IMPROVING THE PRODUCTION PROCESS FOR THE SYNTHESIS OF LEUCOGEN

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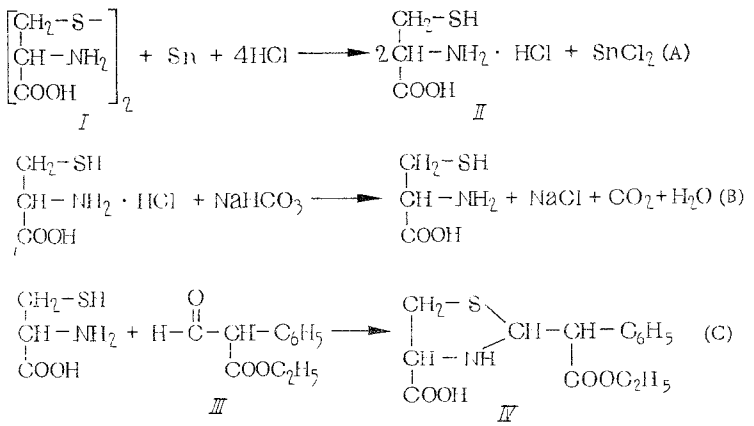
The pharmaceutical preparation leucogen, which is used for the treatment of leukopenia, produced by x-ray radiation or the action of chemical substances which depress hemopoiesis [1], was synthezised by I. T. Strukov [2].

Industrially leucogen is synthesized in accordance with the following scheme:



As can be seen from equation A, the reduction of 1-cystine is carried out with metallic tin in HCl (duration of reaction 24 h).

At the end of the reaction the reaction mixture is diluted with water until the HCl content is 2.5-3% and the Sn(II) ions are precipitated by passing H_2S through the solution, filtering off the $SnCl_2$, and concentrating the filtrate to a syrup-like consistency in vacuo. The 1-cystine (II) in the residue is filtered off and used as a starting material for the production of leucogen.

Leucogen itself, 2-(α-phenyl-α-carboethoxymethyl)-thiazolidine-4-carboxylic acid (IV) is obtained by condensation of 1-cystine with the ethyl ester of formylphenylacetic acid (III) (B, C).

It is clear from what has been said above that the industrial method of obtaining leucogen has numerous disadvantages: 1) the reduction of 1 cystine is time consuming (24 h); 2) special equipment is required for producing H_2S, and also equipment for decomposing the unreacted H_2S before releasing the effluent gases into the atmosphere; 3) to ensure complete precipitation of Sn (II) ions the reaction mixture has to be diluted with water and then concentrated in vacuo; 4) the solution has to be heated so long in order to concentrate it that the quality both of the 1-cystine hydrochloride and of the final product are impaired; 5) the high cost of tin.

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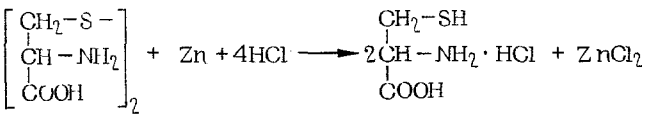
We propose a new method for producing leucogen which does away with the use of H_2S, which is both tedious and dangerous to use on the production scale, and also with tin, which is an expensive raw material and is in short supply. In our process we use zinc instead of tin, Zn being both cheap and easily obtainable, and the process developed involves the production of leucogen in the presence of zinc chloride.

The method of reducing l-cystine by zinc is described in the published literature [3] and is as follows:



This process has not been applied on the industrial scale for the production of l-cystine and leucogen since the direct precipitation of zinc ions is difficult becuase of the high acidity of the solution [4].

We have developed a method of obtaining leucogen without previous removal of the zinc salts. In this method, the solution of l-cystine hydrochloride is neutralized before condensation with the ethyl ester of formylphenylacetic acid to pH 2.0-2.5, i.e., to an acidity at which the zinc salts do not undergo hydroloysis, and at which their presence in the solution does not interfere with the process in accordance with scheme B above. If the pH of the solution exceeds 2.5, basic zinc salts are precipitated in the residue and cause serious contamination of the final product.

Leucogen, produced at pH 2.0-2.5, is filtered off and washed with dilute-1-2% HCl until complete removal of zinc ions from the residue [5]. The final product entirely meets the requirements laid down for this preparation.

EXPERIMENTAL

1-Cystine Hydrochloride (II). To 120 ml of water was added 57.5 g of HCl (sp.g. 1.19) and 30 g l-cystine, and the mixture was heated at 60-70° until the l-cystine was completely in solution, the solution was cooled to 30°, and 11.6 g zinc dust was added in portions. The mixture was then heated at 80° and held at this temperature with stirring for 8 h. It was then cooled to 30°, 3 g of activated carbon was added, the solution was filtered off from the carbon and the residue of zinc dust, and the content of II was determined. This amounted to 15.5-17.5%, i.e., the yield of II was 36.5 g (92.8%).

Leucogen-2-(α-phenyl-α-carboethoxymethyl)-thiozolidine-4-carboxylic Acid (IV). To 60 g of a solution containing 9.3 g of II was added 5.4 g of sodium bicarbonate, and the pH was determined potentiometrically (the pH should be 2.2-2.3). To the mixture was then added 24.8 g of redistilled ethanol and 11.4 g of III, and the mixture was heated to 80-82°. After 2 h at this temperature the mixture was cooled to 30°, 300 ml of water was added, and the mixture was held at room temperature for 12 h. The residue was then filtered off, washed with water to complete removal of zinc ions, and then washed with ethanol (20 ml) and with ether (15 ml). The yield of leucogen was 12.2 g (70.2%).

LITERATURE CITED

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