# SYMPOSIUM ON CHEMICAL ASPECTS OF FLAVOR

## Introduction

To meet the enormous problem of starvation and malnutrition in various parts of the world, new sources of nutritional foods must be found. The food produced from these sources must conform with the flavor habits of the indigenous population—it must have acceptable flavor. Flavor research is necessary to maintain quality of processed foods, which are continuously becoming a larger part of the American diet.

Remarkable advances are being made in ultramicro-analytical methods used in flavor research. Although progress is slower than was expected, it is very encouraging that some organoleptically important compounds are being reported out of the myriad of data being accumulated. The Flavor Subdivision of the Division of Agricultural and Food Chemistry of the American Chemical Society has been organized, mainly by the efforts of Dr. Irving Hornstein, USDA, MQRD, Beltsville, Md., who was appropriately our first chairman, to serve as a focal point, a meeting place for discussion of flavor research.

All papers were delivered superbly at this sympo-sium, and the large audience responded enthusiastically to the interesting topics. Papers which were not submitted by the deadline will be published later, and some will be published elsewhere. We hope that the coverage and promptness of publication of the symposium papers in the JOURNAL of AGRICULTURAL AND FOOD CHEMISTRY will attract many contributions on flavor chemistry to this journal.

We believe that this symposium should be just the beginning of vigorous activity by the members of the Flavor Subdivision to focus attention on the chemistry of flavor, to emphasize the chemistry of the chemical senses. The Flavor Subdivision and the JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY should serve as the means for presenting the latest developments and accomplishments in flavor chemistry research.

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MUSK ODOR

# Olfaction, Musk Odor, and Molecular Properties

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The "penetration and puncturing" theory of olfaction explains quantitatively the olfactory threshold of different types of molecules, but the quality of the odor has proved more difficult to measure and to interpret in fundamental terms. This theory predicts that rates of desorption and molecular cross-sectional areas should be of primary importance. The present work tests the theory as applied to the musk odor, using more than 50 compounds representing most known groups possessing strong musk odor as well as closely related structures with weak or no muski-ness. The study confirms the correlation between musk odor intensity and desorption rate and molecular dimensions and shows that chemical type is not important. The compounds were evaluated for odor strength by a panel of expert perfumers. The muskiness predicted by the theory corresponded to these evaluations, all good musks having standard desorption rates in the range 0.4 to 1.7, molecular cross sections of 40 to 57 sq. A., and ratios of 2.8 to 3.3 of length to breadth of the molecule.

Despite a recent upsurge of interest and consequent substantial activity in the field of olfaction, the mechanism of odor perception is but little understood. The various hypotheses (4, 11, 28) require close scrutiny to determine their validity, but there is a dearth of reliable data for testing them. The present work presents some such data in the form of correlations between intensity of odor and measurable physical properties of a group of compounds possessing the odor of musk.

## Olfactive Process

This process as a whole may be envisioned schematically (Figure 1). An odor vector consisting of a stream of odorant in air passes over the olfactory epithelium which houses the receptors—for example, about $10^8$ in the rabbit—causing nerve ending stimulation. The sensing process is carried as a nerve impulse along the axons ensheathed as nonbranching bundles to the approximate 2000 glomeruli which may well be data-processing centers. The glomeruli are synaptically connected, each with 20 to 30 mitral cells. Finally, the message is carried to the brain. We are concerned here only with the primary stimulus process, which involves the receptor cells.

Figure 2 shows the olfactory mucosa as interpreted from electron photomicrographs. The odor-producing
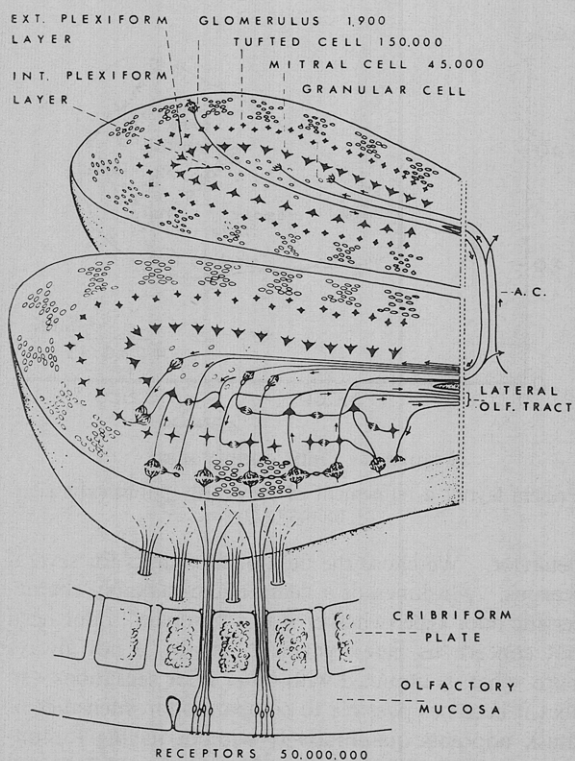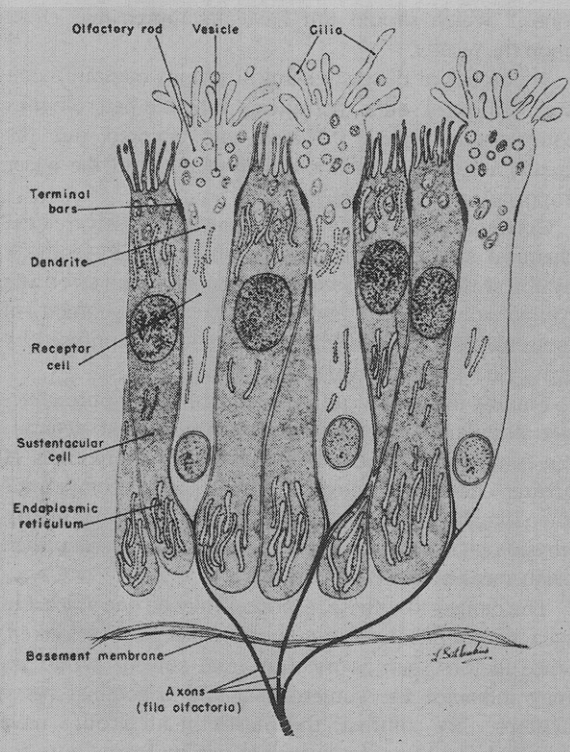
Figure 1.  Olfactory system (*20*)

