

An Aroma Chemical Profile

Indole

By George S. Clark, Commodity Services International, Inc., Easton, Maryland

Indole's long history of use in our industry results in a familiarity that allows many of us to consider it just another aroma chemical. Its early identification in jasmine flowers (along with benzyl acetate) has developed a tradition of its use in floral compositions. It finds its way into most floral creations. Indole is one of the first heterocyclic materials that became available to our industry, and is thus a member of a family of potent aroma chemicals that include the pyrazine subclass responsible for revolutionizing the flavor industry over the past two decades. Indole is often used in conjunction with benzyl acetate, but for every kilogram of benzyl acetate employed in the flavor and fragrance industry, only about 5 grams of indole are used.

The best guide to a superior-grade indole is pure white crystals with a melting point above 52°C and very low heavy metal analysis, particularly regarding iron content.

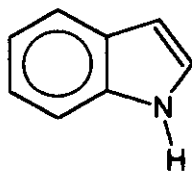
Indole presents a dual organoleptic profile, or, to state it another way, a Dr. Jekyll and Mr. Hyde nature. In very low concentrations, 200 ppm to about 0.01%, indole shows a brilliant, radiant, powerful floral effect which recalls jas-

mine and tuberose. However, when the indole concentrations reach 1% or greater, especially when neat, an aggressive, repulsive, overpowering fecal-decaying impression is encountered. In the 0.01-1% range, indole sometimes is used in special corps formulations such as jasmine fragrances, but even then, the end formulas' levels usually realize concentrations below 1%.

Problems

Storage creep: One problem faced with indole is its tendency to creep across laboratory spaces or storage rooms and invade other containers. Fiber drums are most susceptible, even with poly-seal liners. Solid aroma chemicals seem to have an affinity for picking up indole vapors in trace amounts. The result, for example, is unusable vanillin, coumarin, menthol and heliotropin due to off-indole odors. The reader should be aware that indole easily oxidizes, then couples to form the dye indigo—the dye that gave us the apparel blue jeans and the music "Blue Indigo." Thus, indole, when stored as a solid exposed to air, will discolor due to auto-oxidation. Therefore, indole should be stored in

Indole



Mwt 117 C₈H₇N
FEMA-GRAS 2593
CAS 120-72-9

Classification:

Polycyclic aromatic amine, found in nature

Additional Names: ¹⁻⁴

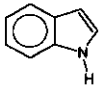
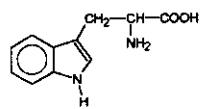
1-Benzo (b) pyrrole
2,3 Benzpyrrole
1-Benzazole
French, German, Portuguese, Spanish: Indol

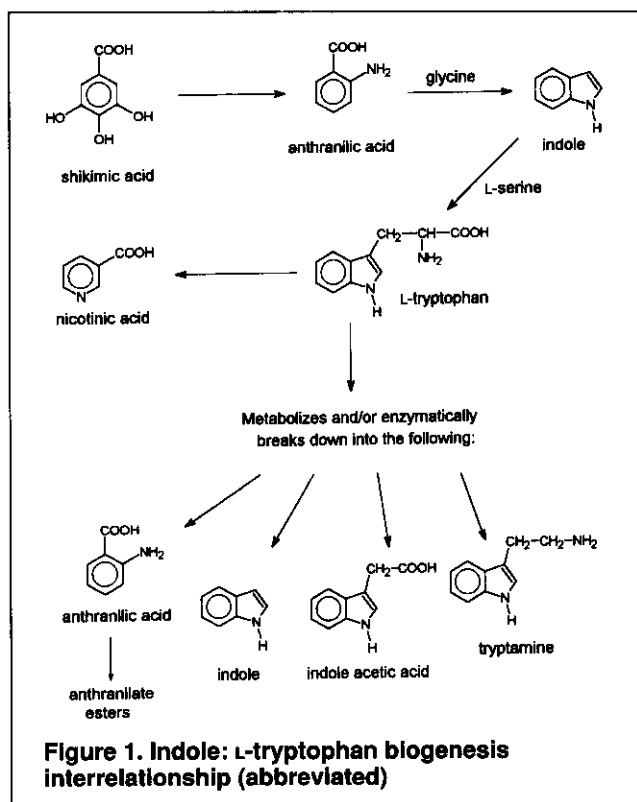
Physical Data:

Appearance: white crystalline solid
Melting Point: 52.5°C
Boiling Point: 254.7°C
Density: 1.0643
Refractive Index: 1.609 (60°C)
Odor Threshold PPB: 140
Solubility: Insoluble in H₂O 20°C
Soluble in hot H₂O
Soluble in most organic solvents, i.e. ethanol, esters, ketones, DEP and chlorinated and aromatic hydrocarbons.

airtight tin, metal or plastic containers and away from other solid aroma chemicals, in a cool room with adequate ventilation.

