METHOD OF OBTAINING HELIOTRINE FROM THE EPIGEAL PART OF Heliotropium dasycarpum

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The technological processes for obtaining heliotrine from the epigeal part of Heliotropium dasycarpum Ledeb. have been studied. A rational method of obtaining heliotrine from the plant raw material has been developed which consists in the extraction of the raw material with 80% ethanol, concentration to an aqueous residue, and reduction of the N-oxide form of heliotrine followed by extraction with chloroform, evaporation, and recrystallization from acetone. The yield of heliotrine corresponding to TU [Technical Standard] 6-09-50-2386-82 is 75-85% of its amount in the raw material.

The alkaloid heliotrine is used in medical practice as a reagent for obtaining an experimental model of hepatitis and cirrhosis of the liver in laboratory animals in the search for effective means of treating hepatitis and other serious diseases of the liver [1, 2].

Heliotrine has been detected in many species of heliotrope [3-7]. The main raw material for obtaining heliotrine is Heliotropium dasycarpum Ledeb. growing in the Bukhara province, Uzbek SSR, the level of heliotropine in which amounts to 0.8-1.0% on the air-dry weight of the raw material.

Heliotrine is obtained from various plants by extracting the raw material with organic solvents and by the ion-exchange method [3-8]. The known disadvantages of these methods are the multistage nature of the process and the low yield of heliotrine. In addition, the heliotrine obtained by these methods has not been standardized, and the pharmacologists of the country have had to determine the dosage of heliotrine for each experiment.

In order to develop a rational technology for obtaining heliotrine, we have studied the distribution of this alkaloid between chloroform and buffer solutions with various pH values. As a result of the experiments we have found $pH_{1/2}$ 7.3 and, therefore, heliotrine is a strongly basic alkaloid.

As is known from the technical classification of methods of obtaining alkaloids [9], heliotrine, as a strongly basic alkaloid, can be isolated not only by the absorption method but also by ethanolic extraction.

In developing an industrial method for obtaining heliotrine from plant raw material we also studied such stages of production as the extraction of the total alkaloids from the plant raw material, the reduction of the N-oxide form of heliotrine to heliotrine, and the production of technical heliotrine, and its purification.

The study of the extraction of the alkaloids from the plant raw material by solutions of ethanol of various concentrations showed that a high yield of alkaloids was obtained from the comminuted plant (particles about 5-10 mm) by the use of an 80% solution of ethanol, the process being performed at room temperature with five extractions.

In the plant raw material, about 50% of the heliotrine is present in the N-oxide form, which, as experiments have shown, is readily soluble in aqueous, acidic, and alkaline media and is scarcely extracted from solutions by organic solvents, while it is readily sorbed on ion-exchange resins and is very difficult to desorb. In the production of heliotrine by the ion-exchange method, when the alkaloids are desorbed from the cation-exchange material the bulk of the N-oxide form of heliotrine remains in the sorbent, which lowers the yield of final product.

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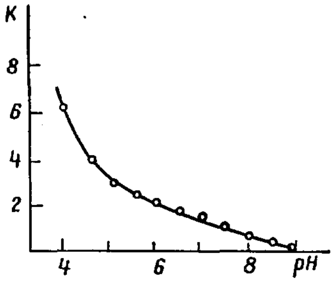

Fig. 1. Distribution of heliotrine between chloroform and buffer solutions with various pH values.

To increase the yield of heliotrine, we reduced its N-oxide form directly in the extract obtained, having first evaporated the ethanol from the extract and having acidified the still residue with sulfuric acid solution. Tin, zinc granules, and zinc dust were used as reducing agents. A high yield of heliotrine was achieved by reducing the heliotrine N-oxide with zinc dust at 70°C with stirring for 4 h.

To purify the combined alkaloids it has been proposed to extract the alkaloids with chloroform from the previously filtered mass after the performance of the reduction process and acidification with ammonia to a pH of 10-11.

