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STUDY REACTION OF GOMOVERATRILAMINE WITH GLYCINE

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ABSTRACT
In the work of quantum chemistry, reactions of condensation and cyclization of homoveratilamine with glycine were studied by constructing the energy profile of the reaction. The structure of the synthesized products is compared with the experimentally obtained and calculated IR spectra with the conformity assessment.

KEYWORDS: homoveratrilamin, glycine, condensation, cyclization, quantum chemical calculation, energy profile, IR spectrum.

I. INTRODUCTION
It is known that isoquinoline derivatives evince a variety of biological, including pharmacological activities due to the presence of a variety of pharmacophore groups [1,2,3,4]. Therefore, now a number of compounds with isoquinoline skeleton have now been introduced into pharmaceutical practice for the effective treatment of a variety of pathological conditions [3,4]. In connection with this, the search for new compounds with isoquinoline skeleton is actual from the point of view of searching selectively acting pharmaceutical preparations.

In the planned synthesis of a substance with a given property, a special place occupies the quantum-chemical substantiation of the reaction process, which is unimportant for the synthesis of compounds with isoquinoline skeleton.

It is known in the literature that amino acids contain pharmacophore groups, i.e. exhibit a variety of biological, including pharmacological activities. Introduction of amino acid residues in isoquinoline skeleton gives the selectively influencing compound with pharmacological activity [5]. Therefore, the study of the synthesis of compounds with isoquinoline skeleton implanted amino acid residues is actual in synthetic organic chemistry.
The goal of the work is to study the reaction of homoveratrilamine with glycine and a quantum-chemical investigation of the reaction course.

II. MATERIALS AND METHODS
Homoveratrilamine (HVA), benzoyl chloride for the protection of amino groups, glycine, Bischler-Napiralsky reaction (reaction of condensation and cyclization followed by reduction). PMR, IR and mass spectroscopy, thin layer chromatography (system: chloroform : methanol = 8:1, developer - Dragendroff solution, quantum-chemical calculations using the Gaussian-09 software package.

The reaction of HVA with glycine was studied in [5,6,7], using carbonyl benzoxy chloride as a protective agent. In this case the condensation reaction proceeds with glycine chloroanhydride at -10 to 0 °C for 5 minutes.
In contradistinction to that benzoyl chloride was used as a protective agent.

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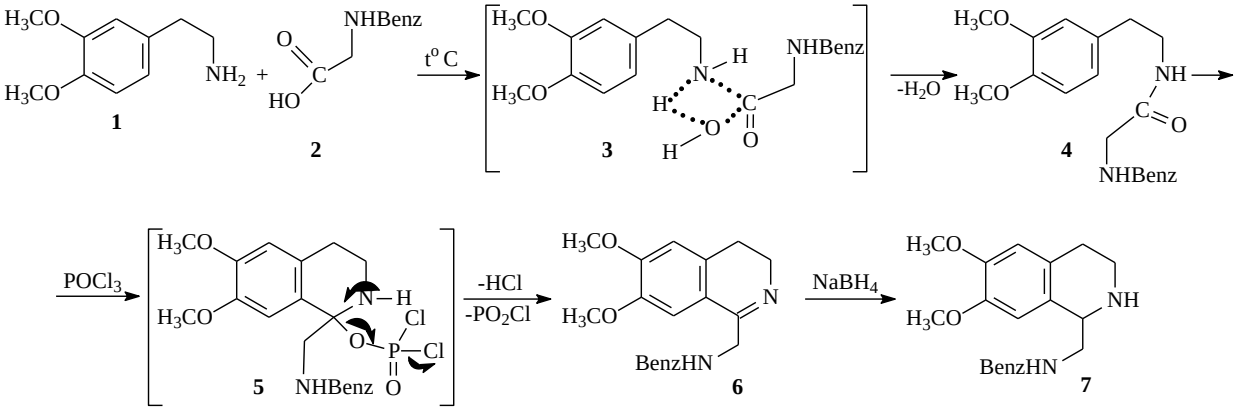
The reactions of HVA with glycine are carried out step by step according to the scheme:



The condensation reactions of HVA with amino group of glycine protected with benzoyl chloride have been carried out at 175-180°C for 2 hours [8,9]. The structure of N- (2- (3,4-dimethoxyphenylethylamino) -2-oxoethyl) benzamide and other products was determined by PMR-, IR- and mass spectroscopy determining the melting point and the R_f value on plates with silica gel LS 5/40 (Czechoslovakia) , using the solvent system chloroform : methanol system = 8:1 (R_f = 0.72 for amide) and chloroform : methanol = 8:1 (R_f = 0.82 for isoquinoline). The yield of amide is 88%, in contrast to work [5] – 62%.

The cyclization reactions have been carried out with the participation of $POCl_3$ for 3 hours. The cyclization product was processed with $NaBH_4$ with the following pulling the protection group off. The yield of N - ((6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-yl) methyline) benzamide is 85%.

We have also studied the course of the reaction of homoveratrilamine with glycine by quantum-chemical methods. For this, a valence-split calculation was used with the help of the basis set VZLYP/6-31G (d, r) by the method of functional density [10,11,12].

III. RESULTS AND DISCUSSION

Energetic and kinetic characteristics of the reactants and products of the reactions N- (2- (3,4-dimethoxyphenylethylamino) -2-oxoethyl) benzamide and the derivative N - ((6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1 -yl) - methylene) benzamide are shown in table 1.

Table 1

Energetic characteristics and rate constant of the reaction of condensation and cyclization of GVA with glycine

N	Energy	Amine	Amide	Isoquinoline
1	$E_{el} + E_0$	-96,23	-288,75	-301,12
2	$E_{el} + E_t$	-96,64	-289,32	-313,46
3	$G = E_{el} + G_t$	-115,29	-369,95	-364,86
4	k_i	$1,56*10^{-38}$	$2,36*10^{-26}$	

From the data in table 1, it is shown that the condensation reaction proceeds under more stringent conditions than the cyclization reactions, and therefore the condensation reaction is limiting in the consecutive reaction studied.

On the basis of quantum-chemical calculations with the use of the TS method, an energy profile is made, i.e. the surface energy potential of the reaction of condensation and cyclization. The energy profile of these reactions in 2D form is presented in Figures 1 and 2.

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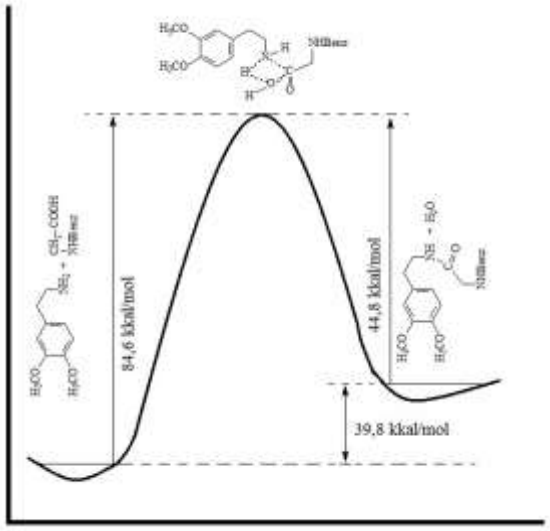

Fig.1. Energy profile of condensation reaction

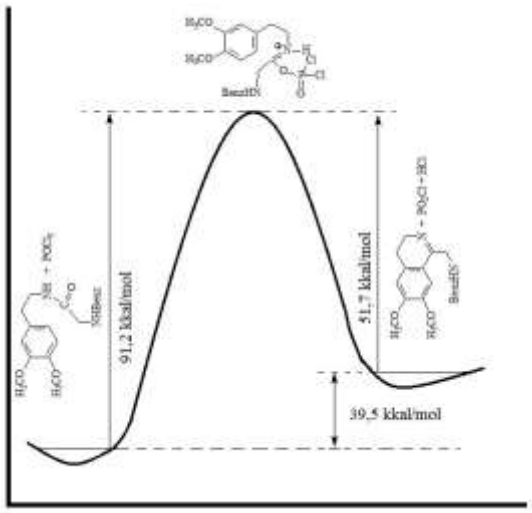

Fig.2. Energy profile of the cyclization reaction

It can be seen from the Figures 1 and 2 that the activation energy is 44.8 kcal/mol for the condensation reaction, 51.7 kcal/mol for the cyclization reaction.