Figure 2.  Olfactory mucosa (idealized) (*14*)

molecules come in contact with the olfactory mucosal membrane, probably at or near the cilia, causing a change in the charge distribution which gives rise to the

signals transmitted ultimately to the central nervous system.

Having reached the limits of resolution of the microscope, further structural details at the sensory membrane must be obtained by deduction.

Figure 3 is a schematic representation of the environment of the olfactory nerve endings.

In order to produce a sensation, the odor molecules must reach the nerve endings.   Therefore they must be adsorbed onto the mucus which surrounds the membrane and must to some extent penetrate this aqueous layer, which has a thickness between 10 and 50 times the molecular diameter of the odor vector molecule, whose molecular weight is a maximum of about 300.   Further requirements may be desorption from the mucus onto the phospholipid-protein structure of the cell membrane itself, and, as postulated (*11*), actual penetration with hole formation into the cell interior, thus permitting a mechanical transfer of $K^+$ and $Na^+$ and, of course, an impulse.

A number of theories explain the mechanism of primary stimulation.   Since the data available are so fragmentary that it has not been possible to apply rigorous tests, these had perhaps better be called hypotheses. Even the ancients had one.   Lucretius (*18*) wrote, "You cannot suppose that atoms of the same shape are entering our nostrils when stinking corpses are roasting as when the stage is freshly sprinkled with saffron of Cilicia and a nearby altar exhales the perfumes of the Orient . . . You may readily infer that such substances as agreeably titillate the senses are composed of smooth, round atoms. These that seem bitter and harsh are more tightly compacted of hooked particles and accordingly tear their way into our senses and rend our bodies by their inroads."

After an interval of approximately 2000 years, three modern approaches sprang up:  the "spectroscopic correlations," the "specific adsorption site" theory, and the "penetration" theory.   The subject has recently been reviewed by Dravnieks (*15*).   As evidence against which to test these proposals, there are now available a considerable number of synthetic odorants, including their isomers and near homologs.   It is, of course, generally agreed that molecular shape and size effects are of basic importance (*1–6, 9, 10, 11, 18, 21, 26, 27*).   It is the detailed evaluation of these effects that is difficult.

**Spectroscopic Theory.**   The spectroscopic theory, as recently modified by Wright (*26, 27, 28*), correlates odor type with the far-infrared spectrum (wave numbers below 500 cm.$^{-1}$).   In spite of certain limited correlations, however, there are inconsistencies, particularly among musks (macrocyclics and others) and among camphoraceous odorants (*15*).

**Specific Adsorption Theory.**   The specific adsorp-
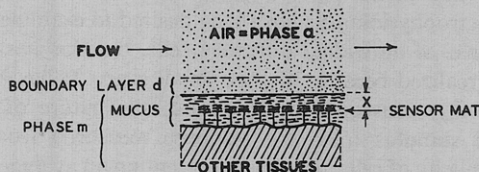
Figure 3.  Olfactory epithelium (idealized) (*16*)

tion site theory of Amoore originally postulated, on the basis of frequency of occurrence, that there are seven "primary odor" types. These include musky and camphoraceous. His earlier theory postulated that molecules which smell musky fit into an oval pan 11.5 A. long, 9 A. wide, and at least 4 A. deep.

After considering many types of musk structures, Beets (5, 6) concluded that "the combination of a sterically accessible functional group and a closely packed profile in a structure with a molecular weight of roughly 220 to 280 are criteria which probably suffice to obtain a musk odor." Amoore's two most recent publications (1, 2) also refer to the profiles of the various types of odorant molecule. Another and simpler example of the profile approach is that of Timmermans (24): He claimed that most molecules smelling like camphor are spherical molecules (though methylcyclopentanol is not). However, the converse statement that all spherical molecules smell like camphor is not true; other factors must be taken into account.

