Oligoaziridines: ring opening with hydrobromic acid

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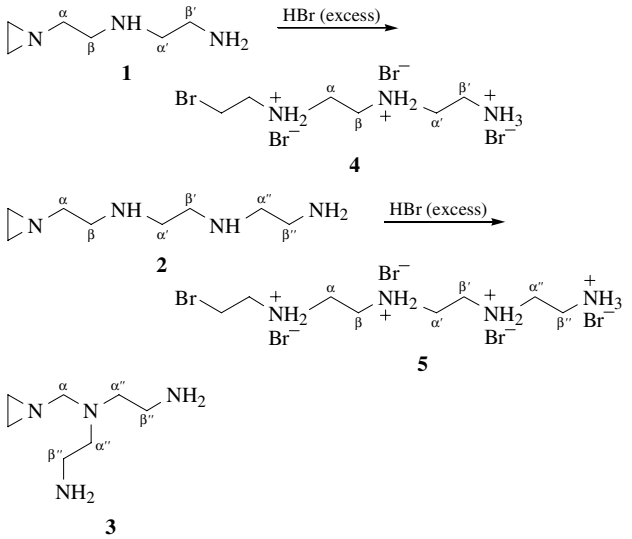
Ring opening in aziridine tri- and tetramers with HBr leads to the stable hydrobromides of corresponding N^1-(β-bromoethyl)-ethyleneamines; an initial mixture of linear and branched tetraethyleneimine isomers yielded only a linear bromo derivative.

Oligoaziridines possess an antiviral activity.[1] Owing to the presence of an electrophilic reaction centre and an oligocationic site, which provides affinity to nucleic acid polyanions, oligoaziridines are promising reagents for the selective inactivation of viral infectivity.[2] However, practical use of these reagents is restricted because of their polymerization susceptibility during long storage, contact with air, pH decrease, or when entering reaction media containing inducers of cationic polymerization. Hydrobromination of oligoaziridines with HBr leads to the formation of N^1-(β-bromoethyl)ethyleneamines, which are also reactive in aminoalkylation, but stable in storage as solid hydrobromides.[3] The products of ring opening in aziridine trimer and tetramer with HBr were characterised in this study.

Aziridine trimer **1** and tetramer (a mixture of **2** and **3**) (Scheme 1) were obtained by fractional distillation of the products of ethyleneimine polymerization at the beginning stage.[4] The ^{1}H and ^{13}C NMR spectra of freshly distilled oligoaziridines did not contain signals due to impurities. An analysis of the integral intensities of ^{13}C NMR signals of aziridine tetramer (fraction with bp 110–112 °C/1 Torr) demonstrated that the tetramer fraction was a mixture of linear and branched isomeric forms in a ratio of ~2:1,† which was consistent with published data.[5]

The synthesis of N^1-(β-bromoethyl)ethyleneamines from oligoaziridines was carried out by the procedure‡ described elsewhere.[6]



Scheme 1

† ^{1}H and ^{13}C NMR spectra were measured on Bruker WM-250 and Bruker AC-200 spectrometers, respectively.

Spectroscopic data for **1** (in D_2O at 297 K). ^{1}H NMR δ: 1.35 [m, 2H, aziridine CH_2 (*cis* to α-CH_2)], 1.75 [m, 2H, aziridine CH_2 (*trans* to α-CH_2)], 2.38 (t, 2H, α-CH_2). ^{13}C NMR δ: 27.68 (2C, aziridine C), 41.08 (1C, β′-C), 49.04 (1C, β-C), 51.94 (1C, α′-C), 59.81 (1C, α-C).

For the mixture of **2** *and* **3** (in D_2O at 297 K). ^{1}H NMR δ: 1.35 [m, aziridine CH_2 (*cis* to α-CH_2), **2** and **3**], 1.75 [m, aziridine CH_2 (*trans* to α-CH_2), **2** and **3**]. ^{13}C NMR δ: 27.68 (aziridine C, **2**), 27.81 (aziridine C, **3**), 38.95 (β″-C, **3**), 41.07 (β″-C, **2**), 48.83 (α′-C, **2**), 49.01 (β′-C, **2**), 49.14 (β-C, **2**), 51.89 (α″-C, **2**), 54.08 (β-C, **3**), 57.35 (α″-C, **3**), 57.76 (α-C, **3**), 59.80 (α-C, **2**).

The assignments for ^{1}H and ^{13}C NMR spectra of both initial substances and products were made using two-dimensional ^{1}H–^{1}H and ^{1}H–^{13}C procedures (COSY) and the ACDLabs database.

