ISOMERIZATION OF THE APORPHINE ALKALOID GLAUCINE INTO THE PHENANTHRENE ALKALOID DES-GLAUCINE IN SUBCRITICAL WATER

[1]M.Kurbanova, [2]I.Jalolov, [3]U.Maraimova, [4]G.Koraboeva
[1,2,3,4]Ferghana state university

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Abstract. *The results of a study on the development of a method for obtaining des-glaucine using direct extraction of an alkaloid or the sum of alkaloids with superheated water from the Glaucium elegans plant are presented. This method provides the production of des-glaucine in one step with good yield and creates the possibility of its further modification under subcritical conditions, both at the phenanthrene ring and at the secondary amino group.*

Keywords: *Glaucium elegans, alkaloids, glaucine, subcritical water.*

Introduction

G. elegans, which include to the family *Papaveraceae*, widespread in Asia and the Caucasus: Afghanistan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, Iran, and the Caucasian republics. Botanically, the plant *G.elegans* characterized as follows: stems 20-30 cm high, slightly branched, leaves thick, bluish, basal petioles - large, 10-15 cm long and 2-3 cm wide. Stem leaves are oval, 4-6 cm in length. The bud is bare, ovate-oblong, acute, 1.5-2 cm long. The flowers are single, large, the petals are yellow with an orange center and a black spot at the base with a diameter of 3 cm. The pods are 6-15 cm long, straight or slightly arched, the seeds are wide about 4 mm. Flowering in April - June, fruiting in June - September[1].

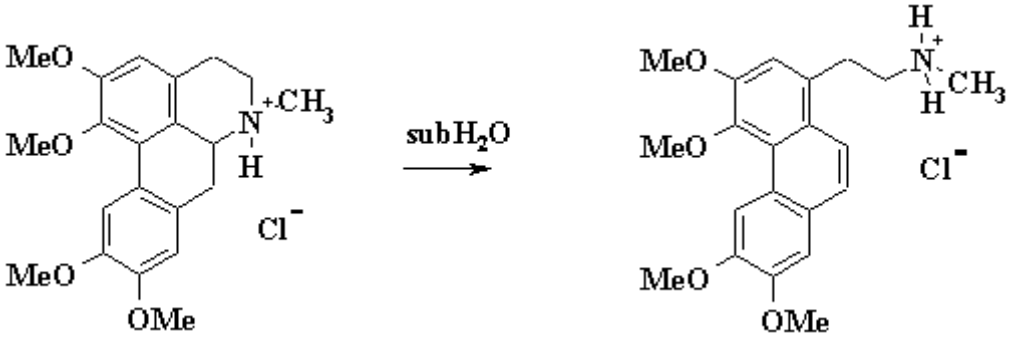
Materials and methods

Research shows that each group of alkaloids has a specific biological effect. Simple isoquinoline alkaloids have hemostatic properties. Benzophenanthridine alkaloids, as well as the sulfate fraction of benzophenanthridine alkaloids of some plants, have a wide spectrum of antimicrobial action, including antibacterial and antifungal activity. Di and three - substituted aporphine alkaloids (coridine) exhibit a convulsive effect. Tetrasubstituted and monohaloid derivatives of aporphine alkaloids, such as glaucine, have antitussive activity and are used to treat bronchial asthma; another aporphine alkaloid, coridine, has an adrenaline effect and is a dopamine receptor blocker. Quaternary aporphine alkaloids have hypotensive properties, and some of them are ganglioblocking. Protopine alkaloids (protopine) have a wide range of applications, so protopine is used for the preparation of analgesics, antiarrhythmic and bile-stimulating drugs and for the treatment of alcohol dependence. Protoberberine – sedantic-tranquilizing and anti-alcoholic properties.

Moderate antitumor activity of sanguinarine and chelirithrine was discovered for the first time. In the future, these same alkaloids can be the starting compounds for the synthesis of effective drugs based on them.

According to many scientists, climate, soil conditions and other factors are important factors for the biosynthesis and accumulation of alkaloids in plants. It has been established that warm weather promotes an increase in the content of alkaloids in plants, cold weather inhibits it, and during frost, alkaloids do not accumulate in the plant. For example, in plants, glaucine occurs

in the form of two enantiomers: (+)-glaucine (the main component) and (-)-glaucine (in minor quantities). Side effects of glaucine (prostate, hallucination) are associated specifically with (-) – glaucine. In this regard, the isomerization of a non-racemic mixture of enantiomers of the natural aporphine alkaloid glaucine into the phenanthrene alkaloid des-glaucine was studied in a subcritical water environment at a temperature of 200-300ºC under hermetic conditions. As a result of the study, des-glaucine was obtained (in English literature seco-glaucine) with a yield of 53%.



