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# ILMIY AXBOROTNOMA

## НАУЧНЫЙ ВЕСТНИК
## SCIENTIFIC JOURNAL

## ANIQ VA TABIIY FANLAR SERIYASI

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# STUDY OF THE REACTIONS OF SYNTHESIS OF 2-BENZYL-6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISOCHINOLINE DERIVATIVES

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**Abstract.** The formation of 2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline through stepwise synthesis reactions involving homoveratrylamine and p-nitro-, m-bromo-, o-methoxybenzaldehyde is described. The reaction stages include imine formation using a Dean-Stark apparatus, reduction in the presence of sodium borohydride, and cyclization in the subsequent stage in the presence of formalin and concentrated hydrochloric acid. The structure of the products was determined based on $^1$H NMR spectral results. This work is significant for the efficient synthesis of isoquinoline derivatives and obtaining their pharmacologically promising analogues.

**Keywords:** isoquinoline; homoveratrylamine; p-nitrobenzaldehyde, m-bromobenzaldehyde, o-methoxybenzaldehyde; benzaldehyde; cyclization; organic synthesis.

## 2-benzil-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin hosilalari sintez reaksiyalarini o‘rganish

**Annotatsiya.** Gomoveratrilamin va *p*-nitro, *m*-brom, *o*-metoksibenzaldegid ishtirokida bosqichma-bosqich olib borilgan sintez reaksiyalari natijasida 2-benzil-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin hosil qilinishi bayon etilgan. Reaksiya bosqichlari Dean–Stark nasadkasi yordamida imin hosil qilish, natriy borgidrid ishtirokida qaytarilish va keyingi bosqichda formalin hamda kontsentratsiyalangan xlorid kislotasi ishtirokida siklizatsiya reaksiyalaridan iborat. Mahsulotlarning tuzilishi $^1$H YaMR spektrlari natijalari asosida o‘rnatildi. Ushbu ish izoxinolin hosilalarining samarali sintezi va ularning farmakologik jihatdan istiqbolli analoglarini olish yo‘lida muhim ahamiyatga ega.

**Kalit so‘zlar:** izoxinolin; gomoveratrilamin; *p*-nitrobenzaldegid, *m*-brombenzaldegid, *o*-metoksibenzaldegid benzaldegid; siklizatsiya; organik sintez.

## Изучение реакций синтеза 2-бензил-6,7-диметокси-1,2,3,4-тетрагидроизохинолиновых производных

**Аннотация.** Описано образование 2-бензил-6,7-диметокси-1,2,3,4-тетрагидроизохинолина в результате поэтапных реакций синтеза с участием гомовератриламина и п-нитро-, м-бром-, о-метоксибензальдегида. Этапы реакции включают формирование имина с помощью насадки Дина-Старка, восстановление в присутствии борогидрида натрия и циклизацию на последующем этапе в присутствии формалина

и концентрированной соляной кислоты. Структура продуктов установлена на основе результатов спектров $^1$H ЯМР. Данная работа имеет важное значение для эффективного синтеза производных изохинолина и получения их фармакологически перспективных аналогов.

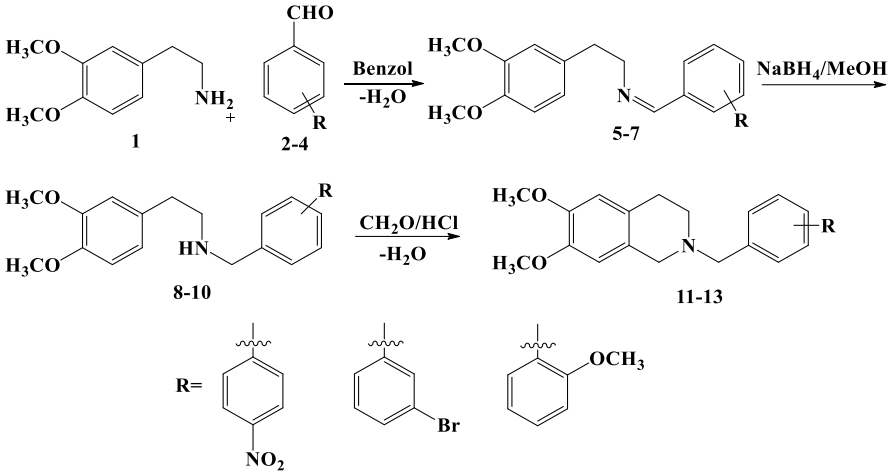
**Ключевые слова:** изохинолин, гомовератриламин, п-нитробензальдегид, м-бромбензальдегид, о-метоксибензальдегид бензальдегид, циклизация, органический синтез.

