SYNTHESIS OF MENTHOLACETYLCHLORIDE WITH MONOCARBOXYLIC ACIDS AND INVESTIGATION OF THEIR STRUCTURES

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Abstract. This study reports the synthesis of novel derivatives of mentholacetylchloride with selected carboxylic acids and investigates the corresponding reaction pathways. The physicochemical properties of the synthesized compounds were systematically characterized, including melting point determination, infrared (IR) spectroscopy, and Rf values obtained by thin-layer chromatography (TLC). The results demonstrate that the newly synthesized derivatives exhibit distinct physical characteristics, differing in appearance, physical state, and melting temperatures.

Keywords: menthol; mentholacetylchloride; menthol acetyl formate; menthol diacetate; menthol acetyl butyrate; menthol acetyl valerate; IR spectroscopy.

Annotatsiya. Ushbu tadqiqotda mentol atsetilxloridining tanlangan karboksil kislotalar bilan o‘zaro reaksiyasi orqali yangi hosilalari sintezi va tegishli reaksiya yo‘llari o‘rganildi. Sintez qilingan birikmalarning fizik-kimyoviy xossalari tizimli ravishda tavsiflandi, jumladan erish haroratini aniqlash, infraqizil (IQ) spektroskopiya va yupqa qatlamli xromatografiya (YQX) usuli orqali Rf qiymatlarini aniqlash amalga oshirildi. Natijalar shuni ko‘rsatdiki, yangi sintez qilingan hosilalar tashqi ko‘rinishi, agregat holati va erish haroratlari bilan bir-biridan sezilarli darajada farq qiluvchi o‘ziga xos fizik xususiyatlarga ega.

Kalit so‘zlar: mentol; mentol atsetilxlorid; mentol atsetil format; mentol diasetat; mentol atsetil butirat; mentol atsetil valerat; IQ spektroskopiya.

Аннотация. В данной работе сообщается о синтезе новых производных ацетилхлорида ментола при взаимодействии с выбранными карбоновыми кислотами, а также исследуются соответствующие пути реакций. Физико-химические свойства синтезированных соединений были систематически охарактеризованы, включая определение температуры плавления, инфракрасную (ИК) спектроскопию и определение значений Rf методом

ISSN 3030-3907

тонкослойной хроматографии (ТСХ). Полученные результаты показали, что вновь синтезированные производные обладают различными физическими характеристиками и отличаются по внешнему виду, агрегатному состоянию и температурам плавления.

Ключевые слова: ментол; ацетилхлорид ментола; ацетилформиат ментола; диацетат ментола; ацетилбутират ментола; ацетилвалерат ментола; ИК-спектроскопия.

INTRODUCTION

In recent years, the use of natural products for medicinal purposes and alternative therapeutic approaches, particularly those based on biologically active compounds of plant origin, has gained increasing attention. The limited efficacy of conventional pharmaceuticals, improper use of synthetic drugs, and issues related to adverse effects and toxicity have further stimulated interest in plant-based medicinal preparations [1–3].

Menthol and its derivatives are widely utilized as auxiliary compounds in the perfumery and pharmaceutical industries, as well as in the production of food and tobacco products, due to their characteristic fragrance and cooling effect. Their extensive application as additives in food, medicine, and cosmetics is attributed to their distinctive flavor and refreshing properties; however, the low water solubility of menthol restricts its practical use [4–7].

Natural menthol is traditionally obtained from *Mentha canadensis* and other related mint species, although it can also be synthesized on an industrial scale through various chemical processes. Menthol exists in eight stereoisomeric forms, among which naturally occurring (–)-menthol and its structurally identical synthetic counterpart are the most preferred isomers for commercial applications. Owing to its broad utility across multiple industries, global demand for menthol remains significant. Recent market analyses indicate that the global menthol market was valued at approximately USD 4.25 billion in 2024, with natural menthol accounting for nearly 75 % of the total market volume, while synthetic menthol constitutes the remaining share [8]. The Asia–Pacific region, particularly India, dominates menthol production and export activities, contributing over 70 % of the global natural menthol supply [9]. Current consumption data suggest that global menthol demand reached approximately 68.6 thousand metric tons in 2023 and is expected to grow further, driven by its applications in pharmaceuticals, oral hygiene products, food flavorings, personal care formulations, and tobacco products [10]. Market forecasts predict continued expansion of the menthol industry through the end of the decade, with steady growth in both production

ISSN 3030-3907

volume and economic value [11]. These trends underscore menthols sustained importance as a multifunctional ingredient with diverse industrial applications.