**Penetration Theory.** The penetration theory (9, 10, 11) of olfaction and of odor type is the modern version of the particles of Lucretius tearing their way into our senses and rending our bodies by their inroads. It permits the calculation of olfactory thresholds (13). Basically, the theory is that one or more odorant molecules must be adsorbed into a thin-walled "site" on the olfactory nerve ending, penetrating it and leading to the formation of a small hole in the membrane through which, by the sudden interchange of $Na^+$ and $K^+$, a generator current and ultimately a nervous impulse are initiated.

Odor type will depend largely, according to this theory (11), on the molecular cross-sectional area, $A$, of the odorant molecules and on their energies—i.e., rates—of desorption, $\Delta G$, from the penetrated membranes (Figure 4). Further, there need be no sharp distinctions between different odors; these are represented by regions on the graph of cross-sectional area vs. energy of desorption; these regions shown in the graph are not sharply delineated but blend one into another.

It has been our purpose in this study to examine closely a very narrow band of the olfactory "spectrum" in order to establish correlations among structure, molecular dimensions, and odor strength.

In terms of the penetration theory, the muskiness will be at a maximum for some particular values of the cross-sectional area of the odorant molecule and of the rate (or energy) of desorption. The preliminary test of this theory (11) suggested that the molecular cross-sectional area of good musks should lie between about 40 and 60 sq. A., and that the desorption energies should lie within a band of high values—i.e., that desorption should be slow—and within certain limits.

Electrophysiologists have long desired to examine the response of individual olfactory cells, but this has not been realized because of their small size. It has been necessary, consequently, to deduce the nature of the initial stimulus from the response measured from a multiplicity of cells and thus representing an average.

Similarly, it has been our goal to focus the microscope of detailed scrutiny upon a very small area of olfactory
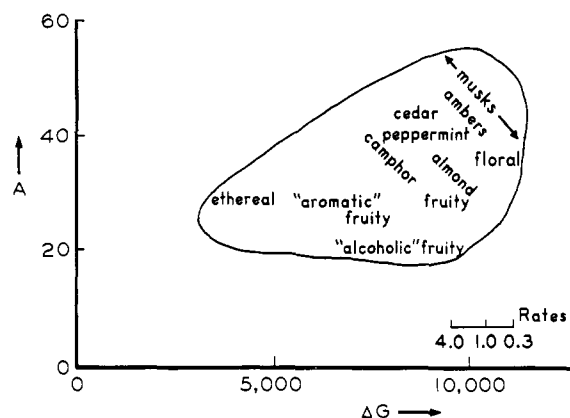


Figure 4. Odor quality map
Present layout a refinement of previously published assignments (11)

behavior. We chose the field of the musks for several reasons. Muskiness is a definite unmistakably characteristic odor type (whether it is a "primary" odor need not concern us here), which is usually if not always pure—that is, unmixed with other odor sensations—so that it becomes possible to compare odor intensities of musk odorants quantitatively without having to consider the disturbing effects of qualitative differences. The trained noses of perfumers can distinguish qualitatively between various groups of musks, but the differences are so small that they may be regarded as "overtones," which should not have an appreciable effect upon the results.

A number of distinct chemical groups contain members with musk odor, permitting valuable heterologous comparisons. Beets (6) long ago pointed out the greater importance of molecular profile and the lesser importance of functional group.

Conversely, and for similar reasons, closely related chemical structures, including homologs and isomers, exhibit wide variations in odor strength, again affording comparisons based upon sophisticated geometrical molecular dimensional differences and not confused by gross electronic or chemical variables.

Finally, the musks can be considered to be pure olfactive stimulants uncomplicated by other stimuli-generating properties such as might arise from compounds of greater chemical reactivity. Such reactive compounds have long been used to study olfaction from the electrophysiological aspect, partly because such materials elicit easily measurable responses.

The danger that these responses may be due at least in part to nonolfactive stimuli must not be overlooked, since factors such as irritation and solvent properties may influence the vomeronasal and trigeminal nerve systems. By contrast, the musks in all groups have minimal functionality, and thus minimal reactivity, together with maximum bulk, which, combined with a very low threshold, avoids to the greatest possible extent the effect of nonolfactive interactions. (The electronegative "nitro musks" such as "musk ketone" and "musk ambrette," long used in the perfumery industry as musk odorants, have been excluded from this study because of possible anomalies. Although they fit more into the

musky odor category than anywhere else, they are so different in odor quality from any of the materials we have used that the possibility of a different response mechanism cannot be completely discounted.)

Although a small change in molecular structure may have a profound effect upon the strength of the musk odor, this effect is quantitative only. The threshold may change greatly, but the odor quality remains musk, or disappears entirely.

A musk molecule in order to give a stimulus must react with a sensory site to change in some way the electrical characteristics of the site. It seems reasonable to assume that since the effect upon the central nervous system is the same for all musks, the interactions must be indistinguishable and the intensity must depend upon the number of such interactions. Maximum response should be the result of an optimum number of reactions $\times$ sec.$^{-1}$ with decrease in response not only with fewer but also with too many interactions. Saturation, conditioning, fatigue, etc., may all be the result of overstimulation. This is turn depends upon the number of molecules that reach the site times the efficiency of interaction.

