

Nitriles in perfumery

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The nitrile function has been studied and used by organic chemists for quite some time but it has not been generally recognized until relatively recently that this class of materials may have wide utility in fragrances. A monograph published in 1949 which deals with synthetic perfumes refers to only one fragrance chemical containing the nitrile group, musk cyanide (1) (see fig. 1).¹ This product, to our knowledge, is nonexistent in modern perfumery and may indeed never have been used to any significant extent in formulation work. A more recent survey on aroma synthetics suggests that a variety of nitrile chemicals has been introduced to perfumers over the years.² However, very few of those shown prior to the early sixties are evident in perfumery today. Myristic nitrile (2), reportedly was first suggested for perfumery use in 1944.³ This synthetic, decanonitrile (3), and dodecyl nitrile (4) are the only products now commercially available which were used in perfume compositions in this earlier era.

Nitriles vs. aldehydes

An inspection of the patent literature shows that interest in the use of nitriles as perfumery ingredients has greatly increased within the past decade. That interest has apparently been bolstered by the successful commercial introduction of geranonitrile (5) and cinnamonitrile (6) as alternatives to the widely used aldehyde counterparts.⁴ The bar graph in figure 1 shows the issuance of patents covering distinctly different chemical types from 1962 through 1978.⁵⁻²⁹ The circled 1964 patent was issued to Sommerville and Shuster; it covered perfumery

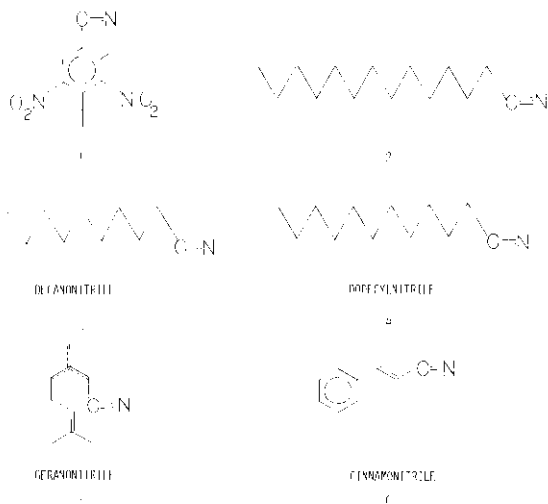
claims for geranonitrile and cinnamonitrile.⁶

There are several reasons why nitriles have been found useful as perfumery components, including their analogy in odor to the corresponding aldehydes and their much greater stability. A comparison of the odor for geranonitrile and cinnamonitrile with the related citral and cinnamaldehyde is displayed in figure 2.⁴ In these cases the odor of the nitrile conveys the generic odor impression of the aldehyde but is

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considerably more pungent, and often has an oily, heavy, metallic character relative to the aldehyde.



Aldehydes are susceptible to a variety of chemical reactions which reduce their odor potency, such as a strong tendency to oxidize and polymerize. The greater stability of nitriles has made them especially useful in perfumes employed in a wide variety of household and consumer products such as soaps, detergents, cleaners, and personal care products in which the fragrance oil can be subjected to rather harsh environments. A summary of the advantages of nitriles is given in figure 3.

Safety considerations

The lowered chemical reactivity of nitriles in comparison with aldehydes, especially unsaturated aldehydes, has further importance in the

potential for providing safer perfume formulations. Table I shows a comparison of toxicity tests conducted as recommended by the Research Institute for Fragrance Materials (RIFM). The oral LD₅₀ values (rats) and the dermal LD₅₀ values (rabbits) do not show any large toxicity differences between the nitriles and aldehydes. The sensitization (Kligman) tests, however, do demonstrate potential advantages in using these particular nitriles where relatively dilute solutions of some aldehydes can be sensitizing.

The reduced sensitizing activity of the nitrile function appears to result from its lowered chemical reactivity, especially with proteinaceous materials in the body. At PFW we have submitted a number of nitrile aroma chemicals for the same tests now used by RIFM and found them generally to have an LD₅₀ of 3g/kg or greater and to give no sensitization reactions.