A high yield of heliotrine is given by treating the combined alkaloids with acetone and recrystallizing them from acetone. A single recrystallization of technical heliotrine is sufficient for the product to correspond to the technical conditions (TU 6-09-50-2386-82, heliotrine, "pure" grade) which was drawn up by T. T. Shakirov, E. K. Dobronravova, and A. D. Rakhimova on the basis of samples of heliotrine obtained by the method described above. A test of the reproducibility of the method on the semi-industrial apparatuses of the institute showed that the yield of heliotrine amounted to 75-78% of its level in the raw material.

Thus, we drew up experimental-industrial rules for the production of heliotrine which were introduced in 1982 in the experimental factory of the Institute of the Chemistry of Plant substances of the Academy of Sciences of the Uzbek SSR.

EXPERIMENTAL

Determination of the $pH_{1/2}$ Value of Heliotrine. From a chloroform solution of the alkaloid with an accurately known concentration (1%) we took 10-ml portions and added the same amount of a buffer solution with a pH from 1.5 to 9.0. The equilibrium distribution of the alkaloids was achieved by shaking the mixtures for 1 h. The chloroform phases were separated off and evaporated to dryness, and the residues were dried to constant weight and weighed. The distribution coefficients were determined from the formula

$$K = \frac{C_1}{C_2},$$

where C_1 and C_2 are the equilibrium concentrations of the alkaloids in the buffer solution and in the chloroform, respectively, and the results were represented in the form of the graph (Fig. 1), K = f(pH) from which the $pH_{1/2}$ value for heliotrine was determined.

Production of Heliotrine. An extractor was charged with 70 kg of the comminuted epigeal part of *H. dasycarpum* and after the addition of 80% ethanol in a ratio of 1:4.2 (300 liters) the mixture was left to steep for 8 h. The ethanolic extract of heliotrine was decanted off. The 160 liters of extract so obtained was evaporated. A second extraction was performed with 160 liters of 80% ethanol. Third, fourth, and fifth extracts were made similarly by steeping for 4, 3, and 3 h, respectively. The extracts obtained were evaporated in a vacuum evaporation apparatus to a residue amounting to 8.0-11.0% of the initial volume. This gave about 60 liters of extract.

This concentrated extract was acidified with 2.5 kg of sulfuric acid (40% solution) and, with stirring, 4 kg of zinc dust was added. The mixture was heated to 70°C and was kept at this temperature with stirring for 4 h, after which the excess of zinc was separated off by filtering the solution.

To eliminate impurities of nonbasic structure, the acid solution of the alkaloids was washed twice with 10-liter portions of chloroform. The purified acid solution of the alkaloids was made alkaline with ammonia to pH 11, and the alkaloids were extracted with chloroform. The chloroform solution of heliotrine obtained was evaporated in a vacuum evaporation apparatus. This gave 560 g of combined alkaloids or 0.8% of the air-dry weight of the raw material.

The combined alkaloids (560 g) were dissolved in 3 liters of acetone, and the solution was left for 12 h. The precipitate of technical heliotrine that deposited was filtered off, washed with acetone, and dried (515 g). To obtain heliotrine satisfying the demands of the TU, the technical heliotrine was recrystallized from acetone. The yield was 470 g on 0.67% of the air-dry raw material.

SUMMARY

A method has been developed for obtaining heliotrine by aqueous ethanolic extraction with a yield of 75% of the amount in the raw material.

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X-RAY STRUCTURAL INVESTIGATION OF A DERIVATIVE OF THE ALKALOID KESSELRINGINE

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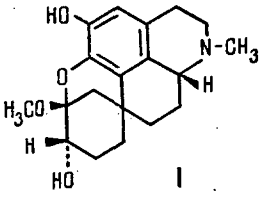
The molecular and crystal structures of 2,6-dimethyl-12-demethylkesselringine methosulfate have been determined by x-ray structural analysis. The relative configurations of the chiral centers in the R, S nomenclature have been established.

Structure (I) has been established for the homoproaporphine alkaloid kesselringine isolated from the Central Asian species of autumn crocus Colchicum kesselringii Regel [1] on the basis of IR, PMR, and mass spectroscopy and chemical transformations [2, 3].



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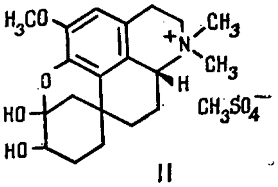

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