**Introduction.** One of the most common among alkaloids is the isoquinoline series, which is divided into more than 20 groups according to their structure [1,2,3] and each has its own specific pharmacological effect: for example, simple isoquinolines have a hemostatic effect, benzylisoquinolines - a spasmolytic effect, 1-arylizoquinolines - an analgesic effect [4, 5]. Even small changes in the molecule can give new therapeutic properties. Therefore, the search for isoquinoline derivatives and their synthesis remains relevant.

The isoquinoline alkaloid was first isolated in its pure form from the quinoline fraction of coal tar. These alkaloids rank second after indole in terms of specificity [6,7]. Their biogenetic precursors are phenylalanine and tyrosine. Isoquinoline alkaloids are divided into several groups: simple isoquinolines (for example, salsalin), 1-benzylisoquinolines (papaverine, drotaverine), aporphins (glaucin), indolo[2,1-a]isoquinolines (cryptaustolin), phenanthrenizoquinolines (morphine), etc. [8, 9, 10, 11]. Plants containing these alkaloids have been used in medicine since ancient times: poppy, barberry, ipecac, salsolidine, and others. Among the synthetic drugs derived from this series of alkaloids, papaverine and drotaverine are the most commonly used antispasmodics [12, 13, 14]. In this context, studying the structure and reactivity of isoquinolines, as well as synthesizing their new derivatives based on existing reagents, is considered important.

**Discussion of the obtained results.** As evident from the above data, aldehydes have been underutilized in the synthesis of tetrahydroisoquinolines. However, heterocycles form the basis of numerous pharmacologically active compounds. Therefore, we focused on attaching aromatic rings with various substituents to the isoquinoline skeleton (at position 1). In our view, this approach could potentially serve as a source of new biological activity. In the synthesis of N-heterocycles, tandem reactions are frequently employed. According to literature analysis, simple isoquinoline alkaloids are particularly relevant from a pharmacological perspective. This work is a continuation of our previous research, with 3,4-dimethoxy-β-phenylethylamine (homoveratrylamine) selected as the primary starting material. Condensation reactions with benzaldehyde derivatives were conducted under Bischler-Napieralski reaction conditions.

Homoveratrylamine and an equivalent amount of benzaldehyde derivative were dissolved in benzene, and a Dean-Stark apparatus and a reflux condenser were installed on the flask. The mixture was refluxed at the boiling point of benzene for 2.5 hours and monitored by TLC every hour. After the reaction was complete, the solvent was distilled off, and the flask was dried under vacuum. The resulting imine was dissolved in methanol and poured into an ice-cold beaker. Then, $NaBH_4$ was added in portions over 1 hour to carry out the reduction. Methanol was distilled off, and the product was extracted with chloroform and water. The solvent was evaporated from the chloroform layer, and the resulting secondary amine underwent cyclization with formalin and concentrated HCl for 3 hours. Excess formalin was distilled off and extracted with chloroform. The resulting 6,7-dimethoxy-2-benzyl-1,2,3,4-tetrahydroisoquinoline was dried and crystallized in acetone. The chemical structure of the obtained product was determined using 1H NMR spectroscopy (Scheme 1).




**Scheme 1.** Synthesis of 2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives.

**Table 1.** Formation times and yields of 11, 12, 13.

| Substances | Time | Performances, % |
|---|---|---|
| **11** | 5 h | 61 |
| **12** | 5 h | 70 |
| **13** | 5 h | 54 |

The structure of the obtained substances (**11, 12, 13**) was established using IR, $^{1}H$, $^{13}C$ NMR spectroscopy methods. According to this, a wide singlet for the NH group (1.5-2.1 ppm), triplets for methylene groups (H-α, H-β) (2.7-3.1 ppm), and singlets for methoxy groups (3.75-3.85 ppm) were recorded in all spectra. Aromatic protons are located in the range of 6.6-7.4 ppm, and their interregions and constants confirm the structure of the aromatic ring. In all compounds, protons of H-α and H-β, belonging to 2 methylene groups, were detected in the form of triplets in the range of ~2.7-3.1 ppm. The spin-spin interaction constant (J ≈ 6.9-7.3 Hz) between these triplets corresponds to their typical ethylene chain structure. Protons belonging to methoxy groups were recorded in the range of 3.75-3.85 ppm in the form of specific singlets. The presence of one (3.84 ppm) methoxy group in some compounds and two or three in others is confirmed by a signal in the form of 2 or 3 separate singlets in the spectrum (for example, 3.75, 3.79 and 3.82 ppm). In particular, the protons of H-2, H-5, H-6 are located around 6.64-6.79 ppm, indicating the presence of symmetric aromatic systems interrupted by the spin-spin interaction between them (J ≈ 1.8-8.1 Hz). The spectra of all compounds have a wide singlet (s) signal of the NH-proton, which is located in the range of 1.5-2.1 ppm. This is due to the labile nature of the proton in forming hydrogen bonds and the influence of its environment. From the spectrum results, we can see that the structure of the substances is correctly demonstrated.

