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The Search for New Aroma Chemicals

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Although up to 10,000 natural and synthetic aroma chemicals exist, the search for new or improved products is ongoing in the flavor and fragrance industry (F-1). The search for new substances starts with the analysis of the possible benefits, the existing knowledge and the routes that can be followed. The hunt for new flavor and fragrance substances can, for example, be initiated by the following guidelines:

- Isolation of new natural products (mixtures or character-impact compounds).
- Searching for open spots in groups of existing natural compounds.
- Studying biogeneration (biochemical formation) of new volatile compounds.
- Investigation of reaction occurring during food processing (e.g. cooking, baking, frying).
- Predicting new groups of substances from structure-odor relationships.

Some recently published programs for the isolation of new products from nature will be discussed herein. In addition, a series of ideas for the development of new or improved flavor and fragrance substances will be presented. These ideas concern new mono- and sesquiterpenoids, substitution of sterical or electronical parts (functional groups) of molecules by more stable ones. New materials with greater organoleptic or olfactive value-for-money will be suggested.

General Introduction

One may question whether the search for new aroma chemicals is economic. In other words, are the costs for research in the flavor and fragrance industry a value for the money? Recent studies of the American Council for Chemical Research revealed that during the period of 1975 to 1998 every $1 invested by 83 chemical industries produced a profit of $2.6. The conclusion: research in the chemical industry does pay off. Recently some interesting publications appeared regarding the search for and the design of new flavor and fragrance materials.[1c,2a,4a-b,6]

The initiation of a research program for new flavor and fragrance materials and improved preparation methods may have the following guiding thoughts:

- What is already known and what has been done in the past?
- How are the materials formed, what are the precursors and (bio)chemical routes to the end products?
- Are there reasonable reliable relationships between a designed molecular structure and expected olfactive and organoleptic qualities, and what is the target?

If one analyzes the search for new materials in the flavor and fragrance industry during the last half century, one may divide this work in different areas, as they are based on:

- ***Natural Products:*** new character-impact compounds, quantification of compounds emitting from new naturals, identification and quantification of existing compounds emitting from living natural products, and quantification in depth of natural isolates.
- ***Chemical or Biogenesis Formation:*** often used for the identification and preparation of new flavor materials: examples are the Strecker degradation of amino acids, the Maillard reaction of amino acids and sugars, followed by Amadori or Heinz rearrangements, the biochemical oxidation of unsaturated fatty acids and the biochemical formation of terpenoids and fatty acids.
- ***Analogues of Existing Odorants:*** the synthesis of analogues of irones (ionones and

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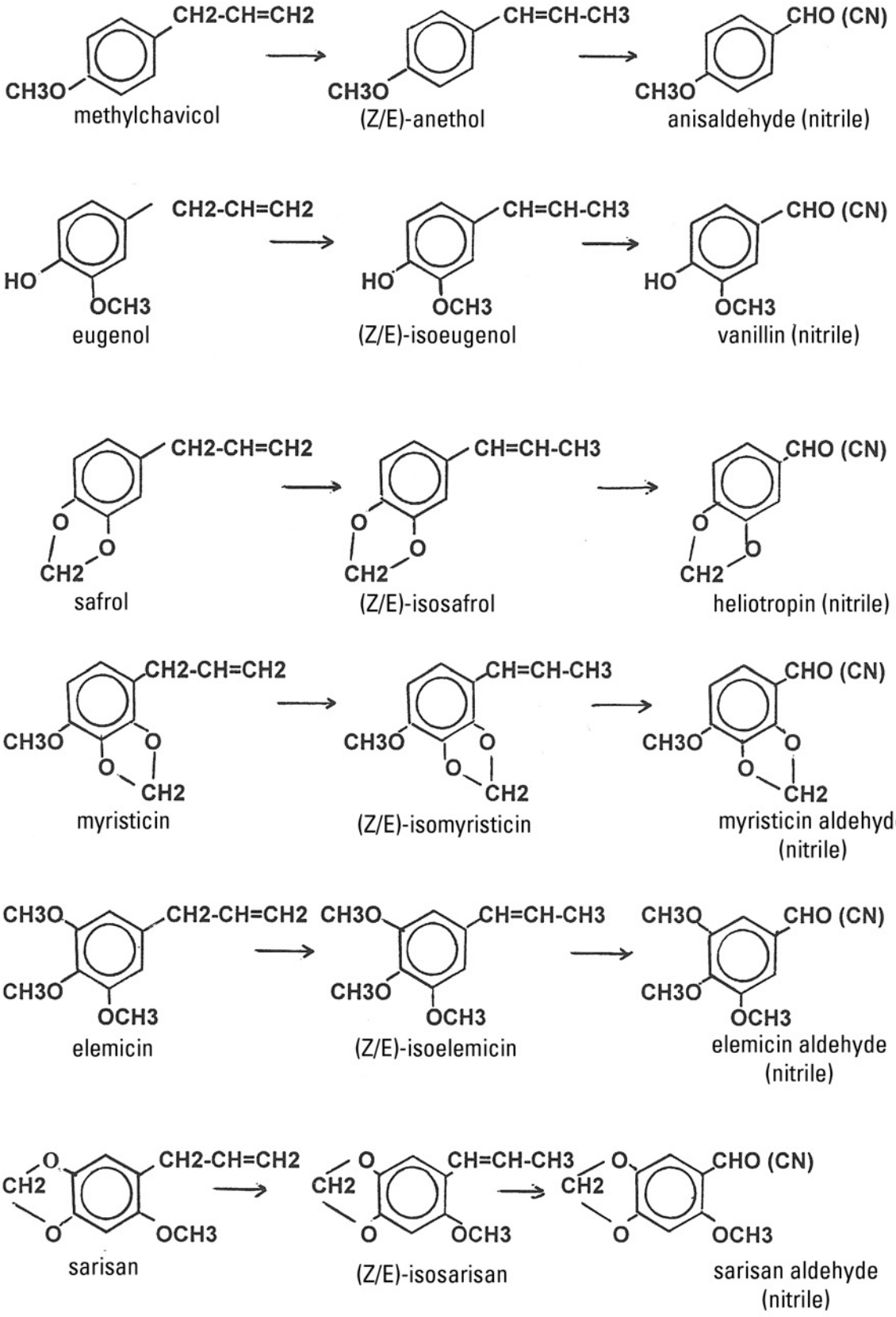
Molecular structures of well-known and little known aromatic compounds

