Fascinating Organic Molecules from Nature
6. Sweet Stimulants of the Olfactory Nerves – Muscone, Civetone and Related Compounds

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Among the traditional five sensory perceptions, colour and smell often go hand in hand, along with taste. Among the objects used for worshipping God, for instance, flowers and incenses occupy prime places. The subject matter of this article is the chemistry of musk and related perfumes derived from natural sources.

Introduction

The sense of smell plays a vital role in the animal kingdom. The olfactory nerves situated in the nasal passages of human beings are sensitive enough to detect, for example, one three-hundred-millionth part of a grain of musk. The olfactory organs of several animals are even more sensitive. Some moths are known to be attracted by odours which humans cannot detect. Dogs cannot see as clearly as we do but their sense of smell is much more acute than ours. Olfactory receptors being chemoreceptors are stimulated by odorous molecules. In animals, several of these compounds act as pheromones. Though no such function in human beings has been definitely established, perfumes do play a major role in the cultural and social activities of men and women. One of the most sought after is the musky odour. The reason for this is two-fold. Being a comparatively less volatile compound, muscone, the principal constituent of natural musk, for example, has a lingering effect and it is also a fixative for other more volatile odorants. The structures of muscone and the related civetone were established by the Nobel Laureate Leopold Ruzicka and his co-workers in the latter half of the 1920s.

Keywords
Muscone, civetone, exaltone, ambrettolide, exaltolide, nitro musks.
Chemistry of Muscone

Muscone was first isolated by Walbaum in 1906. The compound is extracted from a glandular secretion of the musk deer, *Moschus moschiferus*. The secretion collects in a reservoir, the musk pod, located in the abdominal part of the musk deer, which is a native of Siberia, China, and Tibet. From a single musk deer, 25 to 40 g of dried musk grains can be obtained; the muscone content varies from 0.5% to 2%. Though it is possible to extract the material without killing the animal, the traditional method involves killing this very shy herbivore. The structure of muscone was elucidated by the Croatian born Swiss chemist, L. Ruzicka and his co-workers.

Earlier, Walbaum had shown that the compound is a ketone with the molecular formula, $C_{16}H_{30}O$. However, he was unaware of the skeletal structure of the compound. Ruzicka subjected the compound to chromic acid oxidation which resulted in the formation of a series of even-numbered aliphatic dicarboxylic acids ranging from succinic acid to decane-1,10-dicarboxylic acid. By controlled oxidation it was also possible to obtain a dicarboxylic acid, which retained all the carbon atoms of muscone and this was identified as 1-methyltridecane-1,13-dicarboxylic acid. Therefore, muscone could be assigned the structure (2). Natural muscone is laevorotatory and has the (R) configuration as shown in (2); this was established on the basis of an asymmetric synthesis and ORD\(^1\) studies. The first synthetic proof of the structure was provided by Ziegler in 1934 who synthesized racemic muscone using the dinitrile (3) which on treatment with LiNEtC\(_6\)H\(_5\) gave dl-muscone via (4) (Thorpe reaction\(^2\)). To promote the desired intramolecular cyclisation a condition of high dilution was used (Scheme 1).

\[^1\] The change of optical rotation with the wavelength of the incident light is known as Optical Rotatory Dispersion (ORD). It and the related phenomenon of Circular Dichroism (CD) are important tools in stereochemical studies.

\[^2\] The base-catalysed self-condensation of an aliphatic nitrile resulting in the formation of an enamine is known as the Thorpe reaction. In the Ziegler modification, a dinitrile is used as the substrate to obtain a cyclic compound.

\[
\begin{align*}
\text{CH}_3 \\
(\text{CH})_2 \text{-CH-} \text{COOH} \\
\text{CH}_2 \text{-CH-} \text{COOH}
\end{align*}
\]

\[
\begin{align*}
\text{O} \\
\text{H}_2 \text{C}
\end{align*}
\]
Subsequently, several more syntheses of muscone were reported in the literature. For example, Blomquist and co-workers used the following route for the synthesis of \( dl \)-muscone with 14-bromo-3-methyltetradecanoic acid (5) as the starting material. After esterification, (5) was condensed with diethyl malonate, the product was hydrolysed and decarboxylated to obtain the dicarboxylic acid (6). The diacid chloride of (6) was then treated with triethylamine, using high dilution, to bring about intramolecular cyclisation to form (7) via the diketene intermediate (8). On treatment with aqueous methanolic potassium hydroxide, the \( E \)-lactone (7) underwent hydrolysis to yield the carboxylic acid (9) which was decarboxylated to obtain \( dl \)-muscone (Scheme 2).