Discoloration in end products: In end products, indole typically is used at low levels (such as 0.02-0.60 ppm in flavored consumer goods or 200-1,000 ppm in fragranced products). It is such a powerful material that the impurities accompanying it hardly interfere with its organoleptic profile. However, impurities in indole can be critical to its renowned ability to cause discoloration in end products, especially in soap. Synthetic indole minimizes the discoloration problem, but it is no longer available since Givaudan ceased production around 1980.⁵ The present commercially available indole is isolated from a coal tar fraction that contains phenols, other amines and biphenyl, as well as accompanying traces of heavy metals such as iron. None of these organics poses much of an organoleptic problem, but

	1	Indole
	2	L-tryptophan



traces of iron, nickel and other impurities can catalyze the discoloration reaction in which indole participates.

Indole will react with other materials, such as aldehydes, to form colored compounds. In addition, as a mild base, indole will cause aldehydes to condense with themselves to form colored aldol condensation products. In acid media, indole is unstable and reacts with various materials, including other amines and aldehydes, to yield varying highly colored products. One of the earliest chemical tests for the presence of indole was the "Fichtenspahn Reaktion" (pine splint reaction)⁶ which employed a pine wood sliver dipped in hydrochloric acid. When held in a vapor stream of indole or its derivatives, the splint would turn a lovely ("lebhaft") brilliant red to the delight of the early chemist. This test was thought so reliable that it was used well into the twentieth century in organic chemistry laboratory classes as a definitive test for the presence of indole and its derivatives.

Natural Sources

Indole [1] is found in a number of natural products including flowers, seeds, grains, dairy products, fish and animals, but not in amounts practical for isolation. Presently, its major "natural" source is coal tar, from which it is isolated.

Indole's relationship with tryptophan [2] is fascinating because indole serves as both a biological source for the synthesis of L-tryptophan and one of its degradation products, as is anthranilic acid. The main source of L-tryptophan in nature is the plant kingdom, where this amino acid is synthesized via the shikimic acid pathway (Figure 1).

Indole is not very toxic, having an LD₅₀ of 1,100 mg/kg (rats), and if not utilized by mammals it is excreted as is or as derivatives. It has been identified as one of the definitive odor components of mammalian feces,^{7,8} as well as a component of flower volatiles.

Tryptophan seems to act as a reservoir for indole and indole acetic acid, allowing them to reappear in nature at some future time when appropriate. The reappearance coincides with the stage of development we can call "senescence," since indole appears only *after* flowers have fully blossomed and fruit has ripened, not before. Indole has also been identified as part of the aroma of the forest floor.

The positive-negative odor reaction registered by humans can be explained by the theory of human odor preference developed by Irwin Douglass, one of the world's leading sulfur chemists.⁹ Douglass maintained that human repulsion to various odors developed in primitive man as a defense mechanism to protect against dangerous life-threatening circumstances that did not present themselves as immediate danger (such as sudden animal attacks). The presence of organic sulfur compounds (such as methyl mercaptan) in the oxygen-depleted, methane-rich swamp gas often found in caves repulsed man organoleptically and saved him from suffocating in the vapors that hugged the cave floors where he would have slept. Aversion to hydrogen sulfide and sulfur dioxide protected him from volcanic vapor dangers. Thus, man developed acute organoleptic

Table II. Selected materials and their odor threshold

FEMA-GRAS	Material	Threshold in ppb
2716	methyl mercaptan	0.02
2746	dimethyl sulfide	0.30-1.00
3536	dimethyl disulfide	0.16-12.00
3478	n-butyl mercaptan	6
2593	indole	140

sensitivity to these materials, which spilled over to related compounds.