The number that reach the site depends in turn upon: (1) concentration in the air stream (vapor pressure) and (2) rate of adsorption onto the mucus, probably upon (3) rate of desorption from the mucus and adsorption onto the liquid membrane, and possibly upon (4) rate of penetration of the membrane.

Since musk molecules all are within a narrow molecular weight range and have low functionality, it is hardly possible that 1 is an important parameter.

Neglecting differences in energy of individual molecules by taking an average, the efficiency of the interaction may depend upon the "fit" of the molecule with the receptor, which can also be interpreted as the availability and reactivity of the functional group, the size, shape, and general profile of the molecule, and its "synchronism." This may be compared with the effectiveness of a laser beam of light, which because of its synchronous nature has far greater effectiveness per unit energy. Molecules which because of fewer degrees of freedom—i.e., rigidity—can be expected to present fewer facets can thus be expected to produce a greater number of effective collisions, if other criteria are satisfied.

Muskiness (and for that matter other purely olfactory sensations with low thresholds, such as those of amber and cedarwood) is an attribute of compact, usually polycyclic and, therefore, less flexible molecules.

*Discussion*

Having arrived at these conclusions, it was necessary to gather data and, hopefully, correlations. Getting these correlations involved three tasks: assembly of the model compounds, subjective evaluation of their olfactory properties, and measuring of the molecular dimensions and the rates of desorption.

**Step 1.** The project itself was made possible only by an extended historical background of interest in the field of musk odorants among members of the chemical staff of our company (IFF). The compounds made available as a result of this interest included not only those which have achieved commercialization but also many which were the inevitable by-products of the research. In addition, groups of test compounds were made available through the courtesy of Givaudan and Co. and Chemische Fabriek Naarden, which supplied bulky carbonyls and thiomacrocyclics from their research laboratories. Also, a number of macrocyclics and methyl ketone musks were commercially available. These musks can be classified structurally in a number of ways. Perhaps the most meaningful emphasizes those differences which concern the molecular profile.

**Macrocyclics.** The naturally occurring musks and their analogs are lactones and ketones, which may or may not possess other, secondary functionalities such as —S—, —O—, or even another lactone grouping (Figure 5). Replacing one of the oxygens in the bifunctional molecules by sulfur does not destroy the musk odor but affects its intensity radically, depending upon the position of the sulfur relative to the "other" functional group.

**Bulky Carbonyl Compounds.** The pioneering work of Carpenter (8) and Beets (7) opened the way to the first important group of synthetic musk compounds. Strong musks in this group have been made by others also (25). Figure 6 shows the evolution of the present generation of synthetic musks from the less sophisticated synthetic nitro musks. This work was extended to polycyclic analogs, three tricyclic examples of which are shown in Figure 7 (22, 23).

Further researches of Heeringa and Beets (17) resulted in discovery of the new class of musks characterized by the isochroman structure, a typical example of which is shown in Figure 6. If the oxygen in the isochroman ring is replaced by nitrogen, giving a substituted tetrahydroisoquinoline, the compound is still a musk although its intensity is reduced by about one order of magnitude. Whether this is due to a corresponding change in the rate of desorption has not yet been determined. However, in this case the character is not essentially affected, only the strength, even though a different functional group is present. This applies also to the corresponding N-methyl compounds.

Although some of the masks are the subject matter of patents, the original workers plan to present the chemistry of their syntheses in publications in an appropriate chemical journal.

A more specific classification of the bulky carbonyl musks would be misleading. Consider, for example, the series shown in Figure 7. This series ranges from aldehyde to ketone, from monocyclic to bicyclic to tricyclic hydrindacene to fused tricyclic, and from indan to Tetralin; but these classifications are formal and trivial. The significant alteration is the stepwise addition of methylenes to alter the profile, the rigidity, and consequently the physical properties such as adsorption. The characteristic structural feature throughout is the meta orientation of carbons containing *gem*-dimethyl substitution. These compounds have accordingly been called "meta" musks.