In addition, we have calculated the IR spectra of the products of the reactions: N- (2- (3,4-dimethoxyphenylethylamino) -2-oxoethyl) benzamide and N - ((6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-yl) methelyne) benzamide, which were compared with IR spectra, obtained on «FTIR system 2000» (Perkin-Elmer) in KBr tablets. The IR spectra of the obtained products are shown in Fig. 3 and 4.

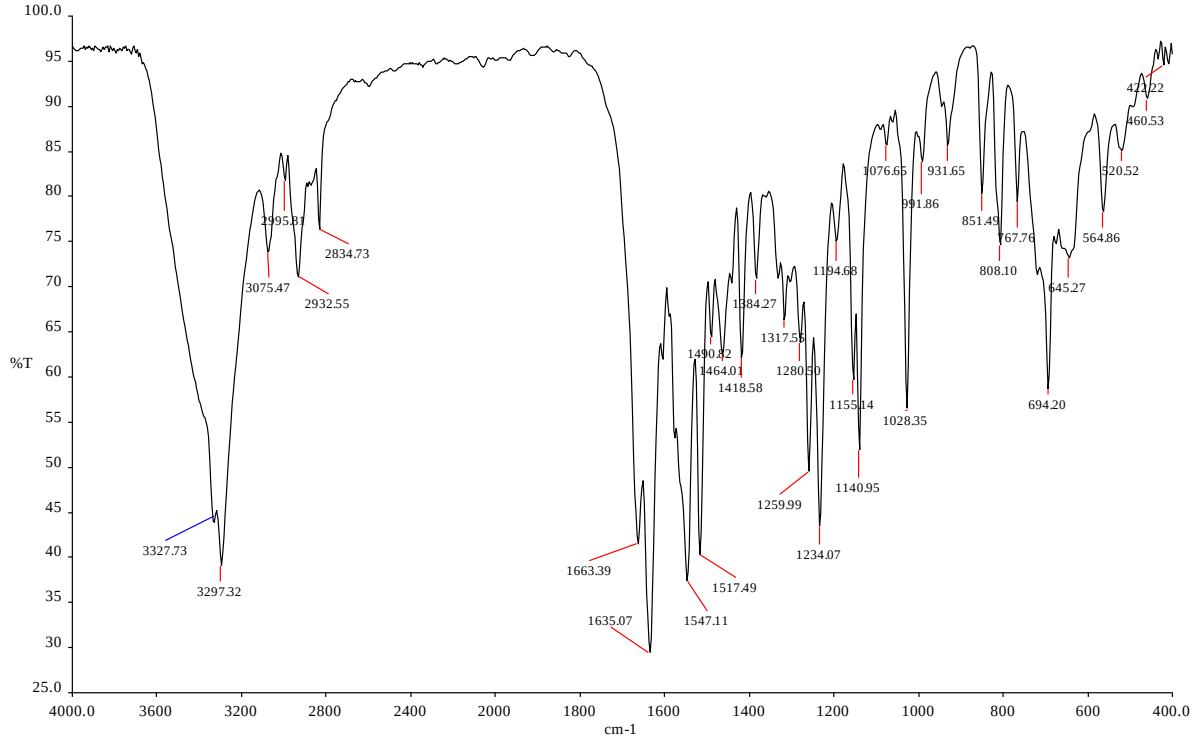

Figure 3. IR spectrum of N- (2- (3,4-dimethoxyphenylethylamino) -2-oxoethyl) benzamide

