IMPROVEMENT OF THE TECHNOLOGICAL METHOD FOR THE SYNTHESIS OF LEUCOGEN

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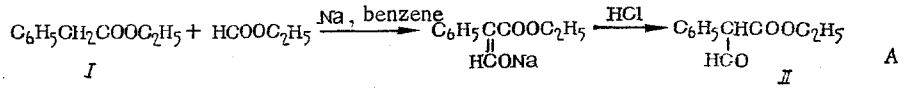
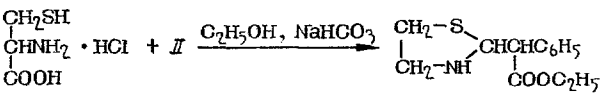
The medicinal preparation Leucogen (L-2-(α-phenyl-α-ethoxycarbonylmethyl)thiazolidine-4-carboxylic acid (IV)), which is used for the treatment of leucoses, was synthesized by I. T. Strukov [1].

Leucogen is synthesized by the route:





In the industrial production of the drug, ethyl phenylformylacetate (II) is prepared as in scheme A as an oil which is purified by vacuum distillation, and Leucogen itself is prepared by reaction of equimolar amounts of the ester II and L-cysteine hydrochloride (III) in aqueous alcohol at 80-82°. The yield of Leucogen in this stage is 70-77% of theory [2, 3].

The thermal instability of the ester II is known to result in reduced yield and purity on vacuum distillation, with the result that under production conditions the yield is no greater than 40% [4]. It is likely also that under the comparatively severe temperature conditions involved in the preparation of Leucogen by scheme B, the ester II similarly decomposes. This appears to be the reason for the fact that even under laboratory conditions the yield of Leucogen does not exceed 79% [5]. When the process is carried out on the industrial scale, therefore, the yield of Leucogen does not exceed 67%. The Leucogen is always contaminated with decomposition products of the ester II, and to obtain material of pharmacopoeia quality extensive and laborious washing is required with alcohol, water, and ether.

For these reasons, we have attempted both to change the conditions for the preparation of the ester II and to select the best conditions (solvent, temperature, concentration, reaction time) for the preparation of Leucogen.

It is known that the ester II can be obtained either as a liquid or in the crystalline state. It appeared to us desirable to use the crystalline form in the industrial preparation of Leucogen. This form is easily obtained by adding a dilute aqueous solution of the sodio-derivative of the ester II to an excess of mineral acid at a temperature of 0-2° [6].

By this means, the need to distill the thermally unstable ester II *in vacuo* would be avoided.

In order to maintain a precise ratio of the components charged to the reactor in the preparation of Leucogen, we have developed a method for estimating the ester II, which is obtained in the form of a paste.

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Satisfactorily reproducible results were obtained by potentiometric titration of the ester with aqueous sodium hydroxide in 50% ethanol at a temperature of 7-10°, using a glass indicator electrode. It was first established that hydrolysis of the ester I did not occur under the conditions of the estimation, and that its presence did not interfere with the determination of II. It should be noted that on storing II in the crystalline form, the content of II decreases, probably as a result of atmospheric oxidation with the formation of formic acid [7].

An investigation of the preparation of Leucogen in aqueous-alcoholic and aqueous-acetone solutions at various temperatures and reaction times showed that the best yield of products (88%) was attained when the process was carried out in aqueous acetone solution at the boil (64-66°) for 4 h.

The product obtained was washed to remove organic impurities with acetone instead of alcohol. It was found that in this way the product was more easily filtered, and the required degree of purity was attained with a smaller volume of solvent. The final product fully complied with the requirements of the State Pharmacopeia (10th edition).

The introduction of this method for the preparation of Leucogen into production resulted in an increase in the final yield of 10%, and in a significant shortening of the technical cycle and simplification of the equipment required for the process.

EXPERIMENTAL

Ethyl Phenylformylacetate (II) in the Crystalline Form. To a mixture of 200 ml of benzene (moisture content not greater than 0.1%) and 14 g of finely divided metallic sodium was added during 3-3$^1/_2$ h at 25-30° a mixture of 54.5 g of anhydrous ethyl formate and 100 g of vacuum-redistilled ethyl phenylacetate. The resulting mixture was stirred at room temperature until the sodium had dissolved completely (around 12 h). When the reaction was complete, 500 ml of water was added to the reaction mixture to dissolve the sodio-derivative of the ester II, and unreacted ester I was extracted with benzene (2 × 65 ml). The solution of the sodio derivative was diluted with water to a volume of 1300 ml, cooled to 5-10°, and 13 g of activated charcoal added. The solution after removal of the charcoal by filtration was added slowly with vigorous stirring at 0-5° to 280 ml of hydrochloric acid (sp. gr. 1.18). The resulting precipitate was filtered off and washed with 50 ml of chilled (2°) water (the pH of the washwater was 4.0-5.0).

The moist product contained 70.2 g of the ester II (60% of theory).

Leucogen, L-2-(α-Phenyl-α-methoxycarbonylmethyl)thiazolidinecarboxylic Acid (IV). To 40 g of a solution containing 6.6 g of L-cysteine hydrochloride was added sodium bicarbonate to pH 2.2-2.3. There was then added a solution of 8 g of the ester II (calculated as 100%) in 35 ml of acetone, and the mixture was boiled under reflux for 4 h (the temperature of the mixture was 64-66°). When the reaction was complete, the mixture was cooled to 15-18°, diluted with 450 ml of water, and stirred for 6 h.

The precipitate was filtered off, washed successively with 50 ml of acetone, 550 ml of acidified water (pH 3.0), and again with 50 ml of acetone, to give 10.9 g of Leucogen (88%, calculated on L-cysteine hydrochloride).

LITERATURE CITED

1. I. T. Strukov, Zh. Obshch. Khim., 22, 1028 (1952).
2. I. T. Strukov, in: Data on the Exchange of the Best Practices and Scientific Achievements in the Chemical-Pharmaceutical Industry [in Russian], No. 1/12, Moscow (1958), p. 62.
3. Yu. A. Ostrovskaya, A. I. Adamovich, M. G. Argitti, et al., Khim. Farm. Zh., No. 3, 45 (1970).
4. A. Michael, Justus Liebigs Ann. Chem., 391, 255 (1912).
5. W. Watanabe, A. Ide, and W. Sugimoto, Yakugaku Zasshi, 83, 1118 (1963).
6. W. Wislicenus, Justus Liebigs Ann. Chem., 389, 273 (1912).
7. W. Dieckmann, Chem. Ber., 50, 1961 (1917).