F-1



methylionones), analogues of methyl jasmonates and damasc(en)ones, nitro-free benzenoid musk compounds.
- ***Petrochemicals and Other Raw Materials:*** fragrance materials derived from dicyclopentadiene and from substituted phenols.
- ***Common Sense and Serendipity:*** functionalization of monoterpenes and sesquiterpenes, C-10 derivatives.

Sometimes new aroma chemicals have been discovered by pure accident.[1c,2a] It seems rather unscientific and uneconomic to carry out random organic synthetic research, to sit and wait until a valuable material comes out. However, even the unexpected discovery of a new aroma chemical as a certain reason for its preparation.

For the production of computerized databases we studied:[5d]

- Forty-two hundred perfumery materials, e.g. aroma chemicals and natural isolates with their performance.
- Fifty-seven hundred fragrances with their qualitative composition.
- Fifty-five hundred flavor raw materials, e.g. natural, nature identical and artificial products.
- The quantitative analysis of 4,000 essential oils with 4,500 constituents.
- Over 7,000 volatile compounds in food products with their qualitative and quantitative occurrence.

Much know-how regarding the search of and the design for new materials was gathered from this study.

To develop a new aroma chemical, the investigation of structure-activity relationships is not just useful/helpful, but necessary. The reasons for studying odor-structure relationships can be, for instance, to produce an aroma chemical (flavor or fragrance material) with:

- Modified, new or unknown sensory properties, e.g. concerning odor quality and appreciation.
- More odor value-for-money, e.g. tenacity, persistence.
- Other improved physiological properties, e.g. better biodegradability, less toxicity.
- Better application properties, e.g. fiber, hair and skin substantivity.
- Improved physicochemical properties, e.g. chemical stability, desired volatility and solubility.

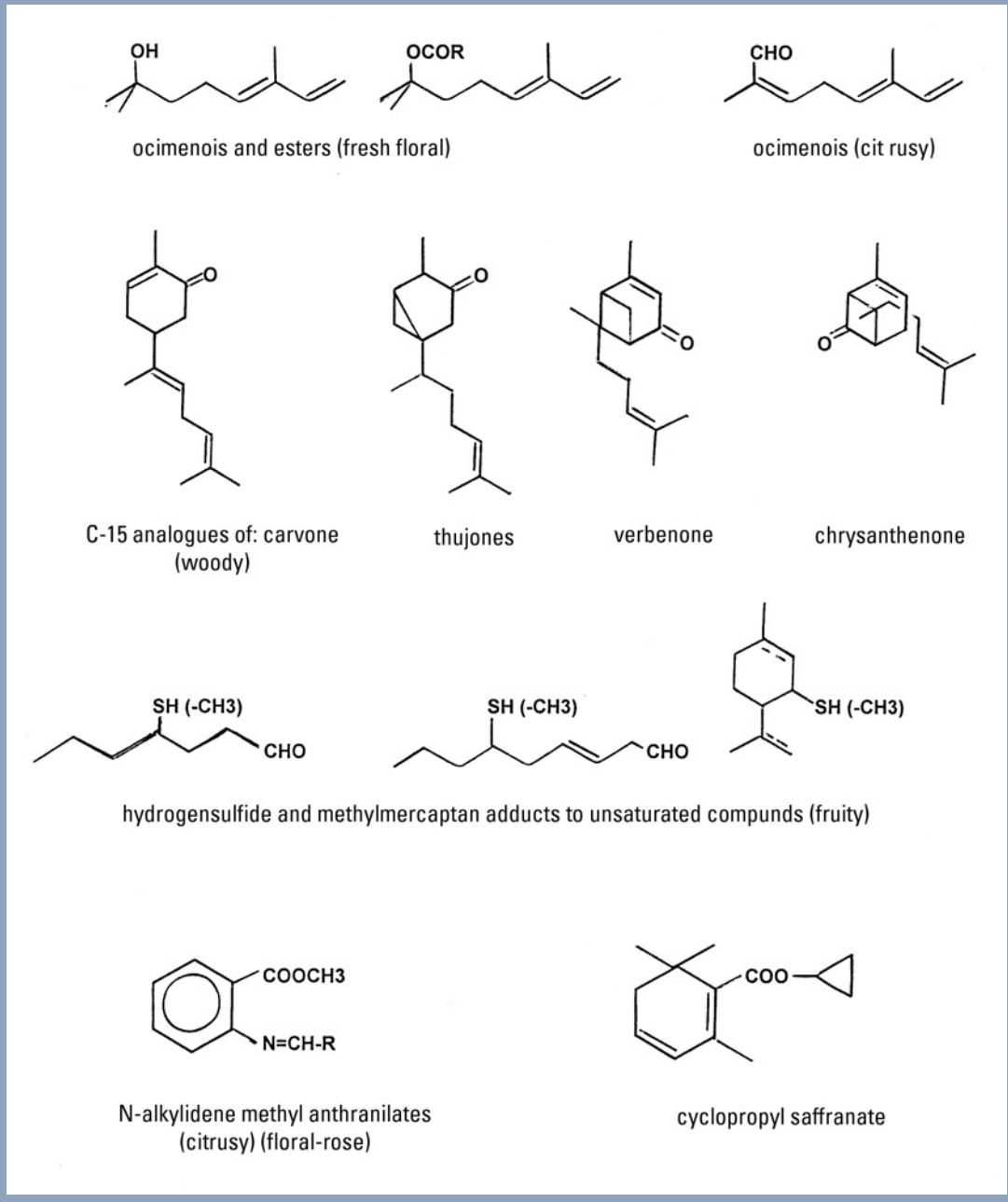
The purpose of the search for new flavor and fragrance materials or improved methods for their preparation has various facets:

- ***Economics:*** less raw material, lower variable, fixed and investment costs, for instance the synthesis of a macrocyclic musk compound.
- ***Sensory Properties:*** organoleptic and olfactive qualities, for instance character-impact compounds from natural isolates or (prepared) food products—preferred odor quality, higher intensity, longer tenacity.
- ***Other Physiological Properties:*** lower toxicity, less negative dermato logical peroperties.
- ***Application Properties:*** better fiber, hair or skin substantivity.
- ***Chemical:*** good stability in functional perfume compounds, less vulnerable for (air) oxidation, hydrolysis, hydration.
- ***Physical:*** optimal volatility, evaporation, diffusion properties.

In the following sections we will discuss:

- Recently published programs for the isolation of new products from nature.
- Improved and new monoterpene alcohols, esters and aldehydes.
- New sesquiterpene derivatives.

Proposal of molecular structures for new flavor and fragrance compounds **F-2**



- Substitution of isobutenyl by phenyl in monoterpenoids.
- Substitution of isopentyl by cyclohexyl in some aroma chemicals.
- Isobutyrates in place of acetates.
- Substitution of functional groups: aldehyde by nitrile, ester by ketone, *cis*-double bond by sulfur, chloro by methyl, allyl and geminal dimethyl by cyclopropyl.
- New natural sulfur compounds by addition of hydrogensulfide and methylmercaptan to unsaturated natural flavor compounds.
- Volatile Schiff bases (F-2).

Recent Research

In 1999, Givaudan carried out an innovative experimental program to discover new tastes, new molecules and new ingredients. A mission took their co-workers deep into the Gabonese rainforest to a place called Foret d'Abeille — one of the last unspoiled forests in Central Africa. In close cooperation with ProNatura, a non-profit rainforest preservation group, Givaudan accomplished a highly challenging expedition. Together with botanists and entomologists, the company's research teams from the United States and Switzerland explored the rainforest's incredible

biodiversity, foraging on foot and hovering above the treetops on the world's largest hot air balloon.[6a] Altogether, more than 250 samples were collected and evaluated. The following new fruit flavors were developed: Ginger Strawberry from *Aframomum giganteum*, Mangolino from *Dacryodes klaineana*, Gabonese Pineapple from *Diospyros mannii*, Rainforest Melon from a *Drypetes* species, Wild Garcinia from *Garcinia epunctata*, Bush Pearl from *Irvingia gabonensis*, jungle fruit from *Landolphia owariensis* and Paradise Fruit from *Pentadesma butyracca*.

In 1998 IFF sent, for the first time, a miniature rose into space to produce three alternatives to the hybrid rose plant under the influence of microgravity. A new rose fragrance was developed from the results of this experiment. IFF is now engaged in a second NASA project exploring new perfumery molecules.[7b] This project will be continued in the coming years.

