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CHOLINE-LIKE NITROSOALKYLUREAS AND THEIR ANTITUMOR ACTIVITY

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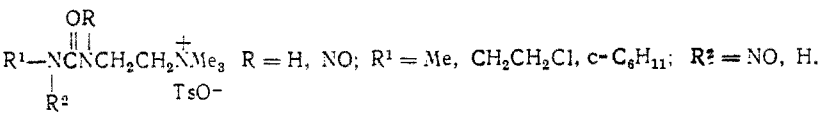
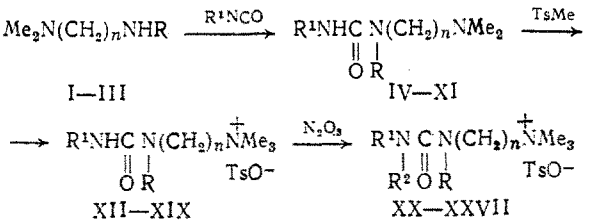
We have previously obtained some nitrosoalkylureas (NAU), derivatives of choline-like alkylammonium salts, which show high antitumor activity and toxicity [1]:



R^1—N(R²)C(=O)NCH₂CH₂N⁺Me₃ TsO⁻ R = H, NO; R^1 = Me, CH_2CH_2Cl, c-C_6H_{11}; R^2 = NO, H.

Reasoning from the mode of breakdown of NAU [6], in order to reduce toxicity by increasing stability or varying the structures of the decomposition products, we have prepared some novel di- and tri-substituted NAU derived from quaternary ammonium salts (XX-XXVII) which differ from previously synthesized compounds in the length of the alkyl chain connecting the urea moiety with the quaternized nitrogen (XX-XXV), or the absence of a urea proton (XXVI-XXVII).



$Me_2N(CH_2)_nNHR$ —R^1NCO→ $R^1NHC(=O)N(R)(CH_2)_nNMe_2$ —TsMe→ (I—III; IV—XI)

→ $R^1NHC(=O)N(R)(CH_2)_nN^+Me_3$ TsO⁻ —N_2O_3→ $R^1N(NO)C(=O)N(R)(CH_2)_nN^+Me_3$ TsO⁻ (XII—XIX; XX—XXVII)

R = H (I, II, IV—IX, XII—XVII, XX, XXIII), Me (III, X, XI, XVIII, XIX, XXVI, XXVII), NO (XXII, XXIV, XXV), H, NO (XXI, mixture of isomers)

R^1 = Me (IV, VII, X, XII, XV, XVIII, XX, XXIII, XXVI), CH_2CH_2Cl (V, VIII, XI, XIII, XVI, XIX, XXI, XXIV, XXVII), c-C_6H_{11} (VI, IX, XIV, XVII, XXII, XXV)

R^2 = H (XXII, XXIV, XXV), NO (XX, XXIII, XXVI, XXVII), NO, H (mixture of isomers, XXI).

n-2 (III, IV, X, XI, XVIII, XIX, XXVI, XXVII), 3 (I, V, VI, VII—XIV, XX—XXII), 4 (II, VII—IX, XV—XVII, XXVIII—XXV).

N,N-Dimethylpropanediamine (I), N,N-dimethylbutanediamine (II), and N,N,N'-trimethylethylenediamine (III) were carbamoylated with the appropriate alkyl isocyanates to give the ureas (IV-XI), which were quaternized with methyl tosylate followed by nitrosation of the quaternary ammonium salts with dinitrogen trioxide in dry acetone or acetonitrile. The resulting NAU (XX-XXVII) were pale yellow crystalline solids which were highly soluble in water (apart from (XXI) and (XXIV), which were of an oily consistency at room temperature). Compounds (IV), (V), (VII), (VIII), (X), (XI), and (XIX) could not be obtained in the crystalline state, and therefore they were not identified, but were used in the subsequent stages without isolation or further purification.

The compositions and structures of the products were confirmed by their elemental analysis and their IR, UV, and PMR spectra, which are shown in Table 1.

