

Human Primary Odors

By Clive Jennings-White, SRI International, Menlo Park, California

That the odor of any substance is determined by the structure of its molecules is generally accepted. These, on arriving at the olfactory clefts, interact with one or more types of receptors embedded in the olfactory epithelium. This triggers a series of molecular and cellular events that result in nerve impulses being sent from the olfactory bulb to the brain. The end result of this process is the subjective experience of smell (Amoore et al., 1964).

It is known that the sensation of colour arises from the stimulation of three distinct types of visual receptors. Each preferentially absorbs light of certain wavelengths, corresponding to one primary colour sensation (red, green, or blue). Therefore, one may ask analogous questions concerning smell:

- How many different types of olfactory receptors are there?
- To what primary odors do these correspond?
- What are the molecular characteristics required for stimulation of each type of olfactory receptor?

The first tentative answers to these questions were suggested by John Amoore in 1952. The rationale is roughly as follows: if we are interested in identifying the primary odors, we should look only at the odors of pure compounds rather than complex mixtures (onion soup or Chanel No. 5) since the latter will surely stimulate more than one type of olfactory receptor. Also it would seem plausible that particularly common odor descriptions might correspond to primary odors. With these considerations in mind Amoore studied the published odor descriptions of hundreds of pure compounds and found that they could be categorized into fourteen groups. Of these he chose the seven largest groups as representing primary odors and found that the structures of the molecules within each group did

indeed show significant similarity (Amoore, 1952).

Amoore and others then sought to confirm by experiment the hypothesis that molecules within these groups correspond to primary odors. Of the several possible modes of attack, the one that has proved most fruitful is the study of specific anosmias (Amoore, 1977). A deficiency in an olfactory receptor protein should result in a specific anosmia for the corresponding primary odor, just as a deficiency in the receptor protein corresponding to the perception of a particular primary colour results in a specific colour blindness. Such specific anosmias are indeed very common. A person with a specific anosmia will not be able to perceive a particular type of odor but will otherwise have a normal sense of smell.

Conversely, if there exists a particular specific anosmia in a certain proportion of the population, then it is likely that this corresponds to a primary odor (Amoore, 1977).

With this in mind Amoore and others began a systematic survey of reputed specific anosmias. They tested the olfactory threshold of a number of compounds which correspond to the same specific anosmia for both a panel of normal subjects and a panel in each class with a particular specific anosmia. The logarithm to the base 2 of the ratio of the average olfactory thresholds for the specifically anosmic panel to that of the "normal" panel gives each compound a number, called the anosmics' defect, which is a measure of its purity of odor that is defined as the extent to which an odorant stimulates a particular type of receptor to the exclusion of others (Amoore et al., 1977). Thus the compound in a particular class that exhibits the highest anosmic's defect represents the purest example of that primary odor. Using this method employing specific anosmias, the molecular characteristics required for generation of eight different primary odors have so far been determined (Amoore, 1977; Pelosi and Viti, 1978; Pelosi and Pisanelli, 1981).

Table I. Odor Classes

<u>Odor Class</u>	<u>Representative Odorant</u>
1. Acidic	Formic acid
2. Alliaceous	Allyl isothiocyanate
3. Almond	Benzaldehyde (Boelens et al., 1978)
4. Ammoniacal	Ammonia
5. Aniseed	Anethole
6. Aromatic	Benzyl alcohol
7. Burnt	Pyridine
8. Camphoraceous	Cineole (Pelosi and Pisanelli, 1981)
9. Citrous	Citral
10. Cocoa	iso-Butyl phenylacetate (Boelens et al., 1978)
11. Cumin	Cuminaldehyde (Boelens et al., 1978)
12. Edible	Maltol
13. Ethereal	Diethyl ether (Amoore, et al., 1964)
14. Fecal	Skatole
15. Fishy	Trimethylamine (Amoore, 1977)
16. Fruity	gamma-Undecalactone
17. Green	Phenylacetaldehyde dimethyl acetal
18. Hyacinth	Cinnamyl alcohol
19. Jasmin	cis-Jasmone (Boelens, 1974)
20. Lily	Hydroxycitronellal
21. Malty	iso-Butyraldehyde (Amoore, 1977)
22. Minty	l-Carvone (Pelosi and Viti, 1978)
23. Musky	6-Acetyl-7-ethyl-1,1,4,4-tetramethyltetralin (Amoore et al., 1977)
24. Oily	Hexadecane
25. Orange Blossom	Methyl anthranilate
26. Oxidizing	Ozone
27. Phenolic	Phenol
28. Putrid	Dimethyl sulfide (Amoore et al., 1964)
29. Pungent	Formaldehyde
30. Rose	2-Phenylethanol
31. Sexual	5alpha-Androst-16-en-3alpha-ol
32. Spermy	1-Pyrroline (Amoore, 1977)
33. Spicy	Cinnamaldehyde
34. Sweaty	iso-Valeric acid (Amoore, 1977)
35. Sweet	Vanillin
36. Urinous	5alpha-Androst-16-en-3-one (Amoore et al., 1977)
37. Violet	alpha-Ionone
38. Woody	Cedryl acetate (Boelens, 1974)

