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Article

Synthesis of Aromatic Amides and Isoquinolines Based on Homoveratrilamine

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Abstract: This paper outlines the synthesis of aromatic amides and isoquinoline derivatives derived from homoveratrylamine. Condensation reactions of homoveratrylamine with cinnamic and mandelic acids gave the corresponding amides in high yields. The cyclization of these amides via the Bischler-Napieralski method facilitated the synthesis of 3,4-dihydro- and tetrahydroisoquinoline derivatives. The synthesized compounds were confirmed through IR and NMR spectroscopy, as well as mass spectrometry. The results highlight the potential of these methods for synthesizing biologically active compounds based on homoveratrylamine.

Keywords: Homoveratrylamine, cinnamic acid, mandelic acid, amide, 3,4-dihydroisoquinoline, tetrahydroisoquinoline, cyclization, Bischler-Napieralski, NMR spectroscopy, mass spectrometry.

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1. Introduction

The synthesis and study of aromatic amides and isoquinolines, in particular those based on homoveratrylamine, is of great importance in modern organic chemistry and pharmaceuticals [1,2]. Heterocyclic compounds such as isoquinolines are widely used in medicine due to their diverse biological activities [3,4]. Isoquinoline derivatives exhibit antioxidant, anti-inflammatory [5], antifungal and antimicrobial properties, making them promising candidates for the development of new drugs [6-8].

Homoveratrylamine, a dimethyl derivative of dopamine, is also of interest due to its properties related to the effect on the central nervous system [9]. Compounds based on it are being studied for the treatment of serious diseases such as Parkinson's disease and heart failure [10]. In addition, these compounds exhibit hemostatic and anti-inflammatory properties, making them important in medicine [11].

Despite active research in this area, the synthesis of new amide and isoquinoline derivatives based on homoveratrylamine with improved properties remains an urgent task [12-14]. Obtaining such compounds and studying them can open up new possibilities for use in pharmaceuticals, especially for the development of effective drugs with minimal side effects.

Thus, the study of the synthesis of amides and isoquinolines based on homoveratrylamine is an important contribution to the development of the chemistry of biologically active compounds and has prospects for implementation in medical practice.

The aim of this work is to develop methods for the synthesis of aromatic amides and isoquinolines based on homoveratrylamine, as well as to study their structure and properties.

Materials and methods of the study. The following reagents were used for the synthesis of aromatic amides and isoquinolines based on homoveratrylamine: homoveratrylamine – the starting material for the synthesis of amides; cinnamic acid, mandelic acid – carboxylic acids used in condensation reactions; methanol, chloroform, acetone, hexane – solvents used for reactions and purification of products; $POCl_3$ (phosphoryl chloride) – an agent for amide cyclization by the Bischler-Napieralski method; $NaBH_4$ (sodium borohydride) – a reducing agent for obtaining tetrahydroisoquinolines; Hydrochloric acid salt, sodium hydroxide – solutions for washing organic layers and equipment: IR spectra were recorded on an FTIR system 2000 instrument (Perkin-Elmer, USA) in tablets with KBr; ^{1}H and ^{13}C NMR spectra were recorded on JNM-ECZ600R spectrometers (JEOL, Japan) ($CDCl_3$ solvents, solvent signal for chemical shifts ^{1}H NMR internal standard - TMS (δ 0.00 ppm) and for chemical shifts ^{13}C NMR ($CDCl_3$ - 77.16 ppm)). The *Rf* value was determined by TLC in silyfol L/W (10x20 cm) with (254 nm) were used to control the purity of the compounds. The melting point of all synthesized compounds was determined using a Stuart SMP20 instrument with an accuracy of ± 0.1°C.

Method of amide synthesis: 1 mole of homoveratrilamine and 1 mole of aromatic carboxylic acids solution and 5 ml of methanol. Then heat the mixture to 180°C for 2 minutes. The progress of the reaction was monitored by TLC. The reaction mixture is dissolved in 100 ml of chloroform. The layer of chloroform is first washed with a 3% solution of hydrochloric acid and hydrogen, then with a 2% solution of sodium hydroxide and hydrogen to a neutral reaction. Poluchennyy chloroformnyy rastvor sushili nad Na2SO4 i parivali. Acetone-hexane trace mixture with residual crystallisation.

