

SYNTHESIS OF QUATERNARY AMMONIUM SALTS BASED ON ETHYLENE CHLOROHYDRIN AND THEIR MODIFICATION WITH CHITOSAN*Iskandar Allaberdiyev**Research Specialist, Uzbekistan GTL LLC**Baxtiyor Bo'rixonov**Associate Professor (PhD), Department of Inorganic Chemistry, Qarshi State University**Arziqul Panjiyev**Qarshi State Technical University**E-mail: borixonov90@mail.ru*

Abstract: A quaternary ammonium salt was synthesized based on ethylene chlorohydrin. Alternative reaction conditions were studied to optimize the synthesis process. The resulting quaternary ammonium salt was subsequently reacted with chitosan. Given the inherently high biological activity of chitosan, its conversion into a quaternized, positively charged form was found to further enhance its bioactivity. The synthesized compounds were analyzed using physicochemical methods, including IR and ¹H NMR spectroscopy. The obtained data confirmed the successful formation of the quaternary ammonium chitosan derivative.

Keywords: Ethylene chlorohydrin, Chitosan, DMF, Ethanol, Choline, Trabectedin, Solifenacin, Noscipine, Quinapril, IR spectrum, ¹H NMR spectrum

Introduction

N-alkylamines are an important class of chemical compounds widely found in natural products and pharmaceutical agents. These compounds are commonly used as structural components in a wide range of drugs, including antidepressants, analgesics, antibiotics, anticancer agents, and antiviral medications targeting hepatitis C, as well as agrochemicals. [1–2] Among the most well-known N-alkylamines are morpholine [3], piperidine [4], pyrrolidine [5], and piperazine [6].

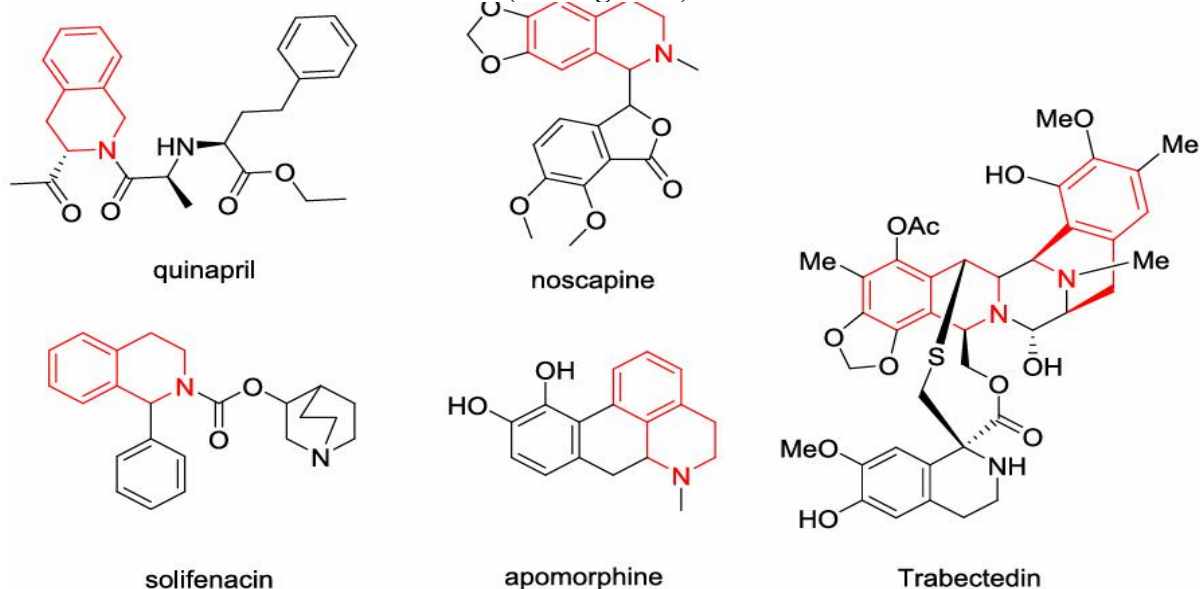
Due to their biological and synthetic relevance, the formation of **C–N bonds** is of great importance in organic chemistry. One of the most frequently used methods for forming C–N bonds is the alkylation of amines using organic halides, which is simple and efficient but often generates large amounts of waste. Alternatively, the catalytic **borrowing hydrogen** methodology using alcohols produces only water as a byproduct, offering a more environmentally benign pathway. [7]

Cancer remains a major public health concern worldwide, posing significant threats to human life and well-being. According to the most recent cancer statistics, cancer has become one of the leading causes of death in China. With a growing and aging population, the cancer burden is expected to increase even further. [8] Thus, the development of antitumor agents continues to be of paramount importance.

