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The animal musks and a comment of their biogenesis

by J.P. Ward and D.A. van Dorp[1]

Unilever Research Laboratorium, P.O. Box 114, NL-3130 AC Vlaardingen (The Netherlands)

Summary. The macrocyclic compounds occurring in animal glandular secretions are reviewed. Early hypotheses for their biogenesis from fatty acids via ω and β-oxidations are found to be inadequate. Radio-active acetate was incorporated into macrocyclic ketones of muskrat (*Ondatra* sp.) preputial glandular secretion, but radio-labelled stearate, oleate, and α, ω-octadecandioic acid were not incorporated.

Introduction

Elbert Hubbard's[2] adage that a perfume is any smell that is used to drown a worse one might have been coined with the animal secretions musk and civet in mind. Significantly, these scents were, and are, favourites with men for their own use. If nowadays more women should be found wearing them, then it is perhaps mainly for their effects on other women!

That civet has long been prized in perfumery is attested to in the plays of Shakespeare: '... he rubs himself with civet ... the sweet youth's in love' (Much ado about nothing, III, 2, 45), 'The courtier's hands are perfumed with civet' (As you like it, III, 2, 60), 'Give me an ounce of civet, good apothecary, to sweeten my imagination' (King Lear, IV, 6, 133). But Shakespeare had no illusions about the nature of civet: '... the very uncleanly flux of a cat' (As you like it, III, 2, 65).

Musk has been described as the most potent of all perfumes. Allegedly, the walls of the Empress

Josephine's chambers still smelled so strongly of it that workmen carrying out repairs in 1900 became senseless[3]. Similar tales exist of the walls of Iranian mosques retaining the smell of musk for centuries after it had been mixed into the mortar with which they were built[4].

The smell of musk is described as sweet and penetrating, but civet is undeniably rank. It has been said that ambergris, musk, civet and castor all possess an olfactory component recalling the smell of human scalp and pubic hair[5], and it seems scarcely coincidental that all 4 are derived from animals. In particular, musk, civet and castor are obtained from certain abdominal glands of the musk deer, the civet cat and the American beaver, having in the case of the deer and the beaver male sexual connotations. A 4th land animal, the musk-ox, although associated with the smell of musk is not a supplier of perfumery material.

Associations in the animal and plant kingdoms with the smell of musk are numerous (tables 1 and 2). Although the animal secretions contain certain chemical components possessing a common structural feature, namely odorous macrocyclic compounds, there seems to be no certainty of a common feature among the plants listed. Nevertheless, there are indications that there is a basis for the appellation 'musk' in these plant names. Ambrettolide (scheme 1), the macrocyclic lactone of 16-hydroxy-7-hexadecenoic acid, is associated with the seeds of *Hibiscus abelmoschus*[6]. Coumarins are frequently described as components, for example, of the *Ferula* species[7], and galbanum and resins obtained similarly from *Ferula* species contain sulphur compounds[8] and pyrazines[9,10], again with possible hints of animal-like smells. The structure of fissinolide, a bridged ketone from the fruits of *Guarea trichilioides*[11], suggests a far-off structural relationship with steroids and the macrocylic ketones. But this is speculation.

Animal perfumes and odours have been reviewed authoritatively by Lederer, and even after 30 years this work is still eminently readable[12]. We shall attempt here to assess the progress since then in the identification of new organic compounds in the animal secretions, and their biogenesis.

Table 1. Animals associated with the smell of musk and civet*

Common name	Zoological name
Musk deer	*Moschus moschiferus* (Moschinae)
Muskrat	*Ondatra zibethicus* (Muridae)
Musk-ox	*Ovibos moschatus* (Bovidae)
Musk-turtle	*Aromachelys odoratus* (Kinosternidae)
	Sternotherus odoratus
Musk-hog	*Tayassu albirostris* (Tayassuidae)
Musk-shrew	*Crocidura* sp.
	Desmana moschata
Musky-rat	*Hypsiprymnodon moschatus*
Musk-mole	*Scaptochirus moschatus*
Civet cat	*Civetticus civetta* (Viverridae)
	Viverra zibetha (Viverridae)

* Lederer's review[12] includes a table listing birds, reptiles, insects and molluscs in addition to animals.