In like manner there is a series shown in Figure 8 with similar structures in ortho position, which we have
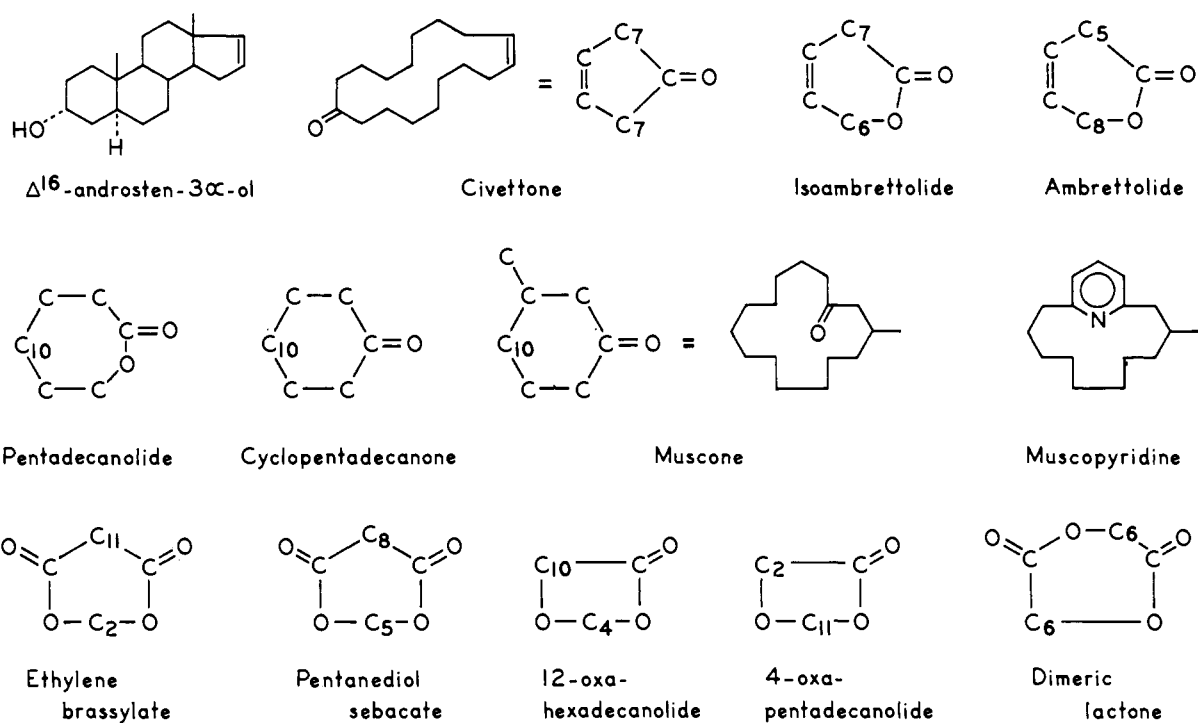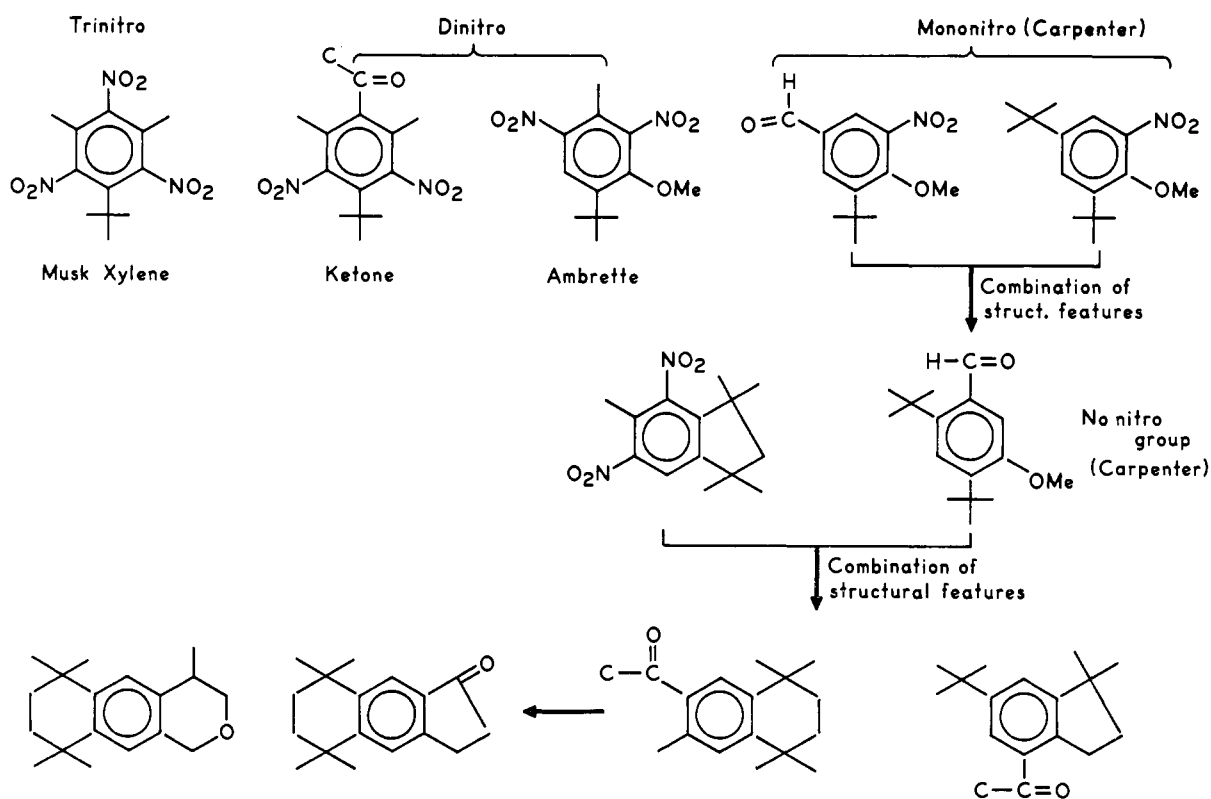
Figure 5. Typical macrocyclic musks and analogs



Figure 6. Reconstructed path from nitro musks to tricyclic musks

called "ortho" musks. The bulky cyclic ethers and analogs can also be considered ortho musks. Having assembled the above musk groups, it was now necessary to determine their muskiness.