Recently, IFF (in the United States) has prepared ground for a new hydroponic greenhouse to complement an existing greenhouse facility. The hydroponics technique concerns the growing of plants in water with essential chemicals in solution, instead of in soil. The new facility will be used for the extraction of fruit and flower aromas from hydroponically grown plants. The addition will feature climate controls for each section, including underground heat. IFF states that there is a high interest in this method of growing plants to discover innovative natural products that will enhance the quality of life of consumers all over the world.[6c]

Quest International, in conjunction with Oxford University and the Ecole Superieur du Science Agronomique, has announced the results of open-air and underwater headspace sampling in Madagascar. The goal was to find new scent molecules, which could be created in vitro later on. Samples were taken from waterfalls, aquatic plants, forest mosses, tropical flowers, uncatalogued species of resinous plants and native woods and barks. New mono- and sesquiterpenoids were discovered in the process. Quest believes that new fragrance profiles will spur new fragrance trends.[6b]

From these and earlier investigations, one may draw the preliminary conclusion that new character-impact compounds are seldom found. These studies often lead to new combinations and concentrations of already existing odoriferous materials as a consequence of new flavor and fragrance bases. Because much of this work is extremely expensive, one may question whether it is not more economic to investigate plant materials that are easily available and which possess unknown sensory properties (e.g. witch hazel, sweet pea, petunia, phlox).

Isolation Techniques and Chemistry

Nature and natural isolates have always stood as the models for the flavor and fragrance chemist. In former times these scientists used classical organic chemistry to synthesize new materials. This chemistry was in principle simple; the organic reactions were divided into ionogenic and radical. The ionogenic reactions could be either electrophile or nucleophile. As reaction types, one could, for instance, recognize additions, eliminations, substitutions and rearrangements. Ionogenic reactions often were carried out in polar solvents with a great deal of inorganic materials and wastewaters. Radical reactions were characterized by rather higher temperatures that allowed the formation of free radicals. Some catalytic processes were known as, for example, hydrogenations and oxidations. What has changed during the past decennium? For one thing, more and more knowledge about biochemical processes has been gained. Approximately 1,500 flavor raw materials are now prepared by these processes.[5d] New techniques and spectroscopic methods have been developed to isolate and analyze constituents from nature down to parts per billion. Is this all old wine in new barrels or new wine in old barrels? No. New isolation techniques, such as the production of important organic compounds from natural products by specific membrane separation at room temperature, will allow progress. In

Odor tests with aliphatic compounds: how seven experienced test persons identified aliphatic methyl ketones and acetates based on their functional groups* **T-1**

Compound		Number of Compounds	Number of Tests	Identified		Most Frequent Type of Mistake
				Correct	Incorrect	
methyl ketone	C-3 to C-63	3	21	76	24	spread
idem	C-7 to C-10	3	26	46	54	ester (50 percent)
idem	C-11 to C-15	3	21	0	100	alcohols (62 percent)
esters	C-3 to C-6	7	52	58	42	methyl ketones (25 percent)
idem	C-7 to C-10	8	51	80	20	spread
idem	C-11 to C-15	9	56	29	71	alcohols (29 percent)

*The methyl ketones C-7 to C-10 and the esters C-3 to C-10 were identified on their fruity odor character; the C-11 to C-15 compounds (methyl ketones, esters and alcohols) were often incorrectly identified because of their fatty odor characteristics.

addition, new membranes will be developed for these techniques. The biochemical (enzymatic) manufacture of flavor and fragrance materials will be improved and extended. These reactions will be carried out with greater specificity and in higher concentrations. Scientists will increasingly realize what is happening in nature, as in the example of the plant exudate labdanum gum on *Cistus ladaniferus* in a subtropical climate at temperatures of up to 100°C in an acidic medium. Complete new reactions will be found as rearrangements (ring contractions) followed by photochemical oxidation (formation of amberoxide). In addition, many new homogenic catalytic enzymatic biological reactions will be discovered.

In flavor and fragrance chemistry it is normally accepted that natural isolates are mixtures of sometimes hundreds of chemical compounds, whereas in the search for new aroma chemicals, one often strives for chemically and olfactively pure compounds. It is far easier and more economic to make olfactively acceptable mixtures, as for instance with the addition of acetic acid to myrcene, acetylation cedarwood terpenes (thujopsene), or for the preparation of amber compounds. In another instance, a mixture of macrocylic biomusk compounds could economically be prepared in a few reaction steps from 10-undecenoic acid and 1,4-butanediol or tetrahydrofuran.

Substitution of Functional Groups

More than 95 percent of the commercially available fragrance and flavor chemicals contain one or more functional groups. One may question, then, whether a functional group is necessary for the odor of a compound. No, it is not, because alkanes and benzenoid hydrocarbons sometimes have very pronounced odors. We wondered whether a trained observer would be able to recognize an odorant by its functional group. Therefore we tested 100 aliphatic (normal C-3 to C-15) compounds with and without functional groups. Seven odor-trained chemists were used. Each observer received known standards with eight carbon atoms and 13 different functional groups, e.g. octane, octanol, octanal, octanoic acid, hexyl acetate, octanethiol, octylamine, and so forth. The chemists received all samples under codes, and upon smelling and comparing with the standards, had to write the general chemical name, e.g. "This is an alkane, alcohol or thiol."

The results were:

- Seven hundred six tests were performed, from which 58 percent were correct and 42 percent wrong.
- For the C-3 to C-6 compounds, more than 80 percent were identified based on their functional groups.
- For the C-7 to C-10 compounds, over 80 percent of the aldehydes, alcohols and thiols were correctly recognized; from the other functional group compounds, more than 50 percent were wrong.
- For the C-11 to C-15 compounds, only the thiols could be identified correctly from the other functional groups; 50 to 100 percent were incorrectly identified.

The results with the methyl ketones and acetates are shown in T-1.