Nitrosation of the disubstituted NAU (XX-XXV) could give two nitrosoderivatives. The site of entry of the nitroso-group was established by PMR spectroscopy. For example, on nitrosation of the ureas (XII) and (XV), the doublet for the protons of the CH_3N group under-

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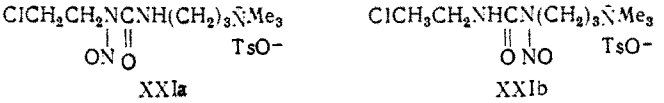
goes a low-field shift such as is characteristic of the $CH_2N(NO)$ group [3], and becomes a singlet, the signal for the urea NH proton being a triplet. Nitrosation of the cyclohexyl compounds (XIV) and (XVII) gives nitroso-compounds the PMR spectra of which show a triplet for the $CH_2N(NO)$ protons and a doublet for the single NH proton. Nitrosation of the chloroethylurea (XVI) results in the appearance in the spectrum of a signal for the protons of the $CH_2N(NO)$ group at 3.80 ppm, overlapping a narrow multiplet for the protons of the $ClCH_2CH_2N$ group, which becomes a singlet when the spectrum is obtained in D_2O. These results show that the disubstituted NAU (XX, XXII-XXV) are pure compounds, although in the case of (XXIV) the presence of a low-intensity triplet at 4.17 ppm, corresponding to the protons of the $CH_2N(NO)$ group in the chloroethyl group [5], indicate that 5% of the isomer with the nitroso-group attached to the nitrogen carrying the chloroethyl group is formed.

When the chloroethylurea (XIII) is nitrosated, a mixture of isomers with respect to the position of the nitro-group (XXIa and XXIb) is obtained,



XXIa XXIb

as shown by the presence of a triplet for the $CH_2N(NO)$ protons of the chloroethyl group in isomer (XXIa) at 4.12 ppm, and a narrow multiplet for the protons of the $ClCH_2CH_2N$ group in (XXIb) at 3.80 ppm, superimposed on a triplet for the CH_2Cl groups in (XXIa) and $CH_2N(NO)$ in (XXIb) at 3.6-3.9 ppm, the signals for the other methylene protons not occurring in this region, as confirmed by the PMR spectra of (XX) and (XXII). The two singlets for the proton of the $\overset{+}{N}(CH_3)_3$ group at 3.04 and 3.08 ppm are apparently also a consequence of the formation of the isomer mixture.

Based on the number of protons of the appropriate groups, and representing the relative amount of the isomer (XXIa) in the mixture by Z and the isomer (XXIb) by (1 − Z), an expression can be written for the ratio of the intensities of the signals in the PMR spectrum at 4.12 ppm [$CH_2N(NO)$ XXIa] and in the region 3.6-3.9 ppm [$ClCH_2$ XXIa, $ClCH_2CH_2N$ and $CH_2N(NO)$ XXIb]:

$$\frac{I_{4.12}}{I_{3.6-3.9}} = \frac{2Z}{2Z + 4(1-Z) - 2(1-Z)} = \frac{2Z}{6-4Z}.$$

The ratio $I_{4.12}/I_{3.6-3.9}$ actually found from the spectrum was 2/15. Solution of Eq. (1) gives the isomer content of (XXIa) as 0.32, and of (XXIb) 0.68. Similar values (0.35 and 0.65) were obtained when the isomer contents were calculated from the ratios of the intensities of the $N(CH_3)_3$ protons, the signal at lower field (3.08 ppm) corresponding to the isomer (XXIa).

A study of the rates of decomposition of the NAU obtained (except for (XXI), which is an isomer mixture) in a phosphate buffer of pH 7.4 at 37°C showed that the disubstituted NAU (XX) and (XXII-XXV) are 2-3 times, and the trisubstituted compounds (XXVI) and (XXVII) 20-100 times more stable than the previously obtained choline-like NAU [2].

Under these conditions, the rate constants for the decomposition of (XX) and (XXII-XXVII) ($k_{decomp} \cdot 10^4$, sec^{-1}) were 0.504, 1.01, 0.306, 1.06, 0.719, 0.01, and 0.176 respectively.

The antitumor activity of the NAU (XX) and (XXII-XXVII) was examined in animals. The activity of the compounds was assessed with respect to leukemia by the increase in the life-span of the animals (ILA, %), and to solid tumors by the inhibition of the growth of the tumor (IGT, %) in the treated animals are compared with the controls. The toxicities of the compounds were measured by the maximum tolerated dose (MTD, mg/kg), which was also the therapeutic dose.