N-(3,4-dimethoxyphenylethyl)-cinnamic amide, $C_{19}H_{21}O_3N$ (4) 2.005 g (0.011 mmol) of homoveratrylamine and 1.6 g (0.011 mmol) of cinnamic acid. Yield 81% (2.27 g), mp 121-122°C (acetone), R_f 0.82 (chloroform:methanol - 8:1).

^{1}H NMR spektrum: (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.78 (2H, t, J=6.9; H-α); 3.57 (2H, m, H-β); 3.78 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 6.20 (1H, broad.s, NH); 6.36 (1H, d, J=5.6 H-1); 6.68 (2H, d, *J*=6.5 H-2.6); 6.73 (1H, d, J=8, H-5); 7.27 (3H, t, J=3.0 H-3'', 4'', 5''); 7.40 (2H, t, J=3.4 H-2'',6''); 7.59 (1H, d, J=5.6 H-2').

^{13}C NMR spektrum: (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 55.96 C-OCH_3; 55.96 C-OCH_3; 39.97 C-α; 41.31 C- β; 111.44 C-2; 112.02 C-5; 147.76 C-3; 149.07 C-4; 120.12 C-6; 120.74 C-6'', 129.96 C-1; 131.12 C-1'', 166.3 C=O; 131.29 C-2'', 131.29 C-6'', 134.70 C-3'', 134.70 C-5'', 141.73 –CH=1'; 35.20 =CH-2'.

Mass spectrum: m/z 311(312)M^+ 218, 165, 112, 60.

N--(3,4-dimethoxyphenylethyl)-2-hydroxy-2-phenylacetamide, $C_{18}H_{21}NO_4$ (5a,b) 1.08 g (0.06 mmol) of homoveratrylamine and 0.97 g (0.063 mmol) of mandelic acid. Yield 75% (1.51 g), mp 105-106°C (benzene), R_f 0.61 (chloroform:methanol - 7:0.5). A mixture of two isomers was obtained.

^{1}H NMR spektrum: (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.68 (2H, m, H-β); 3.45 (2H, m, H-α); 3.77 and 3.79 (overall 3H, s, OCH_3); 3.81 and 3.83 (overall 3H, s, OCH_3); 4.91 and 4.93 (overall 1H, broad.s, H-7); 6.21 and 6.31 (overall 1H, broad.s, NH); 6.55 (1H, d, J=8.0, H-6); 6.61 (1H, s, H-2); 6.71 (1H, d, J= 8.1, H-5); 7.30 (5H, m, H-2'',3'',4'',5'',6'').

2-Oxo-2-(phenylethylamino)-1-phenylethylacetamide $C_{20}H_{23}NO_5$ (10)

A mixture of 1 mol 0.94 g (0.02 mmol) of mandelic acid amide and 1 mol 0.3 g (0.28) ml of acetic anhydride was dissolved in 5 ml of benzene. The mixture was then heated. Excess acetic acid was removed. The progress of the reaction was monitored by TLC. The reaction mixture was dissolved in water-extractable chloroform. The resulting chloroform

solution was dried over Na_2SO_4 and evaporated. The residue was crystallized from acetone-hexane mixture. Yield 70% (0.7 g), mp 126-128°C (acetone), R_f 0.76 (chloroform:methanol - 4:1).

^{1}H NMR spectrum: (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 7.34 (5H, m, H-2'-6'); 6.77 (1H, d, J=8.1; H-5); 6.67 (1H, d, J=2.0, H-2), 6.64 (1H, dd, J=8.0, 2.0, H-6), 6.07 (1H, broad.s, NH); 6.02 (1H, s, H-7'); 3.83 and 3.86 (every 3H, OCH_3); 3.52 (2H, m, H-α); 2.76 (2H, m, H-β); 2.10 (H, s, C(O)CH_3).

^{13}C NMR spectrum: (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 21.03 (C-OCH_3), 35.11 (C-α), 40.56 (C-β), 55.94 (C-OCH_3), 56.02 (C-OCH_3), 75.56 (C-2'), 111.40 (C-5), 112.02 (C-2), 120.79 (C-5), 127.42 (C-5', 7'), 128.82 (C-6'), 129.06 (C-7'), 131.08 (C-1), 131.15 (C-8'), 135.55 (C-3'), 147.87 (C-4), 149.20 (C-3), 168.31 (C-8'), 169.18 (OC(O).