Tetrahydroisoquinolines represent a class of nitrogen-containing heterocyclic compounds that are widely distributed in nature and exhibit various biological activities. These compounds are found in numerous clinically used drugs, such as:

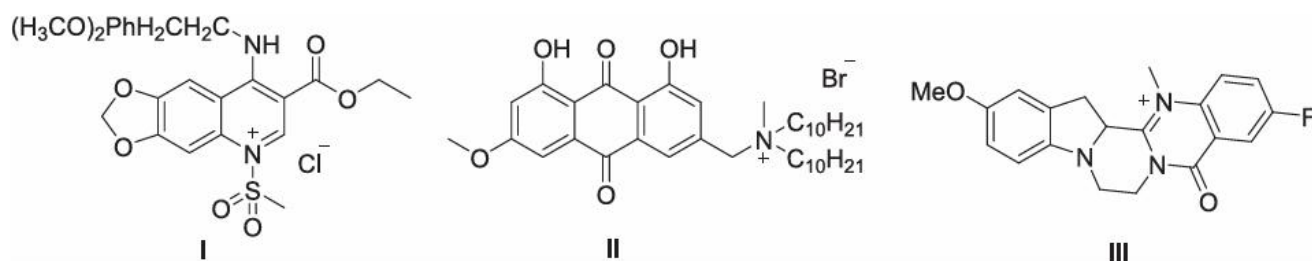
- Quinapril* – an antihypertensive agent
 – *Noscapine* – a cough suppressant
 – *Solifenacin* – used for urological disorders
 – *Apomorphine* – an emetic agent
 – *Trabectedin* – an anticancer drug. [9]

(See Figure 1)



Quaternary ammonium groups are a class of organic compounds that contain positively charged ions. Studies have shown that compounds possessing a quaternary ammonium core structure exhibit significant anticancer activity against tumor cells

(Figure 2).



Materials and Methods

Modern physicochemical techniques were employed to analyze the structural and physical properties of the synthesized compounds. IR spectra were recorded using a Perkin-Elmer Spectrum 2000 FT-IR spectrophotometer in KBr pellets. The ^1H and ^{13}C NMR spectra were

obtained using Unity-400+ (400 MHz) and Jeol-600 (600 MHz) spectrometers with deuterated solvents (CD_3COOD and DMSO-d_6). Tetramethylsilane (TMS) was used as the internal reference (δ -scale).

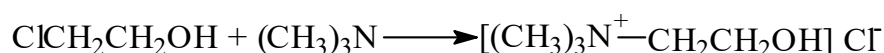
Melting points were determined using a MEL-TEMP apparatus (USA). All synthesis procedures were carried out using thermally and mechanically resistant borosilicate glassware (Borosilicate 3.3 grade).

3. Results and Discussion

3.1. Reaction of Ethylene Chlorohydrin with Trimethylamine

As outlined above, the aim of our study was to synthesize quaternary ammonium salts via the reaction of ethylene chlorohydrin with tertiary amines, investigate their molecular structures, determine their physicochemical properties, and evaluate their potential biological activities.

The first reaction studied was the quaternization of ethylene chlorohydrin with trimethylamine.



