Chemical Constitutions of Natural Musk and Research Progress of Synthetic Musk

Xueqi Zhao*

Oxford International College, Oxford, United Kingdom

* Corresponding Author Email: XueqiZh@stu.sqxy.ed.cn

Abstract. Natural musk, which is released by adult male musk deer, has vital use in medicine, cosmetics, detergents, and other fields. This paper has mentioned that as a result of its predominant composition of macrocyclic ketones, pyridine, alcohols, fatty acids, polypeptides (PEP-tides), proteins, and other desired but uncommon substances, synthetic musk was created. The synthetic musk has been divided into four groups based on its chemical composition: nitrogen-containing musks (NMs), polycyclic musks (PMs), macrocyclic musks (MMs), and alicyclic musk or linear musk (AMs). The history of the creation of compounds with musk odor, the development of four different types of synthetic musk, and the negative impact of NMs, MMs, and PMs had all been mentioned in this article. Also, the creation and use of these different musks have all been discussed in this work. Synthetic musk still struggles with the cost of production and is unable to synthesize all of the components from genuine musk. Thus, there is still a lot of potential for the development of synthetic musk.

Keywords: Musk odor; synthetic musk; macrocyclic musk; polycyclic musk; alicyclic musk.

1. Introduction

Naturally occurring musk is secreted by the musk gland from the mature manly musk deer (Moschus moschiferusL.) which they have been employed as scent accoutrements for several centuries [1,2]. In Shen Nong Ben Cao Jing, which dates back to ancient China, the usage of musk is described as having a lengthy history [3]. Due to it implicit effectiveness, musk has extensively been used in the Traditional Chinese Medicines (TCM) to treat complaint. Further generally used musk containing TCM medications similar as lozenge, power, capsule [4]. For instance, Pien Tze Huang is used for heart cleaning, detoxification, blood rotation formation, and swelling reduction; Angong Niuhuang tablets are used for treating stroke, coma, viral encephalitis and other disease; XingNaoJing is used to treat cerebral infarction and acute ischemic stroke [4]. Clinical procedures have used injection forms for pain treatment, central nervous system issues, and cardiovascular complaints [4]. Musk is utilized as a global medication, a component of fragrances, and has a remarkable cultural significance in many countries [5]. Eventually, the crusaders transported musk from the East to Europe. 1 g of musk cost between 30 and 50 US$ in 1998, making it more expensive than $10 of gold [6].

The natural musk's source, the musk deer, may be found all throughout Asia's hilly and wooded regions, from south of the arctic circle to the border of the north Mongolia and Korea. Apart from the Gobi Desert, the musk deer may also be found in China, North of India, Vietnam, and the area surrounding Hinalayan [7,8]. There are now six different species of musk deer in China which is (1) Forest musk deer M.berezovskii (2) Alpine musk deerM. Sifanicus (3) Blackmusk deerM. Fuscus (4) Himalayan musk deerM.chrysogaster (5) Siberian musk deerM. moschi-ferus and (6) Anhui musk deerM., making it one of the most significant areas for musk deer dispersion. Anhuisheng, a remote territory that spans the majority of China, was designated as a second-class protected wildlife area in 1998 [9]. They have well-developed canines that display the outside of the lips, which is important for musk zoology. The Alpine Musk Deer has wider canines than the Forest Musk Deer. Wild musk deer produce gentle, slithery, and flaccid musk. Uneven globular or grainy bones have sections that are dark brown or unheroic-brown and shells that are primarily grandiloquent-black, slithery, and lustrous with many lines. Grains, short strips, or unformed clumps are the three forms of musk

produced from domestic musk deer. These clumped have an uneven surface that is greasy, somewhat glossy, has a little quantity of hair on it, has an odd scent, and has a mildly spicy, slightly bitter, and salty flavour [2].

In the past, musk deer had to be killed in order to extract musk, which eventually caused the population to drastically fall over the course of the last three to four decades. According to one research, China's musk deer population peaked in the 1950s at 2.5 million, but by the turn of the century it had decreased to less than 0.1 million [2, 10]. Despite the fact that musk deer have been intentionally produced, habitat degradation brought on by deforestation and other human meddling has also promoted to the decrease of the populations as well as it may offer an equally significant threat later on [8]. This experience has made it essential to employ synthetic musk as a replacement for natural musk, which is based on its chemical components and pharmacological effects. Herein, a conclusion of chemical constituents of natural musks and development and application of different artificial musks.

2. Chemical Constitutions of Natural Musks

With components that are both lipophilic and hydrophilic and have a wide range of molecular weights, natural musk has a complex chemical makeup. A general division of the components into water-soluble and water-insoluble components has been made [4].

2.1. Water Insoluble Component

The water insoluble components of the musks have been divided into four parts, macrocyclic ketones, pyridine, steroids and other lipid component.

2.1.1 Macrocyclic Ketones

The primary fragrant constituents of naturally occured musk are macrocyclic ketones, particularly muscone (3-methylcyclopentadecan-1-one), which can range in concentration from 2% to 5% [11]. Walbaum isolated the muscone in 1906, and Ruzicka et al. described it in 1926.