Menthol is not the main component of essential oils, as it is present only in limited quantities in certain aromatic plants. These plants are known to exhibit various in vitro and in vivo biological activities, including antibacterial, antifungal, antipruritic, anticancer, and analgesic effects, and are also effective as fumigants. Moreover, menthol is one of the most efficient terpenes used to enhance the transdermal penetration of pharmaceutical formulations [12–13].

The molecule of menthol ($C_{10}H_{20}O$, molar mass 156.27 $g \cdot mol^{-1}$) is a naturally occurring compound with three asymmetric carbon atoms and exists in four pairs of optical isomers, namely (+)- and (–)-isomenthol, (+)- and (–)-menthol, (+)- and (–)-neomenthol, and (+)- and (–)-neo-isomenthol. Menthol, an organic compound isolated from mint essential oils, belongs to the class of monocyclic terpenes [14].

Building upon the findings of previous studies, we synthesized several novel mentholacetylchloride derivatives of menthol using selected monocarboxylic acids. The synthesis of these new mentholacetylchloridderivatives was achieved through the interaction of the acetyl chloride group in the mentholacetylchloride molecule with the carboxyl group of the corresponding carboxylic acids [15].

The chemical characterization of menthol and its derivatives obtained from carboxylic acids is essential for understanding their structural and physicochemical properties. Modern analytical techniques are widely employed to accurately determine the structure and composition of such compounds. In this study, mass spectrometry (MS), infrared (IR) spectroscopy, and high-performance liquid chromatography (HPLC) were used to investigate the physical properties and confirm the molecular structures of the synthesized compounds. IR spectroscopy was applied to identify the functional groups present in the compounds, particularly the ester functionalities derived from carboxylic acids.

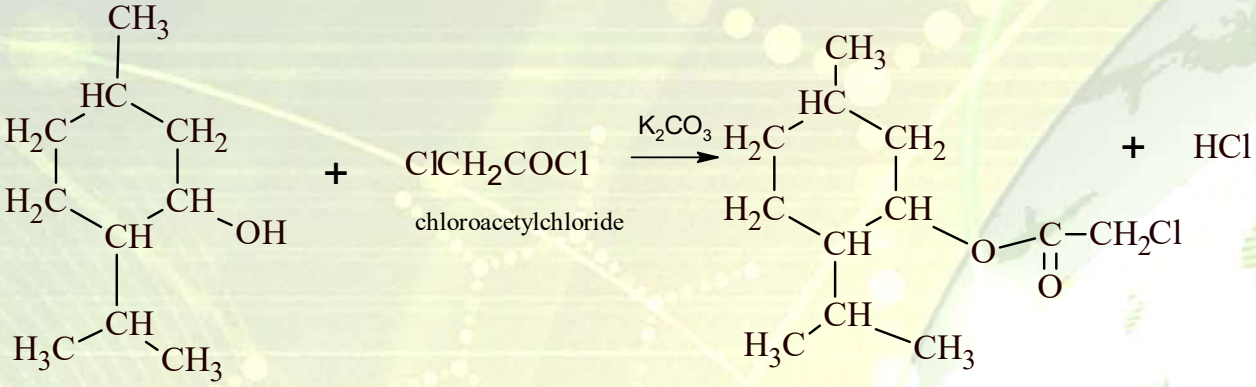
High-performance liquid chromatography (HPLC) was employed to assess the purity of the menthol esters obtained from menthol and carboxylic acids. Determining purity through HPLC enabled more detailed structural analysis of the synthesized compounds using complementary techniques such as nuclear magnetic resonance (NMR) spectroscopy and MS.

These analytical approaches allow for comprehensive structural characterization of new mentholacetylchloride and carboxylic acid derivatives, which is crucial for evaluating their potential efficacy and safety as pharmaceutical agents.