From this experiment it seems likely that experienced odor-perception observers can mistake certain functional groups (ketones) by others (esters), even with the use of odor standards. The same holds true for other functional groups, such as the case of the following substitutions:

- Aldehyde for nitrile in monoterpenoid and benzoid compounds.

Examples of substitution of functional groups with the same odor character **T-2**

Original Functional Group	Example Aroma Chemical	Substituted Functional Group	Substituted Aroma Chemical	Odorl Description
aldehyde	citral	nitrile	geranlynitrile	citrusy, lemon-like
aldehyde	benzaldehyde	nitro	nitrobenzene	aromatic, spicy, bitter-almond-like
acetate	isopentyl acetate	methyl ketone	5-methyl-heptan-2-one	fruity, banana-like
(Z)-ethylene	(Z)-hex-3-en-1-ol (acetate)	sulfur	3-thiapentan-1-ol (acetate)	green, freshly mown grass, slightly sulfurous
chloro	(trichloromethyl)-benzyl acetate	methyl	trimethylmethyl-benzyl acetate	floral, rose-like
nitro	musk ambrette	acetyl	acetyl musk ambrette	musky, erogenic
gem.dimethyl	damasc(en)jone	cyclopropyl	damasc(en)one derivative	floral-fruity, rose- and rum-like
allyl/propenyl	(methyl)ionones	cyclopropyl	(methyl)ionone derivatives	floral-fruity, orris- and strawberry-like

- Aldehyde for nitro in benzenoid compounds.
- *cis*-Olefine for sulfur in straight-chain aliphatic compounds.
- Chloro by methyl in aliphatic and benzoid esters.
- Allyl and geminal dimethyl for cyclopropyl in damasc(en)nones and ionones (F-2).

Some examples of replacement functional groups in odorants with the maintenance of the more or less same odor character are shown in T-2. From this table it is clear that, at times, functional groups can be replaced by others without a big change in the odor character. Substitution of functional groups in molecules with more or less the same electronic charge distribution and similar odor characteristics are examples of "isoelectronic" molecules with similar olfactive properties.

The straight chain aliphatic aldehydes octanal and decanal are organoleptically character-impact compounds of orange peel oil and could have been used a lot more in perfume compounds. In fact, they are used in alcoholic perfumery in several luxury perfumes such as Chanel No. 5. The application of these aldehydes in functional perfumery (soap, detergents and other household products), however, has severe limitations because of the chemical stability of the aldehyde function (oxidation, condensation). Even in alcoholic perfumery, the aldehydes will form hemiacetals. The chemist working on odor-structure relationships will modify the functional aldehyde group.

There are several tools available to accomplish this:

- Substituting of the aldehyde function by a chemically more stable group such as nitrile, acetyl or oxim.
- Preparing a vinyl ether of the aldehyde to give the slow release of the aldehyde in acidic media.
- Making an acetal of a lower alcohol with the same target.
- Forming an equilibrium in a Schiff base with methyl anthranilate.

Isobutyrates in Place of Acetates

Esters of lower fatty acids, e.g. formic and acetic, have fruity-floral odor characters and occur in many food flavors and essential oils. Applications of these esters in functional perfume compounds for alkaline media possess the disadvantage that they can saponify. In some cases, one may substitute the acetate function with an isobutyrate or even a pivalate one without great change in the olfactive character of the compounds. New aroma chemicals of this type are α-terpinyl isobutyrate, phenethyl pivalate and vanillyl isobutyrate. As can be seen from T-3, of the commercially available acetates and isobutyrates there is still room for a series of isobutyrates.

Substitution of Isobutenyl With Phenyl in Monoterpenoids

Various examples of the replacement of an isobutenyl group with a phenyl group are presented in the literature. Substitution of the butenyl group by a phenyl group causes little effect on the odor character of linalool, rose oxide and geranonitrile. Turin could predict with his method for spectrum calculation (inelastic electron tunneling spectroscopy) the similarieites in odor character of these different structural classes.[4b]

The isobutenyl part in the original molecules is more vulnerable to oxidation than the phenyl part in substituted molecules. And while the odor qualities of both molecules show a clear resemblance, the intensities of the phenyl substitutes will sometimes decrease. On the other hand, the odor tenacity of the phenyl derivatives is greater, and their substantivities better. Several of these phenyl substitutes are commercially available. There is room for many more monoterpenoid substitutes, as for instance with: nerol/geraniol (esters), neryl/geranyl hemi-acetals, neric/geranic acid (esters), neryl/geranyl acetone, linalyl esters and hemi-acetals, and citronellyl derivatives (see neryl/geranyl). Examples of commercially available aroma chemicals in which the isobutenyl part is substituted by a phenyl part are shown in T-4.

Examples of commercially available aroma chemicals in which the isopentyl part is substituted by a cyclohexyl part are shown in T-5. Substitution of certain groups in molecules with more or less the same profile (shape, volume) and similar odor characteristics are examples of "isosteric" molecules with reminiscent olfactive properties.

