MENTHOL AND IT IS ORIGIN FOR BIOCHEMISTRY

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ANNOTATION:

The article presents a spectroscopic analysis of the structure of a new menthol derivative obtained using formic acid. Also, the main goal of the research work is to study the chemical characteristics of menthol and the properties of the resulting compounds. This paper presents a method and spectroscopic analysis of menthol acetyl formic ester obtained from menthol and formic acid.

INTRODUCTION.

Menthol is a cyclic monoterpene alcohol known for its distinct cooling sensation and residual minty aroma, derived from the oils it is extracted from. These properties make menthol a key flavoring agent, alongside vanilla and citrus, widely used in various consumer products such as chocolates, chewing gum, toothpaste, and over-the-counter medications for its cooling and therapeutic effects. Its cooling properties extend beyond medicinal use, with approximately 25% of cigarettes containing menthol, and even non-mentholated cigarettes containing small amounts.

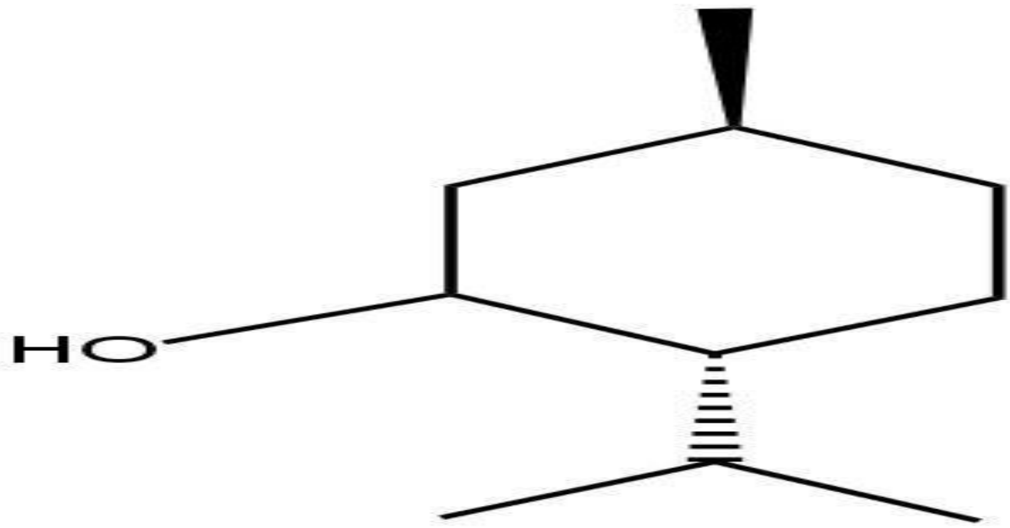
Natural menthol is primarily extracted from **Mentha canadensis**, though it can also be produced synthetically on an industrial scale. While menthol has eight stereoisomeric forms, the preferred one, both naturally sourced and synthesized, is (-)-menthol. The global demand for menthol is substantial, previously estimated at 30,000 to 32,000 metric tonnes annually. Although menthol is not a major component of essential oils, it is found in a few aromatic plants known for their biological activities, such as antibacterial, antifungal, anticancer, antipruritic, and analgesic effects. Additionally, menthol is a potent fumigant and one of the most effective terpenes for enhancing the dermal absorption of pharmaceuticals. This review outlines menthol’s chemical and biological properties, focusing on its cooling effects and toxicity.

Menthol, also known as mint camphor, is a cyclic monoterpene alcohol predominantly found in the essential oils of **Mentha canadensis L.** (cornmint) and **M. x piperita L.** (peppermint). Along with menthone, isomenthone, and other related compounds, menthol contributes to the characteristic cooling minty taste and aroma found in plants, particularly within the **Mentha** genus. Historically, plants were the only source of menthol, and they have been cultivated for medicinal purposes in Japan long before the compound was isolated and identified. Dutch botanist Gambius first isolated menthol as a crystalline substance in 1771.

