5.6 M dimethylamine in ethanol (0.55 mol, 98 mL) and methylacrylate (50 mL, 0.55 mol) to obtain methyl 3-(dimethylamino)propanoate **5a** as a colorless liquid (63.5 g, 88%, b.p. 59-60ºC/15 Hgmm) as a colorless liquid; purity 98% (by GC). The next step was carried out using **5a** (52.5 g, 0.40 mol) and 150 mL of 8 M methylamine (1.2 mol) in ethanol. Vacuum distillation gave 3-(dimethylamino)-*N*-methylpropanamide **5b** as a colorless liquid (47.4 g, 91%, b.p. 90ºC/15

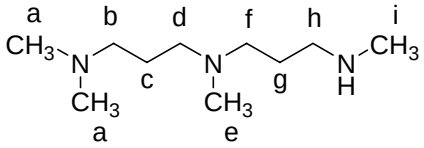
Hgmm); purity 98% (by GC). The general reduction protocol was followed using **5b** (13.0 g, 0.100 mol), 260 mL of dried diethyl ether, $LiAlH_4$ (5.18 g, 0.136 mol), water (9.7 mL), 50% (w/w) solution of potassium hydroxide (14.5 g.), diethyl ether for extraction (2 x 60 mL). Vacuum distillation gave **5** (6.86 g, 59%, b.p. 40ºC/15 Hgmm) as a colorless liquid; purity 96% (by GC). FTIR (film, cm^{-1}): 3300, 2966, 2940, 2856, 2814, 2766, 2725, 1461, 1377, 1298, 1264, 1152, 1123, 1097, 1071, 1041, 839, 744.

N^1,*N*^{1}-Diethyl-*N*^{3}-methyl-1,3-propanediamine 6



The **method C** was followed using diethylamine (40.2 g, 0.55 mol in 100 mL of ethanol) to obtain methyl 3-(diethylamino)propanoate **6a** as a colorless liquid (78.8 g, 90%, b.p. 81 ºC/15 Hgmm; purity 99% by GC). Then **6a** (55.7 g, 0.35 mol) was converted to 3-(Diethylamino)-*N*-methylpropanamide **6b** as a colorless liquid (49.3 g, 89%, b.p. 114ºC/15 Hgmm; purity 98% by GC). The reduction of **6b** (15.8 g, 0.100 mol) gave **6** as a colorless liquid (7.93 g, 55%, b.p. 73-79ºC/15 Hgmm); purity 96% (by GC). FTIR (film, cm^{-1}): 3296, 2969, 2935, 2873, 2839, 2794, 1470, 1449, 1382, 1344, 1294, 1264, 1238, 1202, 1175, 1123, 1071, 1000, 780, 729. ^{1}H NMR (CCl_4): 1.10 ($6H_a$), 1.64 ($2H_d$), 2.45 ($5H_{c,\,f}$), 2.50 ($4H_b$), 2.63 ($2H_e$). ^{13}C NMR (CCl_4): 12.0 ($2C_a$), 27.39 (C_d), 36.43 (C_f), 46.89 ($2C_b$), 50.7 (C_e), 51.33 (C_c). MS (*m/z*): 145 $[M+H]^+$.

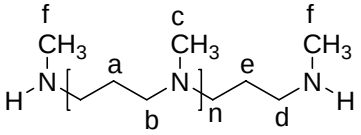
N^1-[3-(Dimethylamino)propyl]-*N*^{1},*N*^{3}-dimethyl-1,3-propanediamine 7



The **method C** was followed using **5** (15.0 g, 0.129 mol) to obtain the propanoate **7a** as a colorless liquid (23.5 g., 90%, b.p. 70-73 ºC/0.5 Hgmm). Then **7a** (55.7 g, 0.35 mol) was converted to the amide **6b** as a colorless liquid (23.4 g., 89%**,** b.p. 130-132ºC/0.5 Hgmm). The reduction of **6b** (20.8 g., 0.111 mol) gave the amine **7** (9.85 g, 51%, b.p. 55-56 ºC/0.5 Hgmm, the overall yield 40.8%). FTIR (film, cm^{-1}): 3289, 2943, 2840, 2813, 2786, 2727, 1463, 1376, 1312, 1265, 1213, 1153, 1122, 1099, 1062, 1040, 969, 829, 751. ^{1}H NMR (CCl_4): 1.55-1.65 ($4H_{c,\,g}$), 2.19 ($3H_e$), 2.20 ($6H_a$), 2.25 ($4H_{d,\,f}$), 2.4 ($5H_{b,\,i}$), 2.58 ($2H_h$). ^{13}C NMR (CCl_4): 25.51 (C_g), 27.39 (C_c), 36.48 (C_i), 42.10 (C_e), 45.36 ($2C_a$), 50.59 (C_h), 55.71 (C_b), 56.10 (C_d). MS (*m/z*): 188 $[M+H]^+$.