**Step 2.** While such odor evaluation of pure com-

pounds may seem a simple matter, the quantization of muskiness in fact, requires much patience, as well as skill. Like the very high frequency audio range which, although piercing, lies just on the border of inaudibility, the musk odor, while intense, may be said to be on the

Figure 7. Meta musks



| WEAK | STRONG | STRONG | WEAK | WEAK |



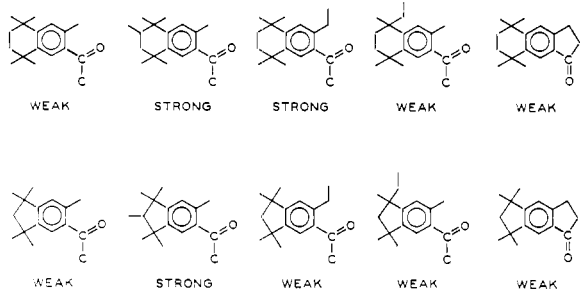| WEAK | STRONG | WEAK | WEAK | WEAK |
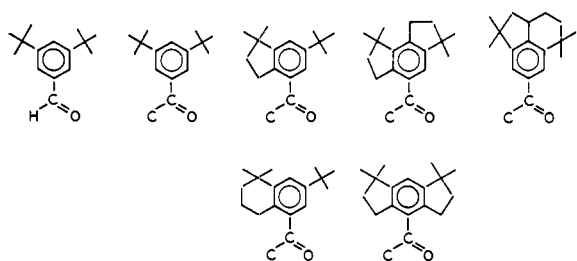
Figure 8. Ortho musks

"Weak" and "strong" refer to odor intensity

borderline of the inodorous, which borderline is crossed by a slight change in the molecular structure. This is not true in the "intermediate" odor range, where slight structural changes result mainly in qualitative odor differences, with odor strength maintained fairly well among isomers and homologs.

An accurate quantitative evaluation of musk odor must take into account a number of factors: the well-known fatiguing effect of musks upon the olfactory sense; the effect of solvent and carrier such as the smelling blotter upon the volatilization and consequently the number of molecules reaching the nose; the loss of precision in comparing samples of different intensity; the personal variable (there are differences in perception even among experts in the musk field); and the temporal variable (not only fatigue but time of day affects sensitivity).

The procedure used was designed to reduce the error effect due to these factors to a minimum. The musks were diluted by a method of successive approximations to a concentration as close as possible in odor strength to a 10% solution of acetyl *tert*-butyldimethylindan chosen as standard. Diethyl phthalate was used throughout as the solvent. Smelling strips of the same quality were wetted to the same depth.

The best available "noses" were used as a panel, and sufficient A to B and B to A (order of smelling) comparisons were made to ensure reliability of the comparisons. Nevertheless, these "quantitative" data cannot be considered accurate in the usual scientific sense. We have found no way to eliminate the fluctuations of opinion due to the personal variable. However, the general relationship can be considered sufficiently reliable to serve the purposes of these correlations.

**Step 3,** measurement of physical characteristics: rate of desorption, molecular cross-sectional area, and $L/B$ value (ratio of length to breadth of molecule).

The effectiveness of an odorant may be written as $\alpha N/t$, where alpha is the fraction of the number $N$ of molecules reaching sensor sites per time $t$ which cause an interaction.

Stereochemical site theory as well as vibrational interaction theory stresses the alpha factor. Desorption rate theory makes $N/t$ the main factor, although the alpha factor need not be disregarded completely. We have no way of knowing the relative importance of alpha and $N/t$ at present and alpha itself is speculation. We can, however, get some insight into the effect of structure on $N/t$, albeit by analogy, by physically measuring the rate of desorption from an aqueous film into air. This rate is a valuable criterion, since it can reasonably be postulated that a similar process of desorption from the mucus at the lipid membrane surface will occur.

**Rates of Desorption, Molecular Structure, and Orientation.** The rate of desorption of any molecule from a water surface into air will depend on $\Delta G$, the energy of desorption for this process:

$$\text{Rate of desorption} = Ae^{-\Delta G/RT} \qquad (1)$$

where $A$ is a constant.

For a single —$CH_2$— group $\Delta G$ is known (12) to be 420 cal. per mole, so that each additional —$CH_2$— group in contact with the surface, and therefore anchoring the molecule to the surface, should reduce the desorption rate by a factor of 2. Knowing this, one may check from the scale models the orientation of the different odorant molecules in the surface.

If the extra methylene group is not in contact with the water, it reduces the rate of desorption by a factor of only about 1.5. The factor of 1.5 arises from van der Waals forces of attraction for the neighboring hydrocarbon groups. Tertiary or quaternary carbon atoms are generally less effective in cohesion and adhesion than methylene or methyl groups. This is one more indication of the fact that the macrocyclic musk molecules clearly do not lie with the whole rings flat in the interface, because the desorption rates of the isomers—e.g., the oxahexadecanolides—are so different, though in a regular sequence.

