

# Indoles: Industrial, Agricultural and Over-the-Counter Uses

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**Abstract** Indole-containing compounds are best known for their medicinal properties in the pharmaceutical industry. Although to a lesser degree, the indole motif none-the-less appears in many significant products across the entire chemical industry. This chapter describes the role that indole plays in a more commodity setting and provides examples illustrating these uses.

**Keywords** Agriculture · Animal health · Cyanine dye · Dietary supplements · Diindolylmethane · Essential oils · Flavoring · Indigoid dye · Indole-3-carbinol · Melatonin · Nutraceutical · Perfume · Pigments · Textile dyes · Tryptophan

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## 1 Introduction

Although the structure of indole was not correctly assigned until 1869 by Adolf von Baeyer, its derivatives have had a prominent role in commerce for centuries [1]. In modern times, analogs based on indole are significant players in a diverse array of markets such as dyes, plastics, agriculture, vitamin supplements, over-the-counter drugs, flavor enhancers, and perfumery. This chapter does not discuss medicinal compounds based on indole, which are covered in a separate chapter in this book.

Powerful internet search engines today place a considerable amount of information at one's fingertips regarding the historical development of indole derivatives in commerce. Beyond providing leading references or search terms, I have kept this type of material at a minimum and have tried to include only enough background information to put that topic in proper perspective. My goal in this chapter is to give the reader an idea of the breadth of commodity markets still impacted by indoles and to discuss some of the most prominent examples in each industry.

## 2 Dyes and Pigments

The global market production of organic colorants in 2010 is forecast to be 2.1 million metric tons valued at 14.4 billion dollars and projected to grow at an annual rate of three to four percent (see <http://www.the-infoshop.com/report/fd87050-dyes-organic.html>). The market for inorganic colorants is roughly 5 times larger [2].

Dyes and pigments differ mainly in the method of attachment to the material that is to be colored. A material to be dyed is immersed in a solvent in which the dye is soluble whereupon the dye adheres to the material through chemical or ionic bonding. The dye is then left behind when the material is removed from the solution, rinsed and dried. Typical materials suitable for dyeing include textiles and paper products where water is the solvent of choice. Traditional photography takes full advantage of sensitizing organic dyes. A great variety of dyes can be applied by controlling the pH of the solution. Pigments are insoluble in the solvent used and are applied either as fine powders or as suspensions or dispersions [2–4]. Many paints are pigment-based. Pigments also are used to color most plastics. Although dyes represent the lion's share of the overall organic colorant market, pigments also are well represented in most segments. Numerous dyes are applied as pigments under different conditions and the reverse is also true.

Indole-based colorants are part of the large, diverse class of organic dyes and pigments. While not the major component of the organic colorant market, indoles never the less play an important role. A complete listing of all colorants sold today that are based on indole would be unnecessarily repetitive. Comprehensive lists can be found in several recent books and registers [2–4]. This segment will give the reader an idea of the breadth of dye and pigment markets still impacted by indole and discuss some of the most prominent examples in each field.

## 2.1 Textile Dyes

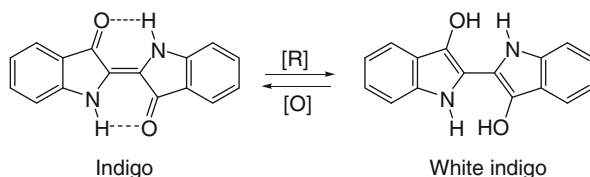
Nearly all textile-dyeing processes are water-based and may be done under acidic or basic conditions. Control of the pH during the process is an important factor in determining attributes such as the intensity of the hue and the strength of the dye-fabric bond (resistance to fading). Many of the indolic dyes and pigments are colored blue to green but nearly all regions of the visible region are represented by analogs having an indole core as part of the structure.