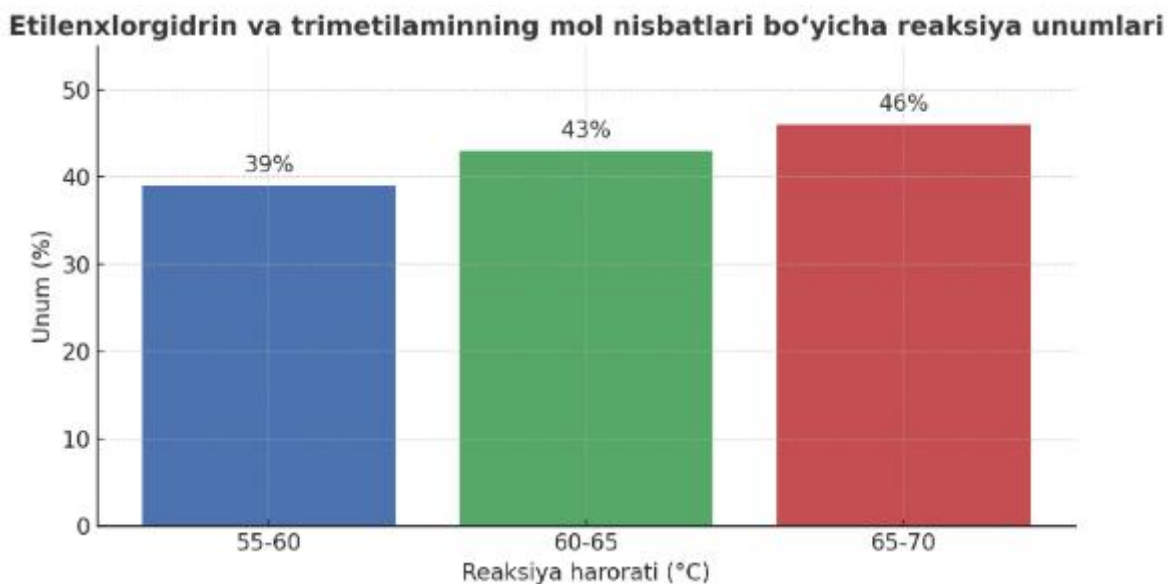
Optimization of Reaction Conditions

To increase product yield and determine optimal reaction parameters, ethylene chlorohydrin was first distilled at 128–129 °C to obtain a purified, reaction-ready form. It was then reacted with a 33% solution of trimethylamine in absolute ethanol at a 1:1 molar ratio.

To study the influence of reaction time and temperature on product yield, reactions were conducted in sealed ampoules at various temperatures for durations of 1 and 2 hours. The corresponding results are summarized in Table

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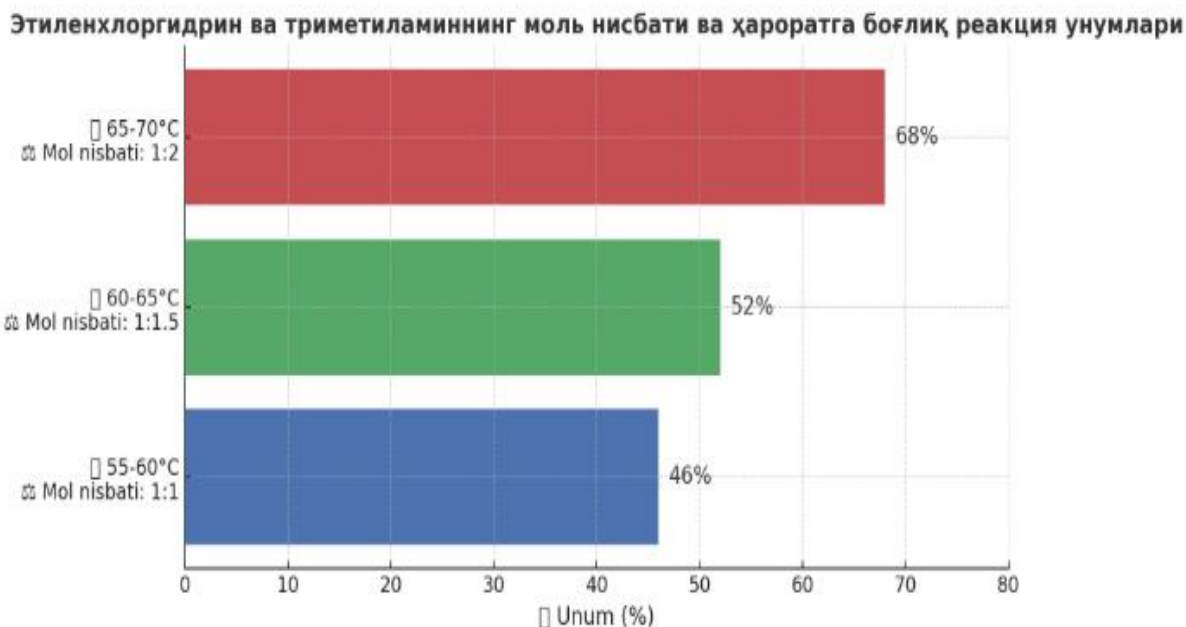
β - Effect of Temperature on the Yield of Hydroxyethyltrimethylammonium Chloride



