Aromatic Substances, Fragrances and Flavors:

The Search for New Active Agents

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The Economic Environment: Everyone seems to agree on one point: the competitiveness of the European chemical industry is primarily a result of its innovative strength. However, in view of the regulatory environment in which we find ourselves in a Europe which is about to unify, there is a great risk that this creative momentum will slow because of a regulatory system which is far too restraining.

Such a development will have serious repercussions on the future of Europe's chemical industry, particularly since research by Europe's principal competitors, both in Japan and the United States, continues to increase (ECU 11,000 million for Japan and ECU 13,000 million for the United States[1]). These considerations must convince the authorities and the general public that research is of crucial importance to the competitive position of European industry.

By spending an estimated 3% of its GNP[2] on research, Switzerland clearly leads the group of industrialized nations. However, although Switzerland is exemplary in this regard, one should recognize that what is important for the pursuit of certain major projects is the value of the critical mass which is required to reach a satisfactory level of efficiency. It is evident that, viewed from this angle, the absolute value for a small country such as Switzerland compares unfavorably with that of the countries in which its major competitors are located.

It is undeniable that in a climate of growing trade liberalization, research and technology play an increasingly decisive role as factors of strategic competition. This is true also for the flavor and perfumery industry. As a genuine driving force in a particularly active economic microcosm, research in this branch not merely determines its development but is also subject to its constraints. As a matter of fact, far from being in the ivory tower where some people imagine it, research in the field of aromatic substances is very close to the market, where it must face a variety of technological challenges and assimilate the changing perceptions of a swiftly changing market consisting of increasingly demanding consumers.

The Objectives

The raw materials of perfumery—essential oils or reconstituted essences, artificial bases, isolated chemical compounds, whether of a natural, nature-identical or artificial type—represent the constituent elements on which modern perfumery and flavoring are built. Now this branch has undergone a constant evolution over time, an evolution which has accelerated in the course of the last two decades in particular. In this paper we'll examine reasons why this evolution must continue, identify some target product areas and review some recent changes in research strategy.

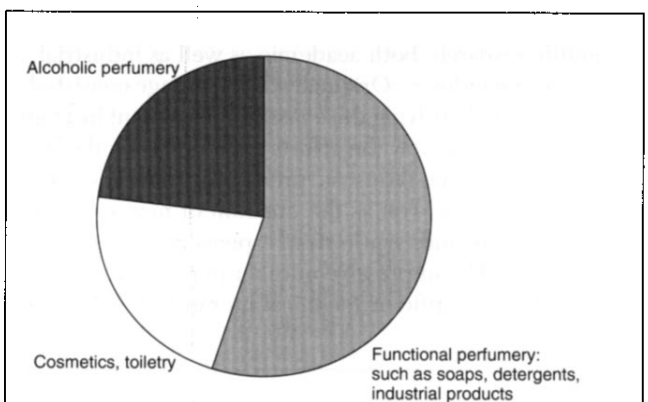

Figure 1. Perfumery sales components.

The growing sophistication in the tastes and perception of consumers, as well as the dynamics imposed by consumerism due to the fact that large segments of the population throughout the world have reached higher income levels, have been the driving forces behind the creation of new scents and the development of new applications. In the eyes of the public at large, our industry is almost invisible. As Figure 1 shows, our industry achieves most of its sales from functional perfumery, which is products used to fragrance detergents, soaps, cleaning agents and deodorants; that requires an exact adaptation of the perfume to the product/substrate, with regard to both its odor and its performance and stability.

Taking into consideration the apparition of new products in a sector as dynamic as that of detergents, for instance, it is not surprising to find that their perfuming requires new odorous materials with properties that satisfy new demands dictated by the presence of active detergent ingredients of

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a frequently aggressive or at least destabilizing nature with regard to traditional perfuming agents.

At the root of the development of the perfumery and flavoring industry we find an obvious fact: the raw materials of natural origin cannot be produced in unlimited amounts at prices that can be used in functional fragrances. Consequently their relative concentration in the compounds decreases as the production of the completed products increases. Since no new natural materials have appeared on the market for the past two decades,[3] it is evident that the consumption of synthetics will increase. At the present time, their proportion with regard to ingredients of natural origin is approximately 4 to 1, and will certainly grow in the future.

The organic chemist has always been an indispensible ally of the perfumer or the flavorist. Rarely has an industry blossomed so harmoniously thanks to the developments of scientific research, both academic as well as industrial, as the flavoring industry. Originally the challenge consisted in isolating and identifying the constituents present in a natural essence, while now the efforts are focused on the study of the synthesis and industrial production of nature-identical compounds as well as the creation of new structures, artificial compounds synthesized especially for their intrinsic qualities. The impressive number of patents and works available in scientific or technical literature testify to this tendency.[4]

One can legitimately ask whether the perfumer/flavorist does not already have at his disposal a sufficient number of active agents. From experience we can reply in the negative and this despite the fact that available spectrum includes thousands of ingredients—the number of ingredients in current use is generally estimated to be between 2,000 and 3,000.

