# SEARCH FOR NEW DRUGS

## $N^{\omega}$-ALKYLNITROSOCARBAMOYL-α,ω-DIAMINOCARBOXYLIC ACIDS. 1. SYNTHESIS AND ANTITUMOR ACTIVITY OF $N^{\omega}$-METHYLNITROSOCARBAMOYL-α,ω-DIAMINO CARBOXYLIC ACIDS

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 30, No. 2, pp. 7 – 10, February, 1996.

*Original article submitted September 21, 1995.*

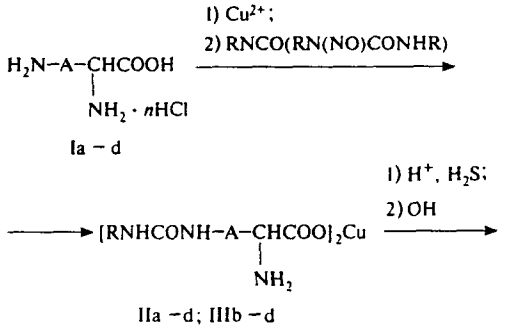
Nitrosoalkylureas are a promising class of organic compounds possessing antitumor activity [1, 2]. However, although these compounds are in some aspects superior to other drugs, their toxicity constitutes a significant shortcoming.

One of the rational approaches to designing compounds with high antitumor selectivity involves the coupling of cytotoxic fragments to carrier molecules that enable the transport of the drug to the target tumor cells. It is known that amino acids and peptides pass through the membranes of tumor cells faster and more easily than through the membranes of normal cells [3]. A large number of compounds have been synthesized in which the cytotoxic N-alkyl-N-nitrosourea group was coupled to amino acid or oligopeptide fragments. In most of these compounds, the α-amino group of amino acid was incorporated into the nitrosourea part of the molecule.

However, we believe that alkylnitrosocarbamoyl amino acid derivatives in which the cytotoxic group forms the side chain of the amino acid, whereas the α-amino group and the carboxyl group, which control the main biochemical properties of amino acids and are essential for active transmembrane transport to the cells, remain intact, are more promising. Hydrolytic decomposition of these compounds *in vivo* can lead to formation of carbamoylating species and formation of α-amino acid derivatives, which are potential antimetabolites and may show a broader spectrum of antitumor activity than the common nitrosoalkylureas. Recently, a number of compounds belonging to this group were synthesized and their efficacy against human immunodeficiency virus was tested [4 – 7].

Previously, we described the synthesis of nitrosocarbamoyl derivatives of 2-(4-aminophenyl)-*L*-alanine, some of which showed noticeable antitumor activity in trials with animals [8]. In continuation of those studies we synthesized nitroso derivatives of aliphatic $N^{\omega}$-alkylcarbamoyl($N^{\omega}$-ANC)-α,ω-diamino acids, both natural [*L*-α,γ-diaminobutyric acid, *L*-ornithine, *L*-lysine (Ia – c)] and their structural analogs [*L*-4-thialysine (Id)], and studied their antitumor activity as a function of the structure of the amino acid fragment and the position of nitroso group. Using methyl ($R = CH_3$) and cyclohexyl ($R = C_6H_{11}$) groups as alkyl substituents, we prepared nitrosoalkylureas with a nitroso group at $N_1$ or $N_3$ atoms of the urea group, respectively. The high antitumor activity of methylnitrosocarbamoyl derivatives is well documented [9]. Studying $N^{\omega}$-cyclohexylcarbamoyl-$N^{\omega}$-nitroso derivatives makes it possible to assess the antitumor activity of the products of amino acid nature, which formed as a result of hydrolytic decomposition of these derivatives.

Compounds (VIa – d) and (VIIb – d) were prepared from hydrochlorides of the corresponding α,ω-diamino acids (Ia – d) according to the following scheme:

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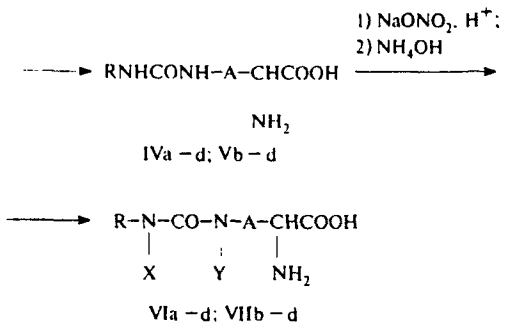
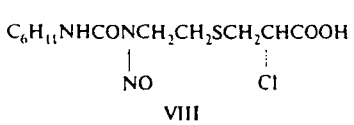