Influence of Reaction Conditions on Product Yield

When the reaction was performed by directly mixing the reagents at room temperature, the reaction vessel heated up significantly, producing white fumes. Under these conditions, the yield did not exceed 46%. However, when the same reaction was conducted under ice bath cooling, the yield increased to 52%, and a colorless, glass-like crystalline product — β -hydroxyethyltrimethylammonium chloride — was isolated.

To further improve the product yield, the reaction was optimized based on literature data. Specifically, 1.7 ml of ethylene chlorohydrin was mixed with 4.6 mL of a 33% solution of trimethylamine in absolute ethanol at 60 °C in an ice bath. The mixture was then sealed in an ampoule and heated in a water bath at a constant temperature of 65–70 °C for 2 hours. Additional experiments were carried out with varying reagent molar ratios to evaluate their effect on yield. The results are presented in Figure 2.



The reaction was conducted at a 1:2 molar ratio of ethylene chlorohydrin to trimethylamine at 65–70 °C, taking into account that trimethylamine, although dissolved in absolute ethanol, is a volatile gas. Therefore, an excess of trimethylamine was used to ensure complete conversion.

After completion of the reaction, the colorless liquid in the ampoule was collected, transferred to an evaporating dish, and the ethanol was removed by evaporation at room temperature. The remaining material was placed in a desiccator over CaCl₂ for drying. As a result, needle-like, colorless crystals of β-hydroxyethyltrimethylammonium chloride were obtained.

To determine product yield, the dried solid was weighed. Under the optimized conditions (1:2 molar ratio, 65–70 °C), the reaction yielded 68% of the desired product.

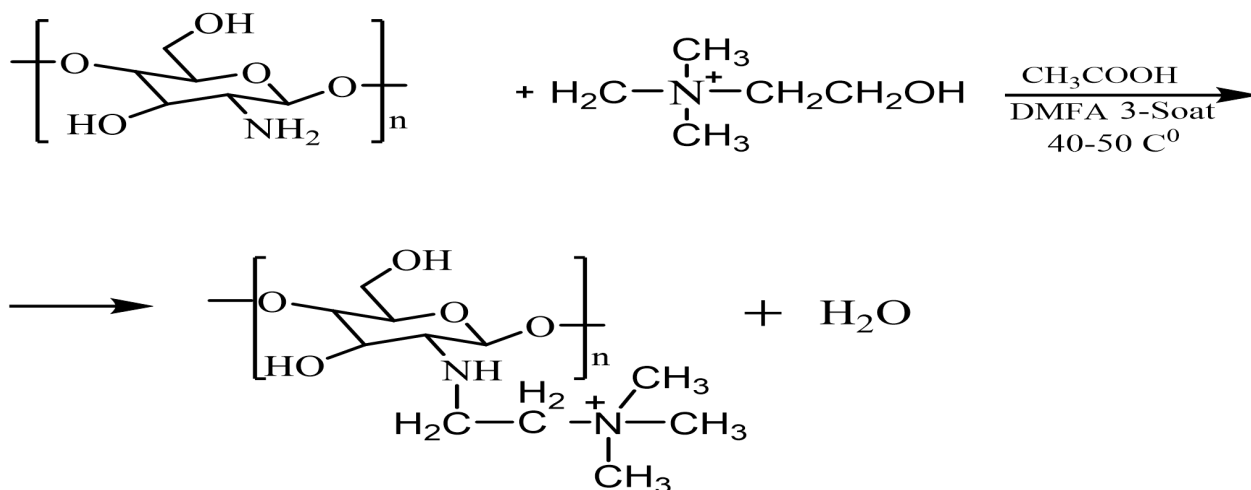
The results clearly show that increasing the molar ratio of the reagents and maintaining an elevated reaction temperature positively influenced the product yield.