Structure types

A scan of selected structural types found in the patent literature, along with odor descriptions, is displayed in figure 4. A variety of nitriles have been made available commercially for perfumery use. The products and current suppliers are shown in figure 5. Citrus-fresh type

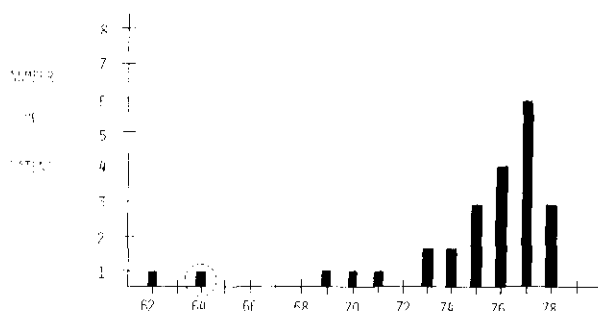


Figure 1 ↑

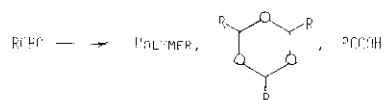
Figure 3 ↓

ADVANTAGES OF AROMA NITRILES

- 1) ODDOR ANALOGOUS TO THE CORRESPONDING ALDEHYDE.
- 2) HIGHLY STABLE TO:
 - A) OXIDATION
 - B) ACIDS AND BASES
 - C) HEAT
 - D) POLYMERIZATION

3) UNIQUE ODDOR EFFECTS.

4) LESS SENSITIZING THAN ALDEHYDES.

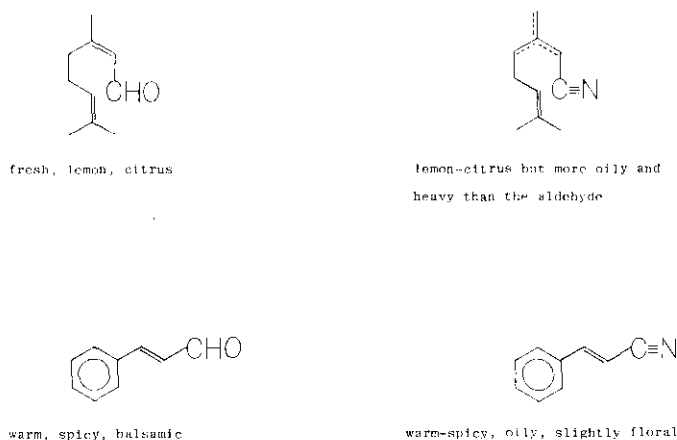


odors predominate in this group.

Synthesis routes

There is a continual challenge for aroma chemists to devise simple, inexpensive, non-polluting processes via readily available and nonhazardous raw materials, especially at this time of heightened concern for our environment. The synthesis of perfume chemicals has been the subject of study for almost 150 years.³⁰ The criteria for today's aroma chemist in providing perfume materials alternative or supplementary to the 5,000 or so products already available to the working perfumer are quite stringent when one attempts to provide novelty, utility, commercial advantage, and safety simultaneously. To compete as an effective addition to the perfumer's palette, a chemical should have a high odor impact in use, provide a unique odor effect or function (such as additional stability), have a relatively low cost-in-use, and be derived by a simple, inexpensive chemical process.

In the aroma chemical industry today manufacturing facilities for specialty chemicals are typically designed for multipurpose batch operations—equipment is used for producing a variety of products rather than just one com-



↑ Figure 2

Table I ↓

	CERANITRILE	CITRAL	CINNAMIC NITRILE	CINNAMIC ALDEHYDE
ORAL LD ₅₀	2.2g/kg.	5.0g/kg.	0.2g/kg.	2.2g/kg.
DERMAL LD ₅₀	0.3g/kg.	2.4g/kg.	>5g/kg.	---
IRRITATION (SOLUTION IN PETROLATUM)	12% NON-IRRITATING	8% NON-IRRITATING	4% NON-IRRITATING	9% IRRITATING 3% NON-IRRITATING
SENSITIZATION (SOLUTION IN PETROLATUM)	12% NON-SENSITIZING	1% SENSITIZING	4% NON-SENSITIZING	2% SENSITIZING