2.1.2 Pyridine

In natural musk, pyridine alkaloids are odoriferous chemicals. Muscipyradine was the initial pyridine alkaloid to be isolated from the raw musk using ether. After that, other pyridine and hydroxymuscopyridine were separated [12,13].

2.1.3 Steroids

The second-largest lipid component of musk, steroids are a changeable component [2]. Thus far, various steroids have been identified from musk, including Cholesterol, Cholestan-3-ol, 5α-androstane-3α, dehy-droepiandrosterone sulfate and so on [2].

2.1.4 Other Lipid Substances

The molecules which contain lipid make about 87% of the entire composition of natural musk. Wax, alcohols, alkanes and fatty acids were shown to be the common constituents, excluding muscone and steroids. A whopping 80% of the diethyl ether extract of natural musk, including 1,1-diethyl-ethane, is made up of hundreds of alkanes, which include aliphatic alcohols with branched-chain Carbon 20-34, fatty acids with Carbon 10-24 compositions with wax [10, 11].

2.2. Water Soluble Components

The high solubility substances of natural musk has also dived into two group, polypeptides with proteins, and other hydrophilic components.

2.2.1 Polypeptides and Proteins

According to early Japanese investigations, this class of compounds is mostly made up of high solubility of active elements of natural musk that are generated from polypeptides (PEP-tides). In one

study, the composition of the musk was examined using liquid chromatography-mass spectrometry (LC-MS), which revealed 41 different types of amino acids as well as tiny molecular acids and bases that are necessary to construct the amino acids group [3].

2.2.2 Other Hydrophilic Components

Japanese researchers discovered allantoin for the first time in 1984 from the methanol extraction of musk. In addition, a series of chromatography was used to separate three aliphatic sulphates from water-soluble compounds [4].

3. History of Compounds with Musk Odor

There were early attempts to develop a substitute due to the declining population of musk deer and the exorbitant cost of the natural musk. By nitrating amber oil in 1979, the chemists Margraf discovered goods with musk-like scents [1]. The first chemically characterised drug was created in 1890 and sold as "Musc Baur" by Buar. Later, what are known as nitro musks were created, which are further members of these chemicals. Contrary to the creation of synthetic musk compounds, research on natural musk ingredients only had its first significant breakthrough in 1906. In 1926, Ruzicka succeeded in identifying muscone and civetone and proved the structural properties by synthesis, establishing a new family of substances known as macrocyclics. After the creation of ambral in 1947, the compounds that resulted from its lack of nitro groups had a subtle, lingering musk scent with a nuance that leans more towards the multi-membraned cyclic type. Two years later 6-Acetyl-1,1,2,3,3,5-hexamethyldihydroindene (AHDI) synthesis was first documented in 1951. With the development of the first member of this category of musks that has economic significance, a broad variety of PCMs have been produced [1, 14].

4. Synthetic Musk

Chemically speaking, artificial musks made up of a variety of substances that may be divided into (1) nitro musks (NMs), (2) polycyclic musks (PMs), (3) macrocyclic musks (MMs) and (4) alicyclic musks (AMs) [15].

4.1. Nitro Musks

Nitro musk was the initial artificial musk to be used in place of natural musk. Dinitrobenzene and trinitrobenzene are also present in the musk, along with extra alkyl, keto, or methoxy groups [15]. The best known NMs are musk ketone, xylene, ambrette, tibetene and moskene [1].

The main reason why musk xylene and ketones (musk ketones) have been utilised for so long as artificial scents in the manufacturing of various durable goods including fabric softeners, laundry detergent, and cosmetics is because of their low cost [16]. A 1992 investigation in Germany also looked into the presence of nitro musk compounds and discovered that they were present in 41.5% of detergents and 55% of cosmetics. The survey found that musk xylene predominated in detergents, musk ketones predominated in cosmetics, and musk ambrette was only recorded in one cosmetic product [17].

The pace of synthesis, however, begins to slow down as a result of the photoallergic responses that musk ambrette causes. The public debate in 1993 advocated against the use of musk xylene in the manufacturing of cosmetics, detergent, and other home goods. Because of the potent phonological properties of musk ambrette, the European Commission banned its use in the formulation of cosmetics in 1995. Also, in 1998, the compounds musk moskene and tibetene were added to the list of substances that were prohibited from use in cosmetics. Also, between 1992 and 1998, the European fragrance industry dramatically reduced its use of nitro musks [1].

4.2. Polycyclic Musk

Before the 1950s, a significant new class of synthetic musk chemicals was created [18]. These are nitro-free chemicals that fall within the categories of tricyclic compounds, indane derivatives, tetrealine derivatives, and coumarin derivatives. After the 1951, synthesis of AHDI, their use began. The two most significant chemicals in this category are 7-acetyl-1,1,3,4,4-hexamethyltetrahydronaphthalene (AHTN) and 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta(g)-2-benzopyrane (HHCB). 4- and 5-acetyl-1,1,2,6-tetramethyl-6-tert-butyldihydroindene (ADBI) and 1,1,2,6-tetramethyl-3-isopropyl-dihydroindene (ATII) [1, 18].