Substitution of Isoamyl by Cyclohexyl in Some Aroma Chemicals

The isoamyl group is a natural degradation product from leucine and often occurs in natural isolates, mostly as an ester. The lower aliphatic isoamyl esters may have strong fruity odors. A disadvantage of the application of these esters is that they are highly volatile and can easily saponify. One may substitute the isoamyl group with a cyclohexyl group without disturbing the odor character to any great extent. Some examples of this substitution can be found in the odors of cyclohexyl salicylate, cyclohexyl phenethyl ether and allyl cyclohexyloxyacetate (see T-5).

In T-6 the commercially available isoamyl and cyclohexyl esters are shown; there is still room for more of the latter.

New Terpenoid Alcohols, Esters and Aldehydes in Natural Products

It is general knowledge that citrus oils contain farnesenes and the corresponding aldehydes α- and β-sinensal. Citrus oils also contain myrcene and ocimenes, but the corresponding aldehydes, myrcenal and ocimenals (see F-2), have not been detected up to now. During our studies of the composition of 3,225 quantitative analyses of essential oils it was noted that more than 50 percent of these oils contained either myrcene or ocimenes. However, less than 1 percent of these oils showed the presence of myrcenol or ocimenols (see F-2), and none of them contained the aldehydes. Synthesis of pure myrcenyl and ocimenyl acetate revealed that they possess excellent olfactive properties, and an extremely fresh floral character that improves those of linalool and its acetate. T-7 shows the frequency of the occurrence and the concentration ranges of some monoterpenoids in essential oils. T-8 shows the commercially available citronellyl, geranyl and linalyl esters. It is clear that more linalyl esters can be prepared; moreover, it is likely that new myrcenyl and ocimenyl esters will be found in nature and manufactured.

New Sesquiterpenoid Derivatives

The allylic oxidation of sesquiterpenes in analogy with that of limonene for the formation of C-15 will lead to analogues of carvone (F-2), perilla aldehyde and isopiperitenone. Sesquiterpene carbonyl analogues should be developed from other olfactively interesting monoterpenoid ketones: thujones, verbenone and chrysanthenone (F-2). These sesquiterpene ketones could

Commercially available acetates and isobutyrates of C-4 to C-10 alcohols* **T-3**

No.	Alcohol Part	Acetate	Isobutyrate	No.	Alcohol Part	Acetate	Isobutyrate
1	butyl	+	+	18	citronellyl	+	+
2	sec.butyl	+	-	19	dihydromyrcenyl	+	-
3	isobutyl	+	+	20	tetrahydromyrcenyl	+	-
4	tert.butyl	+	-	21	tetrahydrolavandulyl	+	-
5	n-pentyl	+	-	22	neryl	+	+
6	2-methylbutyl	+	+	23	geranyl	+	+
7	3-methylbutyl	+	+	24	dimethyloctyl	+	-
8	hexyl	+	+	25	linalyl	+	+
9	2,4-hexadienyl	+	-	26	tetrahydrolinalyl	+	-
10	heptyl	+	-	27	myrcenyl	+	-
11	2-heptenyl	+	-	28	α-terpinyl	+	+
12	(Z)-3-heptenyl	+	-	29	dihydroterpinyl	+	-
13	octyl	+	-	30	benzyl	+	+
14	nonyl	+	-	31	phenethyl	+	+
15	decyl	+	-	32	α-methylbenzyl	+	-
16	2-decenyl	+	-	33	3-phenylpropyl	+	+
17	9-decenyl	+	-	34	cinnamyl	+	+
Total Number:						34	16

*Source: 2002 Allured's Flavor and Fragrance Materials

Commercially available aroma chemicals with isobutenyl by phenyl substitution **T-4**

Original Aroma Chemical (Chemical Identity)	Substituted Aroma Chemical	Commercial Name (Supplier)	Odor Description
6-methyl-5-hepten-2-ol	4-phenylbutan-2-ol	methyl phenethyl carbinol (F-3)	slightly floral, rose-like, sweet aromatic
citronellol (3,7-dimethyloct-6-enol)	3-methyl-phenylpentan-1-ol	Mefrosol (Quest), Phenoxanol (IFF), Phenylhexanol (Firmenich)	diffusive, fresh floral, rose absolute type
citronellal	3-methyl-5-phenylpentanal	Mefranal (Quest)	green aldehydic
citronellylnitrile (3,7-dimethyloct-6-enenitrile)	3-methyl-5-phenyl-pentanenitrile	Hydrocitronitril (Haarmann & Reimer), *Citralis nitrile* (IFF)	citrusy, lime, fresh
geranylnitrile	3-methyl-5-methyl-pent-2-enenitrile	Citronitrile (Haarmann & Reimer)	fresh citrusy, lemon-like, somewhat aromatic-balsamic notes

have useful odor qualities. F-2 to F-3 reveal the molecular structures of some of these sesquiterpenylcarbonyls. There are interesting comparisons to be made between valencene and nootkatone, and α-cedrene and cedrenone.