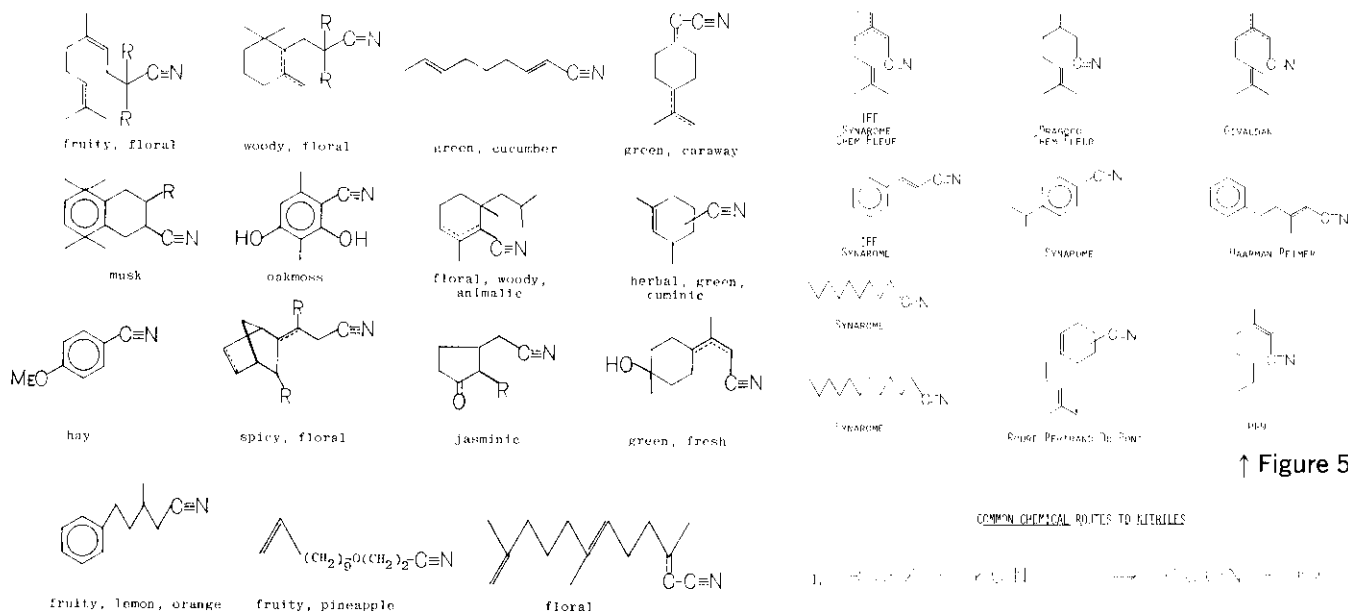
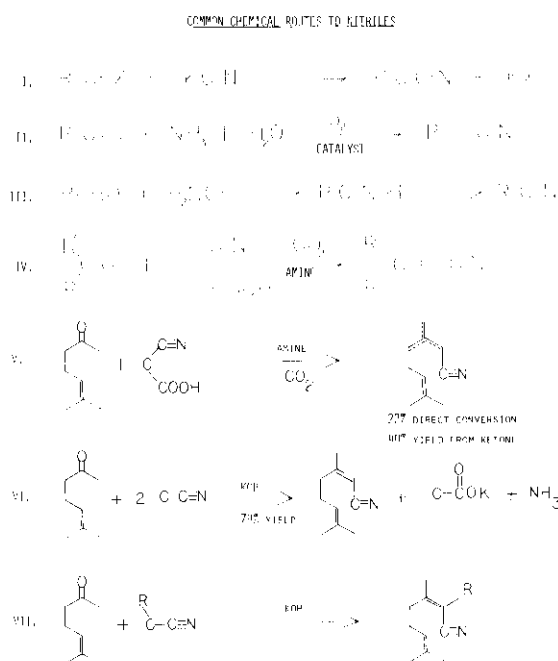


Figure 4 ↑

modity. This is due to the diversity of products required in aroma compositions, along with the small-volume nature of the majority of chemicals used. This restricts the type of chemistry which is feasible for introduction into a typical manufacturing facility.

Figure 6 shows some common reactions for synthesizing nitriles. Route I is simple and facile when employed in the lab. However, it would pose severe problems if brought into a multipurpose plant. This is due to the hazardous nature of KCN, the extraordinary manufacturing precautions necessary for handling, and the cost of waste control and removal. Route II outlines one specific example of a general route to nitriles called ammoxidation.³¹ Although suitable for a large volume operation typical of those run in the petroleum industry, this route requires highly instrumented specialty equipment. Unless the volume of manufacture with such a process is very high, one cannot expect to make the products cheaply due to the low conversions and resulting high recycle rates. In addition, this process is not amenable to having other functional groups in the molecule and the final product may be difficult to separate from a multiplicity of trace components which would be an obstacle to obtaining high odor quality. Routes III and IV, although requiring more expensive starting materials, provide the advantages of suitability for any batch size and ready adaptability to a multipurpose plant. Indeed, many of the commercial products shown in figure 5 are manufactured by either one of these last two routes.