The purpose of the present article is to consider the molecular characteristics of classes of compounds having a particular odor and for which there may or may not be a reputed specific anosmia. Six primary odors plus the five addi-

tional ones that have been determined by the specific anosmia method have been omitted from the discussion since they have been adequately covered elsewhere (Amoore et al., 1964; Amoore, 1977).

Methods

In seeking classes of compounds which may represent primary odors, the starting point was Amoore's "clues to the olfactory code" which lists odor classifications and reputed specific anosmias (Amoore, 1969, 1977).

It became clear that some entries would need to be deleted. For example, the thyme odor, represented by thymol, has been shown to be essentially minty in character. Thymol (figure 1) exhibits an anosmics' defect of 1.8 when tested with a panel selected for anosmia to l-carvone (figure 2) which has a spearmint odor (Pelosi and Viti, 1978). This implies that the odor of thymol is approximately 70% minty. The remainder, possibly "phenolic," would account for the thyme odor which is thus not primary but complex.

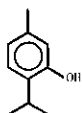


Fig. 1 Thymol

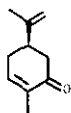


Fig. 2 l-Carvone

Other entries have been combined. For example there is no evidence that "oily" and "waxy" represent different odors. Moreover there do not appear to be any systematic molecular differences in compounds described as having either smell.

The floral primary odor proposed by Amoore can possibly be replaced by a number of specific floral primary odors. It is well known among perfumers that it is possible to imitate the odor of most flowers by proper combination of the essential oils from approximately six types of flower. Moreover, as will be shown, there is considerable molecular similarity between compounds of one flower type. There remains, however, some degree of similarity between most floral compounds and one may speculate on the possible existence of an ancestral floral receptor protein from which our present suggested specific floral receptor proteins may have evolved by mutation. The molecular characteristics of jasmine odorants will not be discussed in this paper since they have been adequately covered elsewhere (Boelens, 1974).

The compounds depicted in the results section have been found partly by thorough literature search of odor descriptions in a manner similar to Amoore's approach of 1952. Additional compounds were found by extensive smelling of as many compounds as the author could lay hands on. Interesting compounds were tested on at least ten individuals for odor description. In

some cases compounds thought to be in the same class were cross-tested for olfactory fatigue desensitization.

This search revealed additional odor classes, for example, sexual, which is represented by androst-16-en-3 α -ol (figure 3). This compound has been isolated from human secretions and has been suggested as a human sex pheromone (Brooksbank et al., 1974; Comfort, 1971; Cleveland and Savard, 1964; Kloek, 1961; Michael and Keverne, 1970; Vierling and Rock, 1967).

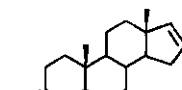


Fig. 3 5 α -Androst-16-en-3 α -ol

It should be emphasized that the odor classes in the results section are not known to be primary odors. However they have been selected with this possibility in mind and may serve as a starting point for experimentation by means of the specific anosmia or some other method.

