6-methylnicotine description

1. Why should 6-methylnicotine not be classified as an alkaloid?

According to the International Union of Pure and Applied Chemistry (IUPAC), which standardizes symbols, nomenclature, and physical property standards for chemists worldwide, alkaloids are defined as a group of naturally occurring organic compounds (generally heterocyclic) of basic nature, primarily plant-derived, and containing nitrogen [1]. This definition explicitly excludes amino acids, peptides, proteins, nucleotides, nucleic acids, amino sugars, and antibiotics from the alkaloid category. Similarly, alkaloids, as compounds produced by plants, are defined in the book titled Alkaloids: Biochemistry, Ecology, and Medicinal Applications [2]. A broader definition is provided in the book The Essential Guide to Alkaloids by D.K. Semwal [3], where alkaloids are described as naturally occurring organic substances containing nitrogen, typically basic in nature. While they do not necessarily have to be plant-derived, they are invariably products of biosynthesis. Although references to synthetic alkaloids exist—for instance, the book Natural Organic Compounds by A. Kołodziejczyk [4] describes alkaloids as "a large group of basic organic compounds, primarily of plant origin or synthetic"—these terms apply to synthetic compounds that also occur naturally. In other words, whether an alkaloid originates from plants or animals, it must exist in nature to qualify as an alkaloid; hence, the term "synthetic alkaloid" refers to laboratory-synthesized compounds that replicate natural substances. This interpretation aligns with further descriptions in Natural Organic Compounds [4], particularly in the section on alkaloid distribution: "Alkaloids, atypical metabolites, are produced by certain plants such as poppies (Papaveraceae), legumes (Leguminosae), and nightshades (Solanaceae), as well as by some lower plants, such as lycophytes, horsetails, and fungi. Even within the same family, not all species produce alkaloids. Rarely are alkaloids found in monocots and conifers. No alkaloids have been found in families like Rosaceae, Orchidaceae, or Lamiaceae. Among animals, they occur in insects, salamanders, certain frogs, and centipedes. In insects, alkaloids are often derived from diet and serve as protection against predators." This text illustrates that alkaloids must originate from living organisms. This is further corroborated by the EU Combined Nomenclature Explanatory Notes (2018/C 191/06), which state that "Cocaine, ecgonine, levomethamphetamine, methamphetamine (INN), racemate of methamphetamine; their salts, esters, and other derivatives" include synthetic alkaloids. However, even in synthetic form, cocaine remains an alkaloid due to its natural occurrence. It is essential to emphasize that the definition of nicotine under the Tobacco Products Directive refers to alkaloids present in tobacco leaves. For instance, nicotine, cotinine, nornicotine, and other alkaloids produced by tobacco

plants qualify as alkaloids irrespective of whether they are extracted or synthesized in a laboratory. In contrast, if a compound is not biosynthesized by living organisms, it does not meet the criteria for being an alkaloid. Numerous nitrogen-containing, basic compounds are not considered alkaloids because they lack natural origin. The IUPAC definition supports this distinction by excluding specific classes of compounds from the alkaloid category. Although 6-methylnicotine is not explicitly listed among excluded groups, other compounds like azines, which meet many definitional criteria, are not classified as alkaloids. To date, no reports confirm that 6-methylnicotine (systematically named 2-methyl-5-[(2S)-1-methylpyrrolidin-2-yl]pyridine) (CAS: 13270-56-9) exists naturally. Its presence has not been detected in tobacco leaves; it is a purely synthetic compound. Consequently, due to its absence from tobacco leaves and its synthetic derivation, various chemical methods have been developed to produce 6-methyl analogs of nicotine, including 6-methylnicotine, to explore their therapeutic potential [5]. One of the earliest and most common synthetic methods for producing 6-methylnicotine involves reacting basic nicotine with methyl lithium [6], a strong nucleophile, in an organic solvent such as toluene. This process yields 6-methylnicotine along with minor amounts of 4-methylnicotine and 2-methylnicotine, as illustrated in Figure 1.

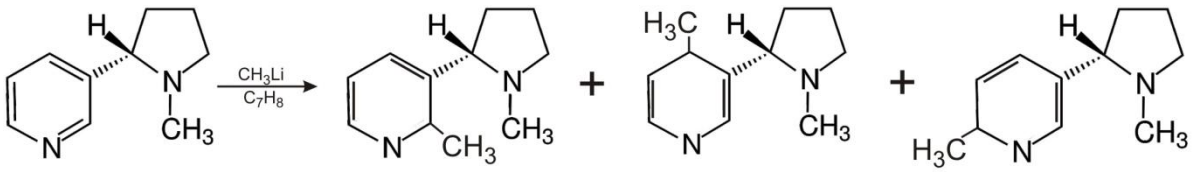

Fig. 1. Reaction of nicotine with methyl lithium in hot toluene.

Another method for synthetically obtaining 6-methylnicotine involves using methyl ester of 6-methylnicotinic acid and γ-butyrolactone as raw materials, followed by ester condensation, ring-opening reaction, reduction, and amination with ring closure [7]. This demonstrates that 6-methylnicotine can be derived from non-alkaloid substrates. The chemical nature of 6-methylnicotine also suggests that it cannot naturally occur in tobacco leaves. Figure 2 illustrates the canonical (resonance) structures of the pyridine ring in the nicotine molecule.