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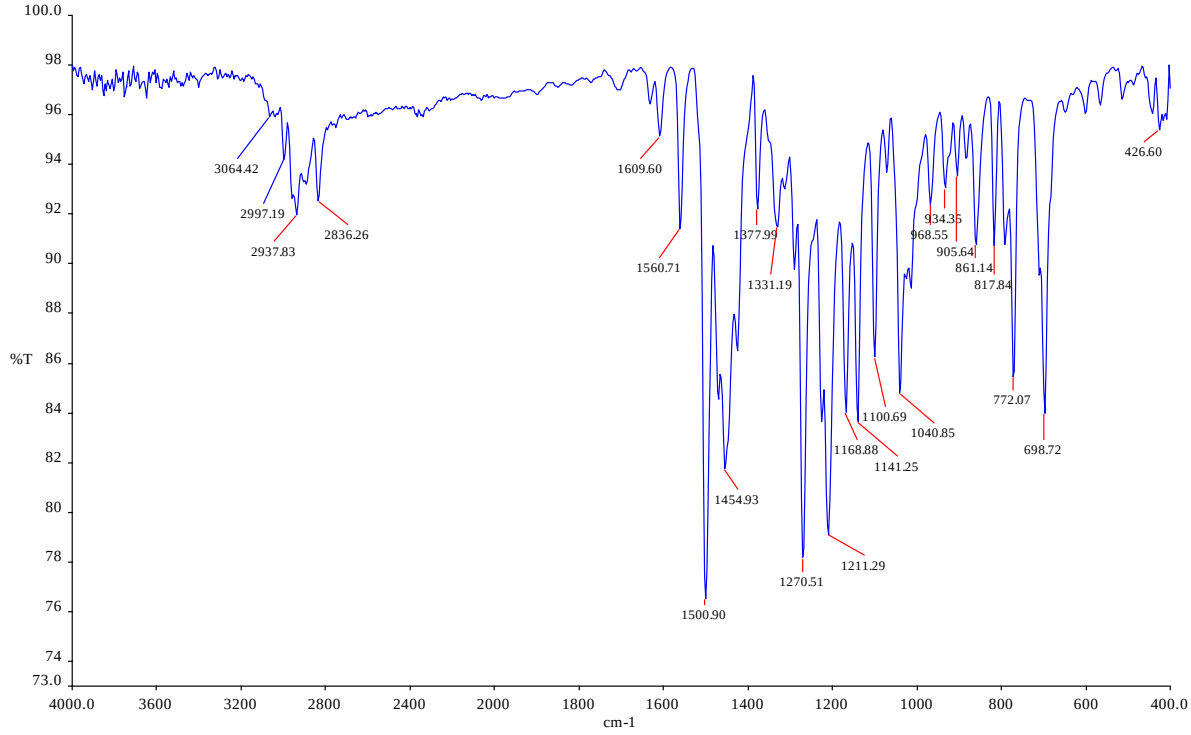

Figure 3. IR spectrum of N - ((6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-yl)methelyne) benzamide

To verify the correspondence between the calculated spectral lines and the experimental ones, the least-squares method was used with the calculation of the correlation coefficient. The value of the correlation coefficient for N- (2- (3,4-dimethoxyphenylethylamino) -2-oxoethyl) benzamide is r = 0.987, and for N - ((6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-yl) methyl) benzamide r = 0.968, which proves the complete correspondence between the calculated spectral data and the experimental data.

Thus, the adequacy of quantum chemical calculations with experimental ones allows to evaluate the course of the reactions of condensation and cyclization of HVA with glycine. The obtained data can be used to carry out the planned synthesis of substances with a given property.

IV. CONCLUSION

1. The reactions of condensation and cyclization of HVA with glycine were carried out obtaining and establishing the structures of the desired products with good yield.
2. The energetic and kinetic characteristics of the reactions of condensation and cyclization of homoveratrilamine with glycine have been studied and compared with experimental data.
3. The adequacy of quantum chemical calculations was confirmed by comparing the correspondence of the calculated IR spectra with the experimental calculation of the correlation coefficient.

V. ACKNOWLEDGEMENTS

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