Scheme 1.

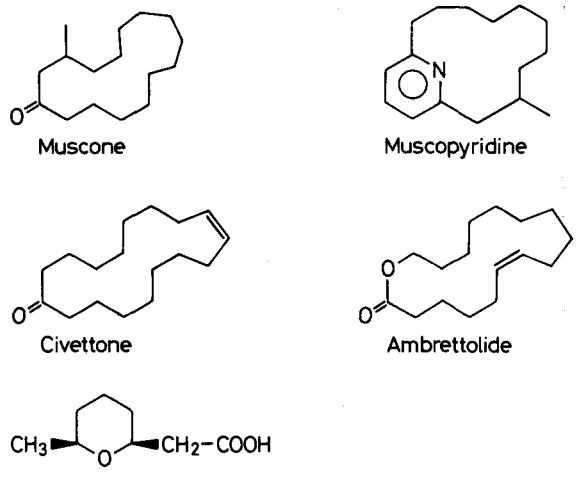


Table 2. Plants associated with the smell of musk

Common name	Botanical name	Literature*
Musk-seed (ambrette)	*Hibiscus abelmoschus* (Malvaceae)	V 33, 38, 42
	Hibiscus moschatus (Malvaceae)	
Musk-root	*Ferula moschata* (Umbelliferae)	VI 566, 586
Musk-plant	*Adoxa moschatellina*** (Adoxaceae)	III 62, 630
	Mimulus moschatus (Scrophulariaceae)	VI 352, 355, 356
	Erodium moschatum (Geraniaceae)	IV 195, 199, 200
Musk-tree	*Trichilia moschata* (Meliaceae)	V 64, 67, 423
	Olearia argophylla (Compositae)	III 455, 486
Musk-wood	*Guarea grandifolia* (Meliaceae)	V 64, 423
	Guarea trichilioides (Meliaceae)	
Musk-rose	*Rosa moschata* (Rosaceae)	VI 84, 92
Musk-melon	*Cucumis melo* (Cucurbitaceae)	III 621
Musk-mallow	*Malva moschata* (Malvaceae)	V 33
Musk-thistle	*Caduus nutans* (Compositea)	-

* The references are to R. Hegnauer, Chemotaxonomie der Pflanzen, Volumes I-VI, Birkhäuser Verlag, Basel (1962 et seq.).

** The scent of this flower contains well-known aroma compounds but no macrocyclic compounds; E.J. Brunke and F.J. Hammerschmidt, Phytochemistry, in press (1981).

Brief description of animals

The musk deer *Moschus moschiferus*[13] is a small antlerless animal found in the wet mountain forests from Siberia and Korea to the Himalayas. After the musk deer had become rare as a result of hunting, attempts were made by the Chinese government to save the animal by breeding it in captivity, and some success was reported[14]. The male has a musk gland, called a pod, in the skin of the abdomen. Its secretion is described as a honey-like mass with a strong odour which may function as a sexual attractant. After this pouch is cut off the secretion hardens, changing colour to blackish brown, and becomes granular. The dried secretion forms the musk grains of commerce which have been an object of trade between China and the West by the overland route since the early Middle Ages at least. Frequently an alcoholic tincture is prepared from them for use in perfumery.

The musk-ox *Ovibos moschatus* is a hoofed ruminant found in arctic North America and Greenland. The male is a shaggy, stoutly built animal covered with brown to black hair which has a musky odour. Little, if anything, is known about the chemical nature of this odour. One might guess that it may have a steroid origin (Lederer[12]).

The muskrat *Ondatra* sp. is also a native of North America. The common muskrat resembles a large house rat but with its tail flattened. Its hind feet are partially webbed between the toes. The fur is shiny brown, with a dense undercoat. It lives solitarily most of the time, either in a burrow in a steep bank, or in winter in a reed hut built in marshy shallows. The burrows are constructed above water level and are connected to an underwater entrance by a tunnel. The muskrats feed mainly on aquatic vegetation, and possibly small animals. Mating occurs in spring and summer, the gestation period being about 30 days. Several litters of 2–6 young may be born each season.

