# OLIGOMERS OF AZIRIDINES AND N-β-AZIRIDINOETHYLAMIDES

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The dimer of aziridine (I) and its derivatives have mutagenic [1], viricidal [2], and antimicrobial activity [3]. Inactivation of viruses and mutagenic and toxic action increases significantly in going from (I) to higher oligomers, which is explained by the increased local concentration of the reagent in the region of the target RNA and DNA polyanions due to the increased total positive charge of the protonated polyamine [4].

The chemistry and spectral characteristics of aziridine oligomers have received little study [3]. The known methods of obtaining (I) are laborious and inefficient. The yields are up to 50% for acidic-catalyzed dimerization [3, 5], 30-95% from complexes with metal salts with large excess of aziridine [6], 30-72% from dimerization by heating with metallic K under pressure [3, 7], and 40% by cyclization of N-β-aminoethylethanolamine according to Venker [8].

In connection with this we report our studies on methods of synthesis, chemical properties, and NMR spectra (Tables 1, 2) of aziridine oligomers $\left|\!\diagdown\!\right\rangle N[(CH_2)_2NH]_nH$, n = 1 (I), 2 (II), 3 (III), $\left|\!\diagdown\!\right\rangle N(CH_2)_2N[(CH_2)_2NH_2]_2$ (IV), and the diastereomers $^{Me-}\left|\!\diagdown\!\right\rangle NCH_2CHMeNH_2$ (Va, b), and $^{Me_2-}\left|\!\diagdown\!\right\rangle N(CH_2CMe_2NH)_nH$, n = 1 (VI), 2 (VII). Compound (VIII), the standard derivative of dimer (I), was obtained by the following scheme

$$\left|\!\diagdown\!\right\rangle NH + Br(CH_2)_2NMe_2 \rightarrow \left|\!\diagdown\!\right\rangle N(CH_2)_2NMe_2 \quad \text{(VIII)}$$

A convenient new two-step synthesis of dimer (I) was developed. Reaction of esters of strong organic acids with two equivalents of aziridine readily gave the acylation product, followed by N-β-amidoethylation. Reaction which ethyl trifluoroacetate proceeds without catalyst and heating (see [3, 9]) to form the crystalline product (X)

$$\left|\!\diagdown\!\right\rangle N(CH_2)_2NHCHO \text{ (IX)} \xleftarrow{HCO_2Et} \left|\!\diagdown\!\right\rangle NH \xrightarrow{CF_3CO_2Et} \left|\!\diagdown\!\right\rangle N(CH_2)_2NHCOCF_3 \text{ (X)}$$

$$\left|\!\diagdown\!\right\rangle NH \xrightarrow[(EtO_2C)_2]{C_6H_6,\ Et_3N} \left[\left|\!\diagdown\!\right\rangle N(CH_2)_2NHCO-\right]_2 \quad \text{(XI)}$$

Bis-β-aziridinoethyloxamide (XI) was obtained according to [3, 9, 10]. This exothermic reaction gives also crystalline product (XI) which can be freed from polymeric impurities by dissolution in $CHCl_3$.

It was shown that N-β-aziridinoethylamides (IX)-(XI) are easily hydrolyzed by aqueous alkali to (I). Considering the high yields of (IX)-(XI), the simplicity of their synthesis and hydrolysis, this method of obtaining dimer (I) is better than the known methods [11].

Dimer (I) cannot be obtained in satisfactory yield from the other potential precursors (XII), (XIII) [12] by alkaline hydrolysis

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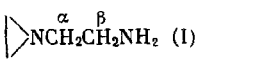
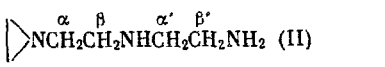
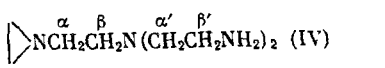
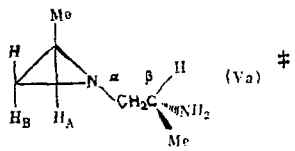
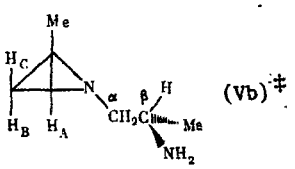
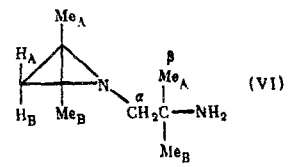
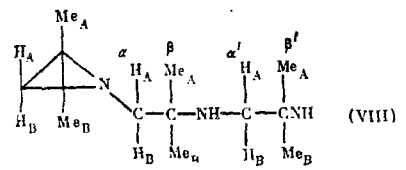
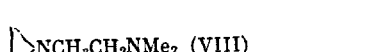
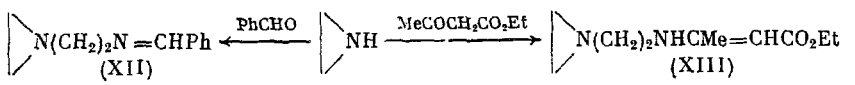
TABLE 1. PMR Spectral Parameters of Aziridine Oligomers in $CDCl_3$ (δ, ppm; J, Hz)