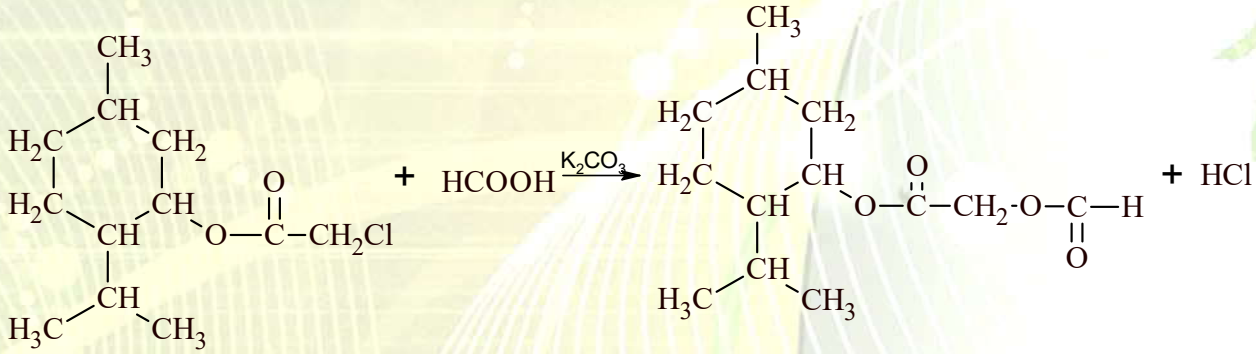
Results and Reaction Process

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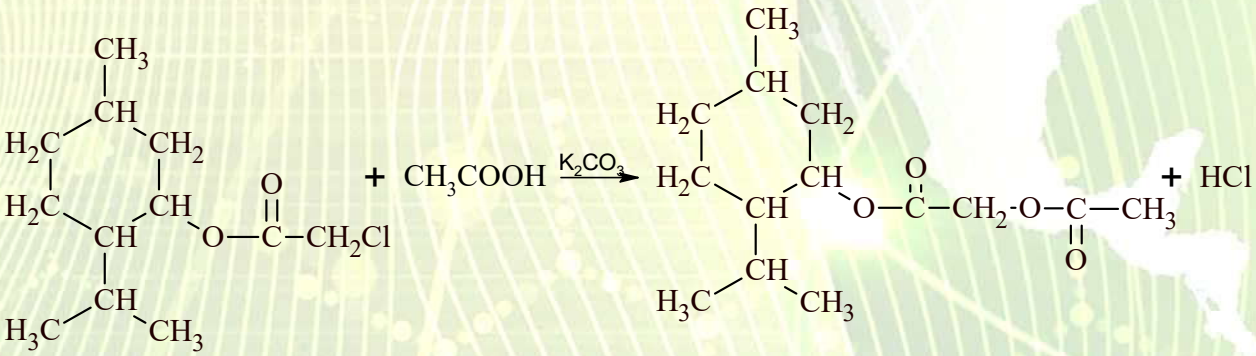
The synthesis of novel mentholacetylchloride derivatives with selected monocarboxylic acids was carried out according to the following reaction scheme:



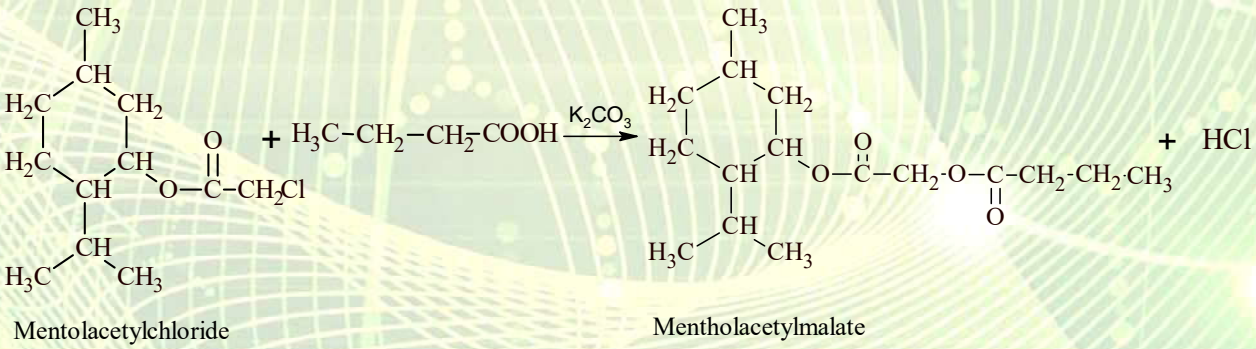
Menthol Mentholacetylchloride



Mentholacetyl chloride Menthol acetylformate



Mentholacetylchloride Menthol diacetate



Mentolacetylchloride Mentholacetylmalate

The reaction was carried out in a round-bottomed (flat-bottomed) flask equipped with a reflux condenser. Initially, 0.58 g (0.01 mol) of

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mentholacetylchloride was dissolved in 20 mL of chloroform, followed by the addition of 1.38 g (0.01 mol) of K_2CO_3. While maintaining the mixture in an ice bath, 0.37 mL (0.01 mol) of the corresponding carboxylic acid was added dropwise. The resulting mixture was stirred at room temperature for 2 hours using an MM-5 TU 25-11834-80 magnetic stirrer.