### 2.1.1 Indigoid Dyes

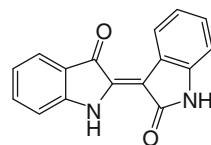
Indigo is probably the oldest and most famous colorant based on indole. It was already being used in civilizations throughout Asia when the ancient Greeks and Romans began importing it from India as a luxury item (see “Indigo dye” [http://en.wikipedia.org/wiki/Indigo\\_dye](http://en.wikipedia.org/wiki/Indigo_dye)). Indigo was a substantial commodity import into Europe from the Middle Ages until well into the nineteenth century. Historically, indigo was obtained from natural sources, but today virtually all indigo is synthetic. Indigo itself is nearly insoluble in water and can be used directly as a pigment when desired. However, its primary use in the textile industry is as a dye because the reduced form, white indigo, is much more soluble in water and can be applied in the same fashion as other dyes. Simple exposure of white indigo to air can reoxidize the molecule back to the highly colored form (Scheme 1).

Production of indigo had dropped to a mere trickle in the mid-twentieth century until blue jeans caught the public eye. The increased demand from this one product line led to over twenty thousand tons of indigo being produced in 2003, primarily as the dye for blue jeans. Indigo also is blended with other dyes under various processing conditions to give hues ranging from blue–green to violet (see [http://www1.dystar.com/products/dyeranges\\_cellulosics.cfm?CFID=508055&CFTOKEN=95928906](http://www1.dystar.com/products/dyeranges_cellulosics.cfm?CFID=508055&CFTOKEN=95928906)). An isomer of blue indigo, indirubin, seen in small amounts in the naturally derived material, is red but it is not used commercially (Scheme 2).

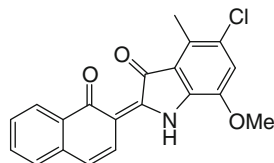
Other dyes based on the indigo motif are known, many with different hues. Tyrian Purple, 6,6'-dibromoindigo, is a natural product isolated from crushed sea shells that was quite valuable in ancient times but is not sold commercially today. However, the (5,7,5',7')-tetrabromo derivative (blue, “Vat Blue 4B”) and the (5,5')-bis-sulfonic acid analog (blue–green, “Blue Saxon”) both are used as dyes in the



**Scheme 1** Indigo-white indigo interconversion

**Scheme 2** Indirubin

Indirubin

**Scheme 3** C.I. Vat blue 8

C.I. Vat Blue 8

Blue to heavy shades  
for cellulose, silk and wool

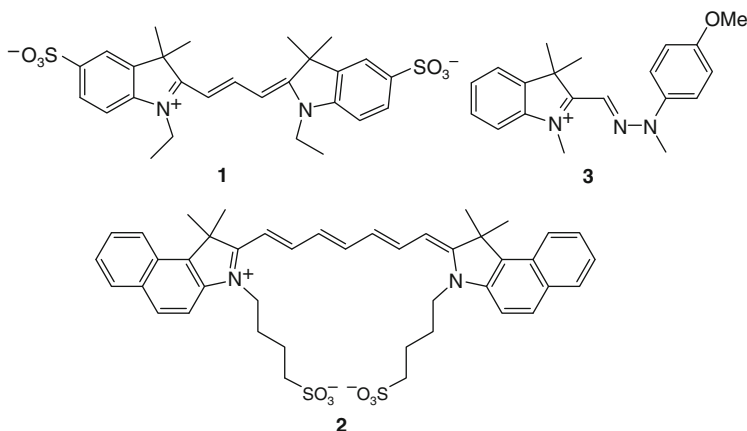
textile industry. Mixed variants such as the indigo-anthrone, C.I. Vat Blue 8, also are sold (Scheme 3).

### 2.1.2 Cyanine Dyes

Cyanine dyes are characterized by a central ethylene or conjugated polyolefin region capped at either end by a heterocyclic group. The length of the polyolefin varies, as do the end-caps that may or may not be the same. The indole moiety is but one of many heterocycles typically found in this large group of dyes. The uses of indolic cyanine dyes are as varied as the structures. Many such as **1** have found broad application as fluorescent probes in nucleic acid imaging [5]. Indocyanine green **2** is used in medical diagnostics to determine cardiac output and other functions. One or more olefin carbons may be replaced by nitrogen, as seen in C.I. Basic Yellow 28 **3**, a common textile dye. A dye such as Basic Yellow 28 could be seen as a cyanine dye or as a carbon variant of the large azo class of organic dyes (Scheme 4) [1].