Ia $n = 2$; Ib – d: $n = 1$;
IIa – d R = $CH_3$;
IIIb – d. R = $C_6H_{11}$;
IVa – d R = $CH_3$;
Vb – d: R = $C_6H_{11}$;
VIa – d: R = $CH_3$, X = NO, Y = H;
VIIb – d: R = $C_6H_{11}$, X = H, Y = NO;
Always a: A = $(CH_2)_2$; b: A = $(CH_2)_3$; c: A = $(CH_2)_4$;
d: A = $(CH_2)_2SCH_2$.

Compounds Ia and Id were prepared according to conventional procedures described in [10, 11]. The α-amino group of α,ω-diamino acids was protected by chelation with $Cu^{2+}$ ions. Copper complexes II, III were prepared by carbamoylation of copper complexes of diamino acids in aqueous solutions by corresponding alkyl isocyanates RNCO at 0°C (method A) or carbamoylation with symmetric dialkylnitrosoureas RN(NO)CONHR at elevated temperatures (method B).

The specific features of the synthesis of copper complexes IId and IIId are explained by the structure of the initial amino acid Id, the molecules of which decompose in alkaline media [12]. Excess $Cu^{2+}$ ions catalyze this process. Therefore, instead of using $CuSO_4 \cdot 5H_2O$ as a source of $Cu^{2+}$ ions in the preparation of copper complex of *L*-4-thialysine as in the case of other copper complexes, $CuCO_3 \cdot Cu(OH)_2$, which is not very soluble in water, was used. Copper complexes IId and IIId were synthesized in high yields only when carbamoylation was carried out with alkyl isocyanates at 0°C (method A).

When copper complexes were decomposed with $H_2S$ in acidic media, corresponding $N^{\omega}$-alkylcarbamoyl derivatives IV and V were obtained, which were then nitrosylated with $NaNO_2$ in dilute hydrochloric acid at pH 1 – 2 at about 0°C. Under these conditions, the α-amino group was not nitrosylated [8], and nitrosylation involved one of the atoms of the urea group only. Compound Vd was the only exception: upon its nitrosylation, 2-chloro-6-(1-nitroso-3-cyclohexylureido)-4-thiahexanoic acid (VIII) formed in addition to compound VIId.



VIII

The direction of nitrosylation in the series of nitroso compounds VI, VII is controlled by the structure of alkyl substituent R and is independent of the structure of amino acid fragment.

It was found that $N^{\omega}$-methylcarbamoyl derivatives IVa – d was regioselective and led to compounds VIa – d with NO group at the atom of nitrogen linked to $CH_3$ group. Indeed, $^1H$ NMR spectra of compounds VIa – d showed a singlet with the chemical shift δ 3.15 – 3.17 ppm assigned to methyl protons in $CH_3N(NO)$ (the $CH_3NH$ group of the initial compounds IVa – d gave a signal at δ 2.63 – 2.64 ppm) and a triplet at δ 3.44 – 3.65 ppm assigned to methylene protons in $CH_2NH$.

Nitrosylation of $N^{\omega}$-cyclohexylcarbamoyl derivatives Vb – d was regioselective and led to compounds VIIb – d with NO group at the $N^{\omega}$ atom of amino acid fragment. This is apparently the result of steric effects due to cyclohexyl radical. In $^1H$ NMR spectra of compounds VIIb – d, methylene protons of the cyclohexyl group gave a multiplet at δ 2.0 – 1.2 ppm, and the methine proton of cyclohexyl radical CHNH gave a multiplet at δ 3.76 – 3.60 ppm, whereas methylene protons of $CH_2N(NO)$ gave a triplet at δ 3.8 – 3.9 ppm.

The structure of the compounds synthesized was confirmed by IR, UV, and $^1H$ NMR spectroscopies. Some physico-chemical characteristics of these compounds are listed in Table 1. UV spectra of compounds VIa – d and VIIb – d show absorption maxima at λ about 230 and 400 nm; these maxima are related to the presence of an NO group. In addition to absorption bands characteristic of amino acids, IR spectra of these compounds reveal bands at ν about 1700 (C = O in nitrosoureido groups) and 1470 (N = O) $cm^{-1}$.