| Compound | Ring H* and Me | α-$CH_2$ | Other |
|---|---|---|---|
|  (I) | 1,15 and 1,73 | 2,28 (5,9) | 2,87 (β), 1,64 (HN) |
|  (II) | 1,15 and 1,74 | 2,35 (5,9) | 2,70 (α′ 5,9), 2,79 (β), 2,82 (β′), 1,38 (HN) |
|  (III) | 1,03 and 1,62 | 2,28 (6,1) | 2,56 (α″ 6,1), 2,64 (α′, β′), † 2,68 (β), 2,69 (β″), 1,68 (HN) |
|  (IV) | 1,01 and 1,68 | 2,26 (6,1) | 2,49 (α′ 5,9), 2,62 (β 6,1), 2,72 (β′), 1,75 (HN) |
|  (Va) ‡ | 1,16 (Me, $^3J$=5,6)<br>1,19 ($H_B$ $^3J_{AB}$=6,2)<br>1,38 ($H_A$ $^3J_{AC}$=3,2)<br>1,44 ($H_C$ $^2J_{BC}$=0) | 2,08 ($^2J$=−11,7, $^3J$=7,6) and 2,14 ($^3J$=4,6) | 1,03 (β-Me, $^3J$=6,3), 3,07 (β) |
|  (Vb) ‡ | 1,17 ($^3J$=5,6)<br>1,28 ($H_B$ $^3J_{AB}$=6,2)<br>1,30 ($H_A$ $^3J_{AC}$=3,2)<br>1,50 ($H_C$ $^2J_{BC}$=0) | 1,97 ($^2J$=−11,7, $^3J$=4,6) and 2,24 ($^3J$=8,1) | 1,029 (β-Me, $^3J$=6,3), 3,07 (β) |
|  (VI) | 1,08 ($H_B$ $^2J_{AB}$=0)<br>1,15 ($Me_A$) 1,19 ($Me_B$)<br>1,74 ($H_A$) | 1,98 and 2,49 ($^2J$=−12,0) | 1,10 (β $Me_A$), 1,12 (β-$Me_B$), 1,67 (HN) |
|  (VIII) | 1,05 ($H_B$ $^2J_{AB}$=0)<br>1,12 ($Me_A$) 1,18 $Me_B$)<br>1,72 ($H_A$) | 1,96 and 2,53 ($^2J$=−12,0) | 1,01 and 1,05 (β-Me), 1,07 (β′-Me), 2,33, 42.36 (α, $^2J_{AB}$=−11,5) |
|  (VIII) | 1,10 and 1,73 | 2,31 (6,6) | 2,48 (β) 2,25 ($Me_2N$) |

*The upfield signal corresponds to the ring protons cis to the N-substituent.
†By iterative analysis on an ASPECT-2000 computer the following values for the AA'BB' spectrum were found: Δν = 20, $^2J$ = −9.5, $^3J$ = 4.0 and 6.0 Hz.
‡The configuration is shown conditionally.



In the reaction of aziridine with dimethyl phthalate in MeOH, instead of the expected bisaziridinoethylphthalamide, the product of the competing β-imidoethylation of methanol (XIV) was obtained

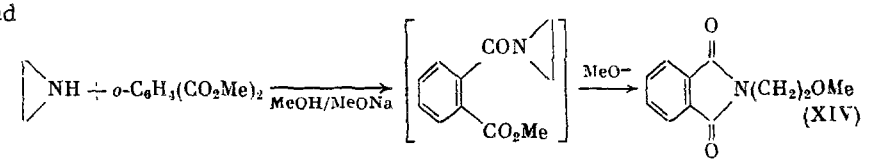
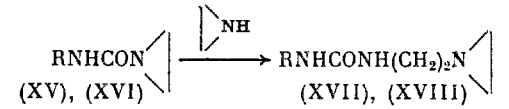


TABLE 2. $^{13}C$ NMR Spectral Parameters of Aziridine Oligomers in $CDCl_3$ (δ, ppm, $^1J$ Hz)

| Compound | Ring $CH_2$ and Me | α-$CH_2$ | β-$CH_2$ | Other |
|---|---|---|---|---|
| (I) | 26,30 (165,4 and 173,3) | 63,95 (133,7) | 41,42 (134,3) | – |
| (II) | 25,67 (165,4 and 173,3) | 60,25 (133,7) | 51,51 (133,1) | 40,52 (β′ 134,3), 48,14 (α′ 133,7) |
| (III) * | 26,93 (162,8 and 173,9) | 62,18 (133,2) | 53,20 (133,2) | 42,42 (β″ 133,2), 49,95; 50,05 and 50,24 (α′, β′ and α″ 132,2) |
| (IV) * | 27,11 (162,7 and 173,8) | 60,94 (133,2) | 54,77 (133,2) | 40,75 (β′ 133,2), 58,78 (α′ 131,3) |
| (Va, b) | 16,57 and 16,73 (Me; 125,5), 32,28 and 32,98 ($CH_2$: 166,7 and 168,5), 32,30 (CH: 163,7) | 68,16 (133,9) | 19,98 (β-Me 124,8) 45,36 and 45,69 (β-C 133,2) | – |
| (VI) | 16,14 ($Me_B$ 125,2), 25,33 ($Me_A$ 126,3), 33,05 ($\underline{C}Me_2$), 41,14 ($CH_2$ 158,9 and 170,5) | 64,38 (132,6) | 27,33 and 27,40 (β-Me 125,2), 48,83 (β-C 4,2) | – |
| (VII) | 17,24 ($Me_B$ 125,5), 26,33 ($Me_A$, 126,2), 34,22 ($\underline{C}Me_2$), 42,27 ($CH_2$; 159,5 and 170,6) | 62,61 (132,5) | 28,29 and 28,36 (β-Me 125,2) 52,57 (β-C) | 53,88 (α′ 130,4), 24,94 and 25,00 (β′-Me 125,1), 49,07 (β′-C) |

*In $C_6D_6$.