6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(phenyl)methanol,$C_{18}H_{19}NO_3$ (7) 0.1 g (0.01 mmol) of mandelic acid amide in 30 ml of anhydrous benzene, 0.4 ml (d=1.64 g/ml) of $POCl_3$ was added. The reaction mixture was boiled for 3 hours under reflux with a $CaCl_2$ tube. The reaction progress was monitored by TLC. After completion of the reaction, benzene and residual $POCl_3$ were removed and the precipitate was crystallized. Yield 52% (0.81 g) T_{mp}=180 °C (acetone), R*f* 0.8 (chloroform:methanol - 4:1).

^{1}H NMR spectrum: (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 7.60 (5H, broad.s, Ar-H); 6.94 (1H, s, H-8); 6.80 (1H, s, H-5); 6.38 (1H, s, H-7); 3.86 (3H, s, OCH_3); 3.83 (3H, s, OCH_3); 3.19 (2H, t, H-4); 3.85 (2H, overlab, H-3).

E-6,7-dimethoxy-1-styryl-1,2,3,4-tetrahydroisoquinoline $C_{19}H_{21}NO_2$ (8).

Obtained from the addition of 1 ml (p=1.64 g/ml) $POCl_3$ in 1.6 g (5.1 mmol) of cinnamic acid amide in 30 ml of absolute benzene. The reaction mixture was boiled for 3 hours with a reflux condenser with a $CaCl_2$ tube. The progress of the reaction was monitored by TLC. After completion of the reaction, benzene and residual $POCl_3$ were removed and the precipitate was crystallized. Yield 67.4% (1.03 g) Tm=143-145°C (acetone), Rf=0.32 (chloroform:methanol - 4:1).

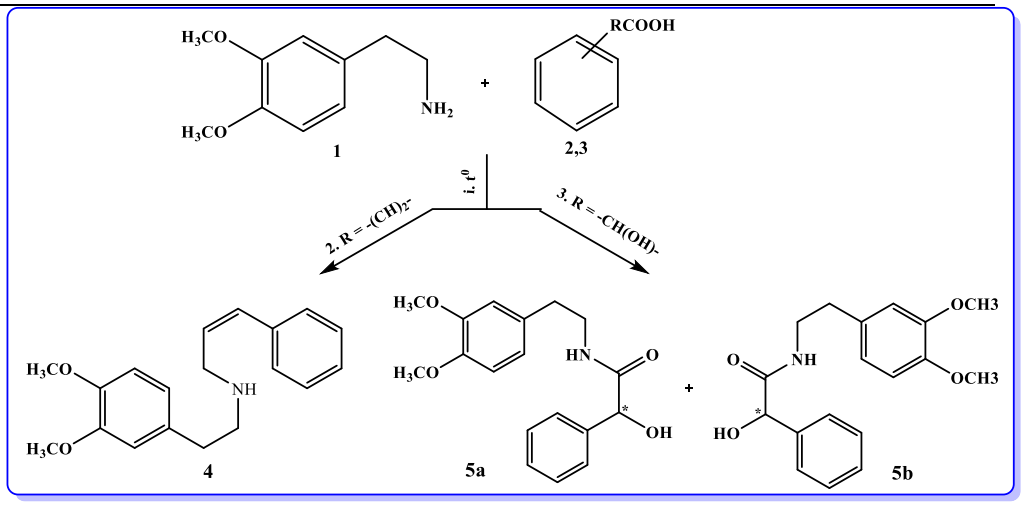
^{1}H NMR spectrum: (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 1,89 (1H, broad.s, NH); 2,71(1H, dt, J=4.9, 16.0; H-4b); 3,27 (1H dt, J=5.3, 12.0; H-4a); 2,85 (1H, dk, J=5.5, 16.0; H-3b); 3,05 (1H. dk, J=4.6; H-3a); 3,77 (3H, s, OCH_3); 3,85 (3H, s, OCH_3); 4,58 (1H, d, J=8.0; H-1); 6,33 (1H, dd, J=8.0; H-9); 6,57 (1H, d, J=16.2, H-10); 6,60 (1H, s, H-5); 6,61(1H, s, H-8); 7,24 (1H, t, J=8.8, H-4'); 7,31 (2H, t, J=7.8, H-3',5'); 7,40 (2H, d, J=7.5, H-2',6').

