of ω-haloalkanals and without ring cleavage with the formation of the corresponding ketones and also, for C_7-C_8, 1,4-epoxycycloalkanes.

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NITROSOALKYLUREAS WITH QUATERNARY NITROGEN ATOM.

5.* STUDY OF DECOMPOSITION PRODUCTS OF THE CHOLINE-LIKE NITROSOALKYLUREAS IN AQUEOUS MEDIUM

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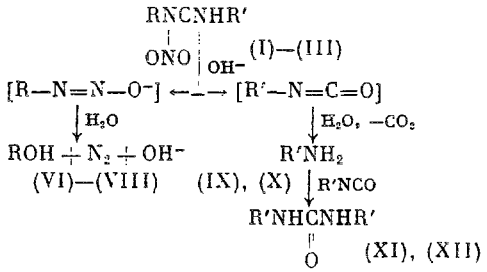
The antitumorigenic activity of nitrosoalkylureas (NAU) is based on their ability to decompose with the formation of reactive cytotoxic products, which are diazohydroxides and isocyanates [2]. In the case of nitrosoureido derivatives of biogenic compounds, the biogenic compounds formed during their decomposition may also influence the biological activity to some extent. It was therefore expedient to study the decomposition products of a new group of choline-like NAU (I)-(V), which we have synthesized [3, 4], during the decomposition of which not only cytotoxic compounds, but also the appearance of choline or its analogs, can be expected.

It can be assumed on the basis of the scheme of decomposition of the known dialkyl-substituted NAU, proceeding by the ElcB mechanism [2] that the decomposition of compounds (I)-(III) leads to the formation of alcohols (VI)-(VIII), amines (IX), (X) and (or) symmetric ureas (XI), (XII). In the case of trialkyl-substituted NAU (IV), (V), the decomposition by the BAc2 mechanism with formation of the corresponding alcohols (VI), (VII) as well as of 2-methylaminoethyltrimethylammonium tosylate (XIII) is most probable (see scheme below)



R = Me, R′ = $(CH_2)_2\overset{+}{N}Me_3 \cdot Cl^-$ (I); R = $(CH_2)_2Cl$, R′ = $(CH_2)_2\overset{+}{N}Me_3 \cdot Cl^-$ (II); R = = $(CH_2)_2\overset{+}{N}Me_3 \cdot TsO^-$, R′ = cyclo-$C_6H_{11}$ (III); R = Me (VI); R = $(CH_2)_2Cl$ (VII); R = $(CH_2)_2\overset{+}{N}Me_3 \cdot TsO^-$ (VIII); R′ = $(CH_2)_2\overset{+}{N}Me_3 \cdot Cl^-$ (IX), (XI); R′ = cyclo-C_6H_{11} (X), (XII).

*For previous communication, see [1].

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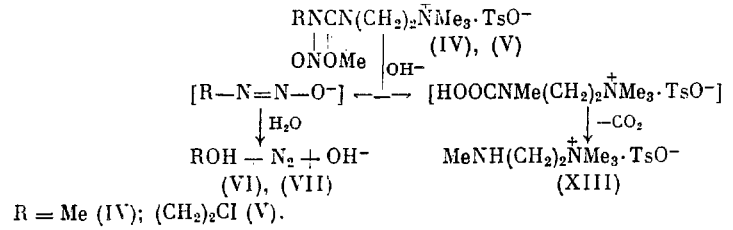
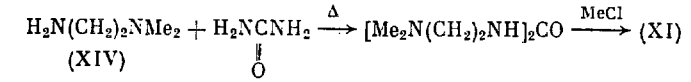
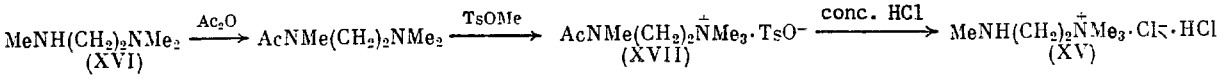


R = Me (IV); $(CH_2)_2Cl$ (V).