H Nozaki et al devised a method for synthesising \( dl \)-muscone from cyclotridecanone (10). On treatment with 3-chloro-2-chloromethylpropene (11), the ketone (10) yielded the bicyclic product (12). Catalytic hydrogenation of the latter gave (13) which on photolysis in methanol yielded the ester (15) via the ketene intermediate (14). A four-step reaction sequence involving hydrolysis, treatment with mercuric acetate–iodine, hydrolysis and oxidation converted (15) to \( dl \)-muscone (Scheme 3).

**Previous articles:**

As is often the case with naturally occurring chiral compounds, the two enantiomers of muscone differ in their olfactory characteristics. The naturally occurring (R)-(−)-enantiomer has a stronger and superior odour than its (S)-isomer. Therefore, several attempts have been made to synthesise this enantiomer. In one such synthesis, reported by Kamat et al., (+)-citronellal (16) was used as the starting material. A key step used for converting this readily available chiral compound to (R)-(−)-muscone was ring closing olefinic metathesis (RCM). In the first step, (16) was subjected to a Grignard reaction with 10-bromo-dec-1-ene (17) in the presence of magnesium in diethyl ether. The resulting alcohol (18) was converted into its TBDMS (tert-butyldimethylsilyl) derivative (19). Ozonolysis of (19) at a low temperature gave the dialdehyde (20), which was subjected to a Wittig reaction to get (21). After hydrolysis, the resulting alcohol (22) was oxidised and the ketone (23) thus obtained was treated with bis (tricyclohexylphosphine) benzylidene ruthenium dichloride (24) (RCM and macrocyclisation protocol). The resulting mixture of the E- and Z-isomers of dehydromuscone (25) was hydrogenated over palladised charcoal to get the desired (R)-(−)-muscone (2) (Scheme 4).

Scheme 3.

Synthesis of Natural (R)-(−)-muscone

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In another route, (+)- citronellol (26) was first converted into its TBDMS derivative which was subjected to ozonolysis followed by a Wittig reaction and a final oxidation using sulphur trioxide–pyridine complex in dimethyl sulphoxide containing triethylamine to obtain (27). The latter on Grignard reaction with 10-bromo-dec-1-ene (17) and magnesium gave (22) (Scheme 5).

A practical method of optical resolution of dl-muscone has also been recently reported. In this procedure, dl-muscone was treated
In 2011, Cheng et al described yet another practical method for the synthesis of di- as well as (R)-(-)-muscone using the commercially available 1,10-dibromodecane (31) as the starting material.

Scheme 6.

with N,N’-dibenzyl-L-tartaramide (28) in the presence of scandium trifluoromethane sulphonate (Sc(OTf)₃) and methyl orthoformate (29). The mixture of diastereoisomeric acetals thus obtained could be fractionally recrystallised to obtain the pure diastereomers. Subsequent hydrolysis of the acetal (30) yielded optically pure (2). One advantage of this procedure is that in the final step, (28) could be recovered and used again for the resolution of another batch of racemic muscone.

In 2011, Cheng et al described yet another practical method for the synthesis of di- as well as (R)-(-)-muscone using the commercially available 1,10-dibromodecane (31) as the starting material. Condensation of (31) with ethyl acetoacetate and subsequent work-up yielded the diketone (32). The latter was subjected to an intramolecular cyclisation reaction aided by propyl zinc iodide to obtain dehydromuscone (25) in good yield. Direct hydrogenation of (25) gave di-muscone. On the other hand, (R)-(-)-muscone could be prepared from (25) by an enantioselective formation of a ketal using (+)-1,4-dibenzyl-D-threitol (33) prior to hydrogenation (Scheme 6).

4 Enantioselective synthesis, also known as chiral or asymmetric synthesis, is a reaction designed to obtain enantiomers or diastereomers of an optically active product in unequal amounts. Ideally, the objective is to synthesise one enantiomer.

Scheme 6.
Exaltone

Exaltone, cyclopentadecanone (34) is a trail pheromone secreted by the American muskrat, a rodent found in the marshlands of Louisiana. It has an odour similar to that of muscone and is used as an alternative to muscone in perfumery compositions. Its synthesis described herein uses the readily available aleuritic acid (9,10,16-trihydroxyhexadecanoic acid) (35) which is a major component of shellac. Treatment of (35) with triethyl orthoformate in the presence of benzoic acid, followed by pyrolysis and esterification gave the olefinic ester (36). Subsequent catalytic hydrogenation followed by oxidation with pyridinium dichromate in DMSO (dimethylsulphoxide) yielded the dicarboxylic acid mono ester (37). A modified Hunsdiecker reaction using mercuric oxide and bromine converted (37) into the bromo ester (38). Treatment of (38) with DMSO in acetic acid containing sodium nitrite followed by esterification yielded the diester (39). In the final step, (39) was subjected to an acyloin condensation (using metallic sodium in xylene) and the product (40) reduced with zinc and acid to obtain exaltone (Scheme 7).

