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SYNTHESIS AND STUDY OF THE REACTION KINETICS OF HOMOVERATRILAMINE WITH BRASSYLIC ACID BY HPLC

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ABSTRACT

In this work, amide, isoquinoline were synthesized and the kinetics of the reaction of homoveratrylamine with brassilic acid was studied by HPLC. The conditions of (high-performance liquid) chromatographic separation were revealed, which allow satisfactory separation of the components of the reaction mixture consisting of reagents, intermediates and products of the reactions of condensation and cyclization. By studying the kinetic laws, it was found that the reactions of condensation and cyclization obey the first-order kinetic equation and the activation energy is, respectively, 172.3 kJ / mol for the amide condensation reaction, and 118.8 kJ / mol for the cyclization reaction.

KEYWORDS: homoveratrylamine, brassilic acid, condensation, cyclization, HPLC, acetonitrile, methanol, intermediate, isoquinoline, tetrahydroisoquinoline, reaction order, activation energy.

1. INTRODUCTION

The synthesis of isoquinoline derivatives is of great theoretical and practical interest in both synthetic organic and pharmaceutical chemistry due to the presence of pharmacophore descriptors [1,2].

Proceeding from this, for many years, research has been carried out on the synthesis of isoquinoline derivatives from homoveratrylamine and carboxylic (mono-, dibasic aliphatic, aromatic and heterocyclic) acids [3-7]. The structure of which was established using spectral and X-ray diffraction methods and entered into the international database of crystal structures [8-10], and also revealed cytotoxic, antifungal, antimicrobial, cardiotropic and antiarrhythmic activity [11-15]. On the other hand, high performance liquid chromatography (HPLC) as a method of separation and analysis makes it possible to identify the individuality of the components from the reaction mixture and to control the content of each component during the reaction [16]. In this regard, the study of the kinetics of the reactions of condensation and cyclization of the synthesis of isoquinoline derivatives is actual.

This work is a continuation of previous works and is devoted to the study of the kinetics of the synthesis of N^1,N^{13}-bis(3,4-dimethoxy-β-phenylethyl)brassyldiamide and 1,11-bis(6,7-dimethoxy-1,2,3,4-tetrahydroiso-quinolin-1-yl) undecane by HPLC.

2. MATERIALS AND METHODS

Homoveratrylamine and brassilic acid were used as materials for the synthesis. To establish the structures of the synthesized compounds, the NMR, IR spectrometer and HPLC were used.

To synthesize the above-shown derivatives, the interaction of homoveratrylamine (1) and brassilic acid according to the scheme was studied [14]:

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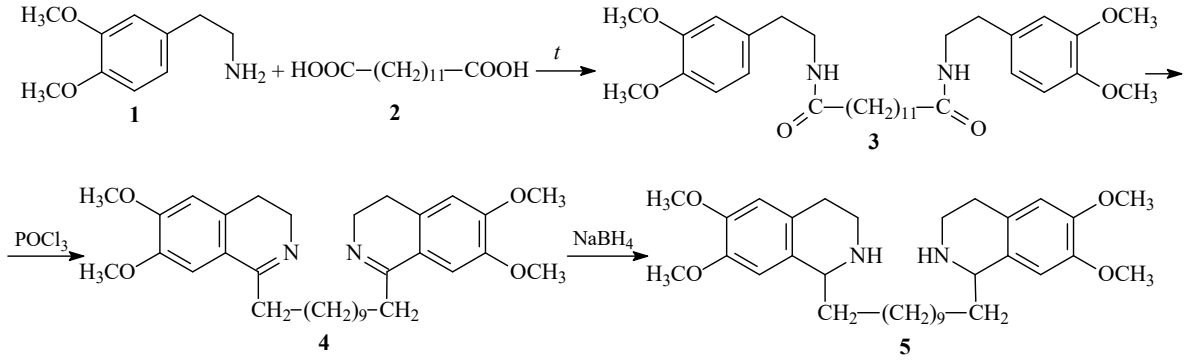

At the first stage, by heating homoveratrylamine (1) with brassilic acid (2) at 178°C for 4 hours amides (3) were prepared with 91% yield. Cyclization reaction (3) was carried out in the presence of $POCl_3$, using it as a hygroscopic reagent and as a solvent for 6 hours. By the reduction of $NaBH_4$ to 3,4-dihydroisoquinoline (4) gave the target tetrahydroisoquinoline (5).