Regarding the epoxidation of sesquiterpenes and the conversion of the epoxide to ketones (isolongifolanone, cedranone, caryophylla-none, etc.), epoxidation can easily be carried out with hydroperoxide and formic acid (or ester) to a mixture of epoxides, diols and formats, which in turn can be

Commercially available aroma chemicals with isopentyl by cyclohexyl substitution **T-5**

Original Aroma Chemical/ Chemical Identity (Commercial Name and Supplier)	Substituted Aroma Chemical	Commercial Name (Supplier)	Odor Description
isopentyl salicylate/ 3-methylbutyl 2-hydroxybenzoate (isoamyl salicylate)	cyclohexyl salicylate	Cyclohexylsalicylat (Cognis)	sweet aromatic- floral, somewhat medicinal-phenolic
allyl isopentoxyacetate/ prop-2-enyl-1 6-methyl-3-oxaheptanoate (A.I.A.A.-Inoue) (Allonate-Quest (Allyfate-Quest) (Allyl amyl glycolate-IFF) (Galballynate-Bell Aromatics) (Isoamylix-Charabot) (Isogalbanate-Dragoco) (Pentyrate-Sensient)	allyl cyclohexoxyacetate	Allyvert (Quest) Cyclogalbanat (Dragoco) Cyclogabaniff (IFF) Hexylix (Charabot) Isoananat (Haarmann & Reimer)	green, fruity, herbal, reminiscent of galbanum, pineapple connotation
isopentyl phenylethyl ether/ 2-isopentoxy-1-phenylethance (Anther-Quest) (Iphaneine-IFF) (phenylethyl isoamyl ether-Toyotama) (Treflon-Takasago)	cyclohexyl phenylethyl ether	Phenafleur (IFF)	floral note with hyacinth associations

Commercially available isoamyl and cyclohexyl esters* T-6

No.	Ester/Acid Part	Ester/Alcohol Part Isoamyl	Ester/Alcohol Part Cyclohexyl	No.	Ester/Acid Part	Ester/Alcohol Part Isoamyl	Ester/Alcohol Part Cyclohexyl
1	acetate	+	+	19	isobutyrate	+	+
2	acetoacetate	+	-	20	isovalerate	+	+
3	angelate	+	-	21	lactate	+	-
4	anthranilate	-	+	22	laurate	+	-
5	benzoate	+	-	23	2-methylbutanoate	+	-
6	butyrate	+	+	24	nonanoate	+	-
7	cinnamate	+	+	25	octanoate	+	-
8	crotonate	+	+	26	phenylacetate	+	+
9	cyclopentenylacetate	-	+	27	3-phenylpropionate	+	-
10	decanoate	+	-	28	propionate	+	+
11	eugenyl	+	-	29	pyruvate	+	-
12	formate	+	+	30	salicylate	+	+
13	4-(2-furan)-butyrate	+	-	31	senecioate	+	-
14	3-(2-furan)-propionate	+	-	32	3-(methylthio)-propionate	+	-
15	geranate	+	-	33	tiglate	+	-
16	heptanoate	+	-	34	undecylenate	+	-
17	heptinecarbonate	+	-	35	valerate	+	-
18	hexanoate	+	+				
Total number						33	13

*Source: 2002 Allured's Flavor and Fragrance Materials

Frequency of the occurrence and concentration of some mono- and sesquiterpenoids in 3,225 essential oils T-7

Monoterpenoid	In Total Number of Oils	Concentration Range (Percent)	In Concentration Range (Precnet)/ Number of Oils	In Concentration Range (Percent)/ Number of Oils
myrcene	2,180	0.01-95	1-95/1,063	10-95/81
myrcenol	20	0.01-8.2	-	-
myrcenyl acetate	2	0.01-6.0	-	-
myrcenal	0	-	-	-
(Z)-ocimene	880	0.01-43	1-43/228	10-43/41
(E)-ocimene	975	0.01-95	1-95/252	10-95/95
(Z)-ocimenol	3	0.01-1.5	-	-
(E)-ocimenol	4	0.01-1.5	-	-
ocimenals	0	-	-	-
menthol	195	0.01-85	1-85/123	10-85/101
menthyl acetate	126	0.01-52	1-52/102	10-52/101
menthone	262	0.01-60	1-60/171	10-54/18
thymol	405	0.01-90	1-90/180	10-90/91
carvone	364	0.01-80	1-80/87	10-80/46
carvomenthone	5	0.01-1	-	-
carvomenthol	0	-	-	-
carvomenthyl acetate	1	0.01-1	-	-
carvacrol	364	0.01-90	1-90/154	10-90/94
α-farnesenes	286	0.01-40	1-40/82	10-40/15
β-farnesenes	530	0.01-90	1-90/150	10-90/16
α-sinensal	71	0.01-3	-	-
β-sinensal	59	0.01-3	-	-

Commercially available citronellyl, geranyl and linalyl esters* **T-8**

No.	Ester/Acid Part	Ester/Alcohol Part Citronellyl	Geranyl	Linalyl	No.	Ester/Acid Part	Ester/Alcohol Part Citronellyl	Geranyl	Linalyl
1	acetate	+	+	+	12	hexanoate	+	+	+
2	acetoacetate	-	+	-	13	isobutyrate	+	+	+
3	anthranilate	+	+	+	14	isovalerate	+	+	+
4	benzoate	+	+	-	15	2-methylbutanoate	+	+	-
5	butyrate	+	+	+	16	phenylacetate	+	+	+
6	cinnamate	-	-	+	17	octanoate	-	+	+
7	crotonate	+	+	-	18	propanoate	+	+	+
8	decanoate	+	+	-	19	tiglate	+	+	-
9	dodecanoate	+	+	-	20	undecylenate	-	+	-
10	ethyl oxalate	+	-	-	21	valerate	+	+	-
11	formate	+	+	+					
Total number							17	19	11

converted into simple sesquiterpene ketones. It should also be noted that methanol may be added to sesquiterpene hydrocarbons (such as IFF's cedryl methyl ether).