The muskrat was introduced into Europe for the sake of its fur, referred to in the trade as musquash. The animal has now become a serious pest, especially in the Netherlands, because of its tunnelling below water level, undermining dykes and canal banks. A recent release in the chemical press[15] indicates that government efforts to halt the spread of the muskrat northwards in the Netherlands by sporadically trapping and killing the animals whenever sighted have not succeeded. The report also contains a suggestion that pheromones might be used to expedite the process of eradication. This raises questions about how much is known of their role in the reproductive cycle of the muskrat, and even more basic questions of age and sexual maturity in muskrats. A method of age determination in muskrats, based on a study of their teeth and in particular the wear of the crown and the simultaneous growth of the root, has been described[16]. Behaviourally significant volatile compounds in the anal gland of the rabbit have been investigated by measuring their effect on the animals' heart rate when sniffed[17], and a similar technique could be envisaged for muskrats.

Civet cats are any of a large group of mainly nocturnal animals of the family Viverridae, and although related to the Felidae they are not true cats. They do have cat-like bodies, long tails, and weasel-like faces. The fur may be grey or brown, and patterned. All civets, male and female, have scent producing glands located in a double pouch near the genital organs. The yellowish fatty secretion of these glands has a musk odour and is used by the animal for territory marking. This secretion is known in commerce as civet and used as a fixative in perfumery. Civet can be removed from captive animals every 14–20 days. The African species *Civetticus civetta* and the Indian *Viverra zibetha* provide most of the civet for perfumery. The amount of civet reported to be secreted by a single civet cat varies from 2–3 g per month to 10 g when mixed with fat (butter) used to fill the gland after each emptying[18]. This practice, putatively to prevent infection of the gland, may account for the wide variation found in the quality and quantity of exported civet. Trade figures indicated that in 1953, 28.7 t of civet were produced in Ethiopia for export. In 1963 this had sunk to 1.4 t.

Chemical constituents of animal musk glandular secretions

Earlier work on structure determination and chemical synthesis of animal musks was discussed by Lederer[12]. By far the most interesting of the known animal glandular constituents are the macrocyclic compounds amounting to no more than a few percent of the total material (scheme 1).

Walbaum isolated muscone[19], identified by Ruzicka as (–) 3-methylcyclopentadecanone[20], from musk. The structure was confirmed by synthesis. Much later, Schinz, Ruzicka, Geyer and Prelog described the isolation of muscopyridine from the same source[21].

Civet was shown by Sack to contain civettone[22], the structure of which was elucidated by Ruzicka to be 9-cycloheptadecenone[21]. This was confirmed by the first synthesis of a macrocyclic ketone by cyclisation of a derivative of an α, ω-dicarboxylic acid[24]. Although many details of this now classical method have been perfected, the principle has been retained in nearly all subsequent commercial syntheses of macrocyclic ketones and lactones. Improvements in methodology and choice of starting material, however, continue to be found. It may be sufficient to mention a synthesis of ambrettolide from a natural product, aleuritic acid, 9, 10, 16-trihydroxypalmitic acid, obtainable from shellac[25], and of muscone from cyclododecanone[26], the latter representing a departure from the original synthesis concept.

Undoubtedly the richest spectrum of macrocyclic compounds is that contained in 'American musk', the glandular secretion of the muskrat. Stevens and Erickson showed that cyclopentadecanone and cycloheptadecanone together with the corresponding secondary alcohols were present[27]. In a later publication Stevens showed that oxidation of the glandular secretion led to the formation of cyclotridecanone and cyclononadecanone, with the implication that the corresponding carbinols were originally present[28].

More recently, Van Dorp, Klok and Nugteren[29] have found that while the 'classical' macrocyclic ketones form the bulk of the ketonic material, numerous other homologues, saturated and unsaturated, are present (table 3). The acetylenic macrocyclic ketones deserve notice, particularly.

For comparison with the natural products 5cis-cyclopentadecenone, 5cis-cycloheptadecenone, 9cis-cyclononadecenone and their acetylenic precursors were prepared as summarized in scheme 2.

Furthermore, skatol and fatty acids were found in civet[22], and the muskrat secretion was also shown to contain fatty acids[28]. More exact data for the fatty acids in civet and American musk were provided by Van Dorp, Klok and Nugteren[29] (table 4).