Gla ucine — Des-glaucine

I — II

Results and discussions

The natural aporphine alkaloid (+)-glaucine ((S)-N-methyl-1',2',7,8-tetramethoxydibenzo[de,g]octahydroquinoline), isolated from yellow poppy (Glaucinum elegans), is a centrally acting antitussive drug . It is part of a number of imported antitussive drugs. In plants, glaucine is present in two forms: (+)-glaucine, a major alkaloid, and (-)-glaucine, a minor alkaloid. The presence of side effects (hypotensive effect) of glaucine is associated with the presence of (-)-glaucine. Upon cleavage of the C-N bond between the chiral carbon atom and the nitrogen atom, glaucine is converted to des-glaucine, which is a derivative of phenanthrene. The target glaucine derivative, des-glaucine, also has a pronounced antitussive effect. At the same time, no side hypotensive effect was found in des-glaucine and des-glaucine is 1.5 times less toxic than glaucine (LD50 = 82.5). In addition, these glaucine derivatives are not chiral compounds, therefore, both enantiomers of glaucine under our reaction conditions give the same product, as a result, increasing the yield of the target product. The spread of des-glaucine as a medicinal product is limited primarily by economic considerations due to the lack of effective methods for its preparation from glaucine itself. Thus, the search for effective methods for producing des-glaucine and its derivatives seems to be a promising direction. It has been shown that in an environment of subcritical water at a temperature of 200-300ºC, isomerization of a non-racemic mixture of (+)- and (-)-glaucine into des-glaucine occurs, which is proven by NMR and mass spectrometry data.

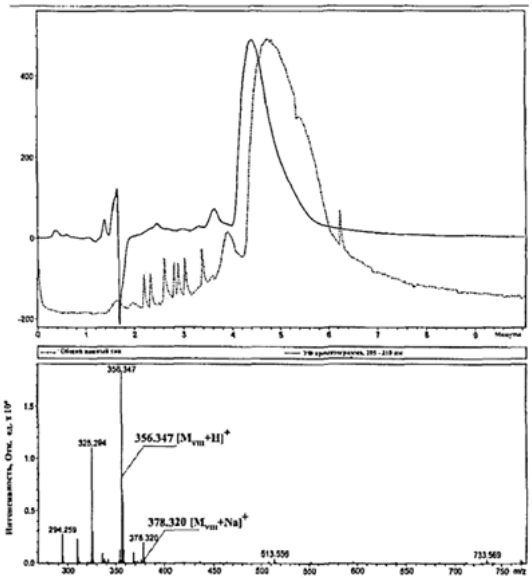


Figure. 1 Mass spectrum of des-glaucine II

Upon direct injection of a solution of des-glaucine preparatively isolated from subcritical water, the mass spectra of positive ions revealed ions with similar ion m/z values, which were attributed to adducts of des-glaucine II with a molecular weight of 355 with the H+, Na+ cation (m/z 356 and 378, respectively) (Fig. 1). 1H NMR spectrum (CDCl3, δ, ppm): 2.53 (t, 3H, CH3), 3.22 (m, 2H, CH2), 3.50 (m, 2H, CH2), 3.90 -4.10 (4s, 12H, 6OCH3), 7.22 (s, 1H, ar), 7.40 (s, 1H, ar), 7.60 (d, 1H, ar), 7, 85 (d, 1H, ar), 9.45 (bm, 2H, NH2).

The use of the proposed method for obtaining des-glaucine opens up a useful perspective. Extraction of an alkaloid or a sum of alkaloids with superheated water from yellow poppy seeds provides the production of des-glaucine in one stage with good yield and creates the possibility of its further modification under subcritical conditions, both at the phenanthrene ring and at the secondary amino group. The presence of yellow luminescence in des-glaucine can make it a promising inexpensive material for use in the synthesis of compounds for molecular electronics (including polymers).

Conclusion

An environmentally friendly method for the isomerization of glaucine to des-glaucine in subcritical water with a yield of 53% has been developed. The proposed approach makes it possible to develop methods for obtaining a wide range of pharmaceutically acceptable salts (chlorides, bromides, phosphates, citrates, etc.) of des-glaucine using an inexpensive, environmentally friendly solvent - subcritical water.

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