Results

Acidic Odorants

At first sight it might appear that these odors could be caused by a pungent smell due to electrophilic character (Amoore et al., 1964) plus stimulation of the acid taste receptor. However, there have been anosmias reported for formic acid and acetic acid (figure 4) (Amoore, 1969). These are not significantly sweaty as, for example, formic acid has an anosmics' defect of less than 1 whereas isovaleric acid has an anosmics' defect of 5.4 for the sweaty odor (Amoore, 1977). Stronger acids such as hydrogen chloride could stimulate the pungent receptor as well and therefore would not exhibit the anosmia. The necessary characteristics for an acidic smell are that the compound should be volatile and capable of donating a proton to the receptor site.

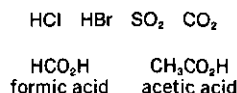


Fig. 4 Acidic odorants

Alliaceus Odorants

The universal feature of alliaceous odorants (figure 5), such as those responsible for the flavour of onions, garlic, and mustard, appears to be that they contain sulfur. Also required is a sufficiently large hydrophobic region. For example, the suspected hamster sex pheromone di-

methyl sulphide, a lower homologue of the alliaceous dipropyl sulphide, does not smell significantly alliaceous, but is putrid by virtue of its nucleophilicity (Amoore et al., 1964).

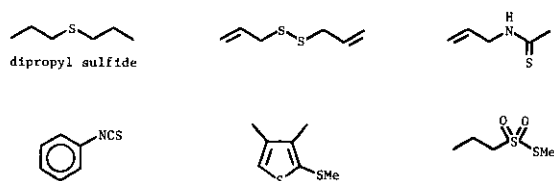


Fig. 5 Alliaceous odorants

Ammoniacal Odorants

Ammonia and various substituted amines do not show a significant fishy anosmics' defect (Amoore, 1977), and yet they are readily distinguishable from the putrid soft volatile nucleophiles. It is possible therefore that these form a separate group which has little structural requirement but quite definite functional group requirements (figure 6). That is, only an amine can smell ammoniacal.

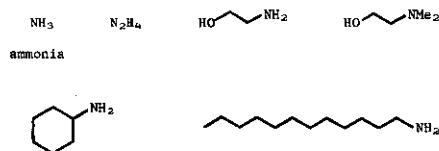


Fig. 6 Ammoniacal odorants

Aniseed Odorants

Specific anosmias to this very characteristic odor have not yet been reported. However there is much similarity between molecules of this odor type, a p-disubstituted benzene ring generally being necessary (figure 7). Ethyl 2,4-hexadienoate might seem exceptional but comparison with ethyl p-toluate resolves the difficulty. There is also a requirement of not being too polar such as in methyl anisate which is a sweet odorant. Indeed, no polar group at all is required for this odor, as in p-diethylbenzene.

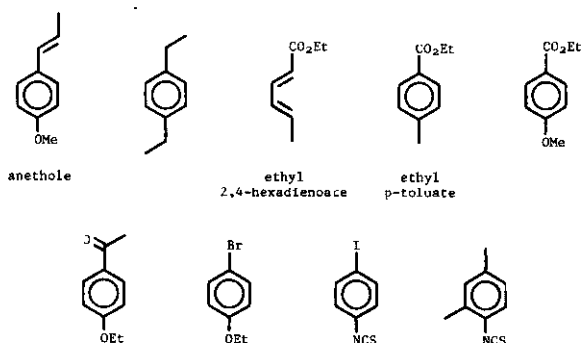


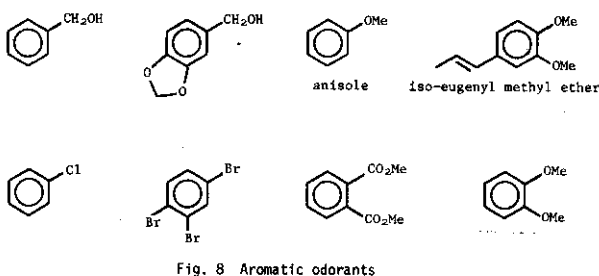
Fig. 7 Aniseed odorants

Primary Odors

Aromatic Odorants

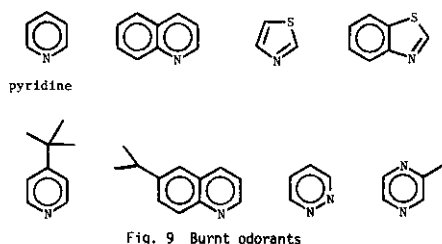
This would appear to be a "garbage can" receptor site for all those aromatic molecules that do not measure up to the specificities of, for example, the almond or aniseed receptor sites. It is well known that olfactory receptor sites vary enormously in their specificity. For example, a huge variety of molecules smell camphoraceous. Virtually any functional or structural type is tolerated so long as the molecule is of suitable dimensions (Amoore et al., 1964). On the other hand, only a tiny handful of molecules that smell spermous are known and they are all small cyclic Schiff's bases (Amoore, 1977).