The reason for this is quite simple: thanks to a new ingredient, the creative perfumer/flavorist will often be able to introduce a novel character which will not merely serve the purpose of establishing in some way the originality of his work, but which will also avoid the risk of being copied since others do not have the same ingredient at their disposal. Resorting to a strategy of protection by patents is a legal weapon which is often decisive in the competitive battle in which the commercial actors are engaged.[5]

According to a perfumer, Arcadio Boix Camps,[6] perfumery has been able to evolve to this stage of perfection only thanks to the fact that research has led to the discovery of new active substances, which, having been made available to creators with a great degree of sensitivity, experience and talent, made it possible to realize a harmonious combination of new fragrances. Boix Camps concludes that great perfumes have always resulted from the development of new chemicals; this situation existed already at the beginning of the century when the discovery of vanillin, ethylvanilline, coumarin, hydroxycitronellal and the ionones made it possible to create perfumes which were truly revolutionary for their time. The relation between the new aromatic products and creative perfumery and flavoring continues today.

Kastner[3] summarizes the critical parameters of a novel perfuming agent in the following way:

- It must have an odor, although rare exceptions are possible.
- Its odor must have a certain degree of novelty.
- It must be harmonious in a complex mixture.
- It must create a perceptible perfuming effect in a composition.
- It must have a sufficient degree of stability.
- It must be synthesizable.
- Its price must be in proportion to its effects.
- It should preferably be patentable—at least with regard to its synthesis or its utilization.
- It must meet dermato-toxicological criteria, be innocuous and satisfy environmental protection requirements, such as those regarding bioaccumulation and biodegradability.

It is therefore not surprising that we can state that despite the considerable investments which have been made in research, the rate of success in the development of a new structure is rather modest. By experience and in the way of citing an example, we can say that in the case of Firmenich, with its laboratories where more than 1,000 new compounds are synthesized each year, only two or

Table I. Classification of aromatic compounds

Natural	Chemical compounds isolated from a natural source
Nature-identical	Compounds found in nature but prepared by way of synthesis
Artificial	Compounds not (yet) found in nature and prepared by way of synthesis

three of all these will eventually be made available to the company's perfumers/flavorists. By the way, it is current practice that the majority of these new compounds remain—at least for a certain amount of time—"confined" and reserved for exclusive use by its own creators before being released for direct sale.

The Target Products

Aromatic compounds can be classified as natural, nature-identical or artificial. (See Table I.) For both nature-identical and artificial compounds, the research strategy has tended toward first designing a molecule and then synthesizing it.

Natural—For certain compounds which belong to this category there is quite often not yet an efficient technical manufacturing process that is price-competetive with the natural product. These compounds include 1,8-cineole, eugenol, cedrol, α-cedrene or α- and β-pinene. On the other hand, total or partial syntheses have been worked out for compounds such as citral, (+)-citronellal and geraniol which now compete with the same products derived from natural sources.

Nature-identical—The number of compounds in this category is growing swiftly. These compounds are popular due to their favorable price/performance ratio, their availability and their toxicological integrity, and they represent the key to the success of most modern flavors. Table II lists some flavoring agents which are the result of research made during the last few years. It is true, however, that the utilization of certain compounds is limited as a result of their instability—this concerns certain heterocyclic or sulphur compounds, for instance. As far as others are concerned, for example the sesquiterpenes, their synthesis still faces certain difficulties.

Artificial—This certainly is the largest category. In flavors, however, these products suffer from significant legislative restrictions which are in force in the different countries. On the other hand, in perfumery, as we have already seen, they find a wider field of application, allowing the creation of novel fragrances. Often they also present a higher degree of performance, stability and safety relative to their natural counterparts.