The ^{1}H NMR spectra of the reaction products contained distinctive low-field chemical shifts of α- and β-$BrCH_2$ groups (~3.75 and 3.65 ppm).§ A correlation between the total intensity of α″- and β″-CH_2 proton signals and that of α-, β-, α′- and β′-CH_2 proton signals in the spectrum of N^1-(β-bromoethyl)-triethylenetetramine allowed us to assume that the isolated product of aziridine tetramer hydrobromination was a linear isomer derivative. The above conclusion was confirmed by

‡ *Preparation of* N^1*-(β-bromoethyl)diethylenetriamine·3HBr* **4**. 0.75 ml of 48% hydrobromic acid (6.6 mmol) were placed in a 5 ml glass vessel with a wide neck supplied with a magnetic stirring bar and cooled to 0 °C in an ice bath with vigorous stirring. 100 mg of aziridine trimer **1** (0.78 mmol) were placed in a glass tube with a capillary and cooled to 0 °C. Then, the capillary end was dipped into cooled stirred hydrobromic acid, and aziridine trimer **1** was added slowly (for ~1 min). Upon the addition, the yellowish colour of the hydrobromic acid solution disappeared. The stirring of the reaction mixture was performed for about 20 min at 0 °C; then, the mixture was brought to room temperature. The mixture was dried in a vacuum dessicator over a solid alkali until the complete evaporation of the liquid (10–12 h). The solid remainder (white crystalline mass) was dissolved in ~20 ml of boiling ethanol and filtered through a hot glass filter. The filtrate was cooled and kept at –20 °C for 24 h. Crystals were filtered off through the glass filter, washed with cold ethanol (3×3 ml) and dried at 25 °C for 4 h. The yield was 140 mg (40%). It was increased by ~120 mg by the slow addition of diethyl ether at room temperature to the stirred mother solution up to the appearance of a white suspension, which gives crystals on standing. The total yield of tribromohydrate of N^1-(β-bromoethyl)diethylenetriamine **4** is 260 mg (75%). White non-hygroscopic crystals were readily soluble in water and insoluble in ethanol and diethyl ether, mp 176–177°C (without decomposition).

Preparation of N^1*-(β-bromoethyl)triethylenetetramine·4HBr* **5**. 1.0 ml of 48% hydrobromic acid (8.8 mmol) were placed in a 5 ml glass vessel with a wide neck supplied with a magnetic stirring bar and cooled to 0 °C in an ice bath with vigorous stirring. 100 mg of aziridine tetramer (mixture of **2** and **3**) (0.58 mmol) were placed in a glass tube with a capillary and cooled to 0 °C. Then, the capillary end was dipped into cooled stirred hydrobromic acid and aziridine tetramer (mixture of **2** and **3**) was added slowly (for ~1 min). Then the reaction mixture was stirred for 20 min at 0 °C. A white thick mass is formed; the mixture was brought to room temperature. The mixture was dried in a vacuum dessicator over a solid alkali until the complete evaporation of the liquid (10–12 h); 3 ml of ethanol were added to the solid remainder. Yellow oily solid formed white crystals, which were dissolved in ~80 ml of boiling ethanol and filtered through a hot glass filter. The filtrate was cooled and kept at –20 °C for 24 h. Crystals were filtered off through a glass filter, washed with cold ethanol (3×3 ml) and dried at 25 °C for 4 h. Yield of tetrabromohydrate of N^1-(β-bromoethyl)triethylenetetramine **5** is 140 mg (40%). White fine non-hygroscopic crystals were readily soluble in water and insoluble in ethanol, mp 157–158 °C (without decomposition).

§ *Spectroscopic data for* **4** (in D_2O at 300 K). ^{1}H NMR δ: 3.43 (t, 2H, β′-CH_2), 3.52 (t, 2H, α′-CH_2), 3.58 (m, 4H, α-CH_2 and β-CH_2), 3.65 (t, 2H, β-$BrCH_2$), 3.74 (t, 2H, α-$BrCH_2$). ^{13}C NMR δ: 26.91 (α-BrC), 36.52 (β′-C), 44.10 (α-C), 44.51 (β-C), 45.79 (α′-C), 50.51 (β-BrC).

For **5** (in D_2O at 300 K). ^{1}H NMR δ: 3.44 (t, 2H, β″-CH_2), 3.53 (t, 2H, α″-CH_2), 3.58 (m, 8H, α-CH_2, β-CH_2, α′-CH_2 and β′-CH_2), 3.67 (t, 2H, β-$BrCH_2$), 3.75 (t, 2H, α-$BrCH_2$). ^{13}C NMR δ: 26.91 (1C, α-BrC), 36.53 (1C, β″-C), 44.19 and 44.61 (4C, α-C, β-C, α′-C and β′-C), 45.82 (1C, α″-C), 50.49 (1C, β-BrC).

the ^{13}C NMR spectrum of this product: the signals of α- and β-$BrCH_2$ groups (26.91 and 50.49 ppm) and those of α′′- and β′′-CH_2 groups (36.53 and 45.82 ppm) were of equal intensity. This fact unambiguously testifies for the linear structure of the product.

The calculated yield of N^1-(β-bromoethyl)triethylenetetramine tetrabromohydrate based on the concentration of the linear isomer in the initial mixture was ~60%.

As the product of branched aziridine tetramer hydrobromination, apparently, remained in the filtrate, the technique used can be applied for the selective isolation of a linear isomer derivative.

The interaction of oligoaziridines with hydrobromic acid allows us to suggest the formation of polymeric side products. However, there were no additional signals in the ^1H and ^{13}C NMR spectra. This indicates that recrystallised products did not contain impurities in detectable amounts.

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