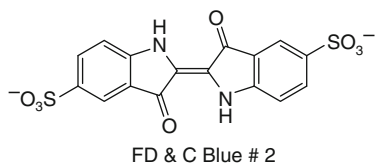
## 2.2 Dyes for Human Use

The list of dyes allowed by the FDA for human use is not large (see <http://www.fda.gov/ForIndustry/ColorAdditives/ColorAdditiveInventories/ucm115641.htm>). Only FD & C Blue No. 2 (indigo carmine) is on the approved list, although it is broadly approved for general use as a dye for food, cosmetics, and drugs and in medical devices, to color sutures (Scheme 5).



**Scheme 4** Cyanine dye examples

**Scheme 5** Indigo carmine  
approved for human  
consumption



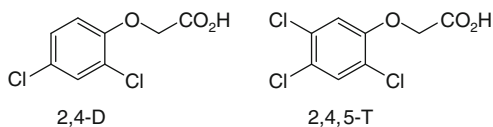
### 3 Agriculture

Natural products containing the indole subunit are found throughout the animal, fungal, microbial and plant kingdoms. The purposes to which the producing organisms put these varied structures often are a mystery. However, many of these components have provided an invaluable basis for research programs targeting diseases or other commercial enterprises. When successful, the vast majority of the marketed products bear little resemblance to the initial lead. The agricultural market is a prime example of this.

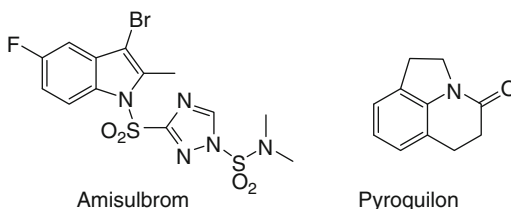
Auxins are one of the five major classes of plant-produced hormones that affect plant growth including bud formation and root initiation (see [http://en.wikipedia.org/wiki/Plant\\_hormone#Auxins](http://en.wikipedia.org/wiki/Plant_hormone#Auxins)). Indole-3-acetic acid is the most common auxin found in plants. Although the small amounts produced internally have the desired effects, auxins are toxic to plants in larger amounts. The nefarious weed-control products 2,4-D and 2,4,5-T target the auxin receptor but bear little resemblance to the natural ligand. Other man-made auxins such as 1-naphthaleneacetic acid and indole-3-butyric acid are used, not to kill weeds, but to stimulate root production in cuttings taken from the parent plant (Scheme 6).

A considerable number of fungicides are based on a heterocyclic core but the indole ring only appears in a few commercial products such as amisulbrom and

**Scheme 6** Herbicides that target the auxin receptor



**Scheme 7** Indole fungicides



pyroquilon ([http://www.alanwood.net/pesticides/class\\_fungicides](http://www.alanwood.net/pesticides/class_fungicides)). A somewhat larger number of fungicides containing additional heteroatoms are based more loosely on the indole core (Scheme 7).

## 4 Animal Health

Many of the same indoles in human medicine could have parallel application in animal health and, indeed, some are used in both arenas. Both livestock and domestic pets may benefit, if only indirectly, from the huge research efforts of the pharmaceutical industry to develop pharmaceutical products. This is fortunate for there are far fewer companies today devoted strictly to veterinary medicine and animal health. However, the registration of a drug for human use does not automatically mean that it can be used in the animal market. The approval process for a new animal health drug is similar to the one for human medicine and the two are distinct.

A number of pharmaceutical agents for humans are restricted in livestock or precluded altogether in order to reduce the risk of these drugs entering our food chain from this source. The risk/benefit of using many drugs in livestock remains a hotly debated topic today between some consumer advocacy groups and the government regulatory agencies. Although this is not an issue for domestic pets and the like, development of drugs for this segment of the veterinary market still often trails the human market.

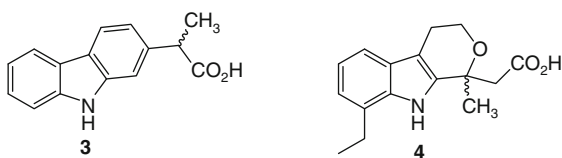
Over five hundred drugs are registered for animal use, not including different formulations and combination products (see Ingredients, section 2: active ingredients of <http://www.accessdata.fda.gov/scripts/animaldrugsatfda/>). The list includes some unusual compounds, such as nitrofurans, arsenic derivatives and toluene (used as a dewormer). Only a handful of drugs on this list contain the indole core. Some are easily recognizable drugs from human medicine while others are only used in animals. Several of these latter are well known indole alkaloids.