It is interesting to note the molecular progression from anisole, an aromatic odorant, to anethole, an aniseed odorant, to iso-eugenyl methyl ether, an aromatic odorant (figure 8). This suggests that if someone lacked the hypothetical aniseed receptor, it would still be possible to smell anethole, but as an aromatic odor. This may explain why specific anosmias to aniseed (and almond) have not been reported.



Burnt Odorants

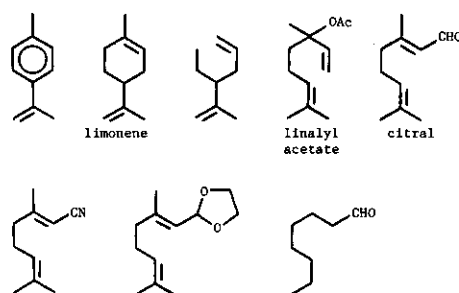
Specific anosmia to pyridine has been reported (Amoore, 1977). The requirement appears to be a nitrogen heteroaromatic ring with a lone pair on nitrogen in the plane of the ring (figure 9).



Citrous Odorants

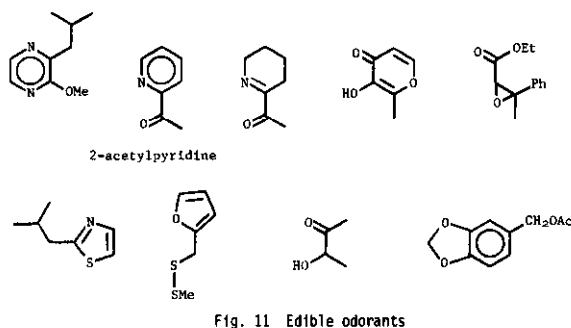
There are two quite different types of compound that smell citrous (figure 10). One is represented mainly by a group of cyclic hydrocarbons, such as limonene, and the other by a group of linear compounds terminating in a polar func-

tional group, such as citral. The clue to a possible explanation is provided by the citrus smell of linalyl acetate, characteristic of the bergamot citrus fruit. This compound appears to have a structure intermediate between the two groups, thus providing a unifying link. An alternative explanation is that there are actually two different citrus receptor sites, one for each citrus subgroup. Specific anosmia has been reported for citral (Amoore, 1977) and measurement of anosmics' defects for the two groups should readily settle the issue.



Edible Odorants

At first sight there is very little to unify the structural types giving rise to this odor (figure 11). However, a close inspection reveals the ubiquitous presence of a 1,4 disposition of heteroatoms (O,N,S). It is possible that the pyrazines represent a different class. However, as with the citrus compounds, the odor of intermediate structural types such as 2-acetylpyridine suggests an underlying unity. The pyrazines have extremely low olfactory thresholds and may be "purer" primaries than other members of this group, although it is possible that they also interact with the hypothetical burnt receptor to a significant extent. It has been proposed that some of the molecules in this group interact with a receptor partly through hydrogen bonding from the hydrogen atom of a hydroxyl group when the hydroxyl oxygen is one of the heteroatoms involved in the 1,4 arrangement (Re et al., 1973; Ohloff and Giersh, 1980). However if some of the



compounds that cannot possess a hydroxyl group show a significant anosmics' defect with a panel selected for anosmia to a compound that does have a hydroxyl group, then an interaction of this type would have to be considered less likely.

Fecal Odorants

It would appear that a suitable disposition of an amine and a benzene ring are the molecular requirements for this hypothetical receptor (figure 12).