According to the proposed scheme, the reaction of homoveratrylamine with carboxylic acids is complex and consists of reactions of condensation and cyclization. However, it is known from the literature that the rate-limiting stage of the interaction process is the addition of homoveratrylamine with a carboxylic acid, i.e. condensation reaction. Based on the principle of anology, it can be assumed that the reaction we are studying is of the first order [14].

3. RESULTS AND DISCUSSION

IR spectra were recorded on an FTIR system 2000 (Perkin-Elmer) in KBr tablets; 1H NMR spectra were recorded on a UNITY-400 + Varian (400 MHz) (solvent $CDCl_3$, CD_3OD, internal standard-HMDS). The Rf values were determined on silica gel plates LS 5/40 (Czechoslovakia) using a solvent system chloroform: methanol - ratio (8: 1), (4: 1).

The melting points of all synthesized substances were determined on a BOETIUS microtable.

N^1,N^{13}–bis(3,4-dimethoxy-β-phenylethyl)brassyldiamide (3).

A mixture of 0.8 g (4.4 mmol) of homoveratrylamine and 0.58 g (2.4 mmol) of brassilic acid was dissolved in 5 ml of methanol, resulting in spontaneous heating. Then the salt was heated in an oil bath for 4 hours at a temperature of 178°C. HPLC results were analyzed every 30 minutes, the reaction mixture was dissolved in 100 ml of chloroform. Then they were washed with 3% hydrochloric acid solution, 2% NaOH solution and water until neutral. Excess chloroform was distilled off, and the residue was crystallized from acetone. The crystals obtained were filtered off. The yield was 91% (1.15 g), m.p. 160-162°C (acetone), R_f 0.77, (system of chloroform: methanol 8:1).

IR spectrum (film, v, cm-1): 3304 (NH), 2919, 2850 (Ar-C), 1639 (N-C = O), 1547, 1519, 1470 (C = C). 1H NMR spectrum (400 MHz, CD3OD, ppm, J / Hz): 0.63 (2H, m, H-7"); 1.22 (10H, br.s, H-4", 5", 6", 8", 9", 10"); 1.50 (4H, t, J = 7, H-3", 11"); 2.07 (4H, t, J = 7.6, H-2", 12"); 2.67 (4H, t, J = 7, H-α); 3.32 (4H, q, J = 7, H-β); 3.73 (6H, s, OCH3); 3.76 (6H, s, OCH_3); 6.68 (2H, dd, J = 2, 8, H-6,6'); 6.76 (2H, d, J = 2, H-2,2'); 6.79 (2H, d, J = 8, H-5,5').

1,11-bis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-yl)undecane (4), $C_{33}H_{42}N_2O_4$.

1.5 ml of $POCl_3$ was added to 0.5 g (0.88 mmol) (3) of brassilic acid diamide and boiled in a water bath for 6 hours under reflux. The HPLC results were analyzed every 30 minutes. The progress of the reaction was monitored by TLC. Ice was added to the reaction mixture and it was alkalized by 25% NH4OH solution to pH = 9 and was extracted with chloroform, the residue after distillation of CHCl3 was dissolved in 40 ml of methanol. 0.05 mol of NaBH4 was added to the resulting solution at a temperature of 0 - 5°C portion-wise. Methanol was distilled off, the residue was dissolved in water and extracted with chloroform. The residue after removal of chloroform was crystallized from acetone. The yield was 87% (0.41 g), R_f 0.44, mp. 115-117°C (acetone), (system of chloroform: methanol 4: 1).