Table 3. Macrocyclic ketones in muskrat gland and civet[29]

Compound	Content (% of cyclic ketones) Muskrat gland	Civet
Cyclopentadecanone	21	
5cis-cyclopentadecenone	16	
Cyclopentadecynone	0.5	
Cyclohexadecanone	0.5	1
Cycloheptadecanone	41	10
5cis-cycloheptadecenone	10	
6cis-cycloheptadecenone		3
7cis-cycloheptadecenone	4	
9cis-cycloheptadecenone		80
5cis, 11cis-cycloheptadecadienone	3	
5-cycloheptadecynone	1	
7cis-cycloheptadecen-5-ynone	2	
Cyclononadecanone	1	
9cis-cyclononadecenone		6

Table 4. Fatty acids composition (%) of total lipids of civet and of musk gland[29]

Fatty acid*	Civet	Musk gland
14:0	35	2
16:0	21	25
16:1	3	6
18:0	6	3
Δ9-18:1	15	45
Δ9, 12-18:2	1	8
20:2	1	-
20:1	0.5	1

* Short hand notation: Δ position of double bond(s)-number of carbon atoms: number of (cis)double bonds.

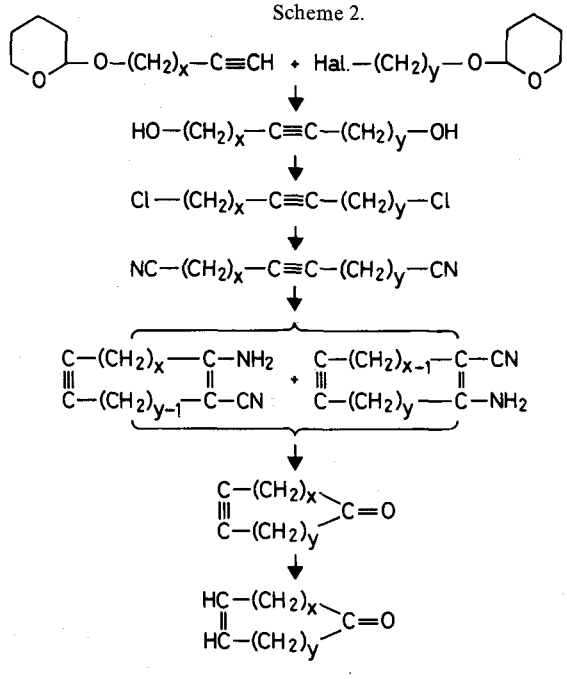
Stevens'[28] percentages of macrocyclic compounds and fatty acids in muskrat gland are in broad agreement with these latest figures if compounds with the same number of carbon atoms are summed, e.g. oleic and stearic acid taken together as C_{18}. Stevens believed on the basis of his analyses that there was 'an intimate biological association of these ketones with the *corresponding* fatty acids' (our italics).

Biogenesis of macrocyclic compounds in animal musk glands

The number of carbon atoms in the macrocyclic ketones, and above all the position of the double bond in civettone, 9-cycloheptadecenone, led (or perhaps misled) Ruzicka to suggest a relationship to palmitic acid and oleic acid; '... Umwandlungsprodukt der Ölsäure ...' (Ruzicka[23], p. 236), and '... das Muscon in ... der Palmitinsäure .... seinen Ursprung haben könnte' (Ruzicka[20], p. 1014). This idea was elaborated by Stevens into a hypothesis[28] for the biogenesis of macrocyclic compounds in muskrat, as given in scheme 3. A similar hypothesis was proposed to describe the formation of muscone (scheme 4).

The essential ideas of ω- and β-oxidations are well known biochemical transformations. However, it is significant that no dicarboxylic acids are known to occur in these animal secretions, despite attempts to find them. Erickson and Hix, moreover, describing the fatty acid analysis of muskrat gland secretion[30],

Scheme 2.