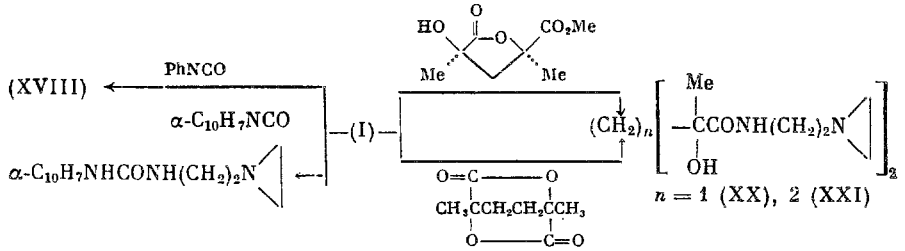
The possibility of synthesizing derivatives of dimer (I) by reaction of N-carbamoylaziridine with aziridine was established (see [3])



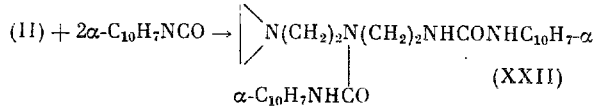

R = Me (XV), (XVII), Ph (XVI), (XVIII).

In (XV) and (XVI) activation of the ring is weakened compared to N-acylaziridines due to competing coupling of the CO group with the N atom of the NHR group. Therefore, (XV) is not changed under the action of a triple excess of aziridine after 12 h at 20°C. However, after 5 days (XVII) was observed in the PMR spectrum of the reaction mixture. The more active (XVI) under these conditions gives (XVIII) in high yield.

A series of stable crystalline derivatives was synthesized directly from dimer (I), i.e., β-aziridinoethylcarbamides (XVIII) and (XIX) were formed from isocyanates and the d,ℓ-bis-β-aziridinoethylamides of α,α′-dioxy-α,α′-dimethylglutaric (XX) and adipic acid (XXI) by reactions with lactones obtained according to [13]



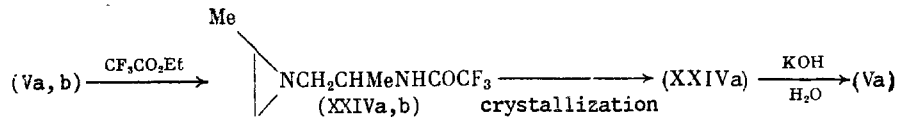

Oligomers (II)-(IV) were obtained by acid-catalyzed polymerization of aziridine according to [5]. From trimer (II) crystalline dicarbamoyl derivative (XXII) was synthesized




In contrast to this it was shown in the reaction of (II) with dimethyl oxalate regiospecific acylation is observed at the terminal amino group with formation of oxamide [ N(CH2)2NH(CH2)2NHCO-]2 (XXIII).

The mixture of linear (III) and branched (IV) tetramers is enriched by column distillation. The last portion of the fraction with bp of 110-112°C (1 mm) contains (III) and (IV) in the ratio (III)/(IV) = 1.7. A pure sample of (IV) was isolated chromatographically.

By acid-catalyzed polymerization of 2-methylaziridine [14] dimer was obtained as a mixture of diastereomers (Va, b) (1:1 according to PMR)




These were transformed into trifluoroacetamides (XXIVa, b), by crystallization of which pure diastereomer (XXIVa) was isolated, and by alkaline hydrolysis of the latter pure diastereomer (Va) was obtained. This allowed complete assignment of all diastereomer signals in the PMR spectra (Table 1).

It was shown that 2,2-dimethylaziridine upon prolonged storage in $CHCl_3$ unergoes complete and regiospecific transformation into dimer (VI) and trimer (VII), which are identical to those described in [15] and were characterized by NMR spectra (Tables 1, 2).

Oligomers (I)-(VII) were identified from their $^1H$ and $^{13}C$ NMR spectra (Tables 1, 2) and those of their derivatives (Experimental). In the PMR spectrum of (I) the methylene proton signals of the N-substituent (upfield $\alpha$-$CH_2$ and downfield $\beta$-$CH_2$) were assigned on the basis of the strong shift of the downfield signal upon substitution on the neighboring amino group and the presence of CH–NH coupling ($^3J_{HCNH}$) in $\beta$-aziridinoethylamides (see Experimental). In the $^{13}C$ NMR spectrum the $\alpha$-C and $\beta$-C signals were assigned by selective heteronuclear double resonance ($^{13}C$ $\{^1H\}$) followed by decoupling from the $\alpha$-$CH_2$ and $\beta$-$CH_2$ protons (Table 2). The NMR parameters found were used to assign the signals of (II). The $\beta$-$CH_2$ signal was assigned by homonuclear double resonance at $\{\alpha$-$CH_2\}$ and $\beta'$-$CH_2$ on the basis of the shift of the farthest downfield signal upon acylation of the $NH_2$ group [see (XXIII)]. The latter was confirmed by selective heteronuclear double resonance with the assumption that the $^{13}C$ signal at 40.52 ppm belongs to the terminal $CH_2$ group by analogy with (I). Similarly, analysis of the spectra of linear (III) and branched (IV) tetramers was carried out. In the $^{13}C$ spectrum of (III) three of the seven signals could not be assigned using selective heteronuclear double resonance due to the low intensity ($\Delta\nu$) of the signals of the $\alpha'$, $\beta'$, and $\alpha''$ protons. In the PMR spectrum of (IV) the signals of the $\alpha$, $\beta$ and $\alpha'$, $\beta'$ protons differ markedly in total intensity.

The signals of the Me groups on the ring and in the substituents on the diastereomers (Va, b) were assigned by homonuclear $\{^1H\}$ and by selective heteronuclear double resonance $\{^{13}C\}$. The trans configuration (Va, b) follows from the data of [16]. The ring proton signals of (VI) and (VII) were assigned on the basis of the shielding effect of the alkyl N-substituent relative to the cis-oriented proton, which was unambiguously proved by the values of $^2J_{^{15}N^1H}$ of aziridine (XXV) (Table 3). The $^1H$ and $^{13}C$ signals of the ring Me groups were assigned from the two-dimensional $^{13}C-^1H$ NMR spectrum of dimer (VI) (Fig. 1) with consideration of the shielding effect of the alkyl N-aubstituent in relation to the cis-oriented Me group, which was proved by us from the coupling constants $^1J_{^{13}C^{13}C}$ [16] and $^2J_{^{15}N^{13}C}$ for (XXV) (Table 3). In the NMR spectra of (Va, b), (VI), and (VII) geminal nonequivalence of the $CH_2$ protons, Me groups, and carbons of the N-substituent Me groups due to asymmetric induction of the ring chiral N atom is observed.

## EXPERIMENTAL

PMR spectra were measured on a Bruker WM-400 spectrometer [400 ($^1H$) and 100 ($^{13}C$) MHz from TMS]. A Bruker LC-31 liquid chromatograph was used with a 0.7 × 25 cm silica gel–$NH_2$ column, and a mixture of hexane–$CHCl_3$–MeOH (50:45:5) as eluent.

By known methods the following compounds were synthesized: (I) with bp of 127°C, (II) with bp of 55-56°C (1 mm), (III), (IV) with bp of 110-111°C (1 mm) [5], and (Va, b) with bp of 32.5-33.5°C (10 mm) [14].

Dimer (VI) and Trimer (VII) of 2,2-Dimethylaziridine. 1.6 g of 2,2-dimethylaziridine in 3 ml of $CHCl_3$ was kept in the cold for 6 months, then evaporated and distilled. There was obtained 1.3 g of (VI) with bp of 37-38°C (6 mm) and 0.2 g of (VII) with bp of 80°C (1 mm) in a total yield of 93.7%. The products were characterized by NMR spectra (Tables 1, 2).

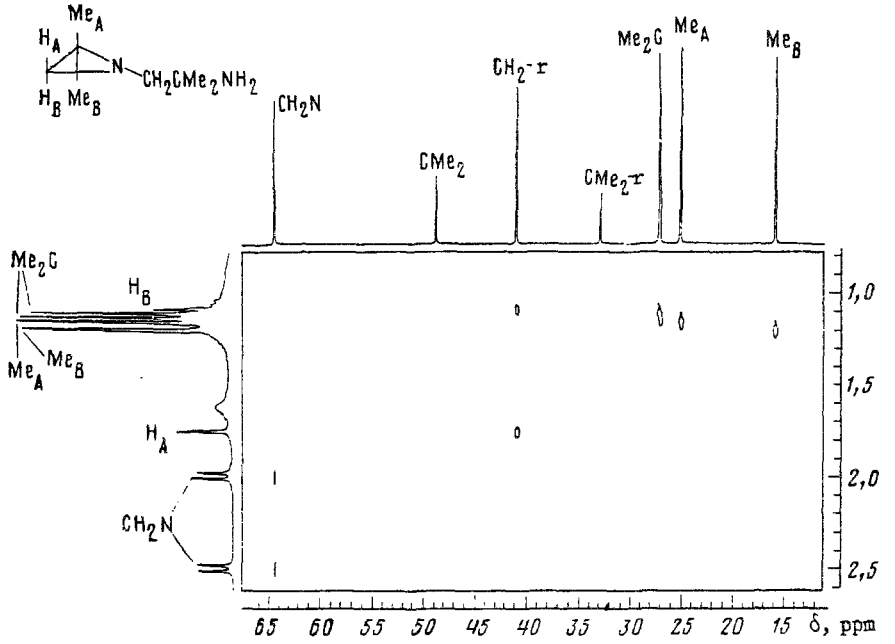
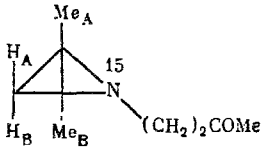



Fig. 1. Two-dimensional $^{13}C-^{1}H$ NMR spectrum in $CDCl_3$ of 2,2-dimethylaziridine dimer (VI) (r – ring).

TABLE 3. $^{1}H$ and $^{13}C$ NMR Spectral Parameters of Aziridine (XXV) in $CDCl_3$




| Nucleus X | Group | δ, ppm | $^{n}J_{^{15}NX}$ ($^{3}J_{^{15}NH}$), Hz |
|---|---|---|---|
| $^{1}H$ | $H_B$ | 1,04 | 0,0 |
| | $H_A$ | 1,62 | 4,9 |
| | $Me_B$ | 1,19 | (0,0) |
| | $Me_A$ | 1,09 | (2,9) |
| $^{13}C$ | $Me_B$ | 16,73 | 0,0 |
| | $Me_A$ | 26,71 | 5,8 |

N-β-Dimethylaminoethylaziridine (VIII). A solution of 3.3 g (21 mmoles) of freshly prepared β-bromoethyldimethylamine {bp 36°C, (13 mm)} in 10 ml of abs. ether was filtered and 8.6 g (0.2 mole) of aziridine and 11.6 g (0.2 mole) of powdered KOH in 10 ml of abs. ether were added. The mixture was shaken until cessation of heat evolution, left for 12 h at ~20°C and, after separation of the precipitate, evaporated. The residue was twice distilled from metallic Na. There was obtained 0.53 g (16%) of (VIII) with bp of 39°C (13 mm). The product was characterized by NMR spectra (Table 1).

N-β-Aziridinoethylformamide (IX). A mixture of 6.45 g (0.15 mole) of aziridine, 3.7 g (0.05 mole) of ethyl formate, and 5 drops of $Et_3N$ in 5 ml of benzene was refluxed for 5 h and, after evaporation, distilled. There was obtained 3.45 g (58.8%) of (IX) with bp of 91-93°C (1 mm). PMR spectrum ($C_6D_6$), δ ppm, J Hz: 0.48 m and 1.24 m (ring $CH_2-N$, AA'BB'), 1.72 t (α-$CH_2$, $^{3}J$ = 5.4), 3.10 d t (β-$CH_2$, $^{3}J_{HCNH}$ = 5.9), 0.06 br t (NH), 7.83 (HCO). Found: C 52.01; H 8.90; N 24.54%. $C_4H_{10}N_2O$. Calculated: C 52.6; H 8.77; N 24.58%.