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IR spectrum (KBr, v, cm-1): 3456, 2929, 2854, 2786, 1613, 1519, 1463. 1H NMR spectrum (400 MHz, CDCl3, ppm, J/Hz): 1.25-1.37 (14H, m, H-4", 5", 6", 7", 8", 9", 10"); 1.46 (4H, m, H-3", 11"); 1.88 (4H, m, H-2", 12"); 2.86-3.05 (4H, m, H-4,4'); 3.25, 3.48 (each 2H, m, H-3,3'); 3.79 (12H, s, OCH_3); 4.33 (2H, t, J = 6, H-1,1'); 6.57* (2H, s, H-8,8'); 6.59* (2H, s, H-5,5').

Separation of the reaction mixture into components was carried out on Shimadzu LC20 liquid chromatograph with a UV detector. Detection was carried out at a wavelength of 210 nm. The sorbent was Exlipse XDB C-18, the particle size was 5 µm. The size of the chromatographic column was 4.6x150 mm. The volume of the mobile phase in the column was taken to be equal to the retention volume of sodium nitrite. As an eluent an acetonitrile - methanol mixture in a volume ratio of 50:50 was used. Elution was carried out in an isocratic mode, the flow rate was 0.5 ml/min. Sorbate solutions (concentration 10-4 mol/l) were prepared by dissolving individual samples in the corresponding mobile phase, the sample was injected in an amount of 1 µL.

The identification of the components of the reaction mixture was carried out by the "comparison" method. For this, the initial reagents and purified products were individually chromatographed with the determination of the retention characteristics.

As a result of identification, the individual composition of the reaction mixture was established, the chromatogram of which is shown in Fig. 1, 2.