The high recognition threshold for indole (140 ppb in Table II) at first seems to contradict this theory. However, at low concentrations man encountered indole in flowers and edible fruits (a positive experience). Man learned to be repulsed by indole only when it was in high concentrations—decaying fish and meat, and areas where sufficient decaying materials or feces were concentrated enough to present a danger from disease.

This theory would explain our acceptance/repulsion toward indole, based on its encountered concentration.

Few other aroma chemicals invoke such a dichotomy. Pyrazines create a powerful rejection effect in humans at high concentrations, but not a reaction of such strong repulsion as that created by indole or its sister skatole.

Indole has been used at low levels for years by perfumers to reconstruct fragrances such as jasmine, narcissus and tuberose. Yet until as recently as 1925, some authorities maintained that indole was not present in fresh jasmine flowers, but only occurred upon maceration of the flowers as a release from some indole-containing glucoside.¹⁰ Such assertions must be doubted by anyone who has stood close to a few tuberose blossoms on a warm summer night. The fragrance of indole that permeates the air is strong enough to give some individuals severe sinus pain and headaches. Mookherjee and Wilson¹¹ finally put this old argument to rest with their research on living flower volatiles (Table III).

According to Lawrence's reports¹² and an interesting paper by Peyron,¹³ as well as numerous other sources,

Table III. Content of indole in volatile oils (weight percentage)

Flower	Weight of Indole*	
	Live (%)	Picked (%)
jasmine	11.0	2.0
paperwhite narcissus	4.5	0.3
purple lilac	2.3	1.5
Easter lily	19.0	2.0
lemon flower	23.0	13.0
tuberose	4.4	2.5
honeysuckle	2.5	none detected

*The indole content of some flowers has been shown to vary with the time of day.

indole has also been identified at significant levels in the following natural products:

- orange flower
- Michelia champaca* absolute 2-3%
- genet flowers concrete 2-12%
- tobacco

And it has been identified by the same sources at trace levels in these natural products:

- clove flowers
- citrus oils
- orchids
- gardenia
- coffee flowers
- Daphne odora*
- putrified dairy products
- tomato absolute
- molasses
- cheese
- roasted sesame seed oil
- rye bread
- aged casein
- aging fish:
 - 4 days old; 11 mgr/100 gr
 - 11 days old; 124 mgr/100 gr

Just as the perfumer uses indole to imitate the very ripe fragrance of flowers, the flavorist can incorporate trace amounts of indole in flavors to induce an overripe (properly decayed) note. Indole, thus used, fits well into banana, pineapple, apricot, peach, plum, grape, aged cheese and various roasted-grain-type flavors.

History

The use of indole as a synthetic chemical goes back about 100 years. Early work (in the 1860s) by Adolf von Baeyer on the structure of the natural dye indigo, resulted in the discovery that indigo was the dimer of an indole derivative, indoxyl, that could be made easily by oxidation of indole. Some processes for the production of synthetic indigo utilized indole, but most circumvented indole by the direct synthesis of indoxyl, which could be directly coupled to yield indigo. By 1897, Badische Aniline und Soda Fabrike (BASF) was offering commercial amounts of synthetic indole. Soon after, Hess discovered its presence in jasmine concrete at levels of 2-2.5%, and his employer, Heine & Co. of Leipzig, Germany, obtained patents for its use in fragrances in 1903. Despite the hindrance of these patents, indole's use in the flavor and fragrance industry increased, though slowly at first because of difficulties in its applications. By 1912, Weissgaber discovered indole in a coal tar fraction. (See *From Coal to Indole*.)

Indole was initially offered by dye firms as a somewhat

pure synthetic chemical, but as the routes to indigo and its derivatives improved, the dye firms ceased production of indole. This left the coal tar producers, usually large steel

Table IV. World producers of F&F-grade indole in 1994

Firm	Market Share
Ruetgerswerke AG, Germany	45%
Osakagodo, Japan	20%
Shanghai Native Prod., China	30%
Hemani Brothers, India	5%
Total	100%

companies, as a sole source of a very crude product, which was usually sold to fragrance houses or to an intermediate producer for upgrading.