After completion of the reaction, the organic solvent was removed under reduced pressure using an IR-1M2 rotary evaporator, and the residue was washed twice with water. During the washing process, the organic layer was separated from the aqueous layer using a separatory funnel. The final product obtained corresponded to the newly synthesized ester. The chemical structure of the synthesized ester was confirmed by infrared (IR) spectroscopy.

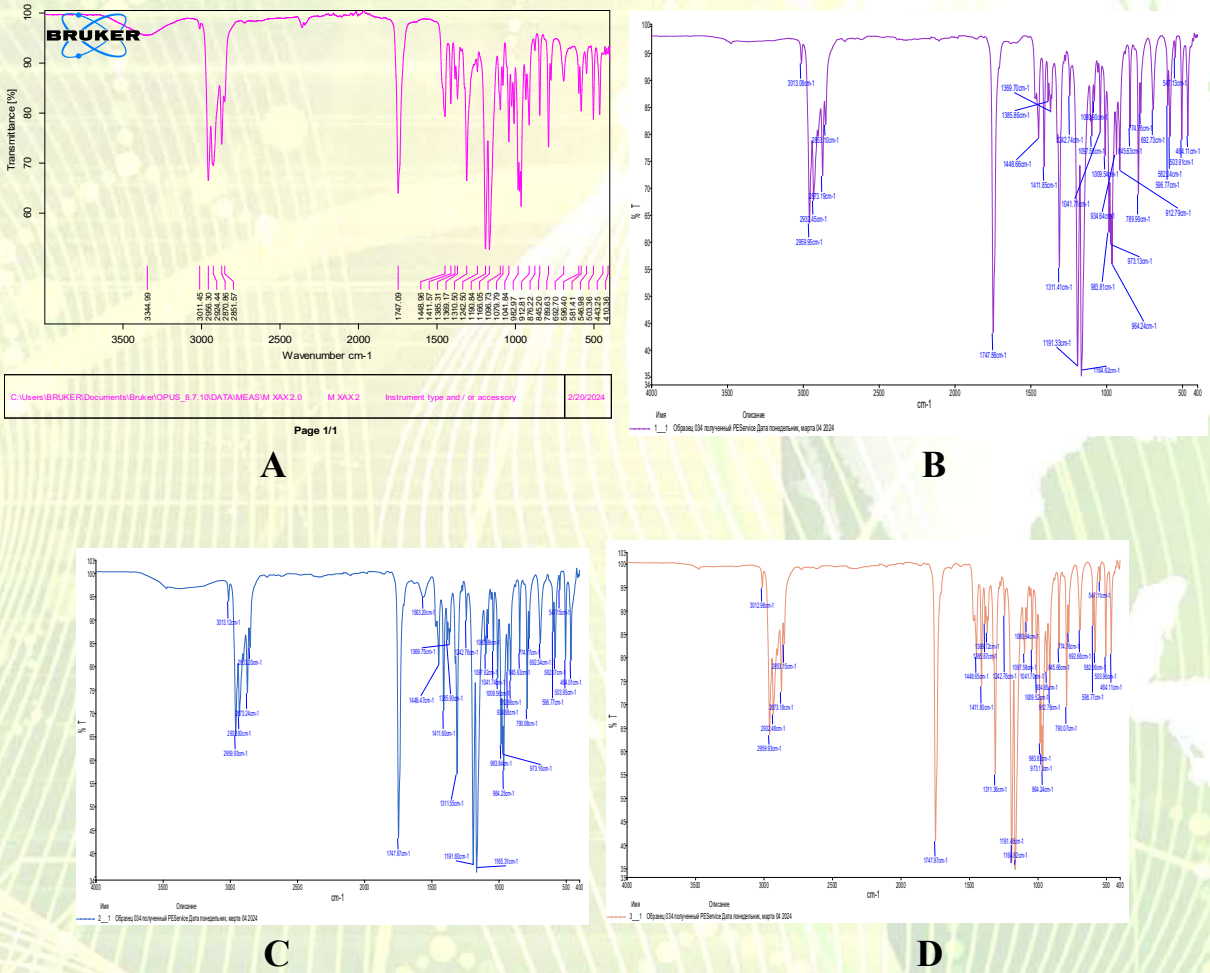


Figure 1. Infrared (IR) spectra of the compounds: (A) Menthol, (B) Mentholacetylchloride, (C) Menthol chloroacetate, (D) Menthol diacetate, (E) Menthol acetyl valerate.