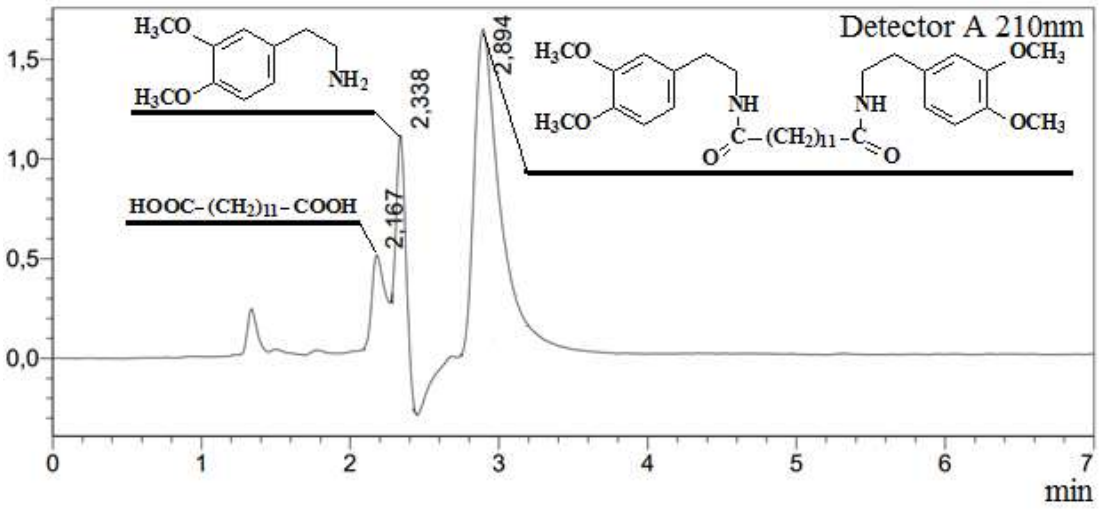

Fig. 1. Chromatogram of the reaction mixture for amide synthesis

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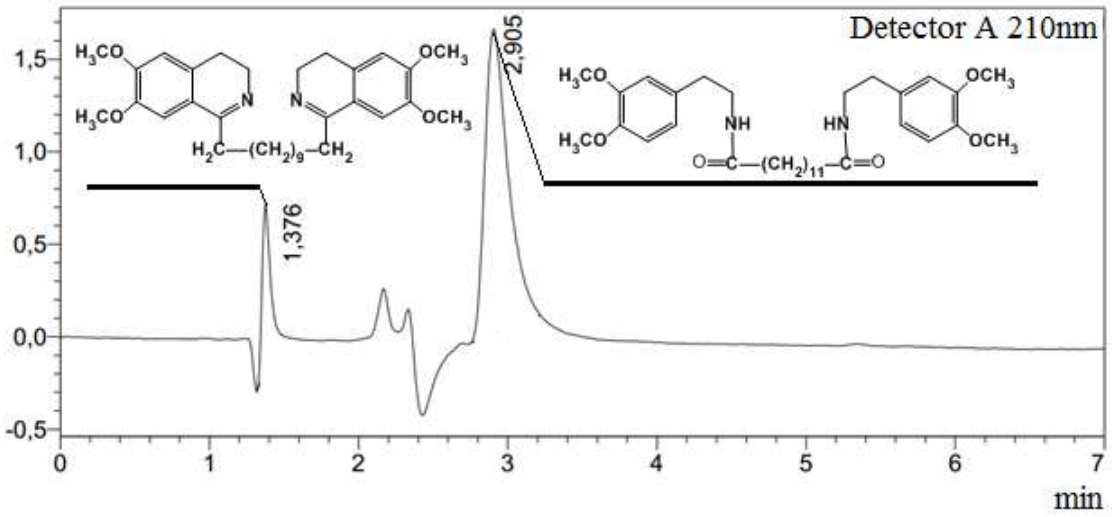

Fig. 2. Chromatogram of the reaction mixture for the synthesis of dihydroisoquinoline

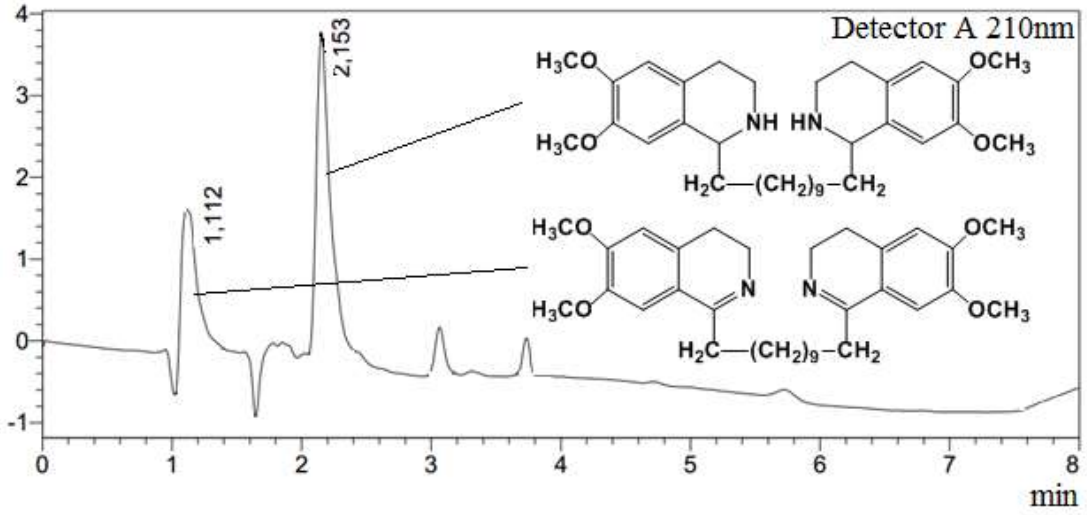

Fig. 3. Chromatogram of the reaction mixture for the synthesis of tetrahydroisoquinoline

To study the kinetics of the condensation reaction, the samples were taken from the reaction mixture every 30 minutes and the results were analyzed by HPLC. The amount of substances from the chromatogram was determined by the method of absolute calibration, which is proportional to the peak area. The results are shown in table. 1.