Modification of Chitosan with the Synthesized Quaternary Ammonium Salt

Following successful synthesis, the obtained quaternary ammonium salt was used to modify chitosan. The reaction scheme is presented below:

Scheme 1.

Synthesis of Chitosan-Based Quaternary Ammonium Salt via Reaction with β-Hydroxyethyltrimethylammonium Chloride



Optimization of Reaction Conditions Using DMF

To identify the optimal conditions for the synthesis, the reaction was performed in DMF (dimethylformamide) at various time intervals. Among the tested durations, the highest yield of the quaternary ammonium salt was obtained after 3 hours of reaction time.

The effect of reaction temperature on product yield was also studied. It was found that reactions conducted at 40–50 °C provided the highest yields, confirming this temperature range as optimal for the synthesis of the quaternary ammonium salt.

IR Spectroscopic Analysis of the Synthesized Compounds

The IR spectra of the synthesized compounds were recorded using SPECORD-75IR and Avatar 360 spectrophotometers with KBr pellets.

Figure 1 displays the IR spectra of chitosan and its quaternary ammonium salt derivative formed by reaction with the pyridinium-based quaternary ammonium compound.

The broad absorption band in the range of 3200–3500 cm^{-1} corresponds to the N–H and O–H stretching vibrations in chitosan. Other characteristic absorption bands observed include: 2878 cm^{-1} – C–H stretching 1600 cm^{-1} – Amide bond vibrations 1156 cm^{-1} and 1078 cm^{-1} – C–O–C stretching and secondary hydroxyl C–O vibrations

Out-of-plane deformation vibrations of aromatic C–H groups were detected in the 650–900 cm^{-1} region, consistent with aromatic ring substitution.

New peaks observed at 1467 cm^{-1} , 1464 cm^{-1} , and 1471 cm^{-1} in the modified chitosan spectrum are assigned to the stretching vibrations of quaternary $-\text{N}^+$ groups, indicating successful quaternization. These spectral changes confirm the successful synthesis of chitosan derivatives containing quaternary ammonium functionality.

^1H NMR Spectral Analysis of Quaternized Chitosan

The ^1H NMR spectrum of the synthesized quaternary ammonium salt of chitosan was recorded at 500 MHz in D_2O . The following chemical shifts were observed:

δ 8.68 (s, 1H, He) δ 8.40 (m, 2H, Hc) δ 8.06 (s, 1H, Hb) δ 7.81 (s, 1H, Hd) δ 4.31 (s, 1H, Hn) δ 4.06 (s, 1H, Ha) δ 3.85–3.69 (m, 4H, H3–H6) δ 3.24 (s, 9H, Ho) – typically attributed to trimethylammonium methyl groups ($\text{N}^+(\text{CH}_3)_3$) δ 2.85 (s, 1H, H2) δ 2.66 (s, 6H, Hm)

Additional characteristic signals supporting structural confirmation:

δ 0.76–1.03 ppm (t, $J = 6.8$ Hz, 3H) – A triplet corresponding to a terminal methyl group ($-\text{CH}_3$) adjacent to a methylene group ($-\text{CH}_2-$). δ 2.97–3.20 ppm (s, 6H) – A singlet with six protons, indicating the presence of two methyl groups attached to nitrogen [e.g., $\text{N}(\text{CH}_3)_2$ or $\text{N}(\text{CH}_3)_3$]. δ 4.55–4.74 ppm (s, 2H) – A singlet typical for methylene protons adjacent to either oxygen or quaternary nitrogen ($-\text{CH}_2-\text{O}-$ or $-\text{CH}_2-\text{N}^+-$).

Conclusion

A quaternary ammonium salt was successfully synthesized by the reaction of ethylene chlorohydrin with trimethylamine. The resulting compound corresponds to choline, which is widely used in the medical field. This synthesized quaternary ammonium salt was further reacted with chitosan, and the optimal conditions for the modification reaction were systematically investigated.

The structure of the obtained chitosan derivative was confirmed using IR and ^1H NMR spectroscopy, and the formation of quaternary ammonium functionalities was clearly evident.

The newly synthesized quaternized chitosan is planned to be further studied for its biological activity, particularly in relation to its antibacterial and antifungal properties.

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