Because to more sophisticated manufacturing techniques and lower pricing, HHCB was utilised more frequently than AHTN in the 1970s; nevertheless, since the 1980s, nearly 95% of the polycyclic musk compounds used commercially were produced [18]. The proof of severe adverse neurotoxic consequences caused the development of ATTN to end in 1980 [17]. Data from a research of the global synthetic musk industry show that polycyclic musk manufacturing has grown yearly, peaking in 1987 at 4300 tonnes annually. Moreover, in 1987, polycyclic musks accounted for more than a half of the global market for artificial musk fragrances. 70% of the global market's total output is made up mostly of HHCB and AHTN, indicating an increased tendency [19]. The grow in PCMs production and the accompanying reduce in NMs manufacture are attributed mostly to the restrictions on musk ambrette usage that were put in place because of certain toxicologically unfavourable consequences [1,17].

However, the PMs in fish and aquatic samples have been recognized by scientists [20, 21]. The initial account of PMs in fish and water was published in 1994 [22]. These findings point to the PMs' notable lipophilicity and persistence, as well as their propensity to biomagnified in fish and other aquatic creatures. From the late 1990s, there has been a noticeable decline in PMs manufacturing because of its lipotropic properties and poor perishability, which can lead to environmental enrichment and biomagnification [15].

4.3. Macrocyclic Musk

After muscone and civetone's structural characterisation in 1926, the development of the MCMs compounds got under way [1]. Macrocyclic musk is highly stable to light, alkaline environments, fixation, and scents of superior quality. These characteristics make macrocyclic molecules very valuable to the fragrance business [1]. One of the most important molecules in this group is dilactone ethylene brassy-late, an economical musk compound because to its straightforward synthesis and low-cost starting materials [23].

There are five different commercial approaches available today to obtain macrocyclic musk molecules. These are polymerization-depolymerization, acyloin condensations, alkyl peroxide rearrangements, ring expansions, and transesterification reactions [23]. The difficulty caused by the unfavorable thermodynamics of macrocyclization is avoided by all of these techniques employing either a chemical or physical procedure; as a consequence, the cost of macrocyclic musks has significantly decreased during the past thirty years [23].

Due to their high manufacturing costs, macrocyclic musks (MMs) have not yet found widespread use. Currently, their usage is almost entirely restricted to fragrances, and their market share is no more than 3-4% [15]. MMs are still expected to become progressively more significant, especially since many of them are naturally occurring and even their synthetic equivalents resemble their actual counterparts [1].

4.4. Alicyclic Musk

Alicyclic musks (AMs) or linear musks, are the newest type of artificial musk. Modified cycloalkyl esters are utilized to create its structure [15]. Although macrocyclic musks are biologically degradable and have even more tenacity and substance than nitro musks and polycyclic musk, certain macrocyclic musks are still rather pricey, especially those that are found naturally. Because of this, it is still common practice to produce musk odorants in environmentally friendly and cost-effective

ways, which has resulted in the creation of a new class of musk perfumes known as alicyclic musks [24].

In 1975, cyclopentene having been discovered, the alicyclic musk started to begin. Giersch et al. discovered Helvetolide as a new member of this class of compound with musk ordor fifteen years later, and it has a fruity and pear-like scent. Romandolide, which Williams discovered can have the $OCMe_2$ ether moiety substituted by an ester function without sacrificing the musk note, is said to have a less fruity and more ambrette-like aroma than Helvetolide. Both of them can be found in various perfume oils for various purposes [24]. Owing to it special properties, the alicyclic musk will be the essential investigation of synthetic musk later if the problems of the high preparation price will be reduced.

5. Conclusion

Natural musk can be used in drug, incense raw accoutrements, and numerous other fields, and is precious, and extensively used all over the world. Thus, the stalking of wild musk deer is getting more and more serious, and artificial parentage and the emergence of artificial musk deer can reduce the payoff of wild musk deer consequently. Still, due to the destruction of natural territories, land reduction, water pollution, and other reasons, the number of wild musk deer is still declining. Polypeptide and protein are still yet unable to be synthesized from natural musk's chemical components. As a result, synthetic musk has mystery components whose influence and function cannot yet be fully understood, while artificial musk still lacks it. Nonetheless, if all of the factors of the natural musk can be synthesized by affordable accoutrements by chemical response to produce the synthetic musk with the same function as natural musk, the price of the drug which contains musk and scents will reduce the price. The stalking of the musk deer will also be reduced.

This paper has covered the introduction and the application of the natural musk, the zoology and geographic location of the musk deer in China where six different types of musk deer have different biological characteristics. Also, this paper has gone through the chemical compositions of the natural musk where the composition has been divided into two groups water soluble and water insoluble. Additionally, this paper has introduced the development of synthetic musk, introduction, development of four types of synthetic musk which are nitro musk, polycyclic musk, macrocyclic musk with five different synthetic method and alicyclic musk and their future perspective.

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