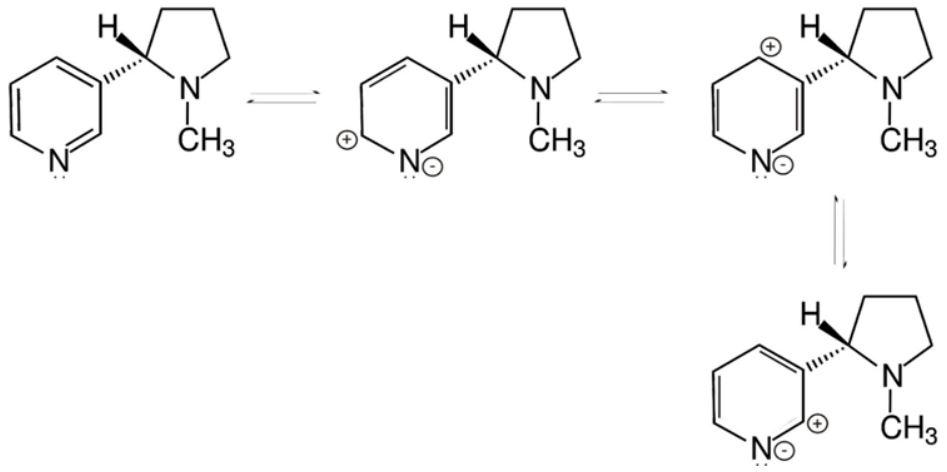

Fig. 2. Canonical (resonance) structures of the pyridine ring in the nicotine molecule

The structure and characteristics of the pyridine ring make it prone to electrophilic addition to the lone pair of electrons on the nitrogen atom, but it is very difficult to undergo electrophilic substitution on the ring. An example of such substitution is alkylation, which involves attaching a methyl (alkyl) group to the ring. This group can be transferred as a radical, carbanion, or carbocation, which forms the basis for the classification of these reactions. Electrophilic substitution on the carbon atom of the pyridine ring is challenging due to the significant decrease in electron density caused by the highly electronegative nitrogen atom. Therefore, the likelihood of such a reaction occurring in a natural environment is greatly reduced, indicating the necessity of using chemical synthesis methods to obtain the compound in question.

Additionally, there are scientific reports referring to 6-methylnicotine as a synthetic compound not derived from tobacco. One such report is the scientific publication “A comprehensive methodology for the chiral separation of 40 tobacco alkaloids and their carcinogenic E/Z-(R,S)-tobacco-specific nitrosamine metabolites,” where in Table 1, 6-methylnicotine is not classified among tobacco alkaloids, but as one of their synthetic derivatives [8].

In summary 6-methylnicotine is a synthetic compound that does not naturally occur in tobacco leaves, and thus, it should not be classified as an alkaloid. Alkaloids are defined as naturally occurring organic compounds, primarily plant-derived, containing nitrogen and are products of biosynthesis. The IUPAC definition excludes synthetic compounds and those not derived from living organisms, such as 6-methylnicotine, which is produced through chemical

synthesis. Since 6-methylnicotine is not found in nature and is synthesized through chemical processes, it does not meet the criteria to be considered an alkaloid.

2. Why do products with 6-methylnicotine have an advantage over traditional solutions?

Scientific reports indicate that the use of 6-methylnicotine in e-cigarettes may offer several benefits compared to traditional solutions based on classic nicotine or its salts. The advantage of 6-methylnicotine also lies in its lower toxicity in the e-liquid to which it is applied, which could be an important step toward creating a less harmful alternative for individuals addicted to nicotine, while still maintaining the effects of its use. In the latest research [9], the toxicity of various nicotine compounds was assessed through experiments on mice using the inhalation method. The analyzed samples included both synthetic and natural nicotine derivatives. The acute toxic effects of individual substances were evaluated based on the LC50 value, which represents the average concentration causing the death of 50% of the tested animals.

Tested Samples:

- Synthetic Nicotine – a yellow solution of synthetic nicotine (nicotine),
- Nicotine Benzoate from Tobacco Leaf Extract – a yellow solution referred to as the leaf salt,
- Synthetic Nicotine Benzoate – a yellow solution of synthetic nicotine salt, known as combined salt,
- 6-methylnicotine – a light yellow solution of the synthetic compound 6-methylnicotine.

The conducted study assessing the acute toxicity of selected nicotine substances in mice using the inhalation method revealed significant differences in their toxicity levels. The lowest LC50 value, indicating the highest toxicity, was recorded for nicotine benzoate derived from tobacco leaf extract (so-called leaf salt). This substance, commonly used in e-cigarette liquids, proved to be the most harmful, particularly to male mice. Slightly less toxic but still highly harmful was synthetic nicotine salt (blended salt). In contrast, nicotine and 6-methylnicotine exhibited significantly lower toxicity compared to nicotine salts. Moreover, although 6-methylnicotine has an LC50 value similar to nicotine, it is used in e-cigarette liquids in much smaller quantities—up to 12-14 times less than standard nicotine. This suggests that, in terms of user safety, e-liquids

containing 6-methylnicotine may be the least harmful alternative. The study results suggest that among the analyzed substances, nicotine salt—especially the plant-derived variant—is the most toxic component used in e-cigarettes. In contrast, both nicotine and 6-methylnicotine exhibit lower toxicity. Additionally, the fact that 6-methylnicotine is used in significantly smaller amounts further reduces potential risks for users. In light of these findings, e-liquids containing 6-methylnicotine may be considered the safest option among available nicotine variants.

In summary, research indicates that 6-methylnicotine in e-cigarettes may be less toxic than traditional nicotine and its salts, especially nicotine salt derived from tobacco leaves, which has proven to be the most harmful. 6-methylnicotine, used in much smaller quantities, could provide a safer alternative for e-cigarette users, reducing the risks associated with its use.

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