***N*[1],*N*[3]-bis[3-(dimethylamino)propyl]-*N*[1],*N*[3]-dimethyl-1,3-propanediamine 8.** This compound was prepared according to **method D**. During seven hours a mixture of 14.00 g. (0.121 mol) of **5** and 2 mL of ethanol was slowly added to a stirred solution of 8.13 g. (0.040 mol) of 1,3-dibromopropane in 20 mL of ethanol keeping the temperature of the reaction mixture at 50˚C. When the addition was completed the reaction vessel was allowed to cool down to room temperature. After keeping for sixteen hours at RT the mixture was stirred at 70˚C for thirty minutes followed by cooling and evaporation of the solvent under reduced pressure. The residue was successively mixed with a solution of 22 g. of potassium carbonate in 30 mL of water and 1.58 g. of potassium hydroxide. The resulted mixture, a bright red oily liquid with a white precipitate, was filtered through a glass filter. The solid on the filter was washed with ether (5 mL). The filtrate was mixed with 10 mL of water and extracted with ether (3 × 5 mL). The combined ether extract was dried with potassium carbonate and evaporated under reduced pressure. The residue was distilled first under 15 Hgmm pressure (2.79 g. of 40-50˚C fraction) then the pressure was reduced to 0.5 Hgmm (3.00 g. of **8,** 27%, b.p. 109-112˚C). FTIR (film, cm^{-1}): 2944, 2857, 2839, 2814, 2784, 2762, 1459, 1375, 1312, 1262, 1203, 1168, 1122, 1098, 1071, 1042, 967, 814, 740. MS (*m/z*): 273 $[M+H]^+$.

Oligomeric amines H_3C-NH-[$(CH_2)_3$-N(CH_3)-]$_n$-H, 9



This compound was prepared according to **method D**. A solution of 5.36 g. (0.0265 mol) 1,3-dibromopropane in 8.9 mL ethanol was dropped in to a stirred mixture of 9.2 g. (0.0531 mol) of *N*[1],*N*[3]-dimethyl-*N*[1]-[3-(methylamino)propyl]-1,3-propanediamine[4] and 2 mL of ethanol at ambient temperature over seven hours and forty minutes. The resulted yellow mixture was left at ambient temperature for sixteen hours.

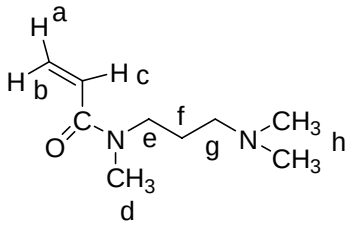
Then the vessel was set to 70 ˚C in a water bath and heated for 30 minutes in which time the solution turned brown with an orange tint. For the next thirty minutes it was allowed to cool to room temperature. Powdered potassium hydroxide (5.91 g., 0.105 mol) was then gradually added to the stirred reaction solution. After stirring for an hour the mixture constituted a white precipitate in a yellow oily liquid. The solid was filtered off on a glass filter and washed with ethanol (4 × 5 mL). The combined filtrate was evaporated with a water pump. The residue was dissolved in 50 mL of water to be extracted first with ether (3 × 100 mL) and then with CH_2Cl_2 (3 × 50 mL). The extraction with CH_2Cl_2 gave a paste. It was dissolved in ether to form a suspension. The solid was filtered off; the filtrate was evaporated and dried in vacuum (150 ºC/0.5 Hgmm, 6 h) to give **9** as a yellow oily liquid (1.50, 33%). ^1H NMR: 1.51-1.75 ($H_{a,\ e}$), 2.16-2.22 (H_c), 2.39-2.43 (H_f), 2.53-2.65 ($H_{b,\ d}$); average polymerization degree (number of nitrogens in the chain) was 15 calculating from intensities of H_c and H_f signals. FTIR (film, cm^{-}

[1]): 3304 (very weak), 2946, 2839, 2785, 2765, 1458, 1422, 1368, 1315, 1246, 1211, 1153, 1121, 1054, 968, 837, 731.

1,5,9-Trimethyl-1,5,9-triazacyclododecane, 10. This compound was prepared according to **method D**. Ethanol solutions of 0.0545 mole of N^1,N^3-dimethyl-N^1-[3-(methylamino)propyl]-1,3-propanediamine (the compound was prepared according to [4]; 9.445 g. diluted with ethanol to a volume of 17.1 mL) and 0.0474 mole of 1,3-dibromopropane (9.570 g. diluted with ethanol to 17.1 mL) were added to stirred ethanol (100 mL) simultaneously by 0.57 ml portions of each solution every ten minutes. The temperature of reaction mixture was kept between 46-50ºC. The addition was completed over five hours followed by stirring at 47ºC for 2.5 hours. Then the reaction vessel was cooled and left at room temperature.