Problems with impurities plagued indole users during the period 1900-1940. Moreover, the list of producers was complex and rapidly changing. At one time or another between 1900 and 1950, every imaginable firm (such as Dow Chemical, Kopper's Coke, Trubek and scores more) offered indole of various specifications. To further confuse matters, every fragrance house attempted to resell the product they bought for inhouse use and often asserted they were producers of indole. A few actually recrystallized crude grades, but for most "producers" the operation was purely repackaging.

Table V. 1994 World consumption of indole and indole mimics in kg

Region	Indole	Derivatives	Mimics
North America	6,800	2,400	6,500
Europe, all areas	11,600	4,600	10,000
Japan	3,000	700	2,000
All others	7,000	2,300	1,500
Total	28,400	10,000	20,000

Thus, the market had no reliable source of this relatively low volume aroma chemical, which was treated as a step-child by the chemical and steel industries.

Finally, in the early 1940s, Givaudan gave to Dr. Gary Kitchens the task of developing a process to manufacture a high purity synthetic indole. Kitchens modified the Madelung Indole Synthesis¹⁴ well enough to obtain a patent,¹⁵ and Givaudan became the world's only source of quality synthetic perfume and flavor grade indole from 1946 until about 1980.

By 1980, the coal tar industry finally caught up to the aroma chemical industry and was able to produce an acceptable grade of indole isolated from coal tar. Givaudan therefore ended its synthetic indole production. Today, the main source of commercially available indole is coal tar.

Producers

Indole is offered by many aroma chemical suppliers, flavor and fragrance houses, dealers and resellers posing as producers. In the past, many flavor and fragrance houses bought crude indole and purified it to a level acceptable for inhouse use. Any excess production was sold on the market. That tradition continues as firms resell part of the indole they purchase for inhouse use. However, few (if any) flavor and fragrance firms reprocess indole today. The major sources of indole in 1994 are reported in Table IV.

No US producer or upgrader could be identified and all US consumption is imported. One should note that the US is a large importer and exporter of coal tar fractions.

Imports

The US imports on average 11,340 kg of indole every year under TSUS, Harmonized Tariff category 2933.90 (previously 401.42) which is duty free. It is estimated that only 9,200 kg of these imports are consumed directly as indole or indirectly as derivatives in the flavor and fragrance industry. The remainder is converted into derivatives for other industries.

World Consumption

For 1994, it is estimated that only 38,400 kg of synthetic isolate indole were consumed by the flavor and fragrance industry worldwide. This figure includes both direct consumption (indole) and derivatives (indoflor-indolal-indolene types). In addition, it is estimated that another 20,000 kg of

indole mimics (indolarome types) were consumed in fragrances. (The regional breakdown is shown in Table V.)

Pricing

Perfume and flavor grade indole is currently selling in the \$25-28/lb range in the United States. Prices for the various grades of indole derivatives and mimics can vary widely due to quality and market conditions.

The pricing trend for indole is steady with little growth. Indole derivatives will show less than a 2% per annum growth over the next 10 years. Indole mimics will show

growth of 3-4% per annum over the next decade. Indole's volume as an aroma chemical is too small to cause much interest for new producers or to induce any aggressive pricing for the market share it enjoys. Expect no surprises with indole.

Derivatives

Several indole derivatives [3,4] that have been used by the flavor and fragrance industry in the past are still in use.

In the past, aldehyde condensation products of indole with other aldehydes (such as citral, citronellal and phenylacetaldehyde) were prepared and used. Few of these products are offered commercially today, but some are still used as inhouse specialties. The more stable non-discoloring indole mimics are displacing these products as well as indole itself.

One indole derivative [5] is found in the genus *Brassica* plant family and has mustard oil-like properties. This isothiocyanate degrades [6] and is found as a residue in the brassica plant.

Some indole derivatives are not of interest to the flavor and fragrance industry, but their structure and properties give the reader a broader view of the indole family.

Indigo [7] is the original blue dye used in Levi's jeans. This bromine derivative gave Tyrian purple and the sulfonated salt produced a carmine color. Tyrian purple was originally produced by the Phoenicians from a Mediterranean mollusk and became the color of nobility in imperial Rome.

Tryptamine [8], a breakdown product of L-tryptophan, is the precursor to the biologically active substance indole acetic acid [9]. Indole acetic acid is nature's internally generated plant growth regulator and is considered the single most important plant growth hormone.

