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SYNTHESIS AND STUDY OF THE ANTIRADIATION PROPERTIES OF SOME DERIVATIVES OF N-ALLYL-N'-SUBSTITUTED THIOCARBAMIDES

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It is known that N-allylthiocarbamide has pronounced radioprotective activity in experiments with model systems [6]; however, the activity of this compound or its derivatives in experiments with animals has not been studied. The pronounced radioprotective activity of isothiuronium derivatives in experiments with animals is also known [2].

For a systematic study of the dependence of the biological activity on the chemical structure it seemed of interest to synthesize and study, in radiobiological experiments, N'-substituted derivatives of N-allylthiocarbamide, as well as isothiuronium derivatives with linear and cyclic structures, that contain one or several thiocarbamide fragments.

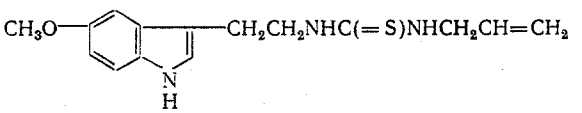
N, N'-Bis(allylthiocarbamoyl)ethylenediamine (I), N,N',N''-tris(allylthiocarbamoyl)diethylenetriamine (II), and N,N'-bis(allylthiocarbamoyl)-1,4-diaminobutane-2,3-diol (III), respectively, were obtained by the reaction of allyl isothiocyanate with ethylenediamine, diethylenetriamine, and 1,4-diamino-2,3-dihydroxybutane:

$CH_2=CHCH_2NHC(=S)NHCH_2CH_2NHC(=S)NHCH_2CH=CH_2$
I

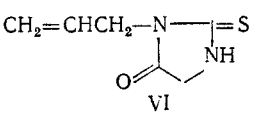
$[CH_2=CHCH_2NHC(=S)NHCH_2CH_2]_2NC(=S)NHCH_2CH=CH_2$
II

$CH_2=CHCH_2NHC(=S)NHCH_2CH(OH)CH(OH)CH_2NHC(=S)NHCH_2CH=CH_2$
III

N-Allyl-N'-[2-(5-methoxy-3-indolyl)ethyl]thiocarbamide (IV) was synthesized by the reaction of allyl isothiocyanate with 3-(2-aminoethyl)-5-methoxyindole hydrochloride in the presence of sodium ethoxide. N-Allyl-N'-carbethoxymethylthiocarbamide (V) could not be obtained when glycine ethyl ester hydrochloride was subjected to a similar reaction. Instead, 1-allyl-5-oxoimidazolidine-2-thione (VI) was isolated.


IV

$CH_2=CHCH_2NHC(=S)NHCH_2COOC_2H_5$
V


VI

This is evidently associated with the ability of V to undergo intramolecular cyclization with splitting out of a molecule of alcohol in the presence of sodium ethoxide. It is interesting to note that the described cyclization is not observed if an alcohol solution of

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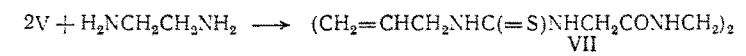
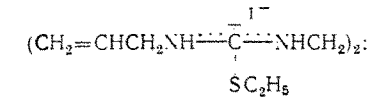
sodium hydroxide is used as the base. In this case the final product is thiocarbamide V; this was confirmed by its subsequent conversion to N,N'-bis(allylthiocarbamoylglycyl)ethylenediamine (VII):



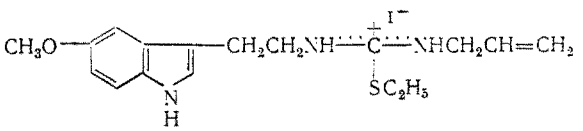
$$2V + H_2NCH_2CH_2NH_2 \longrightarrow (CH_2{=}CHCH_2NHC(=S)NHCH_2CONHCH_2)_2$$

VII

N, N-Ethylenebis(S-ethyl-N'-allylisothiuronium) diiodide (VIII) and S-ethyl-N-allyl-N'-[2-(5-methoxy-3-indolyl)ethyl]isothiuronium iodide (IX) were synthesized by alkylation of I and IV with ethyl iodide:



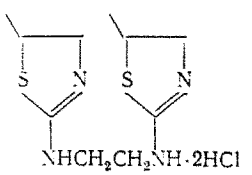
VIII



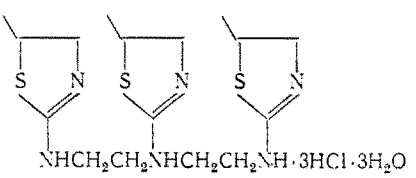
IX

It is known that N-allylthiocarbamide forms 2-amino-5-methylthiazoline when it is heated with hydrohalic acids [9]. It seemed of interest to study the cyclization of bis- and Tris(N-allylthiocarbamides) in order to obtain bis- and Tris(thiazolines).

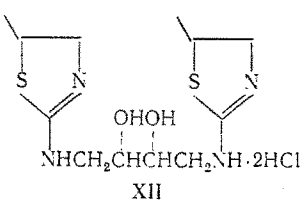
N,N'-Bis(5-methyl-Δ^2-thiazolin-2-yl)ethylenediamine dihydrochloride (X), N,N',N''-Tris(5-methyl-Δ^2-thiazolin-2-yl)diethylenetriamine trihydrochloride trihydrate (XI), and N,N'-bis(5-methyl-Δ^2-thiazolin-2-yl)-1,4-diaminobutane-2,3-diol dihydrochloride (XII) were obtained when I-III were heated in hydrochloric acid:



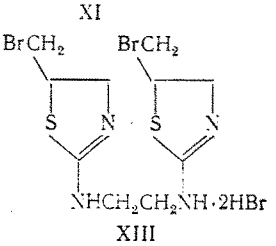
X



XI



XII



XIII

In an attempt to similarly obtain a bis(thiazolinyl) derivative on the basis of VII we were able to isolate only ethylenediamine dihydrochloride. This can evidently be explained by the ease of hydrolysis of the amide CONH bonds. N,N''-Bis(5-bromomethyl-Δ^2-thiazolin-2-yl)ethylenediamine dihydrobromide (XIII) was obtained by bromination of I.

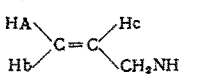
The structures of the substances obtained were confirmed by data from the IR and PMR spectra. Intense bands at 1550-1570 and 1500-1520 cm^{-1}, which belong, respectively, to ν_{NH} symmetrical and asymmetrical vibrations with significant participation of a partially multiple bond (ν_{CN}), are observed in the IR spectra of thiocarbamides I-IV and VII (Table 1). It is interesting to note that for isothiuronium derivatives VIII and IX as compared with thiocarbamides I and IV, from which they were obtained, one observes an increase in $\Delta\nu$ (sym-asym), which should have been expected in connection with an increase in the multiplicity of the C=N bonds and, consequently, an increase in interaction of the indicated vibrations. The change in the bond angles in cyclic derivatives X-XIII changes the pattern in the region of the vibrations of the isothiuronium grouping. The spectra of solutions of the isothiuronium compounds in the region of the NH stretching vibrations have virtually the same character as the spectra of samples in the crystalline state (X). It should also be noted that linear thiocarbamides retain strong intermolecular associations in solutions (I).