Authentic samples of 2-aminoethyltrimethylammonium chloride (IX) were obtained from N,N-dimethylethylenediamine (XIV) by a method described in [5], while 1,3-bis-(2-trimethylammonioethyl) urea dichloride (XI) was synthesized from urea and diamine (XIV) according to a scheme



2-Hydroxyethyltrimethylammonium tosylate (VIII) was obtained by quaternization of 2-dimethylaminoethanol by methyl tosylate. 2-Methylaminoethyltrimethylammonium chloride (XV) was synthesized in the form of a hydrochloride by acetylation of N,N,N'-trimethylethylenediamine (XVI), quaternization of the acetamide formed by methyl tosylate, and hydroylsis of 2-(N-acetyl-N-methylamino)ethyltrimethylammonium tosylate (XVII)



The decomposition of NAU (I)-(IV) was carried out in water at 40°C. To prevent photochemical reactions, in particular denitrosation observed in the case of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea [6], the process was carried out in the dark. After the disappearance, according to the TLC data, of the initial NAU, the precipitate (if any was formed) was filtered, the filtrate was acidified by HCl, and evaporated in vacuo to dryness. The nonvolatile decomposition products were identified by PMR spectroscopy and TLC on acid, neutral and alkaline Al_2O_3 in two or three systems of solvents.

Methanol, the formation of which was expected during the decomposition of methylnitrosoureas (I), (IV), was detected by PMR spectroscopy after the decomposition of the compounds in D_2O from the appearance of a sharp signal at 3.34 ppm. 2-Chloroethanol, the probable product of the decomposition of chloroethylnitrosoureas (II), (V), was identified by GLC.

Our investigation showed that the decomposition of NAU (I)-(V) proceeds in accordance with the data of the above decomposition schemes. Thus, in the case of the dialkyl-substituted NAU (I), (II), methanol and 2-chloroethanol, respectively, were detected in the reaction mixture. The PMR spectrum of the nonvolatile decomposition products of (I) and (II) indicates the formation of 2-aminoethyltrimethylammonium chloride (IX) and a symmetric urea (XI) in a ratio of 2:1. The mobility of the decomposition products on the chromatogram and their color during development with iodoplatinate also correspond to compounds (IX) and (XI). Decomposition of cyclohexylnitrosourea (III) results in the formation of 1,3-dicyclohexylurea (XII). In the residue obtained after acidification and evaporation cyclohexylamine hydrochloride (X) and 2-hydroxylethyltrimethylammonium tosylate (choline tosylate) (VIII) were detected.

During the decomposition of trialkyl-substituted NAU (IV), (V) volatile alcohols (VI), (VII) are formed, which were identified as described above, while the PMR spectrum and the chromatographic characteristics of the nonvolatile residue corresponded to compound (XV). The TLC of compound (XV) was carried out on acid Al_2O_3 or in acid systems, in which the type of anion does not influence the mobility of the cations.

EXPERIMENTAL

For the TLC, acid (Woelm, GFR), neutral and alkaline (LCL_{254}, CSSR) Al_2O_3 were used in solvent systems of chloroform–methanol, 4:1, acetone–water, 9:1, n-butanol–citric acid–water, 87 ml:0.48 g:15 ml. The chromatograms were developed by iodine and iodoplatinate.

The IR spectra were recorded on a Specord IR-75 spectrophotometer in a thin layer of mineral oil. The PMR spectra were run on a Tesla BS-567A spectrometer (100 MHz) in D_2O, using DSS as internal standard. The GLC was carried out at 100°C on a Chrom-5 apparatus with 2.5 m × 3 mm column, filled with a Chromaton N-AW-HMDS carrier with 10% of Leucoprene G-1000,

He as carrier gas, at a flow rate of 40 ml/min.

General Method of Investigation of the Decomposition Products of NAU (I)-(V). A solution of 0.1 g of NAU in 1 ml of distilled water [NAU (IV) was dissolved in 1 ml of 0.1 N NaOH] was held at 40°C in a thermostat up to the disappearance (TLC) of the starting compound (1-6 days). The precipitate which separated in the case of the cyclohexyl derivative, was filtered, washed with water, and dried; mp 230°C, cf. [7]. IR spectrum (ν, cm^{-1}): 3325, 1580 (N—H), 1630 (C=O).

After the decomposition of the chloroethylnitrosoureas (II), (V), 2 μliter portions of the reaction mixture were analyzed by GLC. In both cases, the principal peak corresponded to 2-chloroethanol.