Studying the Biochemical Formation of New Volatile Compounds

The biogenesis of fatty acids and isoprenoids from acetyl-coenzym-A has been known for decennia. Fatty acids are linearly built up via aceto-acetyl-ScoA to higher β-oxo-acyl-ScoA derivatives, followed by reduction, dehydration and again by reduction into fatty acids with the general formula: CH3 (CH2)nCOOH, where n is zero or an even number.

Isoprenoids are biochemically formed via aceto-acetyl-ScoA via β-hydroxy-β-methyl-glutaryl-ScoA and mevalonate to branched-chain (CH3)2C=CH-[CH2-CH(CH3)-CH=CH]- derivatives, where x is zero or a whole number. One could imagine that a combination of the two biogenetic pathways should lead to geminal-methyl- or 3-methyl-alk-2-enyl derivatives. If this combination of the two routes is indeed possible, one could expect a series of these compounds in natural products, which contain the proper precursors and enzyme. We supposed that citrus fruits, containing fatty acid derivatives and isoprenoids, should present a fair chance of finding 3-methylalk-2-enyl derivatives. Therefore, we prepared a series of 3-methylalkenals and searched for their occurrence in different citrus oils. Indeed, it was possible to detect 3-methyloct-2-enal in lemon oil by a combined gaschromato-graphic/mass spectrometric technique. 3-Methyloct-2-enal has a distinct lemon flavor and improves the organoleptic quality of the natural oil. β-Methyl-γ-octanoic lactone has been

found in alcoholic beverages. The compound has a coconut-like odor, but is indispensable for a good flavor of brandy, whiskey or rum. Geminal-dimethyl-alkanoic acids have been found in various meat and in dairy products, e.g. 9-methyl-dodecanoic acid in mutton, and 11-methyldodecanoic acid in powdered milk. Hundreds of new substances can be designed and possibly found in nature following these biochemical guidelines.

So far, up to 70 volatile alcohols and about 60 fatty acids have been detected in food flavors, such as apple, banana, guava, grape, papaya, raspberry and strawberry.[5d] A simple calculation makes it clear that 70 x 60 = 4,200 esters should occur. However, up to now less than 10 percent, or 420 esters in total, have been found in these fruits.

Investigation of Reactions During Food Processing

The most important chemical event during food processing is the Maillard reaction of amino acids and sugars, followed by Amadori or Heinz rearrangements. A European scientific committee was formed from universities and the flavor industry to study this reaction in detail. It was discovered that hydrogen sulfide (from cysteine) and methyl-mercaptan (from methylcysteine) can be added to (Z)-3-hexenol and limonene during flavor formation.

New flavor constituents can be formed by the addition of hydrogen sulfide or methylmercaptan to unsaturated compounds [e.g. (Z)-4-heptenal, (E,Z)-2,6-nonadienal, monoterpenes, sesquiterpenes, damasc(en)ones]. About 10 percent of all published volatile compounds are sulfur compounds.[7,10] An important group of these compounds are disulfides, of which (until now) about 60 have been found in food products. On the basis of all the ca. 50 (= n) thiols one could expect n(n + 1)/2 = 1,275 disulfides. Although not all the 50 thiols occur in the same foods or beverages, many more disulfides surely exist and will be found.

Volatile Schiff's Bases

A Schiff's base of methyl anthranilate with olfactively interesting aldehydes is well known in perfumery. However, this Schiff's base is a mixture of the starting materials in equilibrium with the end product. If one purifies the end product, e.g. by high vacuum distillation, the resulting material is often odorless. One may produce volatile N-alkylidene methyl anthranilates (F-2) (from ethanal, propanal, butanal, isobutanal, pentanal, 2- and 3-methylbutanal, hexanal and hexenal) in pure form, which likely occur in natural products. Only one pure N-alkylidene methyl anthranilates (from 2-methylpentanal, mevanthral from Quest) is commercially available today.

Conclusion

New groups of aroma chemicals can be designed by the substitution of isosteric groups (e.g. isobutenyl by phenyl and isopentyl by cyclohexyl, gem-dimethyl by cyclopropyl) and of isoelectronic groups (e.g. aldehyde by nitrile, acetate by methyl ketone, allyl by cyclopropyl, chloro by methyl).

In closing, new flavor and fragrance materials can be developed by:

- Exploring new natural materials.
- Extending characteristic monoterpenoids to sesquiterpenoids.
- Developing new monoterpenoids from similar sesquiterpenoids.
- Functionalization of mono- and sesquiterpenes.
- New biochemical pathways.
- Volatile Schiff's bases.
- New biochemical pathways.
- New products formed during food processing.
- Extension of esters of naturally occurring alcohols and esters.
- Addition of hydrogensulfide and methylmercaptan to natural and unsaturated compounds.

- Extension of sulfides and disulfides from existing thiols.

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