N-β-Aziridinoethyltrifluoroacetamide (X). To 4.7 g (0.11 mole) of aziridine in 6 ml of abs. ether at −70°C 7 g (0.05 mole) of ethyl trifluoroacetate was added and the mixture was kept for 12 h at ~20°C, then evaporated under vacuum and the residue was recrystallized from abs. ether. There was obtained 6.9 g (77%) of (X) with mp of 62°C. PMR spectrum ($C_6D_6$): 0.48 m and 1.24 m (ring $CH_2N$, AA'BB'), 1.63 t (α-$CH_2$, $^{3}J$ = 5.8) 2.94 d t (β-$CH_2$, $^{3}J_{HCNH}$ = 5.9), 7.99 br m (HN). Found: C 39.39; H 4.97; N 15.10%. $C_6H_{10}N_2OF_3$. Calculated: C 39.34; H 4.91; N 15.30%.

N,N'-Bis-(N-β-aziridinoethyl)oxamide (XI). To a solution of 7.3 g (0.05 mole) of diethyl oxalate (shaken with $NaHCO_3$ to neutrality and distilled) in 20 ml of abs. benzene 9.5 g (0.22 mole) of aziridine (distilled from metallic Na) was added. Over 5-10 min an exotherm was observed. The mixture was maintained at 35-38°C for 1 h by periodic cooling and left for 12 h at ~20°C. Then 20 ml of ether was added, the residue separated by filtration, washed with ether, and dried under vacuum. There was obtained 9 g (80%) of (XI) with mp of 162-163°C {see [3, 9, 10]}. The product is easily soluble in $H_2O$ and $CHCl_3$. PMR spectrum ($CDCl_3$): 1.24 m and 1.75 m (ring $CH_2N$, AA'BB'), 2.35 t (α-$CH_2$, $^3J$ = 6.1), 3.56 d t (β-$CH_2$, $^3J_{HCNH}$ = 6.1), 7.81 br t (HN).

Preparation of Dimer (I) by Alkaline Hydrolysis of N-β-Aziridinoethylamides (IX)-(XI). a) A Mixture of 8.4 g (0.076 mole) of (IX) and 21.9 g (0.39 mole) of KOH in 65 ml of distilled $H_2O$ was boiled for 4 h. After saturation with solid KOH the product was extracted with ether. The extract was dried with granulated KOH, evaporated, and the residue distilled from metallic Na. There was obtained 2.5 g (40%) of (I) with bp of 126-127°C.

b) Analogously from 7.1 g (0.05 mole) of (X) and 16.8 g (0.3 mole) of KOH in 30 ml of distilled $H_2O$ over 1 h 7.6 g (84%) of (I) was obtained.

c) Analogously from 5.8 g (0.026 mole) of (XI) and 8.7 g (0.15 mole) of KOH in 25 ml of distilled $H_2O$ over 1 h 3.5 g (78%) of (I) was obtained.

d) A solution of 113 mg (0.51 mmole) of (XI) and 168 mg (3 mmoles) of KOH in 1 ml of $D_2O$ was thermostatted at 100°C in a sealed NMR tube and at 10 min intervals PMR spectra were taken (80 MHz from TMS). The degree of transformation was determined from the ratio of integrals for signals at 2.65 {groups $\underline{CH_2}NH_2$ (I)} and 3.35 ppm {group $\underline{CH_2}NH$ (XI)}. By least squares processing of the obtained values a logarithmic dependence of the transformation rate on time was found by a known method, which yielded a rate constant (K) at 100°C of $1.37 \cdot 10^{-3}$ $sec^{-1}$ a half reaction time ($\tau_{0.5}$) of 8.4 and a 99% reaction time ($\tau_{0.99}$) of 45. According to the PMR spectrum, complete transformation of (XI) into (I) occurs in 50 min.

N-β-Benzilideneaminoethylaziridine (XII). A mixture of 10.6 g (0.1 mole) of benzaldehyde, 8.6 g (0.2 mole) of aziridine, and 2 drops of $CF_3CO_2H$ in 50 ml of benzene was refluxed for 4 h. After distillation of the benzene–water azeotrope the residue was distilled. There was obtained 7 g (41%) of (XII) with bp of 102-103°C (1 mm) {see (12)}. PMR spectrum ($CDCl_3$): 1.18 m and 1.71 m (ring $CH_2N$, AA'BB'), 2.57 t (α-$CH_2$, $^3J$ = 6.3), 3.84 d t (β-$CH_2$, $^4J$ = 0.7), 7.40 and 7.47 m (Ph), 8.36 t (HC).

Ethyl Ester of 2-(N-β-Aziridinoethylamino)crotonic Acid (XIII). This was synthesized according to [12]. PMR spectrum ($CDCl_3$): 1.11 m and 1.73 m (ring $CH_2N$, AA'BB'), 1.19 t and 4.04 q (EtO, $^3J$ = 7.1), 1.89 d (MeC, $^4J$ = 0.6), 2.32 t (α-$CH_2$, $^3J$ = 6.1), 3.37 d t (β-$CH_2$, $^3J_{HCNH}$ = 6.3), 4.42 q (HC-), 8.70 br t (HN).