## EXPERIMENTAL CHEMICAL PART

The purity of the synthesized compounds was checked with TLC on Silufol UV plates using *n*-butanol – acetic acid – water (6 : 2 : 2) system. The melting temperatures were measured on a Boetius hot stage. UV spectra were recorded in aqueous solutions with a Specord UV-VIS spectrophotometer. IR spectra were measured in vaseline oil suspensions with a Specord IR-75 instrument. $^1H$ NMR spectra were registered with a Tesla BS-497 spectrometer at an operating frequency of 100 MHz in $D_2O$ solutions with a DSS internal standard. The specific rotation was measured with an Al-EPO polarimeter. The data of elemental analyses for the compounds synthesized were consistent with the calculated data.

**$N^{\gamma}$-Methylnitrosocarbamoyl-*L*-α,γ-diaminobutyric acid (VIa).** Method A. To a solution of Ia (6.28 g, 0.033 mole) and KOH (5.53 g, 0.099 mole) in 30 ml of water were added a solution of $CuSO_4 \cdot 5H_2O$ (4.11 g, 0.016 mole) in 12 ml of water with stirring at 30°C and 65 ml of water. The reaction mass was cooled to 5°C. Then 2.82 g (0.050 mole) of methyl isocyanate was added and the mixture was stirred at this temperature for 6 h. The precipitate of cop-

per complex IIa was separated by filtration, washed with water and dried to yield 5.10 g (75%) of IIa.

Method B. To a solution of Ia (4.0 g, 0.021 mole) and KOH (3.49 g, 0.062 mole) in 20 ml of water were added a solution of $CuSO_4 \cdot 5H_2O$ (2.60 g, 0.010 mole) in 10 ml of water with stirring at 30°C, 47 ml of water, and 1,3-dimethyl-1-nitrosourea (3.07 g, 0.026 mole) in 30 ml of ethyl alcohol. The reaction mass was heated on a water bath to 50°C and stirred at this temperature for 5 h. The precipitate was separated by filtration, washed with water, and dried to yield 2.17 g (50%) of IIa.

Compound IIa (5.10 g, 0.012 mole) was dissolved in a mixture of 50 ml of water and 1.33 ml (0.024 mole) of concentrated $H_2SO_4$. The solution was purged with $H_2S$ until all CuS has precipitated. The filtrate obtained after separation of CuS was neutralized to pH 7 with a $Ba(OH)_2$ solution, $BaSO_4$ was separated by centrifugation, and the mother liquor was purged with $CO_2$ until $BaCO_3$ no longer precipitated. The solution was filtered and the filtrate was evaporated in vacuum to dryness. The residue was dried in vacuum over $P_2O_5$ to yield 3.0 g of IVa (70% yield as calculated with respect to IIa).

Compound IVa (3.0 g, 0.017 mole) was dissolved in 30 ml of water and 1.7 ml (0.020 mole) of concentrated HCl was added. The solution was cooled to 0°C and 1.41 g (0.020 mole) of $NaNO_2$ was added. The reaction mass was allowed to stand at this temperature and stirred for 1 h at pH 1 – 2. Nitrogen oxides were removed by evacuation; the reaction mass was neutralized to pH 6 with an $NH_4OH$ solution, and evaporated in a vacuum until a precipitate formed abundantly. The mass was cooled to 0°C; the precipitate was separated by filtration, washed with water and alcohol, and dried in a vacuum over $P_2O_5$ to yield 1.84 g of VIa (53% yield as calculated with respect to IVa).

**$N^{\delta}$-Methylnitrosocarbamoyl-*L*-ornithine (VIb).** Copper complex IIb was prepared from 25 g (0.148 mole) of Ib according to a procedure similar to that used to prepare compound IIa (method B). The yield of compound IIb was 25.0 g (77%). Compound IIb (25.0 g, 0.057 mole) was dissolved in a mixture of 250 ml of water and 6.16 ml (0.114 mole) of concentrated $H_2SO_4$. The decomposition of copper complex with $H_2S$ and isolation of compound IVb were carried out similarly to how it was done with compound IVa. The yield of VIb was 15.2 g (70%, as calculated for IIb). Compound VIb was prepared similarly to compound VIa from 13.52 g (0.071 mole) of compound IVb yielding 12.33 g (79%, as calculated with respect to IVb).