The test results showed that in the case of the disubstituted NAU (XX) and (XXII-XXV), the stabilities of which differed little from the choline-like NAU, the toxicities were maintained at the level of the latter (10-30 mg/kg), but in the trisubstituted compounds (XXVI) and XXVII), the stability of which was greater by 1-2 orders of magnitude, the toxicity was considerably less (MTD 250-300 mg/kg) than that of the choline-like NAU [1].

The highest antitumor activity was shown by (XXVII), which in a dose of 250 mg/kg has a considerable, but evanescent effect (87% IGT in Lewis lung cancer, 88% IGT in mammary adenocarcinoma Ca-755, and 58% IGT in sarcoma 37). Moderate activity was shown by (XXV), which

TABLE 1. Nitrosoaklylureas (XX)-(XXVII) and Intermediates in Their Synthesis

Compound	mp, °C (solvent)	Empirical formula	Found, % / Calculated, %			IR spectrum, ν_{max}, cm^{-1}	PMR spectrum, δ, ppm
			C	H	N		
VI	83 (CH_3CN)	$C_{12}H_{24}N_2O$	63,89 / 63,40	11,53 / 11,08	18,62 / 18,48	3315, 1560 (N—H), 1615 (C=O), 2780—2720 (N—CH_3)	...
IX	79 (CH_3CN)	$C_{13}H_{27}N_2O$	64,71 / 64,67	11,36 / 11,29	17,29 / 17,41	3315, 1575 (N—H), 1615 (C=O), 2780—2720 (N—CH_3)	...
XII	—	$C_{16}H_{27}N_3O_4S$	52,45 / 52,15	8,22 / 7,88	12,18 / 12,16	3300, 1550 (N—H), 1625 (C=O)	6.12 t (NH), 5.90 q (NH), 3.05 s ($\overset{+}{N}(CH_3)_3$), 2.54 d (CH_3N), 3.20 m (NCH_2 and $CH_2\overset{+}{N}$), 1.90 m (CH_2)
XIII	—	$C_{16}H_{28}ClN_3O_4S$	48,57 / 48,79	7,20 / 7,16	10,74 / 10,67	3350, 1560 (N—H), 1650 (C=O)	6.45 m (NH), 3.50 m ($ClCH_2CH_2N$), 3.30 m (NCH_2 and $CH_2\overset{+}{N}$), 3.09 s ($\overset{+}{N}(CH_3)_3$), 1.90 m (CH_2)
XIV	138 (CH_3CN)	$C_{20}H_{33}N_3O_4S$	58,40 / 58,08	8,77 / 8,53	10,21 / 10,16	3360, 3300, 1565 (N—H), 1620 (C=O)	5.95 m (NH), 3.30 m (NCH_2 and $CH_2\overset{+}{N}$), 3.06 s ($\overset{+}{N}(CH_3)_3$), 1.90 m (CH_2), 1.50 m (c-C_6H_{11})
XV	130 acetone—CH_3CN)	$C_{16}H_{29}N_3O_4S$	53,47 / 53,45	7,97 / 8,15	11,50 / 11,50	3340, 1570 (N—H), 1620 (C=O)	6,09 t (NH), 5,86 q (NH), 3,30 m (NCH_2 and $CH_2\overset{+}{N}$), 3.03 s ($\overset{+}{N}(CH_3)_3$), 2.53 d (CH_3N), 1.60 m (CH_2CH_2)
XVI	115 acetone—CH_3CN)	$C_{17}H_{30}ClN_3O_4S$	49,90 / 50,04	7,26 / 7,43	10,28 / 10,30	3320, 1570 (N—H), 1620 (C=O)	6.32 m (NH), 3.50 m ($ClCH_2CH_2N$), 3.30 m (NCH_2 and $CH_2\overset{+}{N}$), 3.03 s ($\overset{+}{N}(CH_3)_3$), 1.60 m (CH_2CH_2)