Table 1. Kinetics of the product formation in condensation reaction (t = 178°C)

τ, min.	S, мм^2	lnS
30	-	
60	3119	8,565
90	5627	8,670
120	6546	8,765
150	7060	8,852
180	7406	8,910
210	7600	8,995
240	7672	9,230

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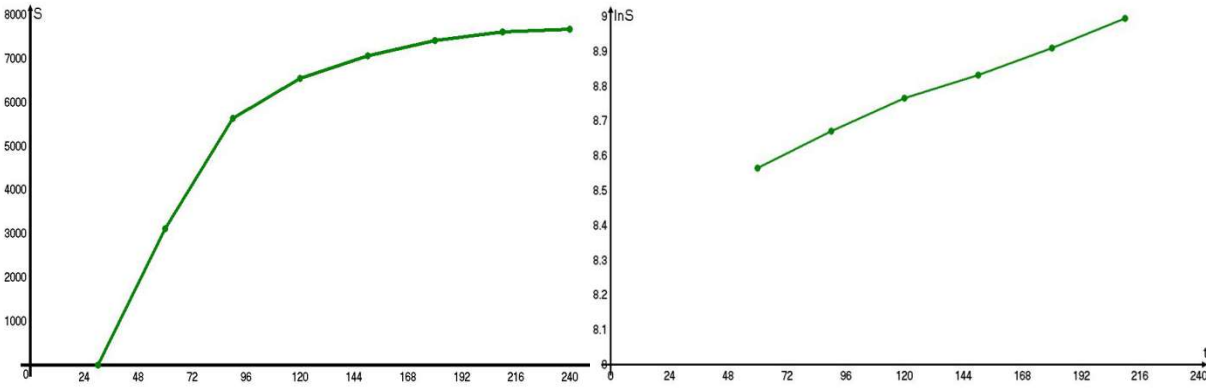
Based on the data shown in Table 1, a graph of the dependence of the amount of product (or peak area) on time was built (Fig. 4).



a ***b***

Figure: 4. The dependence of the reaction rate on concentration (a) and the dependence of the initial rate on concentration in logarithmic coordinates (b).

Thus, a graph of the dependence of S on τ at different temperatures for the condensation reaction and cyclization of homoveratrylamine with brassilic acid has been established.

τ, min.	**S, mm²**	**lnS**
30	4244	8,351
60	6991	8,852
90	9663	9,179
120	11912	9,386
150	15162	9,627
180	17212	9,753

The order of the reaction for the studied stages of the synthesis has been determined. For this, an integral method was used for determining the order of the reaction.
The reaction rate is determined by the equation:

Formulae:

$$\vartheta = k_n C^n, \quad \text{(i)}$$

where C is the equilibrium concentration of homoveratrilamine.

$$lg\vartheta = lgk_n + nlgC. \quad \text{(ii)}$$

Thus, the kinetic curves in (poly) logarithmic coordinates allow to calculate the reaction rate constant.

We have obtained a series of kinetic dependences of the concentration (mol / l) of homoveratrylamine in solution on time for the following ratios of reagents (homoveratrylamine: carboxylic acid) 1:1, 2:1, at a temperature of 20°C.

The reaction order was determined by the differential method:

$$n_i = \frac{\lg(\Delta c_1/\Delta t) - l\ (\Delta c_2/\Delta t)}{lg\ _1 - lgc_2}. \quad \text{(iii)}$$

In this case, the value n_i = 1, i.e. the studied reactions obey the kinetic equation of the first order. In addition to the order, we have determined the activation energy of the reaction, which was calculated using the Arrhenius equation based on the experimentally found values of k_1 and k_2 at different temperatures:

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$$E_{akt} = \frac{R \cdot T_1 \cdot T_2}{T_2 - T_1} ln \frac{k_2}{k_1}. \quad \text{(iv)}$$

The found experimental values for activation energies of the reactions of condensation and cyclization are, respectively, for the condensation reaction E_a = 172.3 kJ/mol and cyclization E_a = 118.8 kJ/mol and correspond to the data of quantum chemical calculations with a deviation of up to 5% [17].
Thus, the following conclusions can be drawn based on the research carried out:

4. CONCLUSION

- The revealed conditions of (High Performance Liquid) chromatographic separation, which allows satisfactory separation of the components of the reaction mixture consisting of reagents, intermediates and products of the condensation and cyclization reaction.
- By studying the kinetic laws, it was found that the investigated reactions of condensation and cyclization obey the first-order kinetic equation and the activation energy is 172.3 kJ/mol for the amide condensation reaction and 118.8 kJ/mol for the cyclization reaction.

5. ACKNOWLEDGEMENTS

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