TABLE 1. Data from the IR Spectra of the Synthesized Compounds

Compound	Spectral recording conditions	Absorption frequency, cm^{-1}		
		νC=C	δNH + νC···N	νNH, OH
I	a	1642	1570 br, int, 1515 s. m	3010, 3040, 3220 on the background from 2900—3500)
	b	1645	1565sh, 1559 int, 1498 s, m	
II	a	1640	1565 sh, 1550, 1540, 1500 s	3060, 3240, 3300
III	a	1640	1560 int, 1515 s	3100, 3240, 3310, 3375 on the background from 2900—3600)
IV	a	1645	1567 int, 1550 sh, 1520 s	3220, 3440 s[d]
VI	a	1650	1520 s, m	3220 br
VII	a	c	1575, 1550	3240, 3300, 3500
VIII	a	1645	1580 int, 1510 s, m	3020, 3100, 3200, 3230 on the background from 2700—3300)
IX	a	1645	1600 int, 1510 s	3150, 3200, 3260, 3300 on the background from 2900—3400)
X	a	—	1655 s, 1640 int, 1550	2800, 2900, 3140, 3200, 3430 on the background from 2800—3450)
	b	—	1650 s, 1640, 1550	2760, 2970, 3140, 3200, 3300 on the background from 2600—3450)
XI	a	—	1655, 1632, 1615, 1550 br	2780, 2860, 2950, 3130, 3420
	b	—	1665 s, 1620 1645 db	1760, 2960, 3100, 3400 on the background from 2600—3500)
XII	a	—	1655, 1630 s, 1550, 1570 int[e]	No. of broad bands at 3100–3600
XIII	b	—	1650, 1645, 1630 s, 1550 br	No. of broad bands at 2700–3200

Note. a-c) Pertains to KBr pellets, b) pertains to solutions in $CHCl_3$, c) indicates that the band is masked by other bands, d) pertains to the indole ring ν_{NH} band, e) pertains to superimposition of the δ_{OH} band, int indicates intense, m is medium, sh is shoulder, s is sharp, br is broad, and db; is doublet.

TABLE 2. Data from the PMR Spectra of I-III and VI (δ, ppm; J, Hz)



Compound	Solvent	δH_A	δH_B	δH_C	δCH_2	δNH	JH_AH_B	JH_AH_C	JH_ACH_2	JH_BH_C	JH_BCH_2	JH_CCH_2
I	d_6-Acetone	5,08	5,20	5,91	4,15	7,21	1,6	10,6	0,7	17,08	0,8	5,3
IIa	d_6-Acetone	5,07	5,20	5,98	4,28	8,13	2,0	10,4	1,0	17,2	1,1	5,8
IIb	d_6-Acetone	5,07	5,20	5,91	4,13	7,35	2,0	10,4	1,0	17,2	1,1	5,2
III	d_6-DMSO	5,07	5,14	5,83	4,04	7,68	2,0	10,3	1,5	17,1	1,3	5,1
VI	d_6-Acetone	5,12	5,18	5,84	4,35	—	2,0	10,9	18,2	18,2	1,3	5,9

Note. For II, a) pertains to the allyl groups attached to the extreme nitrogen atoms, while b) pertains to the allyl groups attached to the tertiary nitrogen atom.

In addition to the absorption bands indicated in Table 1, the spectra of VI and VII contain absorption bands of a carbonyl group at 1750 and 1655 cm^{-1}, respectively, and the spectra of IV and IX contain absorption bands to a substituted benzene ring at 1625 and 1485 cm^{-1}.

The signal of the CH_2=$CHCH_2NH$ group in the PMR spectra of thiocarbamides I-III and VI are presented in Table 2. Let us note that the chemical shifts and the spin-spin coupling constants (SSCC) are in good agreement with the literature data for monosubstituted olefins [8].

In addition to the signals presented in Table 2, the spectrum of I contains two signals with δ 7.21 and 3.70 ppm, which can be assigned to the NH protons and the protons of the ethylene group of the HCH_2CH_2NH fragment. In the spectrum of II the assignment of the methyl-

ene protons (δ 3.90 and 3.72 ppm) was made on the basis of the widths of their multiplets; we proceeded from the fact that the multiplet of the protons of the methylene groups bonded to the tertiary nitrogen atom should be narrower than the multiplet that characterizes the methylene groups bonded to the secondary nitrogen atoms in the $NHCH_2CH_2NCH_2CH_2NH$ fragment. The broader high-field signal at δ 3.72 ppm was assigned to the CH_2 groups bonded to secondary nitrogen atoms.

In addition to the signals presented in Table 2, signals at δ 7.37, 3.52, and 4.84 ppm (intensity ratio 1:2:1), which were assigned to the protons of $NHCH_2$ and CH groups, respectively, are observed in the spectrum of III. The signal of the protons of the hydroxy groups evidently coincides with the signal of the water that is present in d_6-DMSO.

In addition to the signals presented in Table 2, a signal of ring methylene protons at δ 4.18 ppm (J_{CH_2-NH} 1.0 Hz) and a signal of an NH group at δ 8.93 ppm are observed in the PMR spectrum of VI.

The PMR spectra of solutions of X and XIII in d_6-DMSO were recorded. The spectrum of X contains the following signals: a doublet of a methyl group at δ 1.42 ppm (J_{HH} 6.8 Hz), a multiplet of a methylidyne group at δ 4.15 ppm, a doublet of doublets of one of the protons (A) of the ring methylene group at δ 3.60 ppm, a doublet of doublets of the other proton (B) of the same group at δ 3.98 ppm ($J_{H_AH_B}$ 10.7 Hz, J_{CH-H_A} 7.0 Hz, J_{CH-H_B} 4.3 Hz), a broad singlet of four equivalent NCH_2CH_2 protons at δ 3.68 ppm, and a signal of NH protons at δ 10.57 ppm.

The spectrum of XIII contains a doublet of protons of the CH_2Br group at δ 3.87 ppm (J_{HH} 6.2 Hz). The remaining signals are similar to the corresponding signals of X. Their parameters are as follows: δ_{CH} 4.45 ppm, δ_{H_A} 3.89 ppm, J_{H_B} 4.04 Hz, $J_{H_AH_B}$ 10.8 Hz, J_{CH-H_A} 7.3, J_{CH-H_B} 4.0 Hz, $\delta_{CH_2CH_2}$ 3.60 ppm, δ_{NH} 10.23 ppm.

In the spectra of X and XIII, each of which contains two protons bonded to a nitrogen atom, only one signal of H protons is observed; this constitutes evidence for their equivalence [7].

EXPERIMENTAL CHEMICAL PART

The IR spectra were recorded with a Perkin-Elmer 398 spectrometer. The PMR spectra were recorded with a Brucker WM-250 spectrometer with tetramethylsilane as the internal standard.

The yields, constants, and results of elementary analysis of the synthesized compounds are presented in Table 3.

N,N'-Bis(allylthiocarbamoyl)ethylenediamine (I) [10]. A solution of 8.30 g of ethylenediamine in 70 ml of ethanol was added dropwise with stirring (20-25°C) to 27.43 g of allyl isothiocyanate, after which the mixture was refluxed for 30 min. The solvent was removed by distillation, and the residue was recrystallized from benzene–alcohol to give 28.45 g of I.

N,N',N"-Tris(allylthiocarbamoyl)diethylenetriamine (II). A solution of 7.43 g of diethylenetriamine in 30 ml of absolute ethanol was added dropwise with stirring (20-25°C) to 21.36 g of allyl isothiocyanate, after which the mixture was refluxed for 30 min. The solvent was removed, and the residue was recrystallized from hexane–benzene to give 24.8 g of II.

N,N'-Bis(allylthiocarbamoyl)-1,4-diaminobutane-2,3-diol (III). A 10.75-g sample of ally isothiocyanate was added dropwise with stirring (50°C) to 6.51 g of 1.4-diamino-2,3-dihydroxy butane in 150 ml of absolute ethanol, after which the mixture was refluxed for 30 min. The solvent was removed, and the residue was recrystallized from ethanol–acetic acid to give 12.0 g of III.

N-Allyl-N'-[2-(5-methoxy-3-indolyl)ethyl]thiocarbamide (IV). A solution of 3.66 g of sodium ethoxide (from 1.24 g of sodium) in 25 ml of absolute ethanol was added dropwise with stirring at 70°C to a mixture of 12 g of 5-methoxytryptamine and 5.23 g of allyl isothiocyanate in 25 ml of absolute ethanol, after which the mixture was heated at 80°C for 30 min. The solvent was removed, and the residue was recrystallized from benzene–alcohol to give 11.48 g of IV.

1-Allyl-5-oxoimidazolidine-2-thione (VI). A solution of 3.30 g of sodium ethoxide (from 1.12 g of sodium) in 20 ml of absolute ethanol was added dropwise with stirring to a mixture

TABLE 3. Yields, Constants, and Results of Elementary Analysis of the Synthesized Compounds

Compound	Yield, %	mp, °C	Found, %					Empirical formula	Calc., %				
			C	H	Cl	N	S		C	H	Cl	N	S
I	80,0	96—98	46,53	7,02	—	21,94	24,83	$C_{10}H_{16}N_4S_2$	46,51	6,98	—	21,70	24,81
II	86,3	94—96	48,06	7,07	—	21,03	23,95	$C_{16}H_{26}N_6S_3$	48,00	7,00	—	21,00	24,00
III	69,8	171—174	45,07	7,05	—	17,26	19,60	$C_{12}H_{22}N_4O_2S_2$	45,28	6,92	—	17,61	20,13
IV	75,3	113—116	...	...	—	14,58	10,91	$C_{15}H_{19}N_3OS$	...	...	—	14,53	11,07
VI	51,0	85—87	46,17	5,26	—	18,18	20,61	$C_8H_{14}N_2O_2$	46,16	5,13	—	17,56	20,51
VII	51,0	190—192	45,14	6,47	—	22,56	17,28	$C_{14}H_{24}N_6O_2S_2$	45,16	6,45	—	22,58	17,20
VIII	74,5	100—102	29,65	4,91	—	9,88	11,09	$C_{14}H_{28}I_2N_4S_2$	29,50	4,93	—	9,85	11,20
IX	57,8	106—109	45,75	5,47	—	9,53	7,27	$C_{17}H_{24}IN_3OS$	45,80	5,40	—	9,46	7,20
X	76,5	215—218	36,24	6,12	21,56	17,06	19,39	$C_{10}H_{20}Cl_2N_4S_2$	36,25	6,04	21,45	16,92	19,33
XI	40,3	~ 150 (dec.)	...	...	18,58	15,17	16,91	$C_{16}H_{37}Cl_3N_6O_3S_2$	...	...	18,90	14,91	17,03
XII	40,8	158—161	36,71	6,25	18,21	14,31	16,61	$C_{12}H_{24}Cl_2N_4O_2S_2$	36,83	6,14	18,16	14,32	16,37
XIII	43,5	203—205	21,06	3,26	—	9,28	10,86	$C_{10}H_{18}Br_4N_4S_2$	20,80	3,14	—	9,73	11,08

of 4.80 g of allyl isothiocyanate and 6.75 g of ethyl aminoacetate hydrochloride in 70 ml of absolute ethanol, after which the mixture was refluxed for 30 min. The precipitated sodium chloride [2.82 g (99.5%)] was removed by filtration, and the filtrate was refluxed for 30 min with activated charcoal. The charcoal was removed by filtration, the solvent was removed from the filtrate, and the residue was recrystallized twice from hexane–benzene to give 3.81 g of VI.

N,N'-Bis(allylthiocarbamoylglycyl)ethylenediamine (VII). A solution of 8.03 g of potassium hydroxide in 120 ml of absolute ethanol was added dropwise with stirring to a mixture of 14.2 g of allyl isothiocyanate and 20.0 g of ethyl aminoacetate hydrochloride in 200 ml of absolute ethanol, after which the mixture was heated at 70-80°C for 30 min. The precipitated potassium chloride [9.10 g (85%)] was removed by filtration, 3.1 g of ethylenediamine was added dropwise with stirring to the filtrate, and the mixture was heated at 80°C for 30 min. The solvent was removed, the residue was triturated in benzene–acetone (1:1), and the solid was removed by filtration and recrystallized from ethanol–acetic acid to give 9.78 g of VII.

N,N'-Ethylenebis(S-ethyl-N'-allylisothiuronium) Diiodide (VIII). A 2.3-g sample of I and 4.13 g of ethyl iodide were heated with stirring at 90-95°C for 1.5 h in 10 ml of absolute alcohol, after which the solvent was removed by distillation, and the residue was recrystallized from benzene–acetone to give 3.82 g of VIII.

S-Ethyl-N-allyl-N'-2-(5-methoxy-3-indolyl)ethylisothiuronium Iodide (IX). A mixture of 2.5 g of IV and 2.7 g of ethyl iodide was heated with stirring at 100°C for 10 min, after which it was cooled and triturated in acetone. The solid was removed by filtration and recrystallized from benzene–ethanol to give 2.22 g of IX.