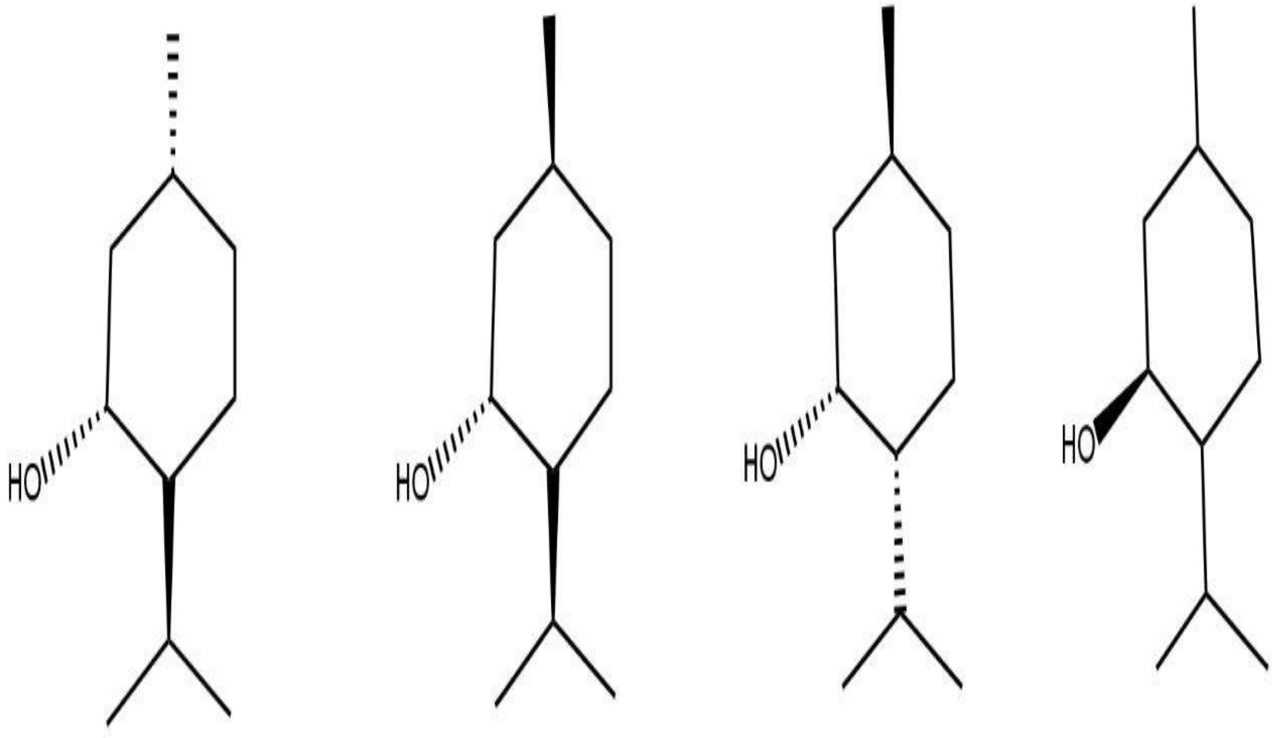
When referring to menthol, it generally implies L- or (-)-menthol, the most commercially significant form. It is estimated that 30,000 to 32,000 metric tonnes of menthol are consumed worldwide each year. After vanilla and citrus, (-)-menthol is considered one of the most important natural isolates.

Menthol is one of the most widely used flavoring substances and is a key component in many tobacco products, first introduced as an additive in the 1920s. Interestingly, even non-mentholated cigarette brands may contain small amounts of menthol, and it is estimated that around 25% of cigarettes sold worldwide contain menthol. The "coolness" provided by menthol enhances the smoking experience, especially for those who prefer mentholated cigarettes, a trend particularly noticeable in the United States.

Menthol is also widely used in various consumer products, including pharmaceuticals, cosmetics, pesticides, candies, chewing gum, liqueurs, toothpaste, shampoos, and soaps, as both a cooling agent and a flavor enhancer. Though menthol is a prominent component in only a limited number of aromatic plants, these plants exhibit several biological activities such as antimicrobial, anticancer, and anti-inflammatory effects, and are also used as insect repellents or fumigants.



Menthol's Structure



Different type of isomers for menthol

Natural Origin and Biosynthesis

Monoterpenes, like menthol, are primarily derived from aromatic plants and act as chemical messengers alongside other organic compounds found in essential oils. Menthol is typically extracted from corn mint oil, which is produced through steam distillation and contains 55–85% menthol content. Natural menthol is often preferred over synthetic L-menthol due to the latter's contamination during crystallization, which affects its scent.

Menthol is synthesized in plants through an 8-step biosynthetic pathway, starting from primary metabolism. This pathway was thoroughly detailed by Croteau et al. (2005), describing the anatomical structures and enzymes involved. A simplified version of this biotransformation begins with the formation of the universal monoterpene precursor, **geranyl diphosphate**, via the condensation of **isopentenyl diphosphate (IPP)** and **dimethylallyl pyrophosphate (DMAPP)**. This precursor undergoes cyclization to produce (-)-limonene.

(-)-Limonene is then hydroxylated, in a reaction dependent on **NADPH** and oxygen, to form (-)-trans-iso piper etenol. Through allylic oxidation, this compound is transformed into **(-)-isopiperitenone**, followed by NADPH-dependent reduction to yield **(+)-cis-iso pulegone**. Isomerization of this intermediate produces **(+)-pulegone**, the precursor for **(+)-mentho furan menthone, and (+)-iso menthol. Reduction of these ketones results in the formation of (-)-menthol, (+)-neomenthol, (+)-isomenthol, and **(+)-neoisomenthol**. 2.1. Cooling Effects of Menthol

Menthol is widely recognized for producing a cooling sensation when inhaled, chewed, consumed, or applied to the skin. This effect occurs because menthol chemically activates the cold-sensitive transient receptor potential cation channel, **TRPM8** (Yusipovich et al., 1996). Research has shown that menthol interacts with TRPM8 receptors by rapidly increasing intracellular calcium levels and facilitating calcium flux through these channels, triggering cold response signals at the site of application (Farco and Grundmann, 2013).