N-β-Methoxyethylphthalamide (XIV). A mixture of 0.54 g (12.5 mmoles) of aziridine, 0.49 g (2.5 mmoles) of dimethyl phthalate, and several drops of a solution of MeONa in MeOH was kept for 3 h at 20°C. The crystalline precipitate was separated, washed with ether, and dried under vacuum. There was obtained 0.5 g (70%) of (XIV) with mp of 152-153°C (from abs. MeOH). PMR spectrum ($C_6D_6$): 3.00 s (MeO), 3.36 t and 3.65 t [$N(CH_2)_2O$, $^3J$ = 5.8], 6.82 m and 7.41 m ($C_6H_4$, AA'BB'). $^{13}C$ NMR spectrum ($C_6D_6$): 37.14 ($CH_2N$, $^1J$ = 139.5), 58.40 (MeO, $^1J$ = 141.0, $^3J$ = 4.4), 69.22 ($CH_2O$, $^1J$ = 142.4), 122.51 ($^1J$ = 165.7, $^2J$ = 4.4), 131.91 ($^2J$ = 2.9, $^3J$ = 5.8), 133.69 ($^1J$ = 164.2, $^3J$ = 7.3, $C_6H_4$), 168.02 (CO, $^3J$ = 2.9). Found: C 64.26; H 5.54; N 6.73%. $C_{11}H_{11}NO_3$. Calculated: C 64.39; H 5.37; N 6.83%.

N-Methylcarbamoylaziridine (XV) and 1-N-β-Aziridinoethyl-3-methylcarbamide (XVII). a) To a solution of 31.4 g (0.55 mole) of methyl isocyanate (distilled from Py) in 150 ml of abs. ether at −40°C a solution of 23.4 g (0.54 mole) of aziridine in 80 ml of abs. ether was added with stirring. The precipitated crystals were separated by filtration, washed with cold ether, and dried under vacuum. There was obtained 44.8 g of (XV) and from the mother liquor another 5 g. The total yield of (XV) was 90.3%, mp 33-38°C, bp 72°C (1 mm) (see [3]). PMR spectrum ($CDCl_3$): 1.98 s (ring $CH_2N$), 2.67 d (MeN, $^3J_{HCNH}$ = 4.9), 5.90 q (HN). Found: N 27.67%. $C_4H_8N_2O$. Calculated: N 27.98%.

b) After keeping (XV) with a threefold amount of aziridine (4 days at 20°C) (XVII) is formed according to PMR. PMR spectrum ($CDCl_3$): 1.14 m and 1.69 m (ring $CH_2N$, AA'BB'), 2.27 t (α-$CH_2$, $^3J$ = 5.9), 2.70 d (MeN), ($^3J_{HCNH}$ = 4.6), 3.28 d t (β-$CH_2$, $^3J_{HCNH}$ = 5.9), 5.34 br m (HN).

N-Phenylcarbamoylaziridine (XVI) and 1-N-β-Aziridinoethyl-3-phenylcarbamide (XVIII). a) From equimolar amounts of aziridine and phenyl isocyanate in toluene compound (XVI) with mp of 82-83°C was obtained (see [3]). PMR spectrum ($CDCl_3$): 2.21 s (ring $CH_2N$), 7.00-7.50 m (Ph).

b) 0.15 g (0.93 mmole) of (XVI) with a threefold amount of aziridine was kept for 5 days at 20°C. After evaporation under vacuum there was obtained 0.15 g (79%) of (XVIII) with mp of 133°C. PMR spectrum ($CDCl_3$): 1.19 m and 1.74 m (ring $CH_2N$), 2.36 t (α-$CH_2$, $^3J$ = 5.6), 3.40 q (β-$CH_2$, $^3J_{HCNH}$ = 5.6), 5.47 br t (HN), 7.07-7.5 m (Ph). Found: C 64.36; H 7.38; N 20.40%. $C_{11}H_{13}N_3O$. Calculated: C 64.39; H 7.32; N 20.49%.

c) To 0.215 g (2.5 mmoles) of (I) in 5 ml of ether 0.3 g (2.5 mmoles) of phenyl isocyanate in 5 ml of ether was added. Heat was evolved and a coarse crystalline precipitate formed which was washed with ether for 1 h and dried under vacuum. There was isolated 4.05 g (78%) of (XVIII).

1-β-Azridinoethyl-3-α-naphthylcarbamide (XIX). To 0.43 g (10 mmoles) of (I) in 10 ml of abs. ether at −70°C 0.85 g (5 mmoles) of α-naphthyl isocyanate in 5 ml ether was added. The mixture was heated to 20°C, the residue separated and dried under vacuum. There was obtained 1.25 g (98%) of (XIX) with mp of 147-151°C. PMR spectrum ($CDCl_3$): 0.98 m and 1.45 m (ring $CH_2N$ AA'BB'), 2.24 t (α-$CH_2$, $^3J$ = 5.6), 3.39 q (β-$CH_2$, $^3J_{HCNH}$ = 5.6), 6.05 br t (HN), 7.42-8.07 m (α-$C_{10}H_7$). Found: C 70.67; H 6.63; N 16.51%. $C_{15}H_{17}N_3O$. Calculated: C 70.56; H 6.71; N 16.46%.

N,N-Bis-(N-β-aziridinoethyl)-α,α'-dioxy-α,α'-dimethylglutaramide (XX). A mixture of 0.1 g (1.16 mmoles) of (I) and 0.1 g (0.53 mmole) of the methyl ester of the monolactone of d,ℓ-α,α'-dioxy-α,α'-dimethylglutaric acid [13] in 2 ml of abs. ether was left in the cold for 12 h. The precipitated crystals were separated, washed with cold ether, and dried under vacuum. There was obtained 0.1 g (57.5%) of (XX) with mp of 140-142°C. PMR spectrum ($C_6D_6$): 0.62 m (ring $CH_2N$), 1.44 s (Me), 1.86 t (α-$CH_2$, $^3J$ = 5.9), 2.45 s ($CCH_2C$), 3.13 d d t and 3.38 d d t (β-$CH_2$, $^2J$ = −13.7, $^3J_{HH}$ = $^3J_{HCNH}$ = 5.9), 7.76 br t (HN). Found: C 54.58; H 8.83; N 17.14%. $C_{15}H_{28}N_4O_4$. Calculated: C 54.86; H 8.59; N 17.06%.