XVII	166 (CH_3CN—acetone)	$C_{21}H_{37}N_3O_4S$	58,71 / 58,98	8,88 / 8,74	9,79 / 9,83	3280, 1565 (N—H), 1630 (C=O)	5,90 m (NH), 3.30 m (NCH_2 and $CH_2\overset{+}{N}$), 3,02 s ($\overset{+}{N}(CH_3)_3$), 1,60 m (CH_2CH_2)
XVIII	135 (acetone)	$C_{16}H_{27}N_3O_4S$	52,43 / 52,15	8,03 / 7,88	12,21 / 12,16	3320, 1530 (N—H), 1615 (C=O)	6,44 q (NH), 3.50 m ($NCH_2CH_2\overset{+}{N}$), 3.09 s ($\overset{+}{N}(CH_3)_3$), 2.82 s (CH_3N), 2.58 d (CH_3N)
XX	140 decomp.	$C_{12}H_{24}N_4O_3S$	47,83 / 48,11	6,89 / 6,94	15,50 / 14,96	3350, 1530 (N—H), 1730 (C=O), 1485 (N=O)	8.85 t (NH), 3,40 m (NCH_2 and $CH_2\overset{+}{N}$), 3.12 s (CH_3H (NO), 3.10 s ($\overset{+}{N}(CH_3)_3$), 2.0 m (CH_2)
XXI	oil	$C_{16}H_{27}ClN_4O_3$	45,38 / 45,44	6,82 / 6,44	13,50 / 13,25	3270, 1535 (N—H), 1720 (C=O), 1485 (N=O)	8.94 m (NH), 4,12 t (N (NO) CH_2), 3.78 m ($ClCH_2CH_2N$), 3,70 m ($ClCH_2$ and N(NO) CH_2), 3.30 m (NCH_2 and $CH_2\overset{+}{N}$), 3.09 s, 3.04 s ($\overset{+}{N}(CH_3)_3$), 2.0 m (CH_2)
XXII	111 decomp.	$C_{20}H_{34}N_4O_3S$	54,41 / 54,28	8,36 / 7,74	12,66 / 12,51	3270, 1535 (N—H), 1720 (C=O), 1480 (N=O)	7,52 d (NH), 3,78 t ($N(NO)CH_2$), 3,25 m ($CH_2\overset{+}{N}$), 3.03 s ($\overset{+}{N}(CH_3)_3$), 2.0 m (CH_2)
XXIII	145 decomp.	$C_{16}H_{28}N_4O_3S$	49,55 / 49,46	7,40 / 7,25	14,33 / 14,42	3400, 1530 (N—H), 1720 (C=O) 1475 (N=O)	8,86 t (NH), 3.30 m (NCH_2 and $CH_2\overset{+}{N}$), 3.10 s (CH_3N), 3.05 s ($\overset{+}{N}(CH_3)_3$), 1,60 m (CH_2CH_2)
XXIV	oil	$C_{17}H_{29}ClN_3O_3S$	46,29 / 46,72	7,03 / 6,70	12,81 / 12,81	3320, 1530 (N—H), 1700 (C=O), 1480 (N=O)	8,93 t (NH), 3.75 m ($ClCH_2CH_2N$), 3.70 t ($N(NO)CH_2$), 3.34 m ($CH_2\overset{+}{N}$), 3.03 s ($\overset{+}{N}(CH_3)_3$), 1.50 m (CH_2CH_2)
XXV	130 decomp.	$C_{21}H_{38}N_4O_3S$	55,21 / 55,23	8,15 / 7,96	12,30 / 12,27	3320, 1530 (N—H) 1720 (C=O), 1485 (N=O)	8,48 d (NH), 3,74 t ($N(NO)CH_2$), 3.24 m ($CH_2\overset{+}{N}$), 3.03 s ($\overset{+}{N}(CH_3)_3$), 1.6 m (CH_2CH_2 and c-C_6H_{11})

TABLE 1 (Continued.)

Compound	mp, °C (solvent)	Empirical formula	Found, % / Calculated, % C	H	N	IR spectrum, ν_{max}, cm^{-1}	PMR spectrum, δ, ppm
XXVI	146 decomp.	$C_{15}H_{26}N_4O_3S$	48.60 / 48.11	7.44 / 6.94	14.57 / 14.96	1680 (C=O), 1470 (N=O)	3.76m (NCH_2CH_2N), 3.13s ($\overset{+}{N}(CH_3)_3$), 3.07s ($CH_2N(NO)$ and CH_3N)
XXVII	133 decomp.	$C_{16}H_{27}ClN_4O_3S$	45.57 / 45.44	6.52 / 6.44	13.42 / 13.52	1690 (C=O), 1485 (N=O)	4.06t ($N(NO)CH_2$), 3.65t ($ClCH_2$), 3.82m ($NCH_2CH_2\overset{+}{N}$), 3.14s ($\overset{+}{N}(CH_3)_3$), 3.09s(CH_3N)