1-(chloro(phenyl)methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, $C_{18}H_{19}ClNO_2^+$ (11, 12)

Prepared from 0.22 g (0.06 mmol) of mandelic acid acetamide and 0.1 ml (d=1.64 g/ml) of $POCl_3$. Yield 40% (0.51 g) oil, (acetone), Rf=0.66 (chloroform:methanol - 4:1).

^{1}H NMR spectrum: (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.72 (2H, m, H-4); 3.53 (2H, m, H-3); 3.81 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 5.04 (1H, broad.s, H-1); 6.60 (1H, s, H-8); 6.66 (1H, s, H-5); 7.32 (5H, m, Ar-H).

Results and discussion. Condensation reactions of homoveratrylamine with cinnamic and mandelic acids were successful, as confirmed by high yields of synthesized amides and their physicochemical properties. In the first stage of the condensation reaction, homoveratrylamine **1** was thermally heated with cinnamic **2** and mandelic acid **3** for **4** hours in an oil bath at 178 °C. As a result of the reaction, amide 4 was obtained with a yield of 81%. As a result of the reaction with 2-hydroxy-2-phenylethanoic acid 3, a mixture of amide enantiomers was obtained with a yield of 54-62%.



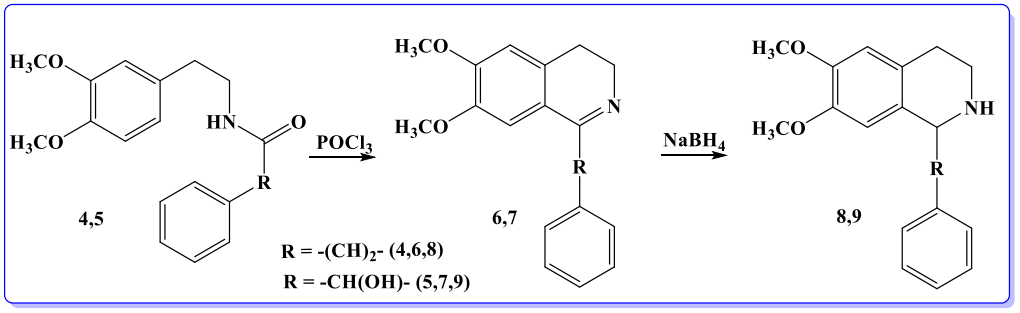
In the ^{1}H NMR spectrum of amides 4,5a,5b obtained as a result of the condensation reaction, the proton of the methylene group (-CH_2-) in the α-state has a resonance at 2.68-2.78 ppm, the proton of the methylene group (-CH_2-) in the β-state is 3.57 ppm was observed as a quartet in the fields. The –OCH_3 groups in the aromatic ring have a length of 3.78 ppm and 3.9 ppm. The protons belonging to H-2, H-5 and H-6 in the aromatic ring are shown in the following field: the doublet of proton H-2 is 6.36 ppm and proton H-5 is 6.73 ppm in the doublet-doublet field and proton H-6 6.68 ppm was observed in the doublet state in the field.

The obtained results confirm the successful course of condensation reactions, which is consistent with the literature data. The methods of synthesis of amides based on homoveratrylamine and carboxylic acids can be successfully applied to obtain compounds with high yields and purity.

The amide cyclization process was carried out using the Bischler-Napieralski method. Amides were reacted with $POCl_3$ followed by reduction to tetrahydroisoquinolines.

The cyclization stage was carried out using the Bischler-Napieralski reaction method. In this case, $POCl_3$ was added to the amide as a water-absorbing reagent, the reaction was heated for 6 hours, and the resulting 3,4-dihydroisoquinolines were reduced to tetrahydroisoquinolines using $NaBH_4$. As a result, tetrahydroisoquinolines were formed with a yield of 52-67.4%.