N,N'-Bis(N-β-aziridinoethyl)-α,α'-dioxy-α,α'-dimethyladipamide (XXI). A mixture of 0.4 g (4.6 moles)* of (I) and 0.34 g (2 mmoles) of the dilactone of α,α'-dioxy-α,α'-dimethyladipic acid [13] in 5 ml of abs. ether was left for 12 h in the cold. The precipitated crystals were separated, washed with cold ether, and dried under vacuum. There was obtained 0.41 g (60.6%) of (XXI) with mp of 165-167°C. PMR spectrum ($CDCl_3$): 1.28 m and 1.78 m (ring $CH_2N$), 1.63 m and 2.00 m {$C(CH_2)_2C$}, 2.28 m and 2.75 m (α-$CH_2$, $^2J$ = −12.0, $^3J$ = 6.4), 3.24 m and 3.55 m (β-$CH_2$, $^2J$ = −8.7, $^3J_{HH}$ = 6.4, $^3J_{HCNH}$ = 5.3), 7.48 br t (HN). Found: C 56.03; H 9.01; N 16.23%. $C_{16}H_{30}N_4O_4$. Calculated: C 56.12; H 9.24; N 16.36%.

N-β-Aziridinoethyl-N,N'-bis-α-naphthylcarbamoylethylenediamine (XXII). To a solution of 0.13 g (1 mmole) of (II) in 10 ml of toluene 0.34 g (2 mmoles) of α-naphthyl isocyanate was added and the mixture was kept for 12 h at 20°C. The precipitated crystals were separated, washed with toluene, and dried under vacuum. There was obtained 0.35 g (66%) of (XXII) with mp of 136-138°C (from a toluene−$CHCl_3$ mixture). PMR spectrum ($CDCl_3$): 1.23 m and 1.80 m (ring $CH_2N$, AA'BB'), 2.46 t (α-$CH_2$, $^3J$ = 4.4), 3.35 d t (β'-$CH_2$, $^3J_{HH}$ = $^3J_{HCNH}$ = 6.1), 3.43 t (α' = $CH_2$), 3.55 t (β-$CH_2$), 6.5 br t (HN), 7.05-7.80 m (α-$C_{10}H_7$). Found: C 71.90; H 6.39; N 14.88%. $C_{28}H_{29}N_5O_2$. Calculated: C 71.93; H 6.25; N 14.97%.

N,N'-Bis-(N-β-aziridinoethylaminoethyl)oxamide (XXIII). To 1.3 g (10 mmoles) of (II) in 5 ml of toluene 0.73 g (5 mmoles) of diethyl oxalate in 5 ml of toluene was added and the mixture was left for 12 h at 20°C. After filtration the solution was evaporated under vacuum. There was obtained 1.5 g (80%) of (XXIII) with mp of 112-113°C (from a MeOH−$Et_2O$ mixture, 1:2). PMR spectrum ($CDCl_3$): 1.12 m and 1.72 m (ring $CH_2N$, AA'BB'), 1.68 br s (HN), 2.31 t (α-$CH_2$, $^3J$ = 5.9), 2.76 t (β-$CH_2$), 2.81 t (α'-$CH_2$, $^3J$ = 5.9), 3.39 d t (β'-$CH_2$, $^3J_{HH}$ = $^3J_{HCNH}$ = 5.9), 7.85 br t (HNCO). Found: C 53.80; H 9.34; N 26.25%. $C_{14}H_{28}N_6O_2$. Calculated: 53.82; N 9.03; N 26.90%.

1-β-Trifluoroacetylaminopropyl-2-methylaziridine (XXIVa, b) and Its Alkaline Hydrolysis to (Va, b). To 0.64 g (5.6 mmoles) of (Va, b) in 10 ml of abs. ether at −60°C 0.8 g (5.63 mmoles) of ethyl trifluoroacetate in 10 ml of abs. ether was added. The reaction mixture was kept for 12 h at 20°C, evaporated under vacuum, and the residue sublimed. There was obtained 0.43 g (39%) of (XXIVa, b) as a 1:1 mixture of diastereomers (according to PMR). By triple crystallization from ether diastereomer (XXIVa) was isolated with mp of 85-87°C. PMR spectrum

*As in Russian original – Editor.

($CDCl_3$): 1.16 d (ring MeC, $^3J$ = 5.6), 1.27 d ($H_B$, $^3J_{AB}$ = 6.6, $^2J_{BC}$ ~ 0), 1.28 d (MeC, $^3J$ = 6.8), 1.41 d d ($H_A$, $^3J_{AC}$ = 3.4), 1.49 d ($H_C$), 2.05 d d ($^2J$ = −12.2, $^3J$ = 4.4) and 2.68 d d ($^3J$ = 4.9) (α-$CH_2$), 4.09 m (β-HC), 7.05 br.m (HN). $^{19}F$ NMR spectrum ($CDCl_3$): 2.78 s. Found: C 45.50; H 6.23; N 13.68%. $C_8H_{13}N_2OF_3$. Calculated: C 45.72; H 6.23; N 13.33%. From the mother liquor crystals were obtained with mp of 60-76°C, enriched in diastereomer (XXIVb) (b/a ratio = 3 according to PMR).

b) 0.12 g (0.57 mmole) of (XXIVa) was heated in a solution of 0.12 g (2.14 mmoles) of KOH in 1 ml of $H_2O$ until dissolution (~2 min), saturated with solid KOH, extracted with ether (twice by 3 ml), dried over $MgSO_4$, evaporated, and distilled. There was isolated 10 mg (15.4%) of (Va). Analogously, from (XXIVb) a sample enriched with (Vb) was isolated. The products were characterized by PMR spectra (Tables 1, 2).