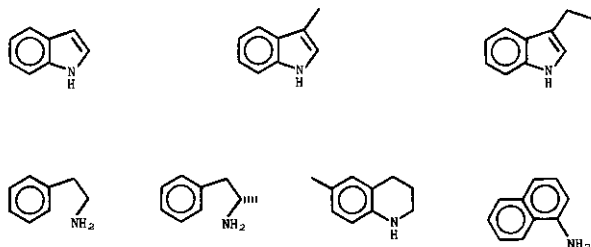


Fig. 12 Fecal odorants

Fruity Odorants

Although most fruity compounds are esters, isostructural ketones also smell fruity. Since most fruity compounds are non-rigid, the receptor site requirements are unclear, except for the required existence of a carbonyl group and a hydrophobic portion (figure 13).

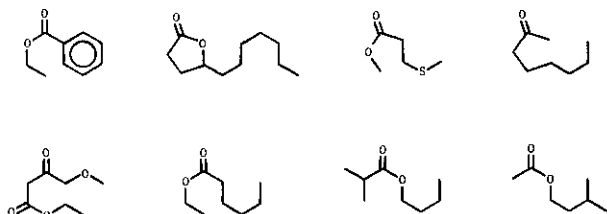


Fig. 13. Fruity odorants

Green Odorants

The rigid molecules in this group (figure 14) give a clue to the receptor requirements. Almost any oxygen or nitrogen functionality in the correct position is tolerated, suggesting an acidic hydrogen atom in the receptor site available for hydrogen bonding.

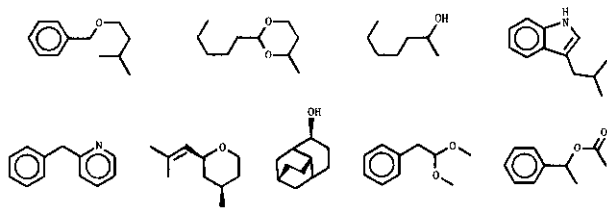


Fig. 14 Green odorants

Primary Odors

Hyacinth Odorants

A word about the hypothetical floral receptors (figure 15) is necessary. It will be noted that molecules belonging to all six floral groups could fit Amoore's "kite" shaped floral receptor (Amoore et al., 1964). It is conceivable that the different groups could all have evolved from an earlier general floral receptor similar to that proposed by Amoore. However, later mutations could have introduced the specificities for each type of flower. If so, then testing by specific anosmia might be more difficult than usual since it is possible that a single mutation would render inoperative several related receptors. Thus distinguishing between the two theories by these means might prove impossible.

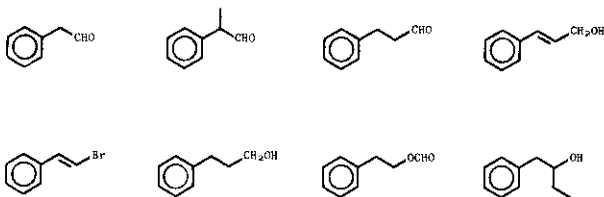


Fig. 15 Hyacinth odorants

Lily Odorants

Ohloff has recently given the molecular requirements for generation of a lily odor (Ohloff and Giersh, 1980). However, all the molecules he considered were bifunctional, and this ignores some compounds commonly used as lily odorants such as α -terpineol, linalol, and dimethyl benzyl carbinol, all of which possess only one polar functional group. Nevertheless, it appears that a tertiary alcohol is necessary for generation of a lily odor, whether or not there is other polar functionality in the molecule (figure 16).

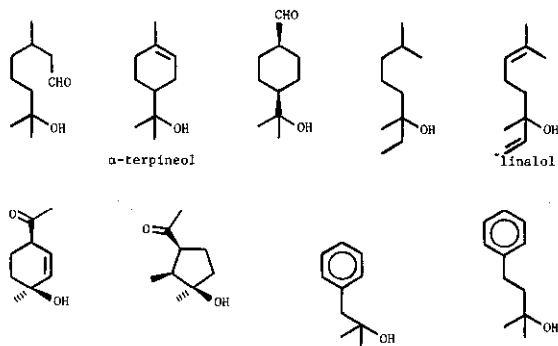


Fig. 16 Lily odorants

Oily Odorants

This hypothetical receptor could be a hydrophobic trough very similar to that proposed by Amoore for the ethereal receptor (Amoore et al., 1964). The difference would be that the oily receptor site is longer. On increasing the length of a simple hydrocarbon chain the odor gradually changes from ethereal to oily (figure 17).