To examine the decomposition products by TLC and PMR spectroscopy methods, the reaction mixture was acifified with HCl to pH 3-5, evaporated in vacuo, and dried. On decomposition on a chromatogram, the residue was dissolved in alcohol, and for recording the PMR spectrum, in D_2O.

The methanol in the decomposition products of methylnitrosoureas (I), (V) was identified by the PMR spectrum taken after the decomposition in D_2O.

2-Hydroxyethyltrimethylammonium Tosylate (VIII). A 0.19-g portion (0.002 mole) of N,N-dimethylaminoethanol was added at ~20°C to a solution of 0.4 g (0.002 mole) of methyl tosylate in 10 ml of acetone. The precipitate that separated was filtered and washed with acetone. The yield of (VIII) was 0.48 g (81%), mp 95°C. Found: C 52.21; H 7.61; N 4.99%. $C_{12}H_{21}NO_4S$. Calculated: C 52.34; H 7.69; N 5.09%.

1,3-Bis-(2-trimethylammonioethyl)urea Dichloride (XI). A solution of 0.62 g (0.01 mole) of urea and 2.25 g (0.025 mole) of N,N-dimethylethylenediamine (XIV) in 4 ml of n-butanol was boiled for 16 h. The reaction mixture was distilled in vacuo (20 mm Hg). The main fraction, bp 190-210°C was dissolved in 20 ml of dry MeCN. A slow current of MeCl, obtained from 5.9 g of NaCl [8], was passed at −10°C into the solution obtained, and the mixture was left to stand overnight in a refrigerator. The crystals that separated were filtered and washed with MeCN. The yield of (XI) was 1.4 g (46%), mp 250°C. IR spectrum (ν, cm^{-1}): 1250 (CO—N), 1540, 3350 (N—H), 1660 (C=O). PMR spectrum (δ, ppm): 3.55 m ($NCH_2CH_2\overset{+}{N}$), 3.18 s [$\overset{+}{N}(CH_3)_3$]. Found: C 43.29; H 9.36; Cl 23.19%. $C_{11}H_{28}Cl_2N_4O$. Calculated: C 43.56; H 9.31; Cl 23.38%.

2-(N-Acetyl-N-methylamino)ethyltrimethylammonium Tosylate (XVII). A 0.96-g portion (0.01 mole) of Ac_2O was added with stirring to a solution of 0.8 g (0.008 mole) of N,N,N'-trimethylethylenediamine (XVI) in 10 ml of dry MeCN at 0-5°C. After 30 min 2.0 g (0.015 mole) of K_2CO_3 were added, the mixture was stirred for 2 h, the suspension was diluted with 50 ml of absolute ether, and the precipitate was filtered. A 1.76-g (0.01 mole) portion of methyl tosylate was dissolved in the filtrate, and the mixture was left to stand overnight in a refrigerator. The crystals that separated were filtered and washed with MeCN. The yield of (XVII) was 2.0 g (77%), mp 139°C. PMR spectrum (in DMSO-d_6, using TMS as internal standard) (δ, ppm): 3.55 m ($NCH_2CH_2\overset{+}{N}$), 3.09 s [$\overset{+}{N}(CH_3)_3$], 2.99 s (NCH_3), 2.00 s (CH_3CO). Found: C 54.89; H 8.06; N 8.59%. $C_{15}H_{26}N_2O_4S$. Calculated: C 54.52; H 7.93; N 8.48%.

2-Methylaminoethyltrimethylammonium Chloride Hydrochloride (XV). A solution of 1.0 g (0.003 mole) of acetamide (XVII) in 16 ml concentrated HCl was boiled for 6 h, and was then evaporated in vacuo at ~100°C, and the residue was recrystallized from ethanol. The yield of (XV) was 0.8 g (78%), mp > 250°C. PMR spectrum (δ, ppm); 3.72 s ($NCH_2CH_2\overset{+}{N}$), 3.27 s [$\overset{+}{N}(CH_3)_3$], 2.83 s (CH_3N). Found: C 38.24; H 9.72; Cl 37.15%. $C_6H_{18}Cl_2N_2$. Calculated: C 38.10; H 9.58; Cl 37.49%.

