SYNTHESIS OF THIOCARBAMIDE DERIVATIVES OF β-ALANINE AND AMINALON AND STUDY OF THEIR ANTIRADIATION ACTION

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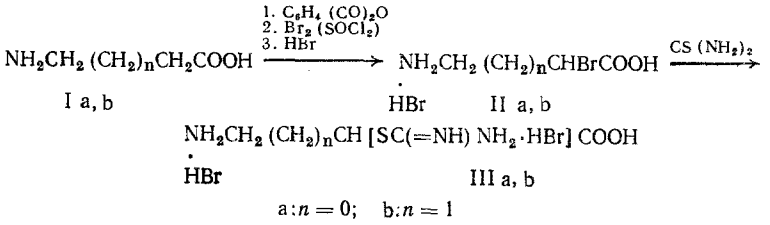
S-(2-Aminoethyl)isothiourea (AET) is one of the most effective anti-radiation agents in experiments on mammals [4, 6]. Numerous attempts to modify the structure of AET to intensify its radiation-protective action by introducing different substituents into the fonctional groups, have not led to any success. S-(3-Aminopropyl)isothiourea (3-APT) [6] also gives a noticeable anti-radiation effect [6].

We have synthesized the carboxyl derivatives of AET and 3-APT, the dihydrobromides of S-(1-carboxy-2-aminoethyl)- and S-(1-carboxy3-aminopropyl)isothioureas, and studied their toxicity and antiradiation effectiveness.

The present work was based on data for the high radiation-protective activity of the corresponding aminoalkylisothioureas [5, 6], on one hand, and on the fact that the introduction of the carboxylic group into the molecule influences the pharmacological properties of a compound, in particular, lowers its toxicity compared with the base compound [1], on the other hand. It should also be noted that S-(1-carboxy-3-aminopropyl)isothiourea can be considered as a new derivative of aminalon, a compound having a wide spectrum of biological activity [2, 3].

The starting compound for the preparation of S(1-carboxy-2-aminoethyl)isothiourea was β-alanine (Ia, n = 0), into a molecule of which a bromine atom was introduced into the α-position with respect to the carboxylic group. By nucleophilic substitution of the latter by thiourea, the desired end product was obtained. Before bromination, the amino group of β-alanine (aminalon) was protected by introducing a pthalyl grouping.



EXPERIMENTAL (CHEMICAL)

The course of the reaction and the preparation of the individual compounds were controlled by the TLC method on the Silufol UV-254 plates in the n-C_4H_9OH—CH_3COOH—H_2O (4:1:5) system.

(β-Phthalimido)propionic Acid. A mixture of 10 g (0.11 mole) of Ia and 14.8 g (0.1 mole) of phthalic anhydride is held at 169°C until water vapor ceases to evolve. The product is cooled and recrystallized from water. Yield 19.5 g (80%). mp 150°C, according to the literature data [7], mp 150-151°C.

2-Bromo-3-aminopropionic Acid Hydrobromide (IIa). A 19 g (0.087 mole) portion of the preceding product is brominated by the action of 13.2 ml (0.25 mole) of bromine and 0.1 g (0.003 mole) of red phosphorus according to a method described in [7], mp 188-190°C.

S-(1-Carboxy-2-aminoethyl)isothiourea Dihydrobromide (IIIa). A 2.5 g (0.01 mole) portion of IIa and 0.76 g (0.01 mole) of thiourea are dissolved in 100 ml of acetic acid, and the mixture is held at 20°C for 72 h. The precipitate that separates is filtered and washed by hot 2-propanol to yield 1.3 g (53%) of IIIa, mp 192°C.

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Dipicrate, mp 241°C. Found, %: C 30.90; H 2.70; N 20.70; S 5.60. $C_{16}H_{15}N_9O_{16}S$. Calculated, %: C 30.90; H 2.40; N 20.30; S 5.20.

S-(1-Carboxy-3-aminopropyl)isothiourea Dihydrobromide (IIIb). A 10.3 g (0.1 mole) portion of Ib and 17.8 g (0.12 mole) of phthalic anhydride are melted together at 160°C, until water vapor ceases to evolve. To the melt cooled to 20°C, 16.7 g (0.14 mole) of $SOCl_2$ are added, and the mixture is held at 80°C until SO_2 and HCl are no longer evolved. The excess of $SOCl_2$ is removed by heating in vacuo. A 9.6 g (0.12 mole) portion of Br_2 is added dropwise to the product obtained, and the mixture is held at 100°C for 2h. It is then cooled, 500 ml of 48% aqueous solution of hydrobromine acid are added, and the mixture is boiled for 6 h. Phthalic acid that separates is filtered and the filtrate is evaporated *in vacuo*. The precipitate is dissolved in 700 ml of glacial acetic acid, and 0.38 g (0.05 mole) of thiourea is added to this solution. The precipitate of IIIb that forms in the course of 24 h at 20°C, is filtered and recrystallized from anhydrous C_2H_5OH to yield 5.6 g (56%) of IIIb, mp 205°C, R_f 0.05. Found, %: C 17.63; H 3.91; N 12.42; S 9.91. $C_5H_{13}Br_2N_3O_2S$. Calculated, %: C 17.71; H 3.84; N 12.39; S 9.44. Mass spectrum: 141 ($C_5H_7N_3S^+$), 117 ($C_4H_7NOS^+$), 116 ($C_4H_6NOS^+$), 76 (CH_4N_2S), 59 (CHNS), 41 (C_3H_5), 30 (CH_4N^+).

EXPERIMENTAL (BIOLOGICAL)

The toxicity and radiation-protective effectiveness of dihydrobromides IIIa and IIIb were studied in experiments on mammals.

The object of the investigation were mice F_1(CBA x C57BL) of both sexes weighing 18-22 g each. In the determination of the toxicity of compound IIIa it was shown that LD_{16}, LD_{50}, and LD_{84} are equal to 335, 412, and 475 mg/kg, respectively. Preparation IIIb is slightly toxic: The LD_{16}, LD_{50} and LD_{84} are equal to 6800, 7200 and 7600 mg/kg. It should be noted that the toxicity of compound IIIb is practically one order of magnitude lower than in the case of the most effective radiation-protective agent among the aminoalkylosothioureas — AET. The toxicity of AET is 500, 530, and 574 mg/kg, respectively, while for 3-APT, the LD_{16} is equal to 350 mg/kg. At the same time, the data obtained show that the introduction of carboxylic acid into the molecule does not always lead to a decrease in the toxicity of the base compound, as has been noted in the literature [1].

In the study of the anti-radiation activity, the compounds investigated were introduced in 0.5 ml of distilled water 1 and 2 h before the irradiation: IIIa in a dose of LD_{16} and $1/2LD_{16}$, IIIb in a dose of $1/2LD_{16}$. The mice were subjected to the action of ^{60}Co-gamma rays in a dose of 9.5 Gy ($LD_{100/30}$) at a dose rate of 1.7 Gy/min. The injury criterion was the rate of survival of the animals for 30 days. The number of mice used in the experiments was 300.

It was shown that for the doses introduced and intervals before the irradiation, neither IIIa nor IIIb have radiation-protective properties, whereas AET and 3-APT, when introduced to the animals at the same intervals before the irradiation under similar conditions, ensure survival rates of 80-90 and 50-60%, respectively.

It was thus found that the introduction of the carboxylic group into the molecules of effective radiation-protective compounds AET and 3-APT [4-6] leads to a loss of the anti-radiation properties.

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