Note. UV spectra of (XX-XXVII), λ_{max}, nm (lg ε): 223 (4.17), 395 (1.93); 223 (4.18), 395 (1.90); 223 (4.16), 395 (7.89); 223 (4.19), 395(1.95); 223 (4.18), 395 (1.90); 223 (4.18), 395 (1.92); 223 (4.16); 380 (1.92); 223 (4.17), 385 (1.90).

in a dose of 30 mg/kg gave 71% IGT with sarcoma 37. The remaining NAU were inactive in nontoxic doses.

Hence, increasing the length of the aliphatic chain between the quaternary nitrogen and the urea group in disubstituted NAU over those previously examined results in a slight decrease in the rate of decomposition, which in practice has no effect on the toxicities of the NAU. Replacement of the amide proton in choline-like NAU by methyl to give trisubstituted NAU results in a decrease in the decomposition rate by 1-2 orders of magnitude, a considerable decrease in toxicity, and the appearance of antitumor activity.

EXPERIMENTAL CHEMICAL PART

The purity of the compounds was checked by TLC on acid (Woelm, West Germany) and neutral (LSL_{254} 5/40, Czech SSR) alumina in the system chloroform–methanol (4:1) and acetone–water (9:1) respectively, the spots being developed with iodoplatinate [4] and by UV. UV spectra were recorded on a Specord UV-VIS instrument in water, IR spectra on a UV-20 in a thin film of vaseline oil, and PMR spectra on a Tesla BS-467A (100 MHz) in DMSO-d_6 (TMS). The rates of decomposition of the compounds were determined as described by Belyaev et al. [2].

1-(3-Dimethylaminopropyl)-3-cyclohexylurea (VI). To a solution of 0.7 g (6.9 mmole) of (I) in 5 ml of dry acetonitrile was added with stirring and cooling at 0°C a solution of 1.03 g (8.2 mmole) of cyclohexyl isocyanate. After 0.5 h, the solid which separated was filtered off and washed with acetonitrile to give 1.07 g (67%) of (VI).

1-(4-Dimethylaminobutyl)-3-cyclohexylurea (IX). Obtained as for (VI), from 0.83 g (7.2 mmole) of (II) and 1.1 g (8.8 mmole) of cyclohexyl ixocyanate. Yield 1.3 g (75%).

3-(3-Methylureido)propyltrimethylammonium Tosylate (XII). To 0.7 g (12 mmole) of methyl isocyanate in 8 ml of dry acetonitrile was added with stirring at −5°C 1.0 g (10 mmole) of (I) in 5 ml of dry acetonitrile. After 1 h, 2.38 g (13 mmole) of methyl tolsylate was added to the mixture, and after a further 2 h the solution was evaporated under reduced pressure. The residue was triturated with dry ether, and recrystallized from a mixture of acetone and acetonitrile to give 2.58 g (75%) of (XII).

3-(3-Cycloexylureido)propyltrimethylammonium Tosylate (XIV). To a solution of 1.07 g (4.4 mmole) of (VI) in 15 ml of abs. ethanol was added at room temperature 1.06 g (5.7 mmole) of methyl tosylate. After 2 h, the mixture was evaporated under reduced pressure to half its initial volume, and the (XIV) crystallized by adding dry ether. Yield 1.65 g (87%).

4-(3-Methylureido)propyltrimethylammonium Tosylate (XV). Obtained as for (XII), from 0.5 g (8.8 mmole) of methyl isocyanate, 0.83 g (7.3 mmole) of (II), and 1.4 g (7.5 mmole) of methyl tosylate. Yield 1.98 g (77%).

4-[3-(2-chloroethyl)ureido]butyltrimethylammonium Tosylate (XVI). Obtained as for (XII), from 0.93 g (8.8 mmole) of 2-chloroethyl isocyanate, 0.83 g (7.3 mmole) of (II), and 1.4 g (7.5 mmole) of methyl tolsylate at −10°C. Yield 2.15 g (74%).