**Exprimental part.** The yield and purity of the compounds were determined using the Shimadzu LC-20 HPLC (Japan) and C18 (Shimadzu LC-20, Japan) instruments. IR spectra were recorded using an FT-IR/NIT Spectrum 3 spectrometer with the ATR system. NMR spectra were recorded on JNM-ECZ400R and JNM-ECZ600R spectrometers (Jeol, Japan) at operating frequencies of 400 and 600 MHz, respectively, for 1H in CDCl3 solutions. TMS (0 ppm) was used as an internal standard in 1H NMR spectra. In the 13C NMR spectra, the chemical shift of the solvent (CDCl3, 77.16 ppm relative to TMS) was used as an internal standard. HR-ESI-MS was recorded on an Agilent Technologies 6420 mass spectrometer with triple LS/MS (electrospray ionization, ESI TIC Scan and CAMAG TLC-MS with ACQUITY QDa detector). IR spectrum was obtained on the "FTIR system 2000" instrument (Perkin-Elmer company) using KBr pellets. Rf values were determined on an LS 5/40 silica gel plate, with benzene:methanol (6:1) used as the mobile phase.

The progress of the reaction and the purity of the resulting compounds were monitored by TLC in various solvent systems using Sigma-Aldrich silufol L/W 10 cm × 20 cm fluorescent indicator 254 nm (Germany). The melting temperatures of all synthesized substances were measured using a Stuart SMP20 microtable apparatus..

*General procedure for the synthesis of 2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives (11,12,13):*

Homoveratrylamine and an equivalent amount of benzaldehyde were placed in a flask. Benzene was added to the mixture. A Dean-Stark apparatus and a reflux condenser were attached to the flask containing the mixture. The mixture was then refluxed at the boiling point of benzene for 2.5 hours. The progress of the reaction was monitored hourly by TLC. After completion, the solvent in the flask was distilled off. Following distillation, the flask was dried under vacuum. The resulting imine was dissolved in methanol, and the flask was placed in an ice bath. Subsequently, a proportional amount of NaBH4 was added in small portions over 1 hour to carry out the reduction. Upon completion of the reduction, methanol was distilled off. The product was then extracted with chloroform and distilled water. The solvent from the extract was distilled off. Formalin and concentrated HCl were added dropwise to the resulting secondary amine, and cyclization was performed for 3 hours. After cyclization, excess formalin was distilled off and the product was extracted with chloroform. 6.7-Dimethoxy-benzyl-1,2,3,4-tetrahydroisoquinoline, formed by distillation of the extract solvent, was dried and crystallized in acetone. The obtained product was analyzed using NMR spectroscopic methods.

**Synthesis of 6,7-dimethoxy-2- (4-nitrobenzyl) -1,2,3,4-tetrahydroisoquinoline, $C_{18}H_{20}N_2O_4$.** 0.2 g of homoveratrylamine and 0.17 g of p-nitrobenzaldehyde were dissolved in 10 ml of benzene, and a Dean-Stark apparatus and a reflux condenser were attached to the flask. The mixture was refluxed at the boiling point of benzene for 2.5 hours and monitored by TLC. The solvent was evaporated, and the flask was dried under vacuum. The resulting imine was dissolved in methanol and transferred to an ice bath. NaBH4 was added in small portions over 1 hour, and the reduction was carried out. Methanol was distilled, and the product was extracted in chloroform and distilled water. The extract solvent was distilled, 4 ml of formalin and 3-4 drops of HCl (conc.) were added to the resulting secondary amine, and it was cyclized for 3 hours. The excess formalin was removed and extracted again with chloroform. The final product - 6,7-dimethoxy-2- (4-nitrobenzyl) -1,2,3,4-tetrahydroisoquinoline - was dried and crystallized in acetone. The reaction yield is 61%. The obtained product was analyzed by methods of TLC, mass spectrum, and $^1$H NMR spectroscopy.

**$^1$H NMR spectrum** (600 MHz, $CDCl_3$, δ, m.f., J/Hz): 1,59 (1H,wide range. -NH); 2,76 (2H, t=6,9, H-α); 2,85 (2H, t=6,9; H-β); 3,84 (1H, s, OCH3); 3,88 (2H, s, CH2); 6,71 (1H dd=1,8, 8,5, H-5); 6.78 1(1H, d=1,8; H-2); 6,79 (1H; d=8,0; H-6); 7,43 (2H; d=8,4; H-2`,3`); 8,14 (2H, d=8,7; H-5`6`).