**$N^{\varepsilon}$-Methylnitrosocarbamoyl-*L*-lysine (VIc).** Copper complex IIc was prepared similarly to compound IIa, starting with 36.5 g (0.2 mole) of Ic and 14.3 g (0.25 mole) of methyl isocyanate (method A) to yield 40.2 g (86%) of the target compound or from 45.7 g (0.25 mole) of Ic and 35 g (0.3 mole) of 1,3-dimethyl-1-nitrosourea (method B) to yield 45.7 g (78%) of the target compound. Compound IIc (10 g, 0.021 mole) was dissolved in a mixture of 150 ml of water and 30 ml of 4 N HCl. The solution was purged with $H_2S$ until the precipitation of CuS was complete. The precipitate was separated by filtration and the filtrate was neutralized to pH 7 with $NH_4OH$ and evaporated in a vacuum to dryness. The residue was extracted with boiling methanol. The precipitate formed upon cooling of the solution was separated by filtration to yield 6.3 g of Ic (73%, as calculated with respect to IIc). Compound IVc was prepared similarly to VIa from 4.5 g (0.022 mole) of compound IVc. It was isolated from the reaction mass by neutralizing it to pH 6 with $NH_4OH$; the separated precipitate yielded 3.8 g of VIc (74%, as calculated with respect to IVc).

**$N^{\varepsilon}$-Methylnitrosocarbamoyl-*L*-4-thialysine (VId).** To a solution of Id (5.0 g, 0.025 mole) in 50 ml of water, which

TABLE 1. Characteristics of $N^{\omega}$-Methylnitrosocarbamoyl- and $N^{\omega}$-Nitroso-$N^{\omega}$-Cyclohexylcarbamoyl-α,ω-diaminocarboxylic Acids (VIa – d and VIIb – d)

| Compound | M.p., °C (decomp.) | $[\alpha]_D^{20}$, deg | $R_f$ (BuAcW) | Empirical formula | $^1$H NMR spectra ($D_2O$)*, δ, ppm |
|---|---|---|---|---|---|
| VIa | 185 – 187 | + 23.6 (s 2, 1 N HCl) | 0.28 | $C_6H_{12}N_4O_4$ | 2.10 – 2.32 (m, 2H, $CH_2CH$), 3.17 (s, 3H, $CH_3$), 3.60 (t, 2H, $NHCH_2$), 3.84 (t, 1H, CH) |
| VIb | > 100 | + 21.6 (s 1.7, 1 N HCl) | 0.30 | $C_7H_{14}N_4O_4$ | 1.5 – 2.0 (m, 4H, $CH_2CH_2CH$), 3.17 (s, 3H, $CH_3$), 3.48 (t, 2H, $NHCH_2$), 3.80 (t, 1H, CH) |
| VIc | > 90 | + 9.5 (s 2, $H_2O$) | 0.43 | $C_8H_{16}N_4O_4$ | 1.3 – 2.0 (m, 6H, $CH_2CH_2CH_2CH$), 3.16 (s, 3H, $CH_3$), 3.44 (t, 2H, $NHCH_2$), 3.76 (t, 1H, CH) |
| VId | 178 – 182 | – 27.2 (s 0.5, $H_2O$) | 0.29 | $C_7H_{14}N_4O_4S$ | 2.85 (t, 2H, $CCH_2S$), 3.08 – 3.11 (d, 2H, $SCH_2CH$), 3.15 (s, 3H, $CH_3$), 3.65 (t, 2H, $NHCH_2$), 3.9 – 4.1 (m, 1H, CH) |
| VIIb | 174 – 175 | + 12.3 (s 1.3, 1 N HCl) | 0.54 | $C_{12}H_{22}N_4O_4$ | 1.2 – 2.0 (m, 14H:10H ($CH_2$)$_5$–cyclohexyl), 4H, $CH_2CH_2CH$), 3.76 (m, 1H, CHNH), 3.88 (t, 2H, $NONCH_2$), 4.09 (t, 1H, CHCOOH) |
| VIIc | 178 – 181 | + 13.2 (s 2, 1 N HCl) | 0.60 | $C_{13}H_{24}N_4O_4$ | 1.2 – 2.0 (m, 16H:10H ($CH_2$)$_5$—cyclohexyl), 6H, $CH_2CH_2CH_2CH$), 3.7 (m, 1H, CHNH), 3.84 (t, 2H, $NONCH_2$), 4.08 (t, 1H, CHCOOH) |
| VIId | 142 – 150 | – 39.7 (s 0.3 $H_2O$) | 0.48 | $C_{12}H_{22}N_4O_4S$ | 1.2 – 2.0 (m, 10H ($CH_2$)$_5$–cyclohexyl), 2.55 (t, 2H, $CH_2S$), 2.98 – 3.06 (dd, 2H, $SCH_2CH$), 3.6 (m, 1H, CHNH), 3.9 (t, 2H, $CH_2NNO$), 4.14 – 4.26 (dd, 1H, CHCOOH) |