Halogen	x	y
Br	3	11
Cl/I	3	9
Cl/I	9	7

sounded a note of caution: 'While it is possible to account for the production of macrocyclic ketones from monobasic acids using biological processes, it would seem difficult now to relate the acids found in muskrat scent glands to macrocyclic carbinols, which must be regarded as the parents of the corresponding ketones'. And later: 'There is nothing to indicate that it is possible to synthesize macrocyclic ketones from saturated monobasic acids; however, if the biological processes of β oxidation .... and ω oxidation ... are recognized, the formation of large ring ketones from these oxidation products can be accounted for on the basis of well known methods of *organic chemical synthesis*' (our italics).

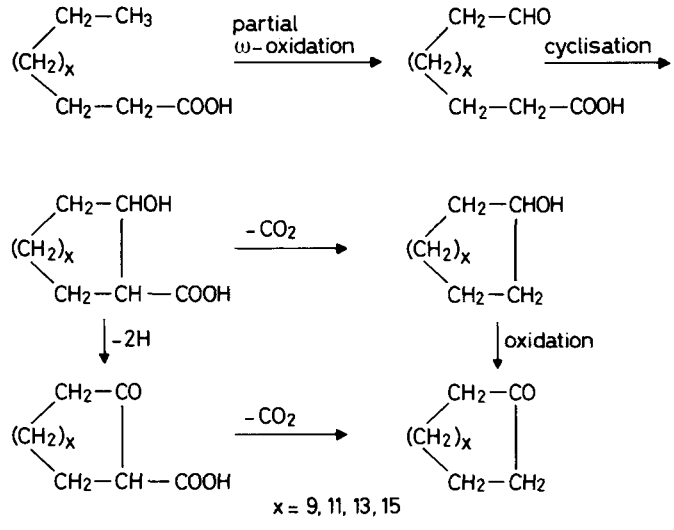
Biemann, Büchi and Walker, however, disagreed outright with these schemes. Instead they invoked, at that early stage, the idea that acetate was the precursor of these macrocyclic compounds, in a scheme based on the polyketide concept, and they proposed that the methyl group of muscone might be derived from propionate or introduced in a biological alkylation step, as known from sterol biosynthesis[31]. It was on the basis of these considerations that these authors proposed, and proved by synthesis, the correct structure for muscopyridine (scheme 1).

Recently, Maurer and Thommen have isolated cis 6-methyltetrahydropyran-2-yl acetic acid (scheme 1) from civet, and shown that it is optically active, possessing the (S,S) configuration[32]. The very low concentration of this compound in civet (2 mg/kg) might be a ground for caution in discussing its origin, especially in view of the practices mentioned above in isolating civet from the cats' musk gland. Nevertheless, the similarity of the heterocycle and carbon skeleton to that of muscopyridine, and the configurational relationship to the macrocyclic (S) carbinols of muskrat seem to warrant the notion that the compound may indeed be a product of an enzyme system involved in the biosynthesis of the macrocyclic musks.

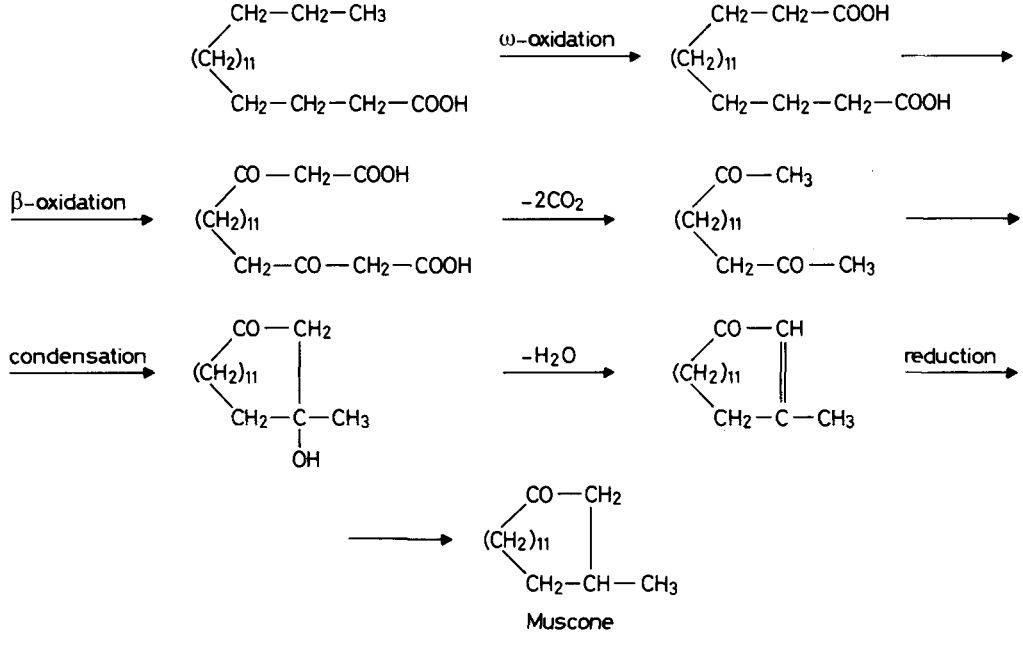
Exploratory work, carried out in our laboratory by D.A. van Dorp and co-workers, on macrocyclic compounds in the muskrat, demonstrated the essential correctness of the above doubts and viewpoints about their origins, and reinforced the point that the macrocyclic ketones in the preputial gland of the muskrats may indeed be sex pheromones.