*Experimental*

The surface films of the musks were studied spread on the surface of redistilled water contained in a silica trough (32 × 15 cm.), measuring the surface tensions with a hanging plate of roughened mica attached by a lever to a torsion wire. They were used at a concentration of 1 mg. per cc. in a 50–50 mixture of redistilled water and redistilled 2-propanol. A few of the musks did not dissolve in this mixture, and for these the ratio had to be altered to 25–75. The deflection of a beam of light reflected from a mirror on the torsion wire was observed on a scale. This technique, and also that of cleaning the surface by dusting a film of talc onto the surface, compressing it, and sucking it off, are now standard procedure (12). The trough was enclosed in a box 63 cm. long, 45 cm. high, and 45 cm. deep. For the desorption measurements, the film was spread to a surface pressure—i.e., a surface tension lowering of the water—of 5.2 dynes per cm. The reduction in this sur-

face pressure in the first 30 seconds as the film desorbed into the air was called the standard rate of desorption of the films. During this process a window measuring the length of the box was raised to leave a gap 32 cm. high. All extraneous air movements in the room were reduced by closing all windows and turning off all fans. The temperature during the desorption runs was 21°. Good musks all have standard desorption rates in the range 0.4 to 1.7.

However, this is a necessary but not a sufficient condition: that a molecule has a desorption rate within the range of the correlation does not necessarily imply that it will be a good musk. It must in addition have appropriate molecular dimensions.

I. The cross-sectional area of the oriented molecule must lie in the range 40 to 57 sq. A.

II. The ratio of the length, $L$, of the oriented molecule (in the plane of the surface—e.g., along the benzene ring) to the breadth, $B$, of the molecule, measured at its polar end, must lie within the range 2.8 to 3.3, inclusive.

Molecular dimensions were measured from models of the musks built up from ICI space-filling atomic models having a scale of 2 cm. to 1 A. The models were first oriented with the polar group pointing as nearly vertically downward as was consistent with the adjacent —$CH_2$— groups being able to adhere to the water surface. For all molecular models the orientations were checked against the desorption rates, making comparisons with homologs and with closely similar structures. These rules may seem arbitrary at first sight, but one interpretation is in terms of the membrane penetration theory of olfaction (as explained below). They also have structural significance: In particular condition II is equivalent, in structural terms, to one or more of the three conditions that:

A good musk must have a total of 8 or more carbon atoms in and on the groups and the ring systems in the position meta and para to the polar group on the benzene ring. If this requirement is not fulfilled, then $L$ is so reduced that ratio of $L/B$ falls below the required value of 2.8, or the rate of desorption may be too high.

If there are three positions vacant on the benzene ring adjacent to the polar group, $B$ may become so low that $L/B$ exceeds 3.3.

A large group (such as $n$-propyl or isopropyl) next to the polar group may not only make the cross-sectional area too great, but may often also make the polar end of the molecule so broad that the ratio $L/B$ falls below 2.8. Again, the odorant will not fulfill the requirements.

*Predicting Muskiness in a Compound*

One can discard all molecules which do not satisfy these substituent group requirements, for if these are not satisfied, $L/B$ will be unsatisfactory. If the compound is not excluded by the above, the scale model is made up from space-filling atoms, and the cross-sectional area (required to be in the range 40 to 57 sq. A.) and the ratio $L/B$ (required to be in the range 2.8 to 3.3, inclusive) are measured. If the structural molecular properties have proved to be within the required limits, the rate of desorption probably can be used to predict

**Table I. Macrocyclic Musks**

| | Intensity | Desorption Rate | Cross Section | L/B |
|---|---|---|---|---|
| $C_{13}$—C=O / C—O | 2.5 | 1.14 | 45 | 2.9 |
| $C_{14}$—C=O / C—O | 2.5 | 0.51 | 45 | 2.9 |
| $C_9$——C=O / O—$C_5$—O | 1.7 | 0.93 | 46 | 2.9 |
| $C_8$——C=O / O—$C_6$—O | 1.2 | 1.20 | 55 | 3.0 |
| $C_{12}$——C=O / C—C | ~1.0 | 1.43 | 42 | 3.0 |
| $C_{13}$——C=O / C—C | 0.8 | 0.80 | 44 | 2.8 |
| $C_4$——C=O / O—$C_{10}$—O | 0.8 | 0.74 | 50 | 3.0 |
| $C_{11}$——C=O / O—$C_3$—O | 0.7 | 0.63 | 46 | 2.9 |
| O=C—$C_{11}$—C=O / O—$C_2$—O | 0.5 | 1.42 | 45 | 2.9 |
| $C_{10}$——C=O / O—$C_4$—O | 0.4 | 0.78 | 47 | 3.0 |
| $C_{10}$——C=O / S—$C_4$—O | 0.3 | 0.43 | 47 | 3.0 |
| $C_{12}$——C=O / O—$C_2$—O | 0.3 | 0.52 | 47 | 3.0 |
| $C_2$——C=O / S—$C_{11}$—O | 0.2 | 0.24 | 44 | 2.9 |
| $C_{10}$——C=O / S—$C_3$—O | 0.2 | 0.71 | 44 | 3.1 |
| $C_{10}$——C=O / S—$C_5$—O | ~0.1 | 0.20 | 47 | 3.0 |

**Table II. Isochroman Musks**

| | Intensity | Desorption Rate | Cross Section | L/B |
|---|---|---|---|---|
| (structure) | 1.8 | 1.47 | 49 | 3.0 |
| (structure) | 0.7 | 1.63 | 44 | 2.9 |
| (structure) | 0.5 | 0.75 | 46 | 3.1 |
| (structure) | 0.3 | 0.60 | 50 | 2.8 |
| (structure) | 0.2 | 2.18 | 46 | 2.9 |
| (structure) | 0.1 | 0.68 | 49 | 1.7 |