The reaction was carried out according to the following scheme:

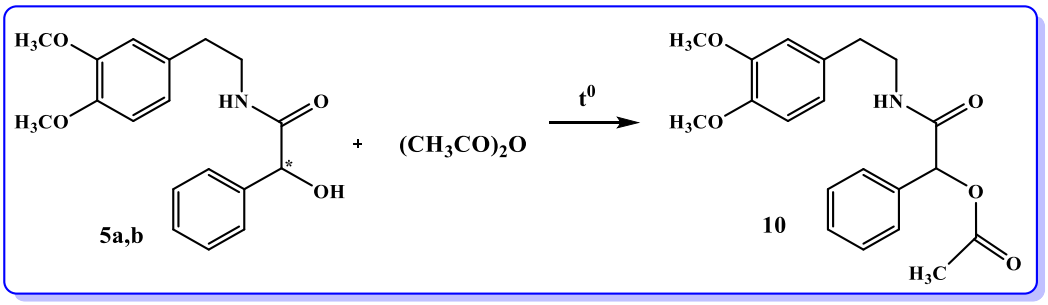


Cyclization of amides using $POCl_3$ gave 3,4-dihydroisoquinoline in 52% yield, which was then reduced to tetrahydroisoquinoline in 67% yield. The ^{1}H NMR spectrum showed key signals confirming the structure: the methylene proton (-CH_2-) in the α-position was observed at 2.72 ppm; the aromatic ring proton H-5 gave a singlet at 6.60 ppm; and the H-8 proton gave a singlet at 6.61 ppm.

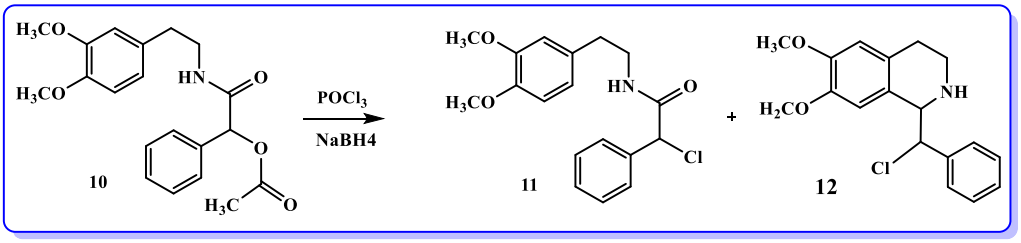
The results confirm the successful cyclization of amides to give isoquinoline derivatives. The introduction of $POCl_3$ facilitated the efficient cyclization, although optimization of the reaction conditions can improve the yield of the products. The reduction of dihydroisoquinolines to tetrahydroisoquinolines using $NaBH_4$ also occurred in high yields, indicating that this method is promising for the synthesis of similar compounds.

The structure of the synthesized amides and isoquinolines was confirmed by NMR

spectroscopy and mass spectrometry. In the ^{1}H NMR spectra, the key signals of methylene and methoxy groups confirmed the structure of the synthesized compounds. Mass spectrometric analysis also confirmed the molecular weights of the synthesized amides and isoquinolines. The hydroxyl group in the mandelic acid amide was converted into an acyl product by acylation.



The second stage of cyclization was carried out by the Bischler-Napieralski reaction. In this case, $POCl_3$ was added to the amide as a water-absorbing reagent, the reaction was heated for 6 hours, and the resulting 3,4-dihydroisoquinoline was returned to tetrahydroisoquinoline using $NaBH_4$.



After the hydrolysis process, the -OH group was formed instead of the acetyl group. The -OH group was replaced by Cl and an amide was formed. The amide was cyclized to give 70% (*R*)-2-chloro-N-(3,4-dimethoxyphenethyl)-2-phenylacetamide and 29% 1-((*R*)-chloro(phenyl)methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was formed.

Conclusion.

In the course of the study, a method for the synthesis of aromatic amides and isoquinoline derivatives based on homoveratrylamine was developed and implemented. Condensation reactions with cinnamic and mandelic acids allowed obtaining amides (81% and 75%, respectively) with high yields and purity. An important stage of the work was the cyclization of amides by the Bischler-Napieralski method, which led to the formation of 3,4-dihydro- and tetrahydroisoquinolines, which is confirmed by high yields and successful identification of structures using NMR and IR spectroscopy.

The results obtained demonstrate that the proposed synthesis methods are effective and can be used to obtain various amide and isoquinoline derivatives, which are of interest as potential biologically active compounds. These compounds can find application in medicine for the development of new drugs, especially in areas related to the treatment of neurological and cardiovascular diseases.

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