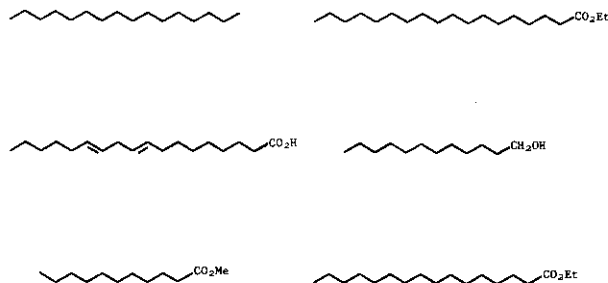


Fig. 17 Oily odorants

Orange Blossom Odorants

The two major groups of orange blossom odorants, anthranilates and β -naphthyl derivatives, are at first sight quite different. However, by drawing the anthranilates in the internally hydrogen bonded form, the similarity of the groups becomes evident (figure 18).

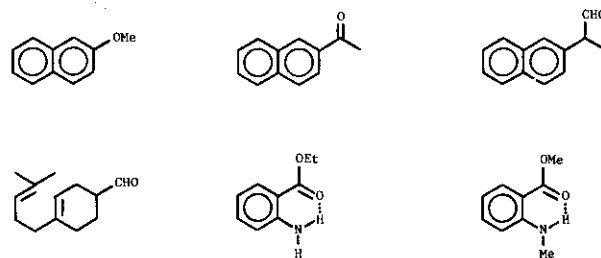


Fig. 18 Orange blossom odorants

Oxidizing Odorants

Volatile oxidizing agents (figure 19) have a characteristic clear, clean smell when dilute. At higher concentrations they are pungent presumably because of their electrophilic character (Amoore et al., 1964).



Fig. 19 Oxidizing odorants

Phenolic Odorants

Evidently phenols smell phenolic (figure 20). However only a small amount of substitution on the aromatic ring is permitted without losing the phenolic odor.

Primary Odors

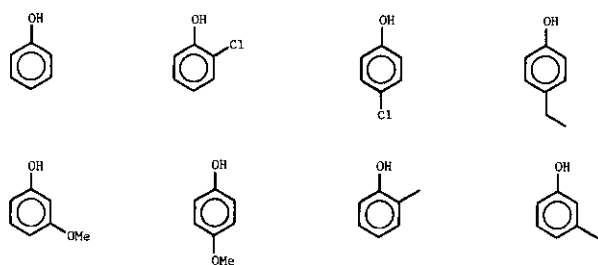


Fig. 20 Phenolic odorants

Rose Odorants

Specific anosmias have been reported for geraniol and β -phenylethanol (Amoore, 1977). The relation between these odorants (figure 21) is only apparent when the very flexible geraniol molecule is depicted in a suitable conformation. In general one expects that more rigid molecules would represent a purer primary odor, that is, exhibit a greater anosmics' defect, than similar flexible molecules since the latter may adapt their conformation to fit other receptor sites.

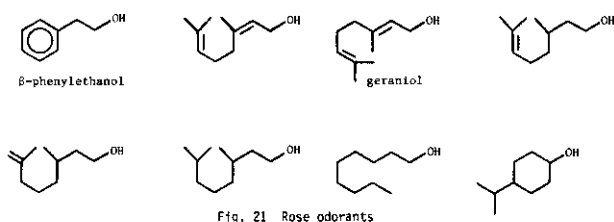


Fig. 21 Rose odorants

Sexual Odorants

5α -Androst-16-en-3 α -ol (figure 22) has been isolated from human urine (Brooksbanks, 1962; Cleveland and Savard, 1964) and human sweat (Brooksbank et al., 1974). There is currently much interest in this compound due to the postulation that it is a human sex pheromone (Brooksbank et al., 1974; Vierling and Rock, 1967). It has already been used in perfumery for several years, for example, "Lydia" by Dinely of London.

Amoore has tested the compound on a panel of anosmics selected for specific anosmia to 5α -androst-16-en-3-one, a urinous odorant, and found that it exhibited a marginally significant anosmics' defect. However, subjective responses to the odors of the two compounds are generally quite different from each other. In addition specific anosmias to each compound can exist independently. Thus it seems unlikely that 5α -androst-16-en-3 α -ol interacts with the urinous receptor to a significant extent.