**Synthesis of 5-N2- (3-bromobenzyl) -6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5b), synthesis of $C_{18}H_{20}BrNO_2$.** 0.4 g of homoveratrylamine and 0.41 g of m-bromobenzaldehyde were dissolved in 20 ml of benzene, and a Dina-Stark nozzle and a reverse cooler were placed in the flask. The mixture was boiled at the benzene boiling point for 3 hours and controlled by TLC. The solvent was distilled, and the flask was dried in a vacuum. The resulting imine was dissolved in methanol and placed in a glass with ice. $NaBH_4$was added in small portions for 1 hour and reduction was carried out. Methanol was distilled, and the product was extracted in chloroform and distilled water. The extract solvent was distilled, 8 ml of formalin and 8-10 drops of HCl (conc.) were added to the resulting secondary amine, and it was cyclized for 2 hours. The excess formalin was removed and extracted again with chloroform. The final product - 2- (3-bromobenzyl) -6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline - was dried and crystallized in acetone. The reaction yield is 70%. The obtained product was analyzed by methods of TLC, mass spectrum, and $^1$H NMR spectroscopy.

**$^1$H NMR spectrum** (600 MHz, $CDCl_3$, δ, m.f., J/Hz): 2,12 (1H,-keng s, NH); 2,77 (2H, t=7,1, H-α); 2,85 (2H, t=7,0; H-β); 3,76 (2H, s, $CH_2$); 3,84 (3H, s, $OCH_3$); 6,71 (1H, d=1,9; H-2); 6,73 (1H, dd=2,81, H-5); 6,79 (1H, d=8,0; H-6); 7,17 (1H, t=7,7; H-5); 6,19 (1H, d=7,7; H-4`); 7,34 (1H, d,t=1,878; H6`); 7,44 (1H, s, H-2`).

**Synthesis of 6,7-dimethoxy-2- (2-methoxybenzyl) -1,2,3,4-tetrahydroisoquinoline (6b), $C_{19}H_{23}NO_3$.** 0.5 g of homoveratrylamine and 0.38 g of o-methoxybenzaldehyde were dissolved in 20 ml of benzene, and a Dina-Stark plug and a reverse cooler were placed in the flask. The mixture was boiled at the benzene boiling point for 3 hours and controlled by TLC. The solvent was distilled, and the flask was dried in a vacuum. The resulting imine was dissolved in methanol and placed in a glass with ice. NaBH4 was added in small portions for 1 hour and reduction was carried out. Methanol was distilled, and the product was extracted in chloroform and distilled water. The extract solvent was distilled, 5 ml of formalin and 5-6 drops of HCl (conc.) were added to the resulting secondary amine, and it was cyclized for 2.5 hours. The excess formalin was removed and extracted with chloroform. The final product - 6,7-dimethoxy-2- (2-methoxybenzyl) -1,2,3,4-tetrahydroisoquinoline - was dried and crystallized in acetone. The reaction yield is 54%. The obtained product was analyzed by methods of TLC, mass spectrum, and $^1$H NMR spectroscopy.

**$^1$H NMR spectrum** (600 MHz, $CDCl_3$, δ, m.f., J/Hz): 1,86 (1H, wide range, NH); 3,01 (2H, m, H-α); 3,07 (2H, t=7,3; H-β); 3,75(3H, s, $OCH_3$); 3,79 (3H, s, $OCH_3$); 3,82 (3H, s, $OCH_3$); 4,12 (2H, t=5,0; $CH_2$); 6,64 (1H, d=1,8; H-6); 6,68 (1H, dd=1,8; 8,1; H-5); 6,74 (1H, d=8,1; H-2); 6,80 (1H, d=7,8; H-3`); 6,90 (1H, t=7,4, H-4`); 7,26 (1H, t=7,6; H-5`); 7,41 (1H, d=7,4; H-6').

**Conclusion.** As a result of the conducted research, the synthesis of 2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives was successfully carried out by stepwise synthesis based on homoveratrylamine and benzaldehyde. The synthesis process included the stages of imine formation, reduction with $NaBH_4$, and cyclization in the presence of formalin. Each stage was monitored using TLC and optimal conditions were selected. The final product was identified by the NMR spectroscopy method, and its structure was confirmed.

This method ensures the effective synthesis of isoquinoline derivatives and can serve as an important basis for the creation of new analogues of biologically active substances in the future. The results will lay the foundation for promising areas of practical importance in the fields of pharmaceutical chemistry and synthetic organic chemistry.

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