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Synthesis and Research of Biologically Active Compounds Based on Aminolupinin

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Abstract The article presents the results of the synthesis and study of a number of lupinin derivatives with an amide bond to search among them for effective biologically active substances that have a certain superiority over known drugs.

Keywords Quinolizidine alkaloids, Anabasis aphylla, Aral Sea region, Aminolupinine, Benzyl esters, Benzoylamidolupinin, Biological activity

1. Introduction

The creation of new biologically active substances and the study of the mechanisms of their action remains one of the most urgent tasks of modern bioorganic chemistry. Modification of natural compounds, especially alkaloids, is considered one of the priorities in its implementation. Modification of quinolizidine alkaloids opens up great prospects in the search for biologically active substances with high efficiency, selectivity and stereospecificity [1].

Quinolizidine alkaloids attract the attention of researchers with their biological activity and structural diversity. In this regard, the alkaloids lupinin and its derivatives isolated from the plant Anabasis aphylla are of considerable practical interest. The poisonous and medicinal properties of this plant have been known since ancient times and it has been used in the treatment of wounds and various diseases, including tuberculosis. Decoctions of the plant were used to control pests of agricultural crops [1-3].

Lupinin is the second alkaloid in terms of content in the plant Anabasis aphylla and a waste product in the production of anabasine hydrochloride. The availability of lupinin and the methods of its isolation are one of the advantages, which makes it possible to synthesize various biologically active substances with specified properties on its basis [1-3,9,10,11].

Currently, there is a lot of factual material on the physiological activity of lupinin and its derivatives. The relatively easy availability of lupinin and the presence of a simple alcohol group in the structure of the quinolizidine system, which makes it easy to obtain various derivatives of this alkaloid, are the reason for the search for active drugs among the derivatives of this alkaloid.

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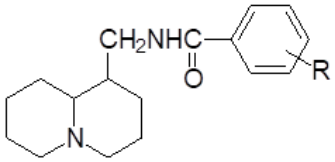
2. Material and Methods

The object of the study was the plants Anabasis aphylla, which grows in the Aral Sea region, the alkaloids lupinin isolated from the plant and its derivative aminolupinin. New modified derivatives of aminolupinin have been synthesized. The individuality of the synthesized compounds was controlled by thin-layer chromatography. The structure of the synthesized compounds was confirmed by the data of IR-, PMR- and mass spectra.

3. Results and Discussion

In order to find new highly effective biologically active drugs among the derivatives of lupinin isolated from Anabasis aphylla plants, we synthesized a number of lupinin derivatives with substituted benzoic acids bound by an amide bond according to the following structure:



R = p-CH_3; p-Br; o-CH_3; o-Br; m-CH_3; m-Br;

To achieve the maximum yield of the reaction product, a short-term heating of the mixture is required after the addition of reagents. The reaction can be carried out without triethylamine. In this case, the reaction mixture must be heated for more than three hours, after which, when potash is added, the base of the aminoester, substituted benzoylamides of lupinine is released from the hydrochloride.

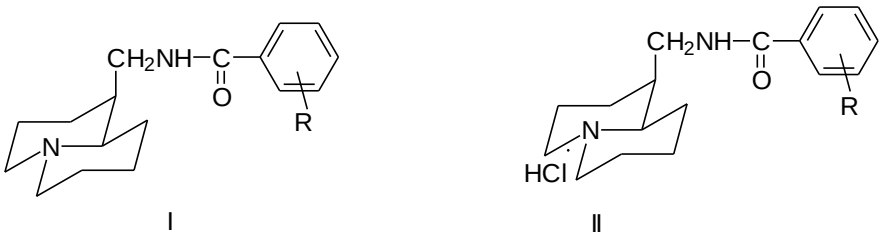
Of all the synthesized compounds, para-bromine- and methane-bromine-substituted benzoylamidolupinins (with prolonged standing, para-bromine- and meta-bromine-substituted benzoylamidolupinins crystallize) are oily, the rest are crystalline substances with a yellowish tinge. The synthesized compounds were purified by recrystallization from benzene. The chlorohydrates of the compounds were obtained by the action of dry hydrogen chloride on a solution of benzoylamidolupinins. All hydrochlorides are obtained clean and do not require further cleaning. The characteristics of the synthesized compounds are given in Table 1.

PMR spectra of lupinin amides (I-VI) contain a complex signal in the range of 3.52-3.98 m.s., related to the protons of the CH_2-N fragment. Signals of aromatic protons are noted at 7.0-7.8 m.s. in the region of 7.35-8.84 m.s. a signal belonging to the NH proton is noted. The signals in the region 1.1-2.2 m.s. belong to the protons of the quinolizidine fragment. The positions of other signals depend on the specific type of substituent and the obtained spectra confirm the structure of the synthesized derivatives of lupinin amides.

The splitting of signals is associated with spin interactions with H7 and NH protons, which indicates a slow rate of proton exchange of NH protons. The two-proton doublet at 2.87 m.s. with 1~10 Hz belongs to the equatorial protons H2e and H10e located in the position to nitrogen. The signals of the remaining protons resonate in the region of "methylene elevation" 1.1.-2.2 m.s.

In the IR spectrum III there is an absorption band at a frequency of 3300 cm^{-1}, due to valence vibrations of the NH groups, and an absorption band at 1530 cm^{-1}, due to deformation vibrations of NH. The composite absorption band with frequencies of 1630 cm^{-1}, 1640 cm^{-1} and with an inflection at 1670 cm^{-1} is caused by valence vibrations of C = O groups.