## Table III. Meta Musks
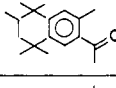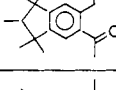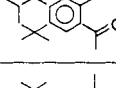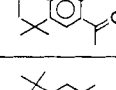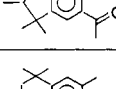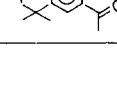
| | Intensity | Desorption Rate | Cross Section | L/B |
|---|---|---|---|---|
| (structure) | 2.5 | 0.96 | 48 | 3.1 |
| (structure) | 1.0 | 1.16 | 48 | 2.8 |
| (structure) | 0.8 | 1.43 | 50 | 3.0 |
| (structure) | 0.4 | 0.65 | 50 | 3.0 |
| (structure) | 0.3 | 0.59 | 53 | 2.9 |
| (structure) | 0.2 | 0.78 | 52 | 3.0 |
| (structure) | 0.1-0.2 | 0.78 | 48 | 2.8 |
| (structure) | 0.1 | 0.52 | 52 | 3.0 |
| (structure) | 0.1 | 2.10 | 50 | 2.3 |

## Table IV. Ortho Musks

| | Intensity | Desorption Rate | Cross Section | L/B |
|---|---|---|---|---|
| (structure) | 2.5 | 0.68 | 52 | 3.1 |
| (structure) | 1.7 | 0.70 | 53 | 3.1 |
| (structure) | 1.3 | 0.43 | 54 | 3.2 |
| (structure) | 0.7 | 0.79 | 54 | 2.9 |
| (structure) | 0.5 | 0.95 | 49 | 3.3 |
| (structure) | 0.2 | 1.00 | 54 | 2.9 |

musk intensity. One either estimates its rate of desorption (from the scale model), or may easily measure it. If the rate lies in the range 0.4 to 1.7, one should have a musk.

### Conclusions

The correlations of the several groups of musks are shown in Tables I through IV.
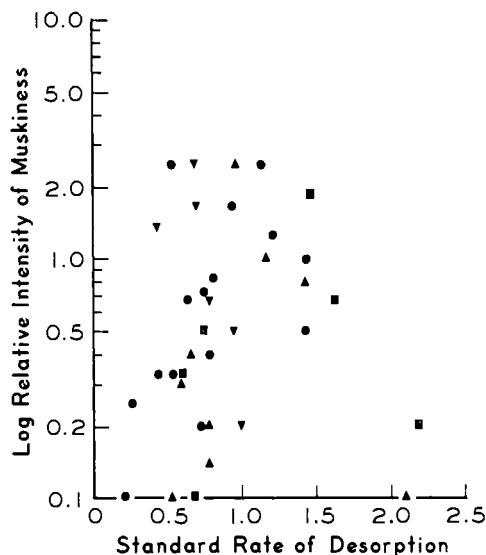
In each group of musks, the odor strength varies sig-



Figure 9. Muskiness as a function of desorption rate

● Macrocyclic musks
■ Isochroman musks
▲ Meta musks
▼ Ortho musks

nificantly with rate of desorption, the spatial requirements all falling within relatively narrow limits. The composite picture shown in Figure 9 not only shows the random distribution of muskiness among the various chemical groups, but also the narrow permissible range of desorption rate associated with strong muskiness. Thus, this rate is a requirement but not a guarantee of muskiness. At least one other, and perhaps many factors, as yet unknown, are involved, for within this narrow band are also many compounds which are weak or odorless, even though possessing the proper molecular dimensions.

We have found indications in recent work that similar criteria apply in other areas of odor, including amber and woody. No generalizations can as yet be drawn, but the rates of desorption and molecular dimensions are different. This work is continuing.

**Significance of $L/B$.** A possible explanation of the importance of this ratio may be the effect of molecular shape at the receptor sites. Some local phase changes involving the physical characteristics of the lipid membrane may occur if $L/B$ is within the appropriate range, thus affecting the fluidity of the membrane walls. Local crystallizations may be important. This suggestion arises out of the work of Lundquist (19), who found that the incorporation of very small mole fractions of "foreign" asymmetrical molecules into a monolayer made up of asymmetrical molecules could cause very marked changes in the physical characteristics of the monolayer. She went on to postulate that "a minor change in the molecular composition of a lipoprotein membrane, especially as regards to the asymmetrical pattern, would induce a complete reorientation of the molecules eventually with a simultaneous change in potential, permeability, etc."

We conclude that the odor type is a purely physical property of the odorant molecules, determined quantitatively by their rate of desorption, molecular cross-sectional areas, and the dimension ratio $L/B$. Though different in many ways from Amoore's site theory of "primary odors," the penetration theory requires that the molecular dimensions fall within defined limits. But that the rate of desorption is quantitatively related to the intensity of muskiness is, we believe, support for the physical adsorption theory, as are also the almost limitless slight variations of odor in the region which we call musky.

*Acknowledgment*

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