4-(3-Cyclohexylureido)butyltrimethylammonium Tosylate (XVII). Obtained as for (XIV), from 1.0 g (4.1 mmole) of (IX) and 0.85 g (4.6 mmole) of methyl tosylate. Yield 1.51 g (85%).

2-(1,3-Dimethylureido)ethyltrimethylammonium Tosylate (XVIII). Obtained as for (XII), from 0.7 g (12 mmole) of methyl isocyanate, 1.0 g (9.8 mmole) of (III), and 2.2 g (12 mmole) of methyl tosylate. Yield 2.8 g (83%).

3-(3-Methyl-3-nitrosoureido)propyltrimethylammonium Tosylate (XX). Into a solution of 1.0 g (2.9 mmole) of (XII) in 15 ml of dry acetonitrile at −10°C was passed gaseous N_2O_3 until a blue coloration appeared. After 0.5 h, the mixture was evaporated under reduced pressure at a temperature no greater than 35°C, and the residue triturated with dry ether. Yield 0.85 g (78%).

Mixture of Positional Isomers of the Nitroso-Group in 3-[3-(2-Chloroethyl)-nitroso-ureido]propyltrimethylammonium Tosylate (XXI). Obtained as for (XX), from 1.0 g (2.5 mmole) of (XIII). Yield 0.88 g (82%).

3-(3-Cyclohexyl-1-nitrosoureido)propyltrimethylammonium Tosylate (XXII). Obtained as for (XX), from 0.75 g (1.8 mmole) of (XIV). Yield 0.68 g (85%).

4-(3-Methyl-3-nitrosoureido)butyltrimethylammonium Tosylate (XXIII). Obtained as for (XX), from 1.0 g (2.8 mmole) of (XV). Yield 0.68 g (88%).

4-[3-(2-Chloroethyl)-1-nitrosorueido]butyltrimethylammonium Tosylate (XXIV). Obtained as for (XX), from 1.0 g of (XXVI). Yield 0.92 g (86%).

4-(3-Cyclohexyl-1-nitrosoureido)butyltrimethylammonium Tosylate (XXV). A solution of 0.5 g (1.2 mmole) of (XVII) in a mixture of 10 ml of acetonitrile and 4 ml of DMF was nitrosated and worked up as for (XX). Yield 0.3 g (56%).

2-(1,3-Dimethyl-3-nitrosorueido)ethyltrimethylammonium Tosylate (XXVI). Obtained as for (XX), from 1.0 g of (XVIII). Yield 1.05 g (97%).

2-[3-(2-Chloroethyl)-1-methyl-3-nitrosoureido]ethyltrimethylammonium Tosylate (XXVII). To a solution of 0.61 g (5.8 mmole) of chloroethyl isocyanate in 5 ml of dry acetonitrile was added dropwise with stirring at −10°C a solution of 0.37 g (3.6 mmole) of (III) in 3 ml of acetonitrile. After 2 h, 1.0 g (5.4 mmole) of methyl tosylate was added, and the solution kept at −10°C for one hour, then evaporated under reduced pressure. The residue was triturated with dry ether to give a viscous oil, which was dissolved in 10 ml of acetone. Gaseous N_2O_3 was passed into the resulting solution at −10°C until a blue coloration appeared, whereupon the (XXVII) separated as a solid, and was filtered off and washed with cold acetone to give 1.0 g (62%) of product.

EXPERIMENTAL BIOLOGICAL PART

The antitumor activity of the compounds was investigated in the biology department of the Problem-Solving Laboratory for the Synthesis of Anticancer and Antitumor Drugs of the S. M. Kirov Urals Polytechnic Institute, and in the Laboratory of Experimental Chemotherapy, NII EdiTO VONTs AMN SSSR by the methods employed at the VONTs AMN SSR. Tests were carried out on mice of strain C57Bl/6, BDFI hybrids, and mongrels. The experimental tumor models employed were La Leukemia, L 1210 lymphoblastic leukemia, Lewis epidermal lung cancer (LLC), mammary carcinoma Ca-755, and sarcoma 37. The compounds were readily soluble in water and physiological saline. Solutions of the compounds were administered to the mice daily by the intraperitoneal route, for five days.

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