Contrary to some popular opinion there does not appear to be any difference between men and women in olfactory response to 5α -androst-16-en-3 α -ol (Kloek, 1961). The author has repeated

Kloek's experiments with 5α -androst-16-en-3 α -ol and found results in very close agreement. The only point of difference was that the author found that of those who could smell the compound 66% described the odor as pleasant (63% of women and 69% of men), whereas Kloek found only 13%. The difference could possibly be explained by a positive change in social attitude towards body odors over the last twenty years (Schneider, 1971).

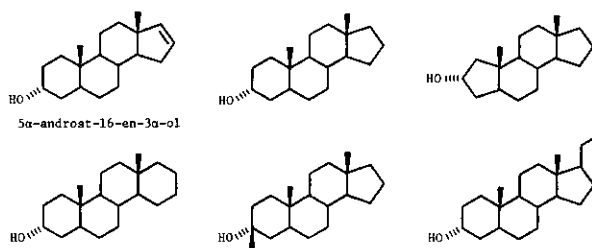


Fig. 22 Sexual odorants

Spicy Odorants

Specific anosmia to cinnamaldehyde has been reported (Amoore, 1977). Other spicy odorants show similar features (figure 23).

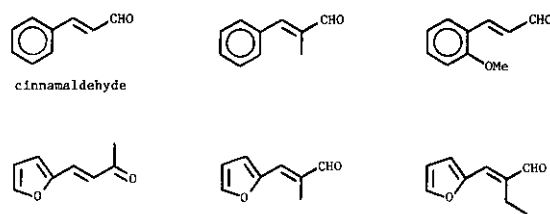


Fig. 23 Spicy odorants

Sweet Odorants

The required molecular characteristics for sweet odorants (figure 24) appear to be an aromatic ring and a carbonyl or similar functional group. Specific anosmia has been reported for vanillin (Amoore, 1977).

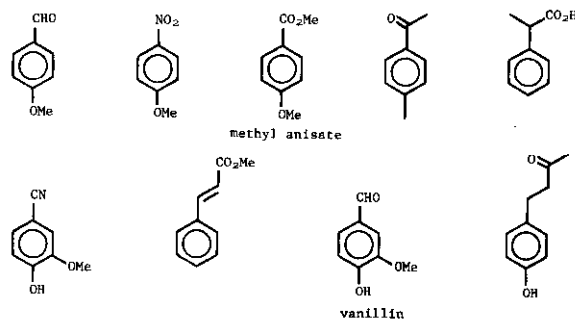


Fig. 24 Sweet odorants

Violet Odorants

These molecules (figure 25) are of the usual floral shape but have the specific requirement of an α,β -unsaturated carbonyl group. However it appears that a pyridine ring can mimic this functionality. Possibly there is a nucleophile in the receptor site that can interact at the β -position, while the carbonyl group is involved in hydrogen bonding. Specific anosmia to ionone has been reported (Amoore, 1977).

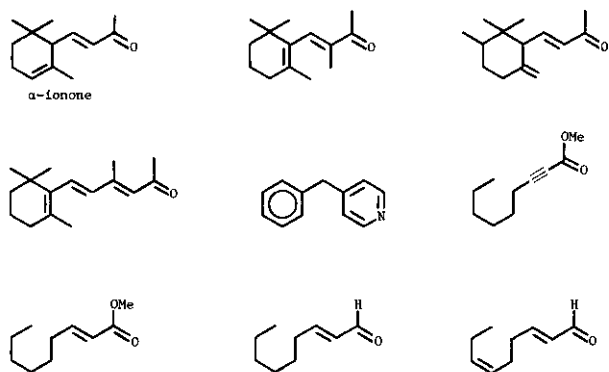


Fig. 25 Violet odorants

Discussion

The odor classes proposed here plus those discussed elsewhere comprise thirty-eight odor classes which are listed in Table I together with a representative odorant of each class. These undoubtedly do not encompass all the human primary odors. Likewise it may well turn out that some of these classes are redundant, in reality being represented by a complex mixture of several primary odors. Nonetheless it is evident from the diagrams that there is considerable molecular similarity between compounds corresponding to the same type of odor whether or not these represent primaries.

