SYNTHESIS AND PROPERTIES OF A NUMBER OF SALTS OF N-SUCCINYLMETHIONINE

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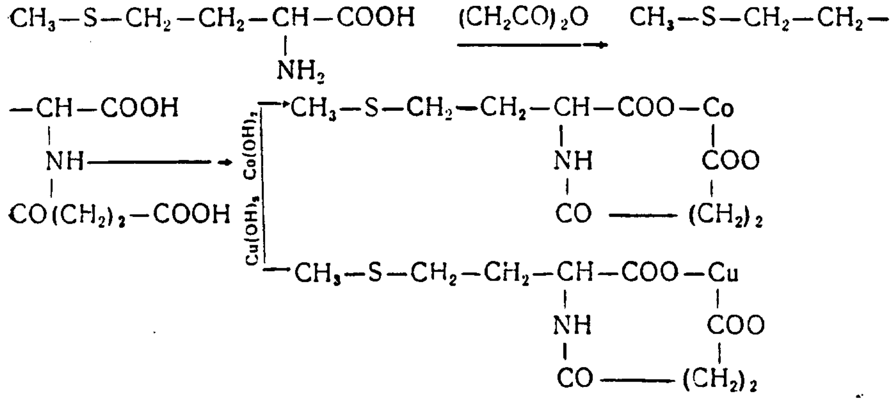
A comparative study has been made of the radioprotector activity of cystamine and the synthesized cobalt and copper salts of N-succinylmethionine. Activity falls in the sequence cystamine-copper salt-cobalt salt.

Sulfur-containing amines and, in particular, cystamine, are among the best radioprotectors — substances protecting the organism from ionizing radiation [1]. The amino acid methionine, which is similar in structure to cystamine, plays a significant role in the vital activity of the organism as a methylating agent.

It appeared of interest to obtain some methionine derivatives with the aim of studying their radioprotector action. As such derivatives we selected cobalt and copper salts of N-succinyl-L-methionine, since succinic acid affects many processes of vital activity, and copper and cobalt are widely used in the treatment of diseases of the blood and disturbances of hematopoiesis. The influence of cobalt on the organism is not limited to hematopoiesis but is also connected with the activity of enzymes, vitamins, and hormones. The compounds mentioned were synthesized by the following scheme:



N-Succinylmethionine was obtained by boiling methionine with succinic anhydride in dioxane solution. The N-succinylmethionine, isolated by the usual method, reacted in aqueous solution with cobalt or copper hydroxide. The desired salt was isolated from the solution, after the elimination of the excess hydroxide, by evaporation in vacuum.

To determine the level of radioprotector action we studied the acute toxicity of the compounds concerned by the generally adopted method, with calculation by the Litchfield—Wilcoxon method [3].

With practically the same LD_{50} values (for the copper salt, 51 mg/kg; and for the cobalt salt, 49.6 mg/kg) there was an appreciable difference in the LD_{84} values which showed that the copper salt was less toxic (71.6 mg/kg) than the cobalt salt (59.6 mg/kg). It is possible that these properties will subsequently be manifested in some difference in their radioprotector actions.

The antiradiation activities of these compounds were studied by the generally adopted method. The radioprotective efficacy was evaluated under the conditions of irradiation with 800 roentgen in a dose of LD_{80-100}. The preparations were added 15 min before irradiation. The radioprotective efficacy of the compounds was evaluated from the percentage of animals surviving for 30 days after irradiation in comparison with the analogous action of cystamine. Thus, the mean survival time of the animals in the control was about 10 days, of those subjected to the action of the copper salt about 13 days and for the cobalt salt 12 days, and the survival rates up to the 30th day were, respectively, 25.0 and 40%.

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EXPERIMENTAL

The elementary analyses of the compounds described corresponded to the calculated figures. N-Succinyl-L-methionine was obtained by a known method [4, 5].

Cobalt Salt of N-Succinyl-L-Methionine. A suspension of 5 g of N-succinyl-1-methionine, 2 g of cobalt hydroxide, and 40 ml of water was boiled for 2 h and was filtered hot from unchanged cobalt oxide. The latter was boiled with water three times, and the water was distilled off from the aqueous part in vacuum.

The lilac-colored residue was dissolved in 20 ml of methanol and the solution was filtered and evaporated to dryness.

In this way, 5.2 g (84.7% of theoretical) of the cobalt salt of N-succinyl-L-methionine was obtained. Lilac-colored crystals soluble in water and insoluble in organic solvents.

Copper Salt of N-Succinyl-L-methionine. A solution of 10.0 g of N-succinyl-L-methionine in 40 ml of water and 30 ml of ethanol was treated with a suspension of 10.0 g of copper hydroxide in 50 ml of water. The remainder of the synthesis was carried out in a similar manner to the preceding case. This gave 9.6 g (79.6% of theoretical) of the copper salt of N-succinyl-L-methionine, soluble in water and insoluble in organic solvents.

LITERATURE CITED

1. L. Juliano and A. C. M. Paiva, *Biochemistry* **13**, 2445 (1974).
2. G. A. Babenko and L. N. Reshetkina, *The Use of Microelements in Medicine* [in Russian], Zdorov'e, Kiev (1970), p. 220.
3. M. L. Belen'kii, *Elements of the Quantitative Evaluation of a Pharmacological Effect* [in Russian], Medgiz, Leningrad (1963), p. 152.
4. L. M. Volovel'skii, I. A. Rastrepina, S. P. Kustova, N. V. Polova, and V. N. Koryukina, *Khim. Prir. Soedin.*, 703 (1985).
5. L. W. Cushman, H. S. Cheung, E. F. Sabo, and M. A. Ondetti, *Biochemistry* **16**, No. 25, 5484 (1977).

OLIGONUCLEOTIDES AND NUCLEOTIDOPEPTIDES. LIII. SYNTHESIS AND PROPERTIES OF THE ETHYL ESTER OF THYMIDYL-(5′ → 3′)-THYMIDINE-(P_m → N)-SERINE

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The phosphoramide analog of the dinucleotide monophosphate EtO-Ser(P_m → N)-(TpT) has been synthesized. It has been shown that the serine amide of the dinucleoside monophosphate undergoes 20% N → O migration in an acid medium (0.1, 0.5, and 1 N HCl, 37°C, 1 h). In an alkaline medium, in contrast to other nucleopeptide phosphoramides, the phosphoramide bond is cleaved.

At the present time, natural covalent compounds of proteins and nucleic acids have been isolated from the most diverse prokaryotic and eukaryotic sources [1-5]. One of the possible types of covalent bond between proteins and nucleic acids is a bond between the functional group of an amino acid and an internucleotide phosphate group of an oligonucleotide. The possibility of the formation of such a bond has been reported previously [6] and has recently been discussed in several papers relating to eukaryotic cells [7]. In the elucidation of the physicochemical principles of the functioning of protein—NA structures a large role is played by synthetic model nucleotidopeptides.

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