The two veterinary drugs Carprofen **3** and Etodolac **4** are better known as Rimadyl<sup>®</sup> and Lodine<sup>®</sup>, the nonsteroidal anti-inflammatory drugs approved for human use. They are especially useful for treating dogs with osteoarthritis, hip dysplasia, and other joint diseases (Scheme 8). Although generic, one estimate placed 2008 sales of Carprofen near \$80 million and predicted an annual increase of ~13% ([http://files.shareholder.com/downloads/GORX/895020712x0x239734/8df627c4-ffd6-420a-a84b-cb79d461562d/GORX\\_090208.pdf](http://files.shareholder.com/downloads/GORX/895020712x0x239734/8df627c4-ffd6-420a-a84b-cb79d461562d/GORX_090208.pdf)).

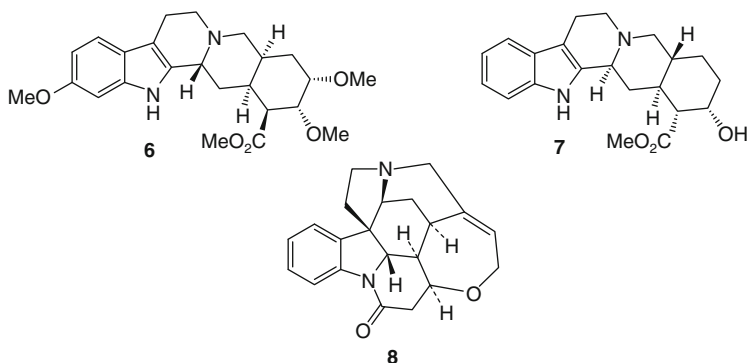
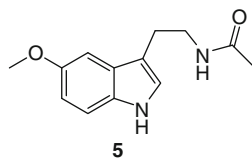
Melatonin **5** is another drug that has application in both animal health and human medicine. In dogs, it is commonly prescribed to calm dogs that are sensitive to loud noises or with separation anxiety (Scheme 9).

The final three indole-containing drugs approved for animals in the U.S. are indole alkaloids. Metoserbate **6** is a water-soluble reserpine alkaloid given to reduce stress and prevent hysteria in poultry. Yohimbine **7** is a central alpha-2 adrenergic antagonist. It is used in dogs to reverse the anesthesia produced by the commonly used anesthetic Xylazine. Strychnine **8** is a rodenticide (Scheme 10). There is no current approved human medical use for metoserbate although yohimbine is prescribed for erectile dysfunction. Strychnine, once used in small doses as a laxative

**Scheme 8** NSAIDs used in veterinary medicine



**Scheme 9** Melatonin



**Scheme 10** Indole alkaloids used in animal husbandry

and as a stimulant to enhance sports performance, is not approved today for any human use (General veterinary use information for 3, 4, 5, 7 and 8 can be found at <http://www.drugs.com/vet/>).

## 5 Over-the-Counter Drugs

The pharmaceutical industry has found numerous leads for its research programs from natural products and from the careful study of key receptors involved in the therapeutic area of interest. Many of these starting points are derived from compounds with an indole core. An eventual commercial product may contain the indole nucleus but is more than likely to bear little superficial resemblance to the initial lead. Separate chapters in this book describe the recent indolic natural product discoveries and new developmental and marketed drugs. This chapter segment covers indole-containing substances that are sold over-the-counter without a prescription. This is a large and rapidly growing market, including vitamins and minerals as well as the two subcategories described below. Overall supplement 2008 sales in the U.S. alone were greater than \$25 billion (<http://nutritionbusinessjournal.com/pressreleases/NBJ-reviews-US-Supplement-Market/>).

### 5.1 *Dietary Supplements*

Dietary supplements are compounds that are found naturally in the human body or are part of a normal diet and are sold over-the-counter, similar to vitamins. There may be no recommended minimum daily requirement established for a dietary supplement. However, the Food and Drug Administration follows reports of adverse events so that maximum recommended doses are known and published when appropriate. OTC supplements are bulk products and as such, these compounds are similar to commodity chemicals even though they are sