# SYNTHESIS AND RADIOPROTECTIVE ACTIVITY OF 3-(2-MERCAPTOETHYL)AMINOPROPIONAMIDES

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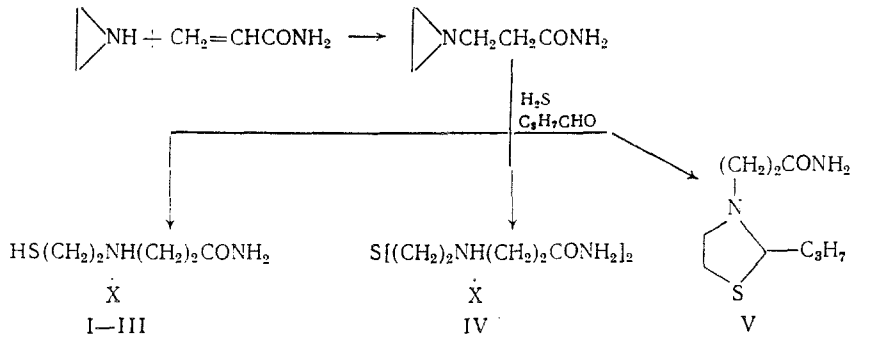
The high radioprotective effectiveness of 3-(2-mercaptoethyl)aminopropionamide tosylate (II) after intraperitoneal administration has already been reported in [6]. We carried out the synthesis of this compound and also of some of its derivatives (I-VI), and studied their radioactive effectiveness with various modes of administration.

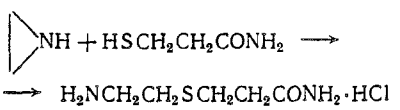



I: X = O; II: X = tosylate III: X = hydrobromide IV: X = dihydrobromide

A convenient method has been developed for the synthesis of compounds I-V, based on the addition of ethylenimine to acrylamide, followed by splitting of the aziridine ring by hydrogen sulfide without preliminary separation of the adduct. Depending on the ratio and order of addition of the reagents at the second stage, the mercaptan I, sulfide IV, or thiazolidine V were obtained.

In the case of a deficiency of hydrogen sulfide, the primarily formed mercaptan I preferentially reacts with 3-aziridinepropionamide, leading to sulfide IV. To obtain thiazolidine V, the reaction is carried out in the presence of butyraldehyde.

3-(2-Aminoethyl)thiopropionamide hydrochloride (VI) was obtained by the reaction of 3-mercaptopropionamide with ethylenimine.




VI

The compounds studied are slightly toxic: their $LD_{50}$ at the two modes of administration is more than 2000 mg/kg, with the exception of compound V, for which the $LD_{50}$ is nearly three times higher, and equal to 630 mg/kg. Compounds II and III displayed a high activity with both methods of administration, which was independent of the type of the salt form. The characteristic feature of the antiradiation action of II and III after peroral administration was the long duration of the increased radioresistance of the animals (up to 1.5 h). However, the same effect is achieved by using large doses (1000 mg/kg) of these compounds.

On transition to the thiazolidine structure (V), the radioresistant effectiveness decreases with intraperitoneal administration. With peroral administration of this compound, the effectiveness is fairly high for the first hour.

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Compound VI was synthesized and tested to clarify the possible mechanism of the radioprotective action of compounds of this series, involving splitting of a highly active radioprotector, mercaptoethylamine, in the organism.

The absence of radioactive activity in compound VI did not confirm this hypothesis. Sulfide IV was found to be ineffective.

Thus, compounds II and III displayed high radioprotective activity for 1.5 h after peroral administration in doses of 750-1000 mg/kg.

## EXPERIMENTAL (CHEMICAL)

All the reactions were carried out in absolute solvents. The synthesized compounds are readily soluble in water. The results of the elemental analyses correspond to the calculated data.

3-(2-Mercaptoethyl)aminopropionamide (I). A 9.46-g portion (0.22 mole) of ethylenimine was added dropwise at 5-10°C to 14.2 g (0.2 mole) of acrylamide. After standing for 24 h at 20°C, the excess of ethylenimine was evaporated under vacuum, and the crystallized 3-ethyleniminopropionamide (mp 105°C) [5] was dissolved in 30 ml of absolute ethanol, the solution was cooled to −70°C and added dropwise, with stirring, to a solution of 17 g (0.5 mole) of $H_2S$ in 30 ml of absolute ethanol. The reaction flask was equipped with a dry carbon dioxide condenser. The reaction mixture was gradually brought up to 20°C, and the white precipitate that separated out was filtered off, washed with absolute ethanol and ether. The yield of I was 5.7 g, mp 77-79°C. $C_5H_{12}N_2O$. The SH group content was 96% (according to the data of iodometric titration).

The mother liquor was evaporated after 24 h under vacuum to yield 24 g of a semisolid residue (contains 95% of I, according to iodometric titration data). The overall yield of I was 95%.

One half (12 g, 0.081 mole) of the semisolid I was added to 20 ml of 40% HBr, and after 1 h, the excess of HBr was distilled under vacuum. To remove the last traces of HBr, 20 ml of water was added to the dry residue, and the mixture was evaporated again under vacuum. Yield 18.2 g (98%) of the 3-(2-mercaptoethyl)aminopropionamide hydrobromide (III), mp 103-105° (from ethanol). $C_5H_{13}BrN_2OS$.

The second half (12 g, 0.081 mole) of the semisolid I was dissolved in 20 ml of benzene, and 4.26 g (0.081 mole) of para-toluenesulfonic acid in 20 ml of benzene was added to this solution. After partial evaporation of benzene under vacuum and addition of ether, 17.4 g (67%) of 3-(2-mercaptoethyl)aminopropionamide tosylate (II) was obtained, mp 122-124°C [7]. The SH-group content was 100%.

Bis[2-(2-carbamidoethylamino)ethyl] Sulfide Dihydrobromide (IV). Under similar conditions, but by adding 5 g of $H_2S$ in 30 ml of ethanol to the adduct of 4.5 g (0.105 mole) of ethylenimine and 7.1 g (0.1 mole) of acrylamide, after the evaporation of the solvent, and grinding the residue with methanol, 12 g of crude bis[2-(2-carbamidoethylamino)ethyl] sulfide was obtained which, after treatment with 40% HBr and recrystallization from ethanol, gave 14.4 g (68%) of dihydrobromide IV, mp 168-170°C. $C_{10}H_{24}Br_2N_4O_2S$.

3-(2-Propylthiazolidine)propionamide (V). A 14.4-g portion (0.2 mole) of butyraldehyde was added to a solution of the adduct of 14.2 g (0.2 mole) of acrylamide and 8.6 g (0.2 mole) of ethylenimine in 50 ml of ethanol. The mixture was then cooled −40°C, and a solution of 7 g of $H_2S$ in 50 ml of ethanol was gradually added. After standing for 24 h at 20°C, the solvent was evaporated under vacuum, and the residue, a thick oil, was ground with benzene into a powder to yield 40 g of crude V. After recrystallization from petroleum ether, the yield of the crystalline V was 18.7 g (46%), mp 70-72°C. $C_9H_{18}N_2OS$.

3-(2-Aminoethyl)thiopropionamide Hydrochloride (VI). A solution of 3.75 ml (3.14 g, 0.073 mole) of ethylenimine in 10 ml of MeOH was added to a suspension of 7.0 g (0.066 mole) of 3-mercaptopropionamide in 80 ml of MeOH. The mixture was heated at 60°C for 8 h to a negative qualitative reaction for the SH group with a sodium nitroprusside solution. The filtered-off mother liquor was evaporated, the residue was treated with an ethanolic solution of HCl, and the alcohol was evaporated under vacuum to yield 6.6 g (54%) of VI, mp 107-109°C (ether-ethanol). $C_5H_{13}VlN_2OS$.

TABLE 1. Toxicity and Radioprotective Activity of 3-(2-Mercaptoethyl)aminopropionamide and Its Derivatives

| Compound | Radioprotective effectiveness | | | | | |
|---|---|---|---|---|---|---|
| | intraperitoneal administration | | | peroral administration | | |
| | dose, mg/kg* | time before irradiation, min | survival, % | dose, mg/kg* | time before irradiation, min | survival, % |
| II | 750 | 20—30 | 80,0 | 750 | 30 | 55,0 |
| | 1000 | 20 | 86,6 | 1000 | 10—30 | 5,0—40,0 |
| | | | | 1000 | 90 | 58,0 |
| III | 300 | 20 | 22,5 | 300—750 | 10—30 | 7,0—25,0 |
| | 500 | 20 | 55,4 | 1000 | 10 | 68,4 |
| | 750 | 20 | 96,0 | 1000 | 20 | 55,0 |
| | 1000 | 20 | 75,9 | 1000 | 30—60 | 85,0 |
| | | | | 1000 | 90 | 50,0 |
| | | | | 1000 | 2 h — 24 h | 10,0—5,0 |
| IV | 235; 940 | 20 | 0 | — | — | — |
| V | 60; 240 | 20—60 | 0—30,0 | 300 | 30—90 | 14,0—46,0 |
| | | | | 600 | 30 | 0 |
| | 60; 240 | 120 | 40,0 | 600 | 60 | 63,6 |
| VI | 1000 | 20 | 20,0 | 600 | 90 | 10,0 |
| | | | | 1000 | 20 | 20,0 |
| | | | | 1000 | 10—90 | 0 |
| Control | — | — | 0 | — | — | 0 |

*The $LD_{50}$ of compounds II-VI was more than 2000 mg/kg for the two modes of administration, only in the case of V for intraperitoneal administration, the $LD_{50}$ was equal to 630 mg/kg.

3-Mercaptopropionamide. A solution of 15.5 ml (16.7 g, 0.22 mole) of thiolacetic acid in 20 ml of $CHCl_3$ was added at 0°C, with vigorous stirring, to a solution of 14.2 g (0.2 mole) of acrylamide. After standing for 24 h at 20°C, the solvent was evaporated to yield 28.4 g (98%) of 3-acetylthiopropionamide, mp 80-82°C [8]. The product was boiled for 5 h with 4.6 g of MeONa solution (from 4.6 g of Na, 0.2 mole) in 100 ml of MeOH. The alcohol was evaporated under vacuum, and the material was extracted from the solid residue with ether in a Soxhlet appratus. Yield 11.5 g (56.7%) of 3-mercaptopropionamide, mp 98-100°C [8]. According to the iodometric titration data, the purity of the product was 93%.

## EXPERIMENTAL (BIOLOGICAL)

The acute toxicity and the radioprotective activity of the compounds was studied in accordance with [3]. The acute toxicity was determined for an intraperitoneal and peroral administration to white nonpedigree male mice, weighing 20-24 g each. The aqueous solutions of the compounds were prepared ex temporae and were introduced in logarithmic scale doses. The results were processed according to the Litchfield and Wilcoxon statistical method in the M. L. Belen'kii modification [1].

The radioprotective effectiveness of the compounds was studied on male mice of the F (CBA × $C_{57}$Bl) line, weighing 20-23 g each. The compounds were introduced intraperitoneally before gamma-irradiation with $^{137}Cs$ in a dose of 900 R, and at a dose rate of 215-213 R/min. To obtain comparable results, the radiative action was carried out at identical times of the day [2]. The data were processed statistically using tables [4].

The results of the investigation of the toxic and radioprotective properties of compounds I-VI are given in Table 1.

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