The cyanoacetic acid synthesis, route V, suffers from the disadvantage that the acid starting



↑ Figure 6

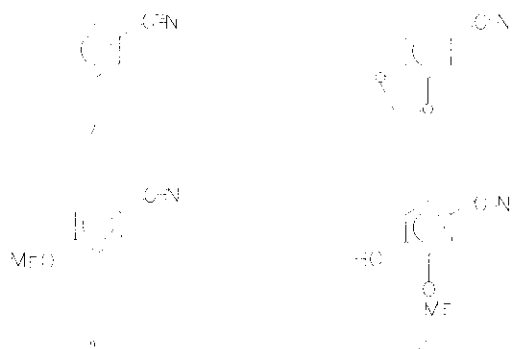
material is expensive and in addition, the yields reported for this route are quite low.³² Upon investigating methods for synthesizing the resulting conjugated nitriles less expensively, we discovered route VI where acetonitrile is condensed directly with methyl heptenone in the presence of alkali and alkali earth hydroxides.¹⁷ In this process, byproduct water is trapped by reaching with an additional mole of acetonitrile, which aids in driving the reaction to completion. Only the conjugated isomers are produced in this method, while with the cyanoacetic acid synthesis, a mixture of conjugated and nonconjugated isomers result.

In a further extension of this latter synthesis, we found it possible to condense higher alkyl nitriles with ketones as shown in route VII, thus greatly expanding the variety of odor types available for evaluation as potential perfume in-

redients.²⁰ It would be very difficult to obtain these skeletal types in a practical fashion through alternative synthetic routes. This class of alpha-dialkyl substituted nitrile was found to be more stable to degradation by heat, light, and hydrolytic processes than the corresponding alpha hydrogen substituted nitrile.

Anomalous odor effects

We have made the point that nitriles frequently have odors analogous to the corresponding aldehydes. This comparison holds up well in the case of benzonitrile (7). In contrast, while investigating the odors of a series of benzenoid nitriles workers at Naarden found quite a different situation with highly purified products (8,9) corresponding respectively to heliotropine, a powerful and widely used floral fragrance chemical, and vanillin, well known for its strong vanilla flavor.¹⁸ These nitriles were observed to be virtually odorless. In addition, p-methoxybenzonitrile (10), which is covered in the Naarden patent claims, did not have the predominant anise note found with the corresponding aldehyde, but was haylike with very little anisic character, making it a good potential



coumarin substitute. There seems to be no good explanation for these nitriles having such a wide variance from odor type of the aldehyde, given the rigid geometry and the similarities of molecular shape, polarity, and volatility with the corresponding aldehydes. Some subtle effects

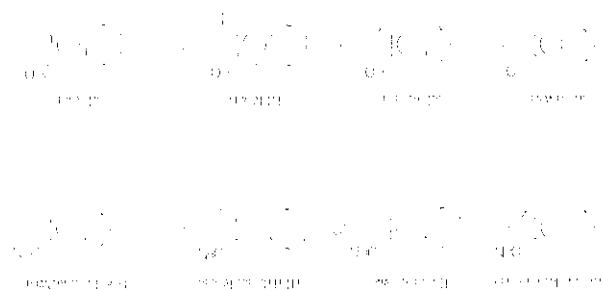


Figure 7 ↑

seem to be in play which have not yet been addressed by current odor theories.

A similar phenomenon arose in other work involving a series of nitrile-substituted indanes and tetralines modeled after a series of commercial keto musks.²² These keto musks exhibit odor strengths in the order shown in figure 7.³³ The nitriles surprisingly showed a reversal in odor strength in that Phantolid nitrile had the strongest odor, even stronger than Tonalid (the strongest keto musk), and Celestolide nitrile exhibited no odor at all.

Conclusion

The secure position that nitriles currently hold on the perfumer's palette can only be strengthened by continued activity in the synthesis and utilization of this most interesting class of aroma chemical.

Acknowledgment

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