The preputial gland in which the musk secretion occurs was found to be developed only in the male

Scheme 3.



Scheme 4.



animal. It was undeveloped in the female. Male muskrats captured in the Netherlands in early autumn (September) could be categorized as young animals born that year, in which the musk gland was scarcely developed, and older animals in which the gland was only partly filled. Ages were assessed on the basis of length, weight, the testes and the teeth (compare van Troostwijk[16]). It was possible to discriminate between very young animals (3 months), and those less than 1 year, more than 1 year, and 2–3 years of age. Male muskrats caught in the spring all had fully filled musk glands. There was a correlation between the size of the musk glands, the sexual activity of the animals and their spring migration (during which most of them were sighted and captured). All the maxima occurred in April, about 10 months after the birth of the animals.

The glandular secretions contained macrocyclic ketones and esterified carbinols (table 5) which were found only in this secretion and not in the liver or other parts of the animal. A number of the macrocyclic compounds were unique, unsaturated compounds, again (like civettone) with a formal resemblance to straight chain olefinic acids. It may be significant that polyisoprenoid compounds were also present. They remain as yet unidentified, but mass spectroscopy indicated molecular weights above 1000. The esterified carbinols could be saponified and oxidized to the corresponding ketones. The $\Delta 5$ olefinic compounds were chiral and have the S-configuration[29].

After s.c. injection into male muskrats captured in the spring (March, April, May) in the Netherlands, ^{14}C-marked acetate was incorporated into the macrocyclic compounds in the preputial gland secretion. Radiomarked stearate, oleate and a, ω-octadecandioic acid were not incorporated, nor were these substrates incorporated into macrocyclic compounds when in vitro experiments were conducted with minced muskrat gland[33]. It is, therefore, clear that biogenetic schemes of synthesis of the macrocyclic compounds in animals musks based on oleate or stearate or palmitate, and concepts of ω-oxidation followed by cyclisation are wrong, certainly as far as the muskrat is concerned. The characteristic positions of the olefinic bonds in civettone and the muskrat ketones and carbinols may be a general result of dehydrogenases participating in the final stages of the biosynthesis. No intermediates have been found between acetate and the macrocyclic end-products in the case of muskrats, but the secretions from the musk deer and civet cat contain unique heterocyclic compounds mentioned above (see also scheme 1) which might serve as markers in investigating the biosynthesis of the macrocyclics.

Table 5. Muskrat gland neutral lipids[33]

Fraction	Type	%
1	Monoesters, waxes, polyisoprenoids	38
2	Macrocyclic ketones	5
3	Triacylglycerols	49
4	Polar lipids	8

Table 6. Products from fraction 1 of muskrat gland lipids (table 5) after saponification[33]

Type	%
Primary alcohols	9
Macrocyclic alcohols	40
Cholesterol	1
Polyisoprenoids	50

1 Acknowledgment. We wish to thank Dr W.J. Doude van Troostwijk, Research Institute for Nature Management, Arnhem, for his assistance in obtaining muskrats, and Mr J. Vellekoop, Leiden, for the Shakespeare quotations.
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