* $^1$H NMR spectra of compounds VIIb – d were measured in $D_2O$ with DCl additive; those of compounds VId, in $D_2O$ with $CD_3COOD$ additive.

was heated to 90°C, was added 5.0 g (0.023 mole) of $CuCO_3 \cdot Cu(OH)_2$. Excess $CuCO_3 \cdot Cu(OH)_2$ was separated by filtration. The filtrate was cooled to room temperature and 1.4 g (0.025 mole) of KOH in 10 ml of water was added. The reaction mass was cooled to 0°C with ice, and 2.28 ml (0.04 mole) of methyl isocyanate was added. The reaction mass was stirred at this temperature for 4 – 5 h. The precipitate was separated by filtration, washed with water and ethanol, and dried to yield 4.67 g of IId (74%). Compound IId (4.67 g, 0.009 mole) was dissolved in 47 ml of water and 1.02 ml (0.019 mole) of concentrated $H_2SO_4$, and compound IVd was isolated similarly to compound IVa, yielding 2.8 g (68% as calculated with respect to IId). Compound VId was obtained similarly to compound VIc from 2.8 g (0.013 mole) of compound IVd. The yield of VId was 2.07 g (65% as calculated with respect to compound IVd).

**$N^{\delta}$-Nitroso-$N^{\delta}$-hexylcarbamoyl-*L*-ornithine (VIIb).** Copper complex IIIb was prepared from 7.52 g (0.045 mole) of Ib and 7.8 ml (0.062 mole) of cyclohexyl isocyanate in a procedure similarly to that used to prepare IIa (method A). The yield was 12.1 g (94%). Compound IIIb (12.1 g, 0.021 mole) was dissolved in 120 ml of water and 2.25 ml (0.042 mole) of concentrated $H_2SO_4$. Compound Vb was isolated similarly to IVa; 3.14 g of Vb (29%, as calculated with respect to IIIb) was obtained. Compound VIIb was prepared from 3.14 g (0.012 mole) of Vb similarly to VIa. The yield was 1.57 g (46% with respect to Vb).

**$N^{\varepsilon}$-nitroso-$N^{\varepsilon}$-cyclohexylcarbamoyl-*L*-lysine (VIIc).** The copper complex IIIc was prepared similarly to IIa. When preparing it according to method A, 5.0 g (0.027 mole) of Ic and 5.2 g (0.041 mole) of cyclohexyl isocyanate were used, yielding 7.4 g (89%) of the target product. According to method B, 36.5 g (0.2 mole) of Ic and 53.2 g (0.21 mole) of 1,3-dicyclohexyl-1-nitrosourea were used, yielding 52.6 g (87%) of IIIc. Compound IIIc (7.0 g, 0.012 mole) was dissolved in a mixture of 100 ml of water and 15 ml of 4 N HCl and $H_2S$ was purged through the solution until the CuS precipitated completely. After separating the precipitate, the filtrate was neutralized to pH 7 with $NH_4OH$. The resulting precipitate was separated by filtration and washed with water to yield 4.2 g (67% with respect to IIIc) of the target product. Compound VIIc was prepared similarly to VIc using 4.0 g (0.015 mole) of compound Vc to obtain 3.5 g (79%, as calculated with respect to Vc) of the product.

**$N^{\varepsilon}$-Nitroso-$N^{\varepsilon}$-cyclohexylcarbamoyl-*L*-4-thialysine (VIId).** The copper complex IIId was prepared similarly to IId from 5.0 g (0.025 mole) of Id and 4.06 ml (0.032 mole) of cyclohexyl isocyanate. The yield was 6.0 g (75%). A solution of IIId (6.0 g, 0.009 mole) in 60 ml of water and 3.2 ml (0.038 mole) of concentrated HCl was purged with $H_2S$ until all CuS precipitated. After separation from precipitate, the filtrate was neutralized to pH 7 with $NH_4OH$. The resulting precipitate was separated by filtration, washed with water and ethanol, and dried in a vacuum over $P_2O_4$ to yield 3.48 g of Vd (64% with respect to IIId). To a solution of Vd (2 g, 0.007 mole) in a mixture of 20 ml of water and 1.3 ml (0.015 mole) concentrated HCl cooled to 0°C, 0.57 g (0.008 mole) $NaNO_2$ was added with stirring. The mixture was allowed to stand at 0°C for 1 h, and the resulting yellow oil was separated, washed with water and alcohol, and extracted with diethyl ether. The ether solution was washed with water and dried with $Na_2SO_4$; then, the solvent was distilled off to yield 0.21 g of VIII (9% with respect to Vd). Compound VIId was then isolated in way similarly to that used with compound VId, yielding 1.35 g (61% with respect to Vd).