Civetone

Civet, the secretion from the perineal glands of the African civet cat, Viverra civetta and V. zibetha is one of the oldest perfumery materials known to mankind. These glands situated below the base of the tail produce a secretion which collects in a large pouch. The chief chemical component of this oily material with a musk-like odour is civetone. One interesting way of collecting civetone without killing the animal is to feed it with coffee beans which get excreted without digestion. However while passing
through the animal the beans get infused with civetone. After a thorough cleaning the beans are used to make coffee having a rich musk-like odour!

Its structure as (9Z)-cycloheptadec-9-en-1-one (41) was elucidated by Ruzicka (see Box 1) and his co-workers. The presence of the carbonyl group was shown by the ready formation of an oxime derivative. Civetone decolourises bromine water indicating the presence of a double bond. Catalytic hydrogenation yields the dihydro derivative (42). The molecular formula of (42), C_{17}H_{32}O, indicates one degree of apparent unsaturation and therefore the presence of a ring. On oxidation with chromic acid, (42) yielded a dicarboxylic acid which was also obtained from civetone by a

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**Box 1.**

Leopold Stephen Ruzicka (1887–1976) was born in a small village in Croatia but worked in Switzerland. He was a student of H Staudinger at the Technische Hochschule in Karlsruhe (Germany). Later, he moved to Zurich along with Staudinger. Much of his research work was conducted at the Eidgenossische Technische Hochschule (ETH), Zurich. His early studies were on the naturally occurring insecticides, pyrethrins. Subsequently, he made important contributions to the chemistry of terpenoids and steroidal hormones. His theory of biogenesis of terpenes was an important milestone in biosynthetic studies on terpenoids. He was awarded the Nobel Prize in Chemistry, 1939 which he shared with Adolf Butenandt.
Clemmensen reduction followed by ozonolysis. It was identified as pentadecane 1,15-dicarboxylic acid (43) by comparison with a synthetic sample. On oxidation with potassium permanganate in the cold, civetone gave a keto dicarboxylic acid (44) which on treatment with sodium hypobromite yielded azelaic acid (45) as one of the products. Stoll confirmed the structure of civetone by a synthesis starting with the dimethyl ester (46) of (44). The ketal derivative (47) of (46) was subjected to an intramolecular acyloin condensation using metallic sodium in xylene. The product (48) was reduced by hydrogenation over nickel and the resulting diol (49) treated with HBr in acetic acid to obtain civetone (Scheme 8).

Blomquist and co-workers used aleuritic acid (35) as the starting material. Reaction of (35) with HBr in acetic acid followed by reduction with zinc in methanol gave the bromo olefinic acid (50). By a series of conventional reactions (50) was converted into the dicarboxylic acid mono ester (51) which gave civetone.
Nitromusks

The great demand for muscone and the ethical and other issues concerning the slaughter of the musk deer triggered the search for synthetic substitutes. A Baur who was looking for compounds with more explosive power than TNT accidentally found that the trinitro derivative (52) of 3-tert-butyl-m-xylene (53) (obtained from m-xylene by a Friedel-Crafts alkylation reaction) possessed a strong musk-like odour though it was inferior to TNT as an explosive (Scheme 10). This compound is known as musk xylene. Subsequently, other closely related compounds, such as musk ketone (54) and musk ambrette (55) were prepared and used in perfumery as substitutes for natural musk. However, following observations that these compounds could be carcinogenic and are not bio-degradable, their use is restricted nowadays.

Musk-like Compounds of Plant Origin

Three macrocyclic compounds of vegetable origin are used in perfumery for their musk-like odour. All of them are lactones. Exaltolide, isolated from the roots of Angelica archangelica, is cyclopentadecanolide (56). Ambrettolide, first obtained from ambrette seeds, Hibiscus abelmoschus, by Kerschbaum in 1927 has the structure (57). Its dihydro derivative, hexadecanolide (58) also possesses the musk-like odour, though to a lesser extent.
Synthesis of Exaltolide

In the section on exaltone, the preparation of methyl-15-bromopentadecanoate (38) from aleuritic acid (35) was described. Hydrolysis of (38) gave the corresponding carboxylic acid (59) which underwent cyclisation in the presence of potassium carbonate to yield exaltolide. Recently, using the enzyme lipase, from Candida Antarctica, methyl 15-hydroxypentadecanoate (60) has been converted into (56) in 80% yield (Scheme 10). A similar strategy was also used for preparing ambrettolide.

Conclusions

Apart from muscone, civetone and ambrettolide, several other compounds of natural origin have been used in perfumery from time immemorial. These include frankincense and myrrh. The chemistry of these materials is as fascinating as those of muscone, etc., described above.

Suggested Reading


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