COMPREHENSIVE STUDY ON THE OPTIMIZATION OF REACTION PARAMETERS IN THE SYNTHESIS OF QUATERNARY AMMONIUM SALTS VIA NUCLEOPHILIC SUBSTITUTION OF ETHYLENE CHLOROHYDRIN WITH TRIETHYLAMINE

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Abstract. This study presents modern approaches to the investigation of nucleophilic substitution reactions involving tertiary amines. The influence of solvent nature, reagent molar ratio, and reaction time on product yield was systematically evaluated. The interaction of ethylene chlorohydrin with triethylamine resulted in the synthesis of a choline analogue — β-hydroxyethyltriethylammonium chloride. Optimization of reaction conditions was found to significantly increase the product yield. Conducting the reaction at lower temperatures promoted crystallization of the product and led to higher efficiency. The synthesized compound was characterized by IR spectroscopy and recommended for further investigation of its biological activity.

Keywords: Ethylene chlorohydrin, butanol, triethylamine, acetone, ethanol, chloroform, tertiary amines, quaternary ammonium salts.

Annotatsiya. Ushbu ilmiy ishda uchlamchi aminlarning nukleofil almashinish reaksiyalarini o‘rganishning zamonaviy yondashuvlari bayon etilgan. Reaksiya jarayoniga erituvchi tabiatining, reagentlarning stexiometrik nisbatining va reaksiyaning davomiyligining ta’siri tahlil qilindi. Etilenxlorgidrin va trietilamin o‘rtasidagi o‘zaro ta’sir natijasida xolin analogi — β-gidroksietiltrietilammoniy xlorid sintez qilindi. Optimal sharoitlarda reaksiyani olib borish mahsulot unumini sezilarli darajada oshirishi aniqlandi. Past haroratda reaksiyani o‘tkazish mahsulotning kristall ko‘rinishda ajralishiga va yuqori unumlilikka olib kelishi isbotlandi. Olingan birikma fizik-kimyoviy xossalari va IR-spektroskopiya yordamida identifikatsiya qilindi hamda biologik faollik bo‘yicha tadqiqot uchun tavsiya etildi.

Kalit so‘zlar: Etilenxlorgidrin, butanol, trietilamin, aseton, etanol, xloroform, uchlamchi aminlar, to‘rtlamchi ammoniy tuzlari.

Аннотация. В данной работе представлены современные подходы к изучению реакций нуклеофильного замещения третичных аминов. Исследовано влияние природы растворителя, стехиометрического соотношения реагентов и времени реакции на выход продукта. В результате

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взаимодействия этиленхлоргидрина с триэтиламином синтезирован аналог холина — хлорид β-гидроксиэтилтриэтиламмония. Установлено, что оптимизация условий проведения процесса значительно повышает выход целевого соединения. Показано, что проведение реакции при пониженной температуре способствует выделению продукта в виде кристаллической соли и обеспечивает более высокий выход. Полученное соединение идентифицировано с использованием ИК-спектроскопии и рекомендовано для дальнейшего исследования биологической активности.

Ключевые слова: Этиленхлоргидрин, бутанол, триэтиламин, ацетон, этанол, хлороформ, третичные амины, четвертичные аммониевые соли.

Introduction.

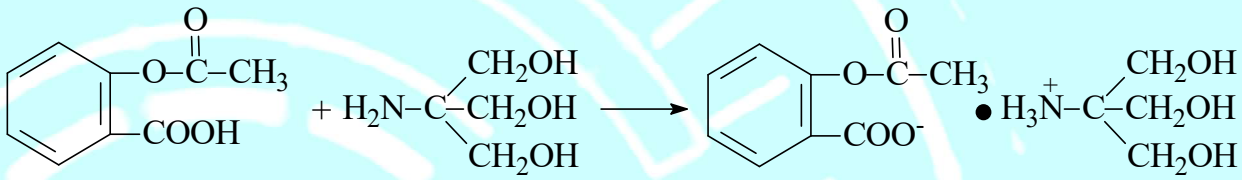
The development and implementation of new catalysts and innovative methods in the synthesis of organic compounds lead to the simplification of technological processes, the creation of more convenient methodologies, the improvement of product yields, and the acceleration of chemical reactions. These advanced approaches can also be successfully applied in the study of nucleophilic substitution reactions involving tertiary amines.

To investigate the interaction between reagents, several groups of structurally related compounds were selected, in which the hydrocarbon fragments within the molecules were systematically varied. These structural factors play a decisive role in determining their reactivity in chemical transformations. In nucleophilic substitution reactions, the reactivity of the amino group is largely controlled by the steric and inductive effects of the substituents attached to the nitrogen atom. [1, 2].

Among the most practically important transformations in organic chemistry are alkylation and acylation reactions. These processes, widely applied both in laboratory and industrial synthesis, introduce alkyl or acyl groups into organic molecules, resulting in electron density redistribution and changes in physicochemical properties of the compounds [3, 4].

One example of such reactions is the synthesis of acetylsalicylate [tris(hydroxymethyl)], a compound exhibiting antipyretic, analgesic, anti-inflammatory, and antiaggregant activities. This substance is highly soluble in water and characterized by low toxicity. Its synthesis is carried out by mixing 13.5 g of acetylsalicylic acid and 9 g of tris(hydroxymethyl)aminomethane in a medium consisting of 9 mL of water and 9 mL of isopropanol, followed by stirring for one hour. The precipitate formed is filtered and washed with 70 mL of isopropanol and 70 mL of ether, resulting in an 85% product yield [5, 6].

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The synthesis of choline analogues derived from tertiary amines was comprehensively investigated through the nucleophilic substitution reaction between ethylene chlorohydrin and triethylamine. Particular attention was given to identifying the optimal reaction conditions that ensure the highest achievable yield of the target β-hydroxyethyltriethylammonium chloride. Since solvent effects play a critical role in determining the efficiency of nucleophilic substitution reactions—primarily through their influence on reagent solubility, ion-pair stabilization, and transition state energetics—the reaction was systematically examined in a range of organic solvents with different physicochemical properties, including polarity and dielectric constant. This approach allowed for the evaluation of how the reaction environment affects both reaction kinetics and product yield.[7,8,9]

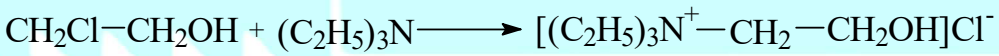
To quantify these effects, a series of controlled experiments was performed under identical temperature and stoichiometric conditions, while only the solvent medium was varied. The experimental results, which reflect the dependence of product yield on the solvent type, are summarized in Table 1.1. Comparative analysis of the obtained data revealed a pronounced increase in yield when the reaction was carried out in ethyl acetate, which may be attributed to improved stabilization of the intermediate quaternary ammonium salt and suppression of competing side reactions. These findings highlight the significant influence of solvent selection on the efficiency of tertiary amine alkylation processes and provide a foundation for further optimization of synthesis parameters.

Table 1.1.

Effect of solvent nature on the yield of β-hydroxyethyltriethylammonium chloride.

№	Ethylene chlorohydrin : triethylamine molar ratio	Solvent	Product yield, %
1.	1:1	Toluol	38
2.	1:1	Xloroform	63
3.	1:1	Etilatsetat	69

As can be seen from the table data, when the reaction was carried out at a 1:1 molar ratio of the reagents, the product yield was 69%.



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Table 1.2.

Influence of reagent molar ratios on the yield of β-hydroxyethyltriethylammonium chloride

№	Ethylene chlorohydrin : triethylamine molar ratio	Solvent	Product yield, %
1.	1:1	Ethyl acetate	69
2.	1:1,5	Ethyl acetate	76
3.	1:2	Ethyl acetate	79

According to the data presented in the table, increasing the molar ratio of ethylene chlorohydrin to triethylamine to 1:2 led to a substantial improvement in the reaction yield, reaching 79%. This enhancement can be attributed to the increased concentration of the nucleophilic reagent, which shifts the reaction equilibrium toward the formation of the quaternary ammonium salt and effectively suppresses competing side processes. These results demonstrate the significant influence of reagent stoichiometry on the efficiency of the nucleophilic substitution reaction.

In order to gain deeper insight into the kinetic behavior of the system, the reaction was subsequently carried out in ethyl acetate using an equimolar (1:1) ratio of the reagents, while extending the reaction time. The objective was to determine whether prolonged reaction duration could compensate for the reduced concentration of triethylamine and thereby enhance product formation. The summarized results of these experiments, which reflect the dependence of product yield on reaction time, are presented in Table 1.3.

Table 1.3.

Effect of Reaction Duration on the Yield of β-Hydroxyethyltriethylammonium Chloride (Solvent: Ethyl Acetate)

№	Ethylene chlorohydrin : triethylamine molar ratio	Reaction time (h)	Product yield, %
1.	1:1	2	69
2.	1:1	4	75
3.	1:1	6	82

According to the data presented in Table 1.3, the yield of the reaction between ethylene chlorohydrin and triethylamine in ethyl acetate at room temperature increases with longer reaction time. It is believed that the yield can be further improved under optimized conditions.

When the reaction was carried out at room temperature, the vessel walls became noticeably warm and white fumes appeared immediately after mixing the reagents. However, when the reaction mixture was cooled in an ice-water bath, the

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product yield increased significantly, and a white crystalline salt — β-hydroxyethyltriethylammonium chloride — was isolated. The obtained salt was placed into a pre-weighed container and stored in a desiccator.

Based on the results of the experiments, it can be concluded that at lower temperatures, the solubility of the salt and the volatility of the reagents decrease, which allows the β-hydroxyethyltriethylammonium chloride to be obtained with higher yield.

Alternative conditions for the synthesis of the compound were also established. The resulting β-hydroxyethyltriethylammonium chloride is a white, crystalline, hygroscopic substance with a melting point of 218–220 °C. To confirm the structure of the obtained product, its IR spectrum was recorded, and the compound was submitted for further study of its biological activity.

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