LITERATURE CITED

1. E. N. Goncharenko and Yu. B. Kudryashov, Chemical Protection from Radiation Damage. A Practical Manual and Lectures in Radiation Biophysics [in Russian], Moscow (1985).
2. V. B. Prozorovskii, M. P. Prozorovskaya, and V. M. Demchenko, Farmakol. Toksikol., No. 4, 497-502 (1978).
3. N. N. Suvorov and V. S. Shashkov, The Chemistry of Pharmacology of Drugs for the Prophylaxis of Radiation Injury [in Russian], Moscow (1975).
4. V. I. Suslikov, Radiobiologiya, No. 6, 880-890 (1963).
5. D. Q. Brown, J. W. Pittock, et al., Int. J. Radiat. Oncol. Biol. Phys., 8, 565-570 (1982).
6. A. Kaluszyner, P. Czerniak, and E. Bergmann, Radiat. Res., 14, 23-28 (1961).
7. Y. S. Kim et al., J. Korean Chem. Soc., 27, 449-456 (1983).
8. D. Klayman et al., J. Med. Chem., 12, 723 (1969).
9. J. R. Piper, C. R. Stringfellow, D. R. Elliott, and T. P. Johnston, J. Med. Chem., 12, 236-243 (1969).
10. Takahashi Iku, Nagai Teruo, Miyaishi Kazuo, et al., Int. J. Radiat. Oncol. Biol. Phys., 12, 935-938 (1986).

SYNTHESIS OF S-(2-AMINO-2-METHYLPROPYL)ISOTHIOUREAS AND THEIR RADIOPROTECTANT ACTIVITY

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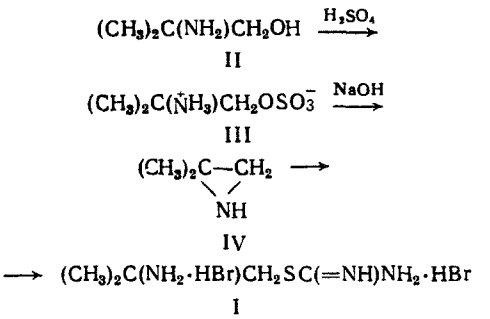
UDC 615.849.1.015.25:547.789.3].012.1.07

The most effective radioprotectant drugs include sulfur compounds such as mercaptoethylamine and mercaptopropylamine, and their derivatives, the corresponding S-aminoalkylisothioureas [5, 6]. It has been found experimentally that increasing the distance between the functional groups by more than three carbon atoms results in a decrease in antiradiation activity [5, 7]. This observation has led to an increased interest in aminoethyl- and aminoisopropylisothioureas.

We have previously found high radioprotectant activity in S-(2-aminopropyl)- and S-(1-amino-2-propyl)isothioureas [3]. S-(3-Aminobutyl)isothioureas show high antiradiation activity in mammals [2].

We now describe a method for the synthesis of S-(2-amino-2-methylpropyl)isothiourea dihydrobromide (I). The starting material used was 2-amino-2-methylpropan-1-ol (II), from which there was obtained 2-amino-2-methylpropyl sulfate (III), followed by 2,2-dimethylaziridine (IV). The desired compound (I) was obtained by reacting (III) with thiourea in dilute aqueous hydrobromic acid.



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0091-150X/89/2306-0505$12.50

TABLE 1. Effects of S-(2-Amino-2-methylpropyl)isothiourea (2-AMPT) and S-(2-Aminoethyl)isothiourea (AET) on Radioresistance in Mice

Agent	Dose of compound, mg/kg	Dose and type of irradiation, min	Time between treatment and irradiation, min	Survival, %	Mean lifespan, days
—	—	10,4 Gy	—	0	4,8±0,8
2-AMPT	114	^{60}Co γ-Rays	60	0	5,7±1,2
AET	500		60	33,3±12,6	9,9±0,6
—	—	9,5 Gy	—	0	9,6±1,6
2-AMPT	114	^{60}Co γ-Rays	60	20±10,7	13,2±0,9
AET	500		60	93,3±6,6	13,0
—	—	7,0 Gy	—	0	13,7±0,8
2-AMPT	114	X-Rays	60	91,7±8,3	18
AET	500		60	100	

EXPERIMENTAL (CHEMISTRY)

The progress of the reactions and the purity of the products were followed by TLC on Silufol UV-254 plates in the system n-butanol–acetic acid–water (4:1:5).

2-Amino-2-methylpropyl Sulfate (III). A mixture of 20 g (0.225 mole) of (II) and 22.1 g (0.225 mole) of sulfuric acid in 100 ml of water was heated to 150-170°C for 4 h. The water was then distilled off, cooled, and the solid residue crystallized from a mixture of 2-propanol and water (1:1). The solid which separated was washed with acetone, to give 35 g (94%) of (III), $C_4H_{11}NO_4S$, mp 282-284°C (285-286°C [1]).

2-Dimethylaziridine (IV). To a solution of 160 g of NaOH (4 mole) in 200 ml of water, heated to 130-140°C, was added dropwise with vigorous stirring a saturated aqueous solution of 35.7 g (0.212 mole) of (III). The azeotropic mixture of (IV) and water was distilled off over the temperature range 75-95°C. Redistillation after drying over sodium hydroxide was carried out at 78-80°C, to give 12.3 g of (IV).

S-(2-Amino-2-methylpropyl)isothiourea Dihydrobromide (I). Thiourea (13.1 g; 0.170 mole) was dissolved in 330 ml of 10% aqueous hydrobromic acid (0.560 mole). To this solution was added at 0°C 12.3 g (0.17 mole) of (IV), and the mixture kept at this temperature for 7 h. The water was distilled off at 20°C, and the dry residue washed with 300 ml of glacial acetic acid, followed by dry acetone, to give 36 g (70%) of (I). $C_5M_{15}Br_2N_3S$. Mp 192-194°C, R_f 0.13.

EXPERIMENTAL (BIOLOGY)

The toxicity and radioprotectant activity of (I) were examined in mammals.

The experimental subjects were mice (CBA × C57B1)F_1 weighing 18-22 g.

The LD_{16}, LD_{50}, and LD_{84} values for the toxicity (I) by the intraperitoneal route were 114, 164, and 240 mg/kg (0.37, 0.53, and 0.78 mmole/kg, respectively). For comparison, the LD_{16} values for its analogs are 420 mg/kg (1.43 mmole/kg) for S-(2-aminopropyl)isothiourea, and 500 mg/kg (1.78 mmole/kg) for S-(2-aminoethyl)isothiourea.

To determine the antiradiation activity of the compound, it was administered intraperitoneally in 0.5 ml of physiological saline 60 min before irradiation. This timing was chosen on the basis of our earlier work on the time required for maximum accumulation in the organs and tissues of the conversion products of aminoalkylisothioureas and their cyclic derivatives, to which we attribute radioprotectant activity [4]. The animals were irradiated with supralethal (10.4 Gy) and minimum absolute lethal doses (9.5 Gy; ^{60}Co x-rays, dose rate 1.7 Gy/min), and a dose of 7.0 Gy of γ-rays (the dose causing the deaths of 90% of the animals in 30 days). The irradiation conditions were: voltage 210 kV, current strength 15 mA, filters 0.5 mm Cu and 1.0 mm Al, dose rate 0.66 Gy/min. The criteria for radiation injury were: survival of the animals for 30 days, and the mean lifespan at this time.

It was found that (I) was ineffective with the supralethal dose, but had a slight effect at $LD_{100/30}$, and a very significant effect at $LD_{90/30}$ (see Table 1). According to our findings [3], S-(2-aminopropyl)isothiourea at $LD_{100/30}$ gave a survival of approximately 40-50%. The S-(2-aminoethyl)isothiourea used in the present investigation as a representative of the group of aminoalkylisothioureas similar to (I), as well as a standard of radioprotectant activity, was more active than either of the above-mentioned compounds (Table 1).

It has therefore been shown that the introduction of a methyl group into the β-position of the S-(2-aminoethyl)isothiourea molecule results in a marked increase in toxicity. It is likely that it is this factor which is responsible for the reduction in the radioprotectant activity of S-(2-aminomethylpropyl)isothiourea as compared with the original aminoalkylisothioureas.

LITERATURE CITED

1. P. A. Gembitskii, D. S. Zhuk, and D. S. Kargin, The Chemistry of Ethyleneimine [in Russian], Moscow (1966).
2. G. V. Dontsova, M. M. Konstantinova, A. A. Mandrugin, et al., Khim.-farm. Zh., No. 3, 306-307 (1986).
3. I. V. Nekrasova, A. A. Mandrugin, É. I. Gintsburg, et al., Radiobiologiya, 16, No. 2, 215-217 (1974).
4. A. G. Tarasenko, E. Ya. Graevskii, M. M. Konstantinova, et al., Dokl. Akad. Nauk SSSR, 187, No. 2, 203-206 (1969).
5. D. G. Doherty and W. T. Burnett, Proc. Soc. Exp. Biol. (N.Y.), 89, 312-318 (1955).
6. J. Earley, O. O'Rourke, L. Clapp, et al., J. Am. Chem. Soc., 80, 3458-3462 (1958).
7. R. Shapira, D. G. Doherty, and W. T. Burnett, Radiat. Res., 7, 22-28 (1957).

ANTISILICOTIC ACTIVITY OF FRACTIONS OF THE COPOLYMER OF ETHYLENE GLYCOL VINYL GLYCIDYL ETHER AND N-VINYLPYRROLIDONE

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UDC 615.235.012.1.07

There are literature reports of the use of macromolecular compounds for the prophylaxis and treatment of silicosis [4, 7, 9]. The best known of these compounds is poly(vinylpyridine N-oxide) [9]. Polymers of this type must meet definite requirements in respect of molecular and compositional homogeneity, since some fractions may have different pharmacological effects. The presence of oligomolecular fractions which are rapidly eliminated from the body reduces the effectiveness of polymer fractions, while the presence of fractions of mass greater than 70,000 is undesirable as a result of elimination, from the body being too slow, and in some instances incomplete, with accumulation in the liver and kidneys [1, 4].

We have previously shown that copolymers of ethylene glycol vinyl glycidyl ether (I) with N-vinylpyrrolidone (II) display antisilicotic activity in experimental silicosis [3]. In the series of polymers tested, the most active was the vinylidone copolymer containing 16 mol. % of (I) and 84 mol. % of (II). Since vinylidone, like many synthetic polymers, possesses a considerable range of molecular masses, it was desirable to separate this copolymer into fractions according to molecular mass, and to examine the antisilicotic activity of each fraction.

EXPERIMENTAL (CHEMISTRY)

The copolymers were obtained by free-radical initiation as described in [3], molecular mass 31,000, ratio (I):(II) = 0.16:0.84.

Fractionation was effected by successive precipitation of a 5% solution of the polymer in chloroform with hexane [2]. The fraction which separated as an emulsion was reprecipitated from diethyl ether, and the final fraction was obtained by complete evaporation of the solution followed by reprecipitation from ether.

The system, which was insensitive to the composition of the copolymer, was chosen bearing in mind the requirements for the fractionation of the copolymers using the turbidimetric

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 6, pp. 711-713, June, 1989. Original article submitted April 11, 1988.

0091-150X/89/2306-0507$12.50