In the IR spectra of the newly synthesized menthol, chloride, and the monocarboxylic acid derivatives (Figure 1), the C=O stretching vibrations were observed in the region of 1730–1710 cm^{-1}, corresponding to the carbonyl groups of the acyl and ester functionalities. In contrast, menthol exhibits O–H stretching

ISSN 3030-3907

vibrations in the 3500–3250 cm^{-1} region. The disappearance of the hydroxyl stretching band in the spectra of the synthesized esters indicates that the hydroxyl group of menthol reacted with the carbonyl group of the monocarboxylic acid to form the ester linkage.

The physicochemical properties of the obtained complex esters were determined, and their structures were confirmed by comparing their IR spectra with those of the starting materials. Notably, in the IR spectra of the esters, no –OH stretching vibrations were observed around 3245 cm^{-1}, further confirming the formation of the ester bond between the hydroxyl group of menthol and the carbonyl group of the monocarboxylic acid. Additionally, the appearance of strong carbonyl stretching vibrations at 1747 cm^{-1} is consistent with literature data and provides further evidence for successful esterification.

CONCLUSION

Mentholacetylchloride esters were successfully synthesized using several monocarboxylic acids. The physicochemical properties of the newly synthesized compounds were determined, and their structures were elucidated using infrared (IR) spectroscopy. Future work will focus on evaluating the biological activities of these new compounds to assess their potential pharmacological applications.

REFERENCES

1. Smith, J., & Brown, L. (2020). *Plant-derived bioactive compounds in alternative therapies*. Journal of Natural Products, 83(4), 1023–1035.
2. Zhang, X., Li, H., & Wang, Y. (2019). *Evaluation of plant-based medicinal preparations for therapeutic applications*. Phytotherapy Research, 33(11), 2880–2895.
3. Patel, R., & Kumar, S. (2018). *Natural products in modern medicine: challenges and opportunities*. Current Medicinal Chemistry, 25(22), 2637–2652.
4. Johnson, P., & Williams, T. (2017). *Menthol and its derivatives in pharmaceuticals and food products*. Industrial & Engineering Chemistry Research, 56(12), 3456–3465.
5. Lee, S., & Chen, Y. (2016). *Properties and applications of menthol in cosmetics and oral hygiene products*. Journal of Cosmetic Science, 67(3), 145–157.
6. Kim, H., & Park, J. (2015). *Menthol as a flavoring and cooling agent: solubility and application issues*. Food Chemistry, 173, 1123–1130.
7. Zhao, L., & Li, Q. (2014). *Water solubility limitations of menthol and its impact on pharmaceutical formulations*. International Journal of Pharmaceutics, 473(1–2), 98–105.
8. Gupta, A., & Singh, P. (2013). *Industrial production and global demand of menthol*. Journal of Industrial & Engineering Chemistry, 19(5), 1631–1638.

ISSN 3030-3907

9. Tanaka, M., & Sato, K. (2012). *Biological activities of menthol-containing plant extracts*. Journal of Ethnopharmacology, 141(1), 450–456.
10. Wang, F., & Li, J. (2011). *Enhancing transdermal drug delivery using terpenes: role of menthol*. International Journal of Pharmaceutics, 407(1–2), 1–12.
11. Khalmuratova, Z.T., Turemuratov, Sh.N., & Abdurakhmanova, U.K. (2025). *Synthesis of mentholacetylchloride derivatives with monocarboxylic acids*. Uzbek Journal of Chemistry, 7(2), 45–53.
12. March, J. (1992). *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (4th ed.). New York: Wiley.
13. Smith, M.B., & March, J. (2007). *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (6th ed.). Hoboken, NJ: Wiley.
14. Silverstein, R.M., Webster, F.X., & Kiemle, D.J. (2005). *Spectrometric Identification of Organic Compounds* (7th ed.). New York: Wiley.
15. Pavia, D.L., Lampman, G.M., Kriz, G.S., & Vyvyan, J.R. (2015). *Introduction to Spectroscopy* (5th ed.). Boston, MA: Cengage Learning.

ISSN 3030-3907