Musks in perfumery

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Since Baur discovered the musk odor in nitrated benzene derivatives,[1] a tremendous amount of work has been carried out in this field. The chemistry and olfactive properties of musk compounds have intrigued scientists for a long time and still do. Ruzicka was awarded a Nobel Prize for his excellent work on macrocyclic musk compounds.[2] Thorough reviews by Belov and Skvortsova, Beets, Wood, and Abe and Etoa have appeared in the literature.[3-6]

Musk odors were found in -polynitro benzene derivatives, -macrocyclic compounds, -steroids, -heterocyclic compounds, -nitro free benzene derivatives, and -aliphatic compounds.

Although all musk compounds have a musky odor quality in common, trained observers can easily distinguish between macrocyclic and nitro musks. A musk compound usually has, apart from its musk quality, several other perfumery notes. It is not surprising that muscone and civettone, being found in excretions of animals, have a rather strong animal note. Ambrettolide and pentadecanolide have vegetable-like connotations. These compounds have been isolated from ambrette seed oil and angelica root oil respectively. Ambrettolide even shows a weak fruity character.

The odor aspects of synthetic musk compounds may be different. There is a rather strong floral note in 11-oxa-hexadecanolide. Nitro free benzene musks sometimes have an earthy note. Nitro musks and particularly musk ketone, usually have powdery odor connotations. Theimer and Davies compared the degree of muskiness of different compounds.[7]

Not only may the odor quality of the different compounds vary, but also the odor intensity can differ. d'Andrea measured threshold values and determined intensities in relation to the concentration of macrocyclic, nitro musks and nitro free musks.[8] He found that the perceived intensity of a nitro free musk was ten times higher than that of a nitro musk at the same concentration.

The nitro musks, musk ambrette, musk xylene, musk ketone, and musk tibettene were discovered first and still are very important. The well known natural musk compounds muscone, ambrettolide, civettone, and pentadecanolide belong to the macrocyclic group. The commercially most important macrocyclic musk compounds, 11-oxa-hexadecanolide, 12-oxa-hexadecanolide, ethylene brassylate, and cyclohexadec-5-enone-1, are synthetic. A very important group consists of the nitro free benzene musks, acetyl hexamethyl indane, acetyl t. butyl dimethyl indane, acetyl hexamethyl tetraline, and hexamethyl indanopyrane. A musky odor is also observed in certain steroid and aliphatic compounds, 5-alpha-androstene-16-ol-3-alpha, 5-alpha-androstanol-3-alpha, citronellyl ethyl oxalate, and ethyl undec-2-ynoate.

Musks are indispensable in modern perfumery. The annual world production of musks reaches over 2,000 tons, with an average value of more than 300 million dollars. These amounts are totally consumed by the perfumery industry.

The total production can roughly be divided into:

- 5% macrocyclic musks
- 45% nitro free benzene musks
- 50% nitro musks

A rough indication of the mean concentration of the different musk types in the most important applications is given in Table 1. Until 10 years ago, the percentage of musk compounds in a perfume composition was seldom over 2%. Today, a content of 5-10% musk is not unusual.

Table 1

Type	Detergents	Soap	Cosmetics	Toiletries
Macrocyclic	0.5 - 1 %	0.5 - 2 %	0.5 - 2 %	0.5 - 1.5%
Nitrofree Benzene	2.5 - 10 %	1.0 - 2.5%	2.5 - 4 %	2 - 5 %
Nitro	0.5 - 3 %	2 - 3 %	1.5 - 3 %	1 - 4 %

Overlooking the whole field of musk compounds, their performance, stability, and price, one realizes that the best chance for a new musk compound lies in the group of nitro free benzene musks. A tremendous amount of work has already been carried out in this field to search for new musk compounds. Nevertheless, we decided to explore this area in more detail. We realized that success could only be achieved if the following requirements were fulfilled:

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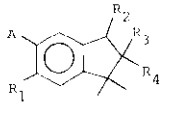
- starting materials readily available
- practical and feasible chemistry
- a unique position
- an excellent performance

Since Carpenter discovered the first nitro free benzene musk, many compounds of this type have been prepared.[9,10] Wood has given an excellent review about the chemistry and olfactive properties of these compounds.[5]

Looking at the structures of the most important representatives of this group, one recognizes the following structural features:

- an aromatic ring substituted with a functional group
- two quaternary carbon atoms, either in ortho position or in meta position (in ortho position, both are part of a 5 or 6 membered ring condensed to the benzene nucleus)
- moreover, in all cases an isolated lower alkyl group is present, sometimes condensed to another ring together with the functional group, or with one of the bulky groups

We wanted to know whether two quarternary carbon atoms are really necessary, because if one such group could be replaced by a tertiary carbon atom, substituted with a bulky group, a convenient synthesis and a unique position could be achieved. We decided to synthesize products with the general structure:

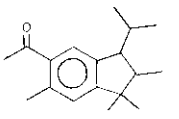


These products can easily be synthesized by:

- acylation of a substituted benzene derivative, followed by reduction and halogenation
- cyclo-alkylation of the substituted benzylhalide with an iso-alkene
- functionalization of the obtained indane derivative

According to the third method, we prepared 15 different compounds. As a functional group we introduced the aldehyde, acyl, nitro, or nitrile functions. For substituent R_1 hydrogen, methyl, and ethyl were investigated. As a bulky group R_2 isopropyl and t.butyl were introduced. Finally for substituents R_3 and R_4 hydrogen or methyl groups were used. However, if R_4 is hydrogen, two possible isomers, cis and trans exist; both have been prepared separately.

It turned out that the product which we have called Traseolide met all of our requirements. This compound has a very powerful musk odor with an excellent performance in all types of perfume compositions.



All compounds had some musky odor; however, the intensity varied strongly. Where Traseolide, which in fact is a trans-isomer, is a powerful musk, its cis-isomer has only a moderate musk connotation.

Variation in the functional group causes quite a difference in the olfactive properties. The nitrile derivative had a very weak musk odor but a rather strong earthy note. The aldehyde possessed a normal musk quality, but also an earthy note, whereas the nitro derivative had only a moderate musk odor. Variations of the acyl group demonstrated that the acetyl group gives the most powerful musk compound. Changing R_3 and R_4 results only in a decrease in musk odor.

Today a lot is known and understood. Nevertheless, this field continues to present a challenge for research workers interested in the chemistry and olfactive properties of musk compounds.

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