## EXPERIMENTAL BIOLOGICAL PART

Trials were carried out with mice of lines C $57Bl_6$; $DBA_2$; CBA; $BalB_C$, and $BDF_1$ hybrids. Leukemia was induced by intraperitoneal injection of $1.0 - 1.2 \times 10^6$ cells to each mouse; solid tumors were induced by subcutaneous injection of 50 mg of tumor suspension in the axillary region. The antitumor activity was studied in mice with lymphoblast leukemia L 1210 and hemocytoblastosis La. The antitumor activity was also studied against solid tumors: mammary adenocarcinoma (Ca-755), large intestine cancer (AKATOL),

TABLE 2 Antitumor Activity of $N^{\omega}$-Methylnitrosocarbamoyl and $N^{\omega}$-Nitroso-$N^{\omega}$-cyclohexyl-α,ω-diaminocarboxylic Acids

| Compound | Dose, mg / kg (intraperitoneal injection 5 times a day) | Leukemia | | Solid tumors | | | |
|---|---|---|---|---|---|---|---|
| | | LTI index, % | | RTG, % on the 1st, 7th, and 13th days after the completion of treatment | | | |
| | | L 1210 | La | Ca-755 | AKATOL | LLC | RShM-5 |
| VIb | 500 – 700 | 200 | 25 | 73 – 91 | – | 73 – 86 – 73 | – |
| VIc | 500 – 700 | 156 | 49 | 94 – 94 – 83 | 9 – 32 – 30 | 30 – 20 – 11 | 82 – 89 – 78 |
| | 800 – 1000* | – | – | 77 – 99 – 93 | 60 – 69 – 36 | – | – |
| VId | 500 | 90 | – | – | – | 53 – 30 (12% lethality) | – |
| VIIc | 500 – 700 | 0 | – | 98 – 77 – 54 | – | 59 – 15 | – |
| VIId | 500 | 19 | – | – | – | 63 – 43 (50% lethality) | – |
| | 600 | 5 | – | – | – | 86 (lethality) | – |
| MNU | 20 – 25 | 75 | 48 | 67 – 4 | 52 – 51 | 45 | 18 |

* Two injections during four days.

Lewis lung carcinoma (LLC), and cervical carcinoma (RShM-5). The antitumor activity was compared with that of the nearest analog, 1-methyl-1-nitrosourea (MNU), which was synthesized at the Institute of Chemical Physics of the Russian Academy of Sciences.

The treatment's efficacy was assessed by the retardation of tumor growth (RTG; for the number of animals tested in this study, the minimal significant value amounts to 50% RTG) and an increase in the lifetime of animals (LTI index; the minimal significant value is 25% LTI). The compounds were administered in maximally tolerated doses. The results of the studies are summarized in Table 2.

It was found that $N^{\omega}$-methylnitrosocarbamoyl derivatives VIb and VIc show high activity, which exceeded that of MNU, both against solid tumors Ca-755, AKATOL, LLC, and RShM-5 and against leukemia L 1210. Cyclohexyl compound VIIc was effective only against Ca-755.

Studies of the antitumor activity of $N^{\omega}$-ANC derivatives of *L*-4-thialysine revealed that the cyclohexyl derivative VIId did not affect the course of L 1210 leukemia, whereas the methyl derivative VId increased the lifetime of mice suffering from this leukemia by 90%. Both compounds showed only slight and rapidly disappearing effect on the growth of LLC lung carcinoma; moreover, some of the animals perished because of the toxicity of the compounds.

Comparison of these results with those for the hydrocarbon analogs (VIc and VIIc) led us to the following conclusions. The antitumor effect and the efficiency spectrum of $N^{\omega}$-ANC derivatives of α,ω-diamino acids are significantly controlled by the structure of alkyl substituent; replacing the methylene group with an S atom in the fourth position in the amino acid fragment reduces the antitumor activity and increases the toxicity.

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