Table 1. Physical and chemical characteristics of monosubstituted benzoylamidolupinins (I) and their hydrochlorides (II)



I II

№	R	Product Output ,%	Melting point, C (I)	R_f	Melting point, C of hydrochlorides (II)
I	p-CH_3	75,3	115-117	0,76	Hygroscope
II	p-Br	57,6	146-147	0,82	177-178
III	o-CH_3	65,8	114-116	0,44	143-145
IV	o-Br	69,2	105-106	0,72	146-147
V	m-CH_3	59,0	87-89	0,54	142-143
VI	m-Br	72,5	194-195	0,76	200-201

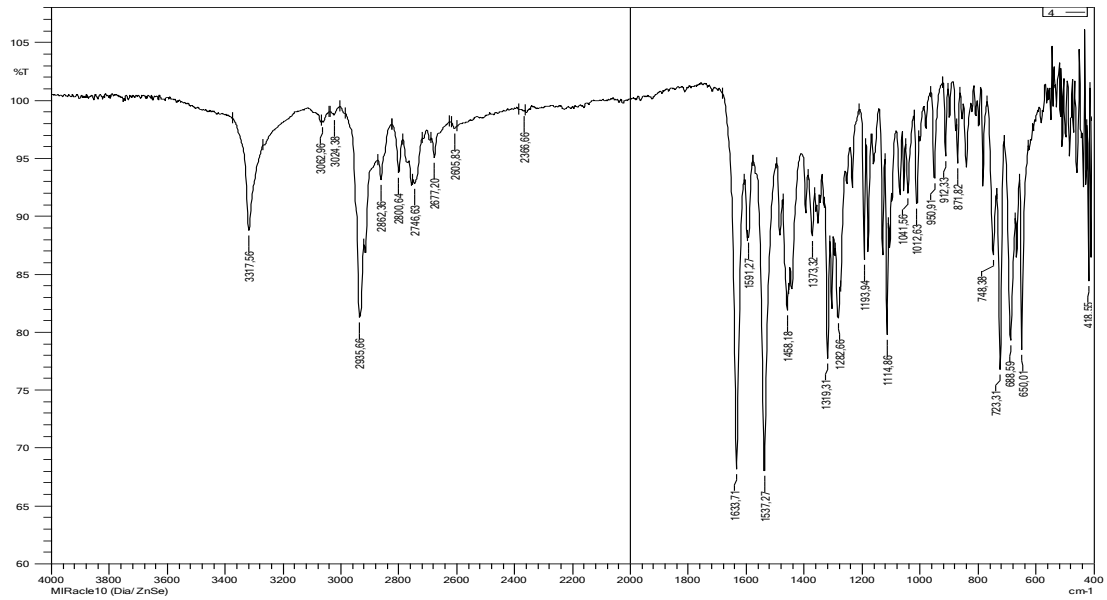


Figure 1. IR spectrum of 2-methylbenzoylamidolupinin (III)

The benzene part of molecule III corresponds to the following absorption bands: absorption bands at frequencies of 3020 cm^{-1}, 3060 cm^{-1}, caused by valence vibrations of the C-H bonds of the benzene ring; the absorption band at a frequency of 1600 cm^{-1} is caused by valence vibrations of the carbon skeleton of the benzene ring and planar deformation vibrations of the CH bonds of the benzene ring; absorption bands at frequencies of 710 cm^{-1}, 680 cm^{-1}, 640 cm^{-1} are caused by out-of-plane oscillations of the bonds of the CH benzene ring; most of the absorption bands between 1200 cm^{-1} and 800 cm^{-1} are also caused by fluctuations in the benzene part of molecule III [6].

In the IR spectrum I, all absorption bands caused by fluctuations in the benzene part of the molecule differ significantly compared to spectra III and V. Consequently, in molecules I, the CH_3 group, apparently through conjugation, strongly affects the electronic structure of the benzene part of molecules I.

The absorption bands caused by the fluctuations of the benzene part of molecule IV differ little from the corresponding absorption bands in spectrum VI, but in the IR spectrum II, these absorption bands differ significantly. Consequently, in molecule II, the bromine atom most strongly affects the electronic structure of the benzene part.

The mass spectroscopic decay of lupinin and epilupinin derivatives, in particular organophosphorus, esters and esters, and a number of other derivatives has been studied in some detail [4,5].

It has been shown that β- or β1-decay is characteristic of the alkaloids of lupinin and epilupinin, as a result of which ions with m/e 111, 110, 97, 83 can be formed directly or subsequently. Ions with m/e 138, 137, 136 can be formed from the molecular ion as a result of decarboxylation.

Indeed, in the mass spectra studied by us there is an intense peak of the molecular ion with m/e 362 and intense peaks of the reduced ions are observed [6-8].

4. Conclusions

Modified derivatives of lupinine with an amide bond have been synthesized on the basis of aminolupinine with chlorohydrides of substituted benzoic acids. Based on a comprehensive physico-chemical study of synthesized compounds, their structure has been established. All the obtained spectra confirm the structure of synthesized benzyl esters of aminolupinin.

The study of the biological properties of synthesized compounds can lead to the creation of new effective drugs that have a certain superiority with known drugs in medicine or in agriculture to increase the yield and quality of crops.

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