

## Arguments questioning the statement that 6-methylnicotine (CAS: 13270-56-9) is an alkaloid.

According to the definition of the International Union of Pure and Applied Chemistry (IUPAC), which standardizes symbols, nomenclature and physical quantity standards used by chemists around the world, alkaloids are defined as a group of naturally occurring basic compounds organic, mainly heterocyclic, mostly of plant origin containing nitrogen [1]. Clearly alkaloids as chemical compounds produced by plants are also defined in the book titled: Alkaloids. Biochemistry, ecology and medicine applications [2]. The constitutive feature of an alkaloid is not whether a given type of compound is produced by the plant or not. For example, nicotine, cotinine, nornicotine and other alkaloids produced by the tobacco plant will be alkaloids regardless of whether they were synthesized in a laboratory or extracted. This is due to the fact that these compounds are produced by plants. DK Semwal understands this concept in a similar way, in his book "The essential guide to alkaloids" [3] states that alkaloids are "naturally occurring organic substances" containing, among others: nitrogen and having an alkaline nature. They do not have to be of plant origin because they can be synthesized by other living organisms, including some animals. Nevertheless, their inherent feature is their origin from biosynthesis. Accordingly, if a given compound is not produced by living organisms, it is not an alkaloid, and there are many examples of compounds that contain nitrogen, have an alkaline environment, but are not produced by a plant and are therefore not considered an alkaloid. To date, there are no reports that the chemical compound known as 6-methylnicotine (systematically 2-methyl-5-[(2S)-1-methylpyrrolidin-2-yl]pyridine) occurs in nature in its pure form. Due to the above and due to the great interest of researchers in the use of nicotinic acetylcholinergic receptors due to their therapeutic potential, various methods have been developed for obtaining 6-substituted nicotine analogues by chemical synthesis, including 6-methylnicotine [4]. One of the first and most common synthetic methods of obtaining 2-methyl-5-[(2S)-1-methylpyrrolidin-2-yl]pyridine is the method involving the reaction of basic nicotine with methyllithium [5], which is a strong nucleophile in one of the organic solvents (e.g. toluene), which leads to the isolation of 6-methylnicotine with small amounts of 4-methylnicotine and 2-methylnicotine as shown in Figure 1.

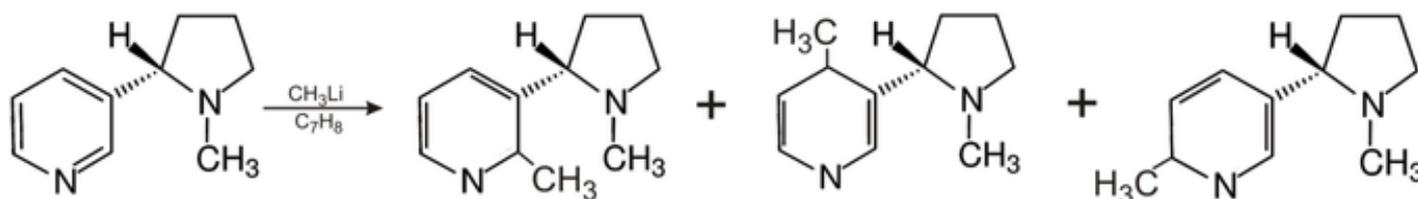
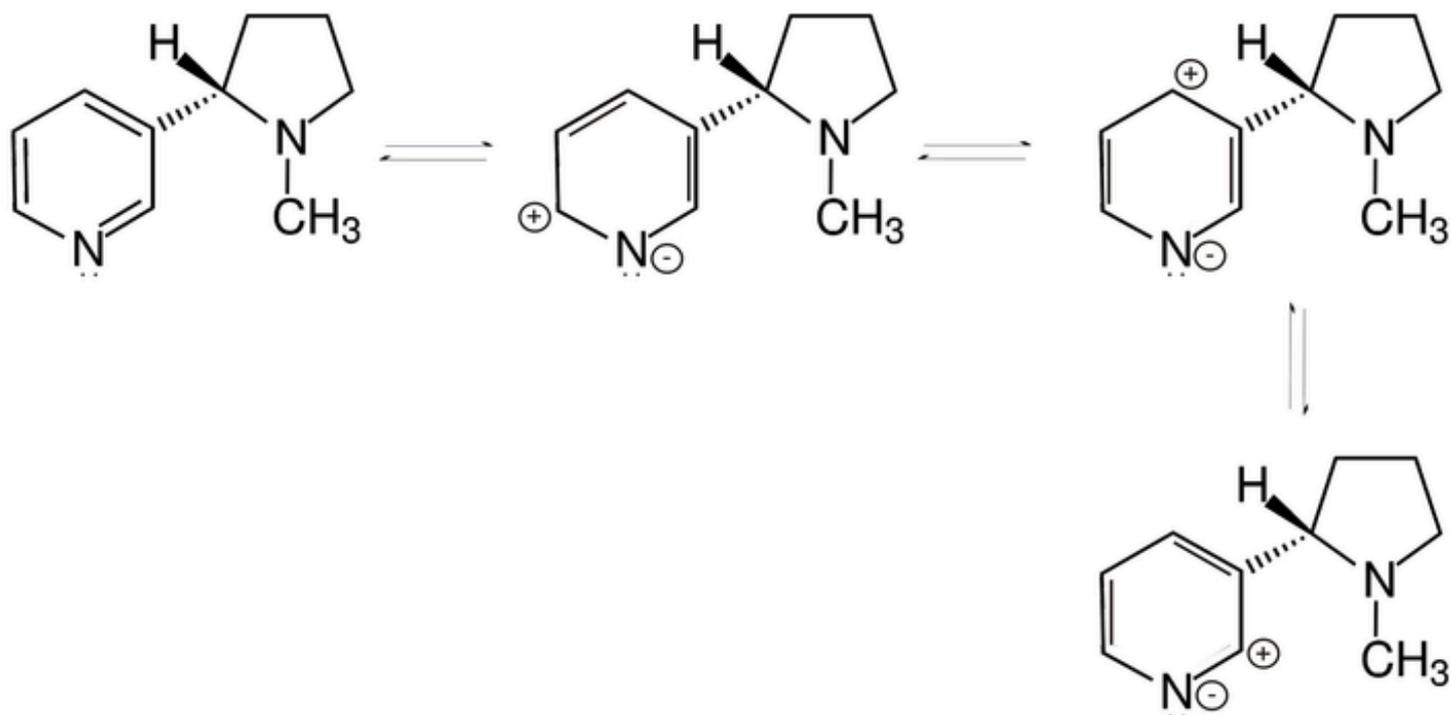