Serotonin [10] is found in mammals and thought to be responsible for the state of well-being effect in the human brain. Serotonin antagonists produce the opposite effect, such as insanity-like actions and hallucinations.

Psilocin [11] is a hallucinogenic indole derivative found in the teonanacatl mushroom (the sacred mushroom of Mexico) as well as its phosphate ester, psilocybin.

Other indole derivatives include lysergic acid diethylamide (LSD) and the anti-carcinogenic drugs vinblastine, found in periwinkles, and reserpine.

Substitutes and Analogues

Indole is such a minor additive to flavor compositions that little consideration is given to a substitute. In fragrances, the best-known substitute is Indolarome* [12].

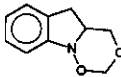
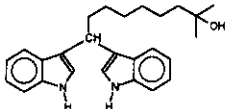
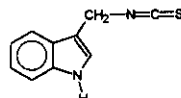
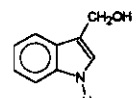
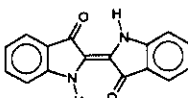
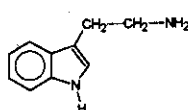
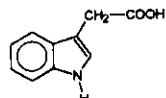
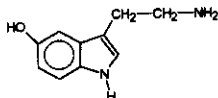
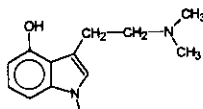
The indole analogue skatole [13] can be used as a substitute in fragrances if a twist is desired.

The early isolation of skatole from civet, coal tar and other natural sources inspired chemists to synthesize every imaginable methyl derivative of indole. The results were lackluster. A few [14-17] are presented in Table VII.

Four indole analogues [18-21] from the early 1900s were reported in the literature,⁶ but little has been stated as

* Indolarome is a registered trademark of IFF, New York, NY.

Table VI. Indole derivatives

	3	Indoflor—Haarmann & Reimer Corp. Indolal—Dragoco
	4	Indolene—IFF Indolique—(Fritzsche Dodge & Olcott) Givaudan-Roure
	5	isothiocyanate
	6	isothiocyanate degradation product
	7	indigo dye (blue)
	8	tryptamine
	9	indole acetic acid
	10	serotonin
	11	psilocin

to their organoleptic qualities. One might guess the answer, as history has spoken.

Six additional analogues [22-27] have been reported and are included here for curiosity's sake. The only conclusion one can glean from these structures is that straying too far from the basic indole structure destroys the impression. A basic rule of organic chemistry still holds: the first structure of a series is unique. However, the organoleptic profiles reported for these structures suggest that a reinvestigation using pure materials and a valid organoleptic comparison might result in different descriptions.

References

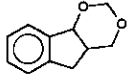
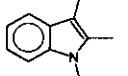

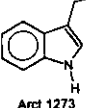
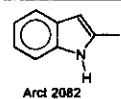
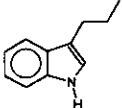
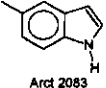
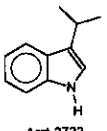
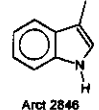
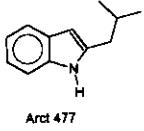
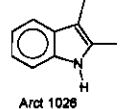
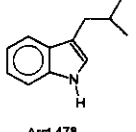

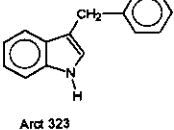
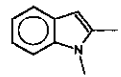
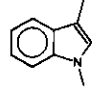
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Table VII. Indole substitutes and analogues

	12	indolarome		21	1,2,3-trimethyl indole
	13	skatole	 Arct 1273	22	3-ethyl indole animal-tarry
 Arct 2082	14	2-methylindole animalic indole	 Arct 2721	23	3-n-propyl indole dry naphthalenic
 Arct 2083	15	5-methylindole weak indole	 Arct 2722	24	3-iso-propyl indole heavy floral
 Arct 2846	16	3-methylindole skatole, fecal, overripe, indole	 Arct 477	25	2-iso-butyl indole mild indole
 Arct 1028	17	2,3-dimethylindole weak, sweet floral	 Arct 478	26	3-iso-butyl indole mild skatole
	18	1-methyl indole	 Arct 323	27	3-benzyl indole floral-earthy
	19	1,2-dimethyl indole			
	20	1,3-dimethyl indole			