Table II. Examples of some special flavoring agents*

Cyclic ethers	Sulphur compounds	Pyrazines
Ambrox[a]	dimethyl sulphide	acetylpyrazine
menthofuran	1-p-menthene-8-thiol	3-ethyl-2,6-dimethylpyrazine
rose oxide	2-methyl-4-propyl-1,3-oxathiane	2,6-dimethylpyrazine
theaspirane	8-mercapto-p-menthane-3-one	2-isobutyl-3-methoxypyrazine
vitispirane		tetramethylpyrazine

Ketones	Unsaturated alcohols, aldehydes, esters and hydrocarbons	
α-damascone	(Z)-4,7-ethyl-octadienoate	(Z)-4-hexenol
β-damascone	(2E, 4Z)-2,4-ethyl-decadienoate	(E,E)-2,4-octadienal
β-damascenone	(Z)-3-hexenal	(2E, 6Z)-2,6-nonadienal
cis-α-irone	(Z)-4-hexenal	(3E, 5Z)-1,3,5-undecatriene
4-(p-hydroxyphenyl)-2-butanone		

[a]Firmenich
* according to F. Näf et al. *Flavour Sci & Techn* Weurman Symposium (1990)

In the course of the last 30 years some 200 new perfuming agents have been introduced on the market. One could mention among them the rose ketones, various musks, several compounds of a woody nature (including compounds with a typical quality of sandalwood), as well as different esters, lactones, acetals and nitriles. Compounds of an amber type as well as macrocyclic compounds have been studied in a particularly thorough manner.

Research Strategy

Research strategy is based essentially on two distinct approaches. The first approach makes use of empirical or semi-empirical methods while the second approach is based on numerical methods.

Empirical methods—This approach groups together the traditional research methods which rely primarily on the intuition of a chemist who can also make use of certain observations and correlations which may exist between the properties of a generally uniform series of compounds with analogous structure.

This is an application of various theories. As examples one could cite Ohloff's triaxial rule,[7] Amoore's stereochemical rule[8] as well as the principles of conformational analysis of certain compounds with sandalwood[9] or patchouli odor.

Numerical methods—This approach, on the other hand, resorts to quantitative relations of structural activity, to techniques of pattern recognition or even molecular design, methods which can be completed by resorting to artificial intelligence or expert systems.

One must acknowledge that despite the increasing use of these numerical methods, the synthetic chemist's intuition largely still rests on the experience acquired in the course of many years of patient work performed in the laboratory. In spite of everything it is the conjunction of the empirical methods combined with a good amount of luck which is at the origin of the creation of most new molecules. Certainly, the remarkable progress which has recently been achieved with regard to understanding the mechanism of olfaction relating to the determination of the structure of the proteins of the receptors, of their active sites and of the nature of the complex ligand/receptors, makes us think that developments which only recently seemed to us to be utopian, will one day become reality and that chemists will thus have a reliable tool at their disposal for the creation of new and outstanding molecules.

Analytical chemistry—One cannot conclude these remarks on the subject of aromatic substances research without paying homage to the considerable contribution made to this process by analytical chemistry. It is actually the extraordinary advancement of the techniques of instrumental analysis, gas chromatography, mass spectrometry and nuclear magnetic resonance in particular, which has made it possible to isolate the active principles of most of the natural essences and to identify their molecular structure.

Biotechnology—We must also mention the indispensible assistance offered by biotechnology. Its importance for the industry of aromatic substances has constantly increased since the beginning of the 1980s. The growing demand for natural aromatic ingredients has been at the origin of this development. The use of food-grade microorganisms in controlled fermentation processes will henceforth make it possible to obtain a large number of aromatic metabolites of current use considered to be natural substances from the point of view of the regulations which are presently in force. The interest in such processes is all the more evident since they make it possible to obtain complex aromatic mixtures such as milk, bread, meat or fruit flavors.

On the other hand, the biological processes making use

of purified enzymes are utilized in order to develop flavors designed for a variety of products such as soya, sausages, wine, beer and dairy products. The use of lipases, for instance, will be a standard procedure for producing cheese flavors (EMC) and the use of esterases will be a standard procedure for obtaining certain esters with a fruity flavor.

One could also mention the application of biological techniques which are related to the culture of vegetable tissue of which the somaclonal variations and the fusion of protoplasts are examples.

Conclusions and Outlook

The search for new aromatic, perfuming or flavoring agents has certainly undergone an extraordinary and rapid expansion from the 1960s through the 1980s, thanks to the unprecedented development of analytical techniques. Such a degree of development will certainly be difficult to match during the years ahead. Nevertheless, there must be no doubt that the need for new compounds remains. This irrefutable fact constitutes a constant challenge to the synthetic chemists who have to resort to innovative approaches to manufacture these compounds.

The new strategies of research will be inherently influenced by the use of numerical techniques. Their development remains subordinated to the development of computer science and dependent on the understanding of the mechanism of perception of our olfactory and gustatory senses.

Finally, one should state that the mastery of biotechnology will play a decisive role.

It follows from all this that teams of highly qualified and motivated researchers, having at their disposal substantial resources within a framework of integrated and multidisciplinary research, will be able to face the challenge which a market in constant evolution poses to our industry. Accordingly this may well limit the number of candidates for success.

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