In a study by Yusipovitch et al. (1996), it was observed that menthol's cooling effect could last for 70 minutes or longer in 65% of the human subjects tested. Another study by Almeida et al. (2006) demonstrated that low doses of menthol, when administered intravenously, caused rats to seek warmer environments. Interestingly, in one human subject, menthol intensified the sensation of warmth. Additionally, Green (1985) noted that at temperatures above 37°C, solutions containing 0.02% menthol were perceived as warmer than water without menthol. In a related study, when 40% menthol was applied to human subjects, 10% reported sudden sensations of warmth.

Conclusion

Menthol is a significant component of essential oils from the **Mentha** genus and has been utilized in traditional medicine for centuries to treat various ailments. Its applications span multiple industries, including pharmaceuticals, cosmetics, tobacco, and food, where it serves as a flavor enhancer, preservative, and cooling agent. Menthol is associated with several biological properties, including antibacterial and analgesic effects, with one of its primary attributes being the sensation of coolness experienced when it is chewed, inhaled, or applied to the skin. Additionally, menthol may enhance the skin penetration of various drugs. Thus, topical formulations incorporating menthol, combined with an anti-inflammatory analgesic like indomethacin, could potentially yield synergistic effects. Given its low toxicity, it is not surprising that menthol has attracted considerable research interest and commercial value.

Despite the promising findings, there remains a significant lack of information regarding other aspects of menthol. The mechanisms through which it exerts its effects in vitro and in vivo are still not well understood. Furthermore, as menthol exists in various forms, the structure–activity relationships require further exploration. Essential oils, in general, and individual compounds, in particular, are widely recognized as fumigants and insect repellents. There are notable gaps in the scientific literature, particularly concerning menthol's effects on malaria vectors, such as **Anopheles mosquitoes**, and its potential impact on **Plasmodium falciparum**, the causative agent of malaria, a leading cause of death in many developing countries.

It is clear that menthol, with its extensive documented applications, has vast potential for development into medicinal compounds, whether in its natural form or as a basis for synthetic modifications. Beyond medicinal uses, the annual production of menthol in significant quantities indicates that interest in this compound continues to grow, as evidenced by the numerous patents related to menthol products and synthesis methods. For instance, a search on freepatentsonline.com yields 49,738 results for menthol. As new applications are frequently discovered, the future of this molecule, which has been used as a medicine in Japan for over 2,000 years, looks promising.

Reference:

1. Syntheses of menthol acetyl formic ester, Xoliqov M.I, Yettibaeva L.A, Turlibekov O.A, Xolmuratova Z.T, Matchanov A.D,
Science and Education in Karakalpakstan. 2024 №2/2 ISSN 2181-9203

2. Z.T. Khalmuratova, L.A. Yettibaeva, U.K. Abdurahmanova. "Synthesis of new derivatives of

menthol". Current status and prospects of the science of functional polymers. Tashkent-2020. Page 429.

3. Tolstikov, L.A., Baltina E.E. Shults A.G. Pokrovsky// Glycyrrhizinovaya acid. 1997.T 23. No. 9 P.691-

709.

4. Vasilenko A. Yu., Frolov A. V., Chapaeva S. Ch.,// Chem. - pharmacist. journal. 1985. T. 19 S. 1335-

13395.

5. L.A. Yettibaeva, U.K. Abdurahmonova, A.D. Matchanov, D.M. Allanazarova, and Z.T. Halmuratova. Influence of Glycyrrhizic Acid, Menthol and Their Supramolecular Compounds on the Functional Activity of Rat Mitochondria in in-vitro Experiments /Journal of the Korean Chemical Society 2021, Vol.65, No.5 Printed in the Republic of Korea https://doi.org /10.5012/jkcs.2021.65.5.1.

6. Douglas A. Klumpp, Robert M. Sobel, Smaro G. Kokkinidou, Brian Osei-Badu Synthesis of Menthol Glycinates and Their Potential as Cooling Agents // ACS Omega, 2020, Vol. 5, N 8, pp. 4043–4049.

7. Patent US 6566545B2, 2016 Menthol derivatives and process for preparing the same // Jae Won Yoo, Duck Hee Kim, Seong Joon Moon, Min Soo Noh.

8. Yi Li, Feng Zhou, Ying Wen, Kayin Liu (−)-Menthol-based thixotropic hydrogel and its application as a universal antibacterial carrier // Soft Matter, 2014, Vol.10, pp.3077-3085.

9. MuLi, Li-RongYang, GangXu, Jian-PingWu Highly diastereoselective acylation of L-menthol by a lipase from Stenotrophomonas maltophilia CGMCC 4254 // Biochemical Engineering Journal, 2016, Vol. 109, pp. 81-87.

10. Pooneh Khaligh, a Peyman Salehi, Morteza Bararjanian, Atousa Aliahmadi Synthesis and in Vitro Antibacterial Evaluation of Novel 4-Substituted 1-Menthyl-1,2,3-triazoles //Chem. Pharm. Bull., 2016, Vol. 64, N 11, pp. 1589–1596.