N,N'-Bis(5-methyl-Δ^2-thiazolin-2-yl)ethylenediamine Dihydrochloride (X). A 2.6-g sample of I was heated with stirring (140-150°C) in 5.8 ml of concentrated hydrochloric acid for 10 min, after which the acid was removed by distillation, and the residue was recrystallized from acetone–ethanol to give 2.54 g of X.

N,N',N"-Tris(5-methyl-Δ^2-thiazolin-2-yl)diethylenetriamine Trihydrochloride Trihydrate (XI). A 2.0-g sample of II was heated with stirring (140-150°C) in 4.0 ml of concentrated hydrochloric acid for 15 min, after which the hydrochloric acid was removed by distillation, and a mixture of 15 ml of absolute benzene and 15 ml of absolute ethanol were added to the residue. The solvent was removed in vacuo (this operation was repeated three times) to give 1.14 g of XI.

N,N'-Bis(5-methyl-Δ^2-thiazolin-2-yl)-1,4-diaminobutane-2,3-diol Dihydrochloride (XII). A 3.2-g sample of III was heated with stirring (125-130°C) in 5.8 ml of concentrated hydrochloric acid for 5 min, after which the excess hydrochloric acid was removed by distillation, and a mixture of 15 ml of absolute benzene and 15 ml of absolute ethanol were added to the residue. The solvent was removed in vacuo, and the residue was recrystallized from acetone–ethanol to give 1.6 g of XII.

N,N'-Bis(5-bromomethyl-Δ^2-thiazolin-2-yl)ethylenediamine Dihydrobromide (XIII). A solution of 3.7 g of bromine in acetic acid was added dropwise with stirring (20°C) to a solution of 3.0 g of I in acetic acid, after which the mixture was heated at 145°C for 10 min. The acetic acid was removed by vacuum distillation, and the residue was recrystallized from ethanol–acetic acid to give 2.9 g of XIII.

Reaction of VII with Concentrated Hydrochloric Acid. A 1.86-g sample of VII was heated with stirring (135-140°C) with 5.4 ml of concentrated hydrochloric acid for 10 min, after which the excess hydrochloric acid was removed by distillation, and 10 ml of absolute ethanol was added to the residue. The precipitated crystals were separated to give 0.63 g (95.5%) of ethylenediamine dihydrochloride. Found, %: C 17.86, H 7.40, N 21.01, $C_2H_{10}Cl_{12}N_2$. Calculated, %: C 18.05, H 7.52, N 21.05.

EXPERIMENTAL BIOLOGICAL PART

The study of the radioprotective activities and acute toxicities of the synthesized compound was carried out in conformity with [4]. The toxic properties of the compounds were determined [4]. The toxic properties of the compounds were determined by intraperitoneal injection of mongrel male white mice with masses of 20-24 g. Aqueous solutions and suspensions of the substances were prepared ex temporae and administered in doses of the logarithmic

TABLE 4. Radioprotective Efficiencies and Acute Toxicities of the Synthesized Compounds

Compound	LD_{50}, mg/kg	Radioprotective efficiency			
		preparation dose, mg/kg	No. of animals		survival time
			total	% survived	
$CH_2=CHCH_2NHC(=S)NHCH_2CH_2OH$ IV	>800*	300	19	21,0	9,8
IV	>800*	200	11	0	10,8
I	>800*	300	18	0	9,0
II	>800*	300	20	0	8,0
III	>800*	300	15	0	7,2
VII	>800*	300	15	7,0	12,0
VI	>800*	300	21	0	9,0
$CH_2=CHCH_2$	200	80	20	0	9,0
	(234—171)	20	20	0	7,8
$C_2H_5S-C(=NH^+)-NH_2$ I^- VIII**	200	70	15	0	10,1
IX	180	67,5	16	6,0	6,3
	(207—156)	17	19	0	6,0
X	300	85	20	0	8,3
	(402—224)	21,3	16	0	6,4
XIII	130	50	19	0	4,7
	(147—115)	12,5	20	0	5,7
XII	290	115	18	16,7	8,5
	(328—256)	29	17	5,0	9,8
XI	84	25	20	0	9,7
	(108—65)	6,3	20	0	9,6

*Death of the animals was not observed when the given doses were administered.