Fig. 1. Reaction of nicotine with methyllithium in hot toluene.

Another method of synthetically obtaining 6-methylnicotine is to use 6-methylnicotinic acid methyl ester and -butyrolactone as starting raw materials and carry out ester condensation reactions, ring opening, reduction, and ring closing amination reactions [6].

The canonical (boundary) structures of the pyridine ring in the nicotine molecule are shown in Fig. 2



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

The structure and nature of the pyridine ring causes it to easily undergo electrophilic addition to the lone electron pair of the nitrogen atom, but it is very difficult to undergo electrophilic substitution in the ring. The alkylation reaction, i.e. the attachment of a methyl (alkyl) group to a ring, is an example of such a substitution. This group can be transferred in the form of a radical, carbanion or carbocation, which is the basis for the systematics of these reactions. Electrophilic substitution at the carbon atom of the pyridine ring occurs difficult due to the significant reduction of electron density by the highly electronegative nitrogen atom. Therefore, the probability that such a reaction may occur in the natural environment decreases significantly and indicates the need to use chemical synthesis methods. Moreover, there are numerous scientific reports referring to 6-methylnicotine as a synthetic compound, not derived from tobacco or nicotine. According to the above-mentioned arguments, the compound 6-methylnicotine cannot be considered an alkaloid.

#### Literature:

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- [2] Rodger, M. F., & Wink, M. (1998). *Alkaloids Biochemistry, ecology and medicine applications*.
- [3] Semwal, D. K., (2023). *The Essential Guide to Alkaloids. Nova Science Publishers, Inc.*
- [4] Dukat, M., Dowd, M., Damaj, M. I., Martin, B., El-Zahabi, M. A., & Glennon, R. A. (1999). Synthesis, receptor binding and QSAR studies on 6-substituted nicotine derivatives as cholinergic ligands. *European journal of medicinal Chemistry*, 34 (1), 31-40.
- [5] Seeman, J. I., Secor, H. V., Howe, C. R., Chavdarian, C. G., & Morgan, L. W. (1983). Organometallic methylation of nicotine and nicotine N-oxide. Reaction pathways and racemization mechanisms. *The Journal of Organic Chemistry*, 48 (25), 4899-4904.
- [6] SHENZHEN ZINWI BIO-TECH CO LTD(Shenzhen Zhenwei Biotechnology Co., Ltd.), 06 May 2022, Patent Application.