It is hoped that eventually all of these thirty-eight odor classes will be subjected to Amoore's method of specific anosmia to provide answers to the uncertainties posed above.

Acknowledgements

Thanks are due to Dr. Graham A. Mock and Ms. Eileen Mayes for helpful discussions. I am especially appreciative of discussions with Dr. John E. Amoore, without whose prior work in the field this paper would have been impossible. Financial support was provided by Dinely of London, fine perfumery company, who also supplied odorants for olfactory evaluation.

Primary Odors

References

Address correspondence to Clive Jennings-White, PhD, SRI International, 333 Ravenswood Avenue, Menlo Park, California 94025, U.S.A.

- J. E. Amoore, 1952, The stereochemical specificities of human olfactory receptors, *Perfum. Essent. Oil Rec.* **43**, 321-323, 330
- J. E. Amoore, 1969, A plan to identify most of the primary odors, in *Olfaction and Taste III*, Pfaffman, C. (ed.) New York, Rockefeller, 158-171
- J. E. Amoore, 1977, Specific anosmia and the concept of primary odors, *Chem. Sens. Flavor* **2**, 267-281
- J. E. Amoore, J. W. Johnston, Jr. and M. Rubin, 1964, The stereochemical theory of odor, *Sci. Am.* **210**, 42-49
- J. E. Amoore, P. Pelosi and L. J. Forrester, 1977, Specific anosmias to 5 α -androst-16-en-3-one and ω -pentadecalactone: the urinous and musky primary odors, *Chem. Sens. Flavor* **2**, 401-425
- M. Boelens, 1974, Relationship between the chemical structure of compounds and their olfactive properties, *Cosmet. Parfum.* **89**, 70-78
- M. Boelens, L. M. van der Linde, D. de Rijke, P. J. de Valois, J. M. van Dost and M. J. Takken, 1978, Molecular structure and organoleptic quality, *Chem. Soc. Reviews* **7**, 167-176
- B. W. L. Brooksbank, 1962, Urinary excretion of androst-16-en-3 α -ol. Levels in normal subjects, and effects of treatment with trophic hormones, *J. Endocrin.* **24**, 435-444
- B. W. L. Brooksbank, R. Brown and J. A. Gustafsson, 1974, The detection of 5 α -androst-16-en-3 α -ol in human male axillary sweat, *Experientia* **30/8**, 864-865
- W. W. Cleveland and K. Savard, 1964, Studies of excretion of androst-16-en-3 α -ol, *J. Clin. Endocrinol. Metab.* **24**, 983-987
- A. Comfort, 1971, Likelihood of human pheromones, *Nature* **230**, 432-433, 479
- J. Kloek, 1961, The smell of some steroid sex-hormones and their metabolites. Reflections and experiments concerning the significance of smell for the mutual relation of the sexes, *Psychiat. Neurol. Neurochir. Neerl.* **64**, 309-344
- R. P. Michael and E. B. Keverne, 1970, Primate sex pheromones of vaginal origin, *Nature* **225**, 84-85
- G. Ohloff and W. Giersh, 1980, Stereochemistry-activity relationships in olfaction. Odorants containing a proton donor/proton acceptor unit, *Helv. Chim. Acta.* **63**, 76-94
- P. Pelosi and A. M. Pisanelli, 1981, Specific anosmia to 1,8-cineole: the camphor primary odor, *Chem. Sens. Flavor* **6**, 87-93
- P. Pelosi and R. Viti, 1978, Specific anosmia to l-carvone: the minty primary odor, *Chem. Sens. Flavor* **3**, 331-337
- L. Re, G. Maurer and G. Ohloff, 1973, Ein einfacher zugang zu 4-hydroxy-2,5-dimethyl-3(2H)-furanon (furanol), einem aromabestandteil von ananas und erdbeere, *Helv. Chim. Acta.* **56**, 1882-1894
- R. A. Schneider, 1971, The sense of smell and human sexuality, *Medical aspects of human sexuality* **5**, 156-168
- J. S. Vierling and J. Rock, 1967, Variations in olfactory sensitivity to exaltolide during the menstrual cycle, *J. Appl. Physiol.* **22**, 311-315