β-(N-2,2-Dimethylaziridino)ethylmethylketone (XXV). This was obtained by A. S. Moskalenko according to [3]. PMR spectrum ($CDCl_3$): 1.04 s ($H_B$), 1.62 d ($H_A$, $^2J_{^{15}NH}$ = 4.9), 1.09 d ($Me_A$, $^3J_{^{15}NH}$ = 2.9), 1.19 s ($Me_B$), 2.47 m and 2.74 m ($CH_2CO$, $^2J$ = −11.7, $^3J$ = 6.6 and 7.1), 2.65 m ($CH_2N$, Δν = 29.0, $^2J$ = −12.7). $^{13}C$ NMR ($CDCl_3$): 16.73 ($Me_B$, $^1J$ = 124.5), 26.71 ($Me_A$, $^1J$ = 125.1, $^2J_{^{15}N^{13}C}$ = 5.8), 30.41 (MeCO, $^1J$ = 127.1), 35.98 ($CMe_2$, $^1J_{^{15}N^{13}C}$ = 8.7), 41.2 (ring $CH_2N$, $^1J_{CH_A}$ = 172.9, $^1J_{CH_B}$ = 161.8, $^1J_{^{15}N^{13}C}$ = 7.9), 44.5 ($CH_2N$, $^1J$ = 126.3, $^2J$ = 4.9, $^1J_{^{15}N^{13}C}$ = 2.9), 48.03 ($CH_2CO$), $^1J$ = 133.1), 207.88 (CO, $^2J$ = 3.7). The coupling constant $^1J_{^{13}C^{13}C}$ is found in [16].

## CONCLUSIONS

1. An efficient method of aziridine dimer synthesis is presented involving reaction of aziridine with esters of strong organic acids followed by alkaline hydrolysis of the resultant N-acyl derivatives.

2. New N-acyl and carbamoyl derivatives of aziridine dimer and trimer were synthesized.

3. Linear and branched isomers of aziridine tetramer and also diastereomers of 2-methylaziridine dimer were isolated and characterized.

4. An efficient regiospecific synthesis of 2,2-dimethylaziridine dimer and trimer was developed.

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# SYNTHESIS, STRUCTURE, AND PROPERTIES OF BENZOSULFINYL-11-CROWN-4

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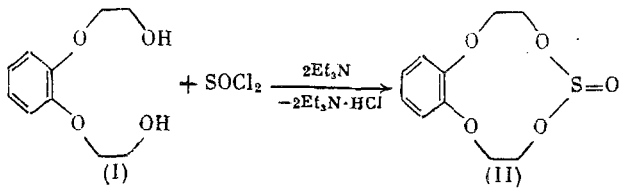
Several crown ether derivatives containing sulfinyl functional groups in the ring have been synthesized previously [1, 2]. As part of our continuing systematic search for compounds with valuable properties among macrocyclic polyethers with a variety of functional groups [3-6], we have recently synthesized a novel 11-membered ring crown ether containing a sulfinyl functional group. The synthesis was carried out starting from 1,2-di(2-hydroxyethoxy)-benzene (I) via reaction with thionyl chloride in the presence of triethylamine.




Benzosulfinyl-11-crown-4 (II) is a colorless crystalline substance which is readily soluble in polar organic solvents and stable under storage conditions. Its structure was confirmed on the basis of elemental analysis, IR, NMR, and mass spectroscopic analysis, and also by x-ray structural analysis.

It was also found that compound (II) appears to be a physiologically active compound. At a dose of 50-100 mg/kg (intraperitoneal) compound (II) produces a sharp decrease in the spontaneous mobility (activity) of mice, inducing ptosis and making them catatonic. In addition, compound (II) also exhibits significant antihypoxia activity on a hypoxia model featuring hypercapny in hermocapacity (volume); at doses of 50, 100, 150, and 200 mg/kg it increases the lifetime of animals under hypoxia conditions by 1.15 ± 0.06, 1.42 ± 0.12, 1.93 ± 0.23, and 2.95 ± 0.10 times, respectively. Unfortunately, however, its relatively low therapeutic index (ca. 4-5) makes it impossible to utilize compound (II) clinically. Nevertheless, the demonstrated substantial antihypoxia activity of this compound makes it of continuing interest and also has stimulated the present detailed investigation of its structure.

## EXPERIMENTAL

Synthesis of Benzosulfinyl-11-crown-4 (II). The reaction was carried out in a half-liter four-necked flask, equipped with a stirrer, reflux condenser, two dropping funnels, and a gas outlet tube. One of the funnels was charged with a mixture of 0.025 mole (I), 0.05 mole triethylamine, and 50 ml of anhydrous acetonitrile, while the second dropping funnel was charged with a solution of 0.025 mole thionyl chloride in 50 ml acetonitrile. To the reactor, which contained 50 ml acetonitrile, the two solutions from the dropping funnels were added simultaneously and slowly (over ca. 2 h), while the temperature was maintained at 1-3°C and the mixture was stirred vigorously under a stream or Ar. The reaction mixture was then maintained for 5 h at ca. 20°C. The resulting precipitate of triethylamine hydrochloride was removed by filtration and the filtrate was evaporated and the residue treated with 150 ml

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