**This compound was studied by T. N. Tuzhilkova and co-workers.

scale with an interval of 0.1. The results were processed by the method of Litchfield and Wilcoxson [1].

The radioprotective effectiveness of the compounds was studied with respect to male mice of the $(CBA \times C57Bl)F_1$ strain with masses of 20-23 g. The preparations were administered intraperitoneally in doses of 1/2 and 1/8 of the LD_{16} 20 min prior to γ-irradiation at a dose of 8.6 GR and a dose rate of 2 GR/min. To obtain comparable results the radiation exposure was realized at the same time up to 12 h [3]. The data obtained were treated statistically by the method presented in [5].

The results of the study of the toxic and radioprotective properties of the compounds are presented in Table 4.

The investigated compounds can be arbitrarily divided into three groups: N-allylthiocarbamide derivatives that contain one, two, and three thiocarbamide fragments, mono- and bis(isothiuronium) derivatives, and substances that contain two and three thiazolidine rings.

It is apparent from Table 4 that all of the N-allyl- thiocarbamide derivatives, viz., I, IV, VI, VII, and N-allyl-N'-(2-hydroxyethyl)thiocarbamide, have low toxicities.

The isothiuronium derivatives, viz., N-allyl-S-ethylisothiuronium iodide and VIII and IX, can be classified as moderately toxic substances.

Approximately the same degree of toxicity is observed in the case of bis(thiazolidine) derivatives X and XII. Compound XIII, which differs from X with respect to the presence of bromomethyl substituents, displays definitely higher toxicity. Compound XI, which contains three thiazolidine rings, has the most pronounced toxic properties.

Thus alkylated derivatives of thiocarbamides prove to be more toxic than the thiocarbamides themselves. An increase in the number of thiazolidine rings in the compound also leads to a significant intensification of the toxic properties.

Substances that have radioprotective activity were not detected among the investigated compounds.

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SYNTHESIS AND STUDY OF THE ANTIVIRAL ACTIVITY OF PROPANOLAMINE DERIVATIVES

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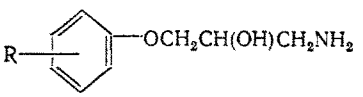
The process of developing new preparations for viral infection chemotherapy has shown that the oxyethyl [7] or propandiolamine [3] fragment is frequently encountered among the various chemical groups that enhance antiviral action. On the other hand, it is generally recognized that quaternary derivatives are active against certain viruses [3, 4]. However, there has been no special study of the effect that the oxyalkylammonium fragment has on the antiviral activity of the ammonium derivatives, and there is no information about the activity of its simplest derivatives. For that purpose we employed a method we previously developed [9] to synthesize the series 1-aryloxy-2-oxypropylamines, having the general formula:



(I — IX),

where R = H (I); 4-CH_3 (II); 4-Br (III); 2-Cl (IV); 3-CH_3 (V); 4-CH_3O (VI); 2-Br (VII); 2,4-Cl_2 (VIII); 3-CH_3-4-iso-C_3H_7 (IX).

We also synthesized the N-phthalimide (compounds XIV-XVII and N-acyl (XVIII-XXI) derivatives of aryloxypropylamines. There has been particular interest [5] in obtaining the substituted thioureas:

$$ArXCH_2CH(OH)CH_2NH_2 + S{=}C{=}NC_6H_5 \longrightarrow \underset{XXII - XXVII}{ArXCH_2CH(OH)CH_2NHC(=S-)NHC_6H_5},$$

where (enumerated compounds, Ar, X): XXII, C_6H_5, O; XXIII, C_6H_5, NC_6H_5; XXIV, $C_6H_4CH_3$-2, NH; XXV, $C_6H_3(CH_3)_2$-2,4, NH; XXVI, $C_6H_3(CH_3)_2$-2,5, NH; XXVII, C_6H_4Br-2, NH.

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