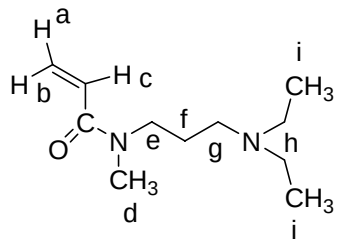
After sixteen hours the mixture was warmed from RT to 47ºC and stirred for three hours followed by refluxing for 1.5 hours. To the cooled reaction vessel powdered potassium hydroxide (5.35 g.) was added. After twenty minutes of stirring the mixture was filtered and evaporated using a water pump. The viscous red residue was diluted with 25 mL of water and extracted with ether (25 mL x 3). The combined ether extracts was dried with potassium hydroxide powder. After evaporation of the solvent the residue was distilled under vacuum of an oil pump to give **10** as a yellowish liquid (0.43 g., 4.2%, b.p. 70-80ºC/ 0.5 Hgmm). FTIR (film, cm^{-1}): 3075, 2947, 2837, 2787, 1460, 1371, 1344, 1316, 1276, 1244, 1224, 1191, 1136, 1118, 1105, 1076, 1059, 1051, 995, 963, 916, 862, 833, 806, 741, 708. MS (*m/z*): 214 $[M+H]^+$.

***N*-[3-(Dimethylamino)propyl]-*N*-methylacrylamide, 11**



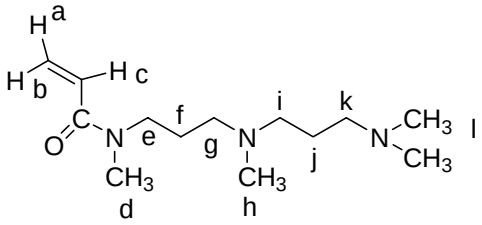
The **method E** was followed using a solution of **5** (13.94 g., 0.120 mol) in 45 mL of methylene chloride, a solution of acryloyl chloride (10.86 g, 0.120 mol) in 250 mL of methylene chloride, 34 g. of a potassium carbonate water solution (50% w/w), anhydrous potassium carbonate (40 g.) to obtain **11** as a colorless oily liquid (16.55 g., 81%, b.p. 80ºC/ 0.5 Hgmm). FTIR (film, cm^{-1}): 2942, 2860, 2816, 2765, 1651, 1612, 1460, 1416, 1403, 1379, 1264, 1218, 1164, 1108, 1058, 1041, 979, 956, 795. ^{1}H NMR: 1.69-1.79 ($2H_f$), 2.20-2.32 ($6H_h$, $2H_g$), 3.0-3.08 ($3H_d$), 3.40-3.50 ($2H_e$), 5.64-5.70 ($1H_b$), 6.28-6.37 ($1H_a$), 6.53-6.72 ($1H_c$). MS (*m/z*): 171 $[M+H]^+$.

***N*-[3-(Diethylamino)propyl]-*N*-methylacrylamide, 12**



The **method E** was followed using **6** (17.31 g., 0.120 mol) to obtain **12** as a colorless liquid (18.08 g., 76%, b.p. 105-108 ºC/0.5 Hgmm). FTIR (film, cm^{-1}): 2968, 2934, 2874, 2803, 1648, 1613, 1469, 1455, 1443, 1416, 1404, 1379, 1290, 1260, 1214, 1162, 1101, 1070, 979, 956, 795. ^{1}H NMR: 0.98-1.02 ($6H_i$), 1.68-1.77 ($2H_f$), 2.21-2.34 ($2H_g$, $4H_h$), 2.98-3.07 ($3H_d$), 3.41-3.50 ($2H_e$), 5.64-5.71 ($1H_b$), 6.29-6.38 ($1H_a$), 6.51-6.73 ($1H_c$). MS (*m/z*): 199 $[M+H]^+$.

***N*-3-[[3-(Dimethylamino)propyl](methyl)amino]propyl-*N*-methylacrylamide, 13**



The **method E** was followed using **7** (22.48 g., 0.120 mol) to obtain **13** as a colorless liquid (20.27 g., 70%, b.p. 125 ºC/0.5 Hgmm). FTIR (film, cm^{-1}): 2943, 2857, 2840, 2814, 2785, 2765, 1650, 1614, 1460, 1416, 1402, 1377, 1315, 1262, 1218, 1167, 1128, 1099, 1062, 1043, 979, 958, 826-894, 795. ^{1}H NMR: 1.58-1.78 ($2H_f$, $2H_j$), 2.18-2.40 ($3H_h$, $2H_g$, $2H_i$, $2H_k$, $6H_l$), 2.9-3.09 ($3H_d$), 3.31-3.50 ($2H_e$), 5.64-5.70 ($1H_b$), 6.29-6.37 ($1H_a$), 6.54-6.72 ($1H_c$). MS (*m/z*): 242 $[M+H]^+$.

Acknowledgements

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