CONCLUSIONS

During the decomposition in water of choline-like nitrosoalkylureas, choline and its analogs are formed, which are potential cholinergic compounds. The formation of symmetric ureas during such a decomposition indicates the occurrence of the ElcB mechanism.

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NITROSOALKYLUREAS WITH A QUATERNARY NITROGEN ATOM.

6. STUDY OF REACTION KINETICS OF THE DECOMPOSITION IN AQUEOUS MEDIUM OF NITROSOALKYLUREAS BASED ON MONOQUATERNARY ALKYLAMMONIUM SALTS

A. A. Belyaev and L. B. Radina

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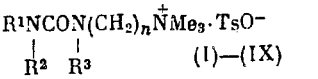
We have previously studied the reaction kinetics of the decomposition of choline-like dialkyl-substituted nitrosoalkylureas (NAU) (I)-(III) in aqueous medium [1]. The data obtained for the decomposition reactions of these compounds conform with the ElcB mechanism. In the present work, we studied the kinetics of the decomposition of NAU over a wide range of pH, and also the kinetics of decomposition of its analogs with a longer alkyl chain between the quaternary N atom and the urea-grouping (IV)-(VII), and the trialkyl substituted NAU (VIII) and (IX), having no amide proton, and therefore not decomposable by the ElcB mechanism

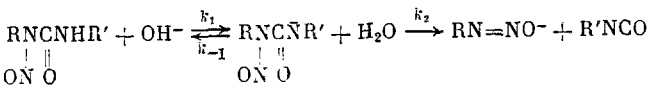


(I)—(IX)

$R^1 = Me$, $R^2 = NO$, $R^3 = H$, $n = 2$ (I); $R^1 = (CH_2)_2Cl$, $R^2 = NO$, $R^3 = H$, $n = 2$ (II); $R^1 = cyclo\text{-}C_6H_{11}$, $R^2 = H$, $R^3 = NO$, $n = 2$ (III); $R^1 = Me$, $R^2 = NO$, $R^3 = H$, $n = 3$ (IV); $R^1 = cyclo\text{-}C_6H_{11}$, $R^2 = H$, $R^3 = NO$, $n = 3$ (V); $R^1 = Me$, $R^2 = NO$, $R^3 = H$, $n = 4$ (VI); $R^1 = cyclo\text{-}C_6H_{11}$, $R^2 = H$, $R^3 = NO$, $n = 4$ (VII); $R^1 = R^3 = Me$, $R^2 = NO$, $n = 2$ (VIII); $R^1 = (CH_2)_2Cl$, $R^2 = NO$, $R^3 = Me$, $n = 2$ (IX).

The reactions were carried out in 1/15 M phosphate buffer solutions. As in [1], the dependence of the spectrophotometrically determined analytical concentration of (I)-(IX) [NAU_{anal}] on time (τ) is linear in the $\ln([NAU_{anal}]/[NAU_{anal}]_0)$ vs. τ coordinates at all pH values ($[NAU_{anal}]_0$ is initial concentration of NAU). The pseudofirst order reaction rates k_{obs} for the reactions of (I)-(IX) at 37°C were calculated by the method of least squares (Table 1). With increased distance between the quaternary N atom and the nitrosoureido group, the stability of NAU (IV)-(VII) increases compared with (I)-(III), clearly due to the weakening of the electron-acceptor action of N^+. The trialkyl-substituted NAU (VIII) and (IX) are 20-100 times more stable than the corresponding disubstituted compounds (I) and (II).

The pH dependence of $\log k_{obs}$ for dialkyl-substituted (I)-(VII) is in general nonlinear; over the whole pH range, the tangent of the angle of slope of the tangential line to the curve (m), i.e., the order of the reaction with respect to OH^- [1], is equal to 0.5-0.7 on an average, and does not exceed 0.8. As well as the composition of the decomposition products of the dialkyl-substituted NAU, [2], these data do not contradict the ElcB mechanism



The realization of the following equation has been shown previously [1]

$$k_{obs} = \frac{k_2 \cdot K_1^{eq} \quad [OH^-]}{K_1^{eq} \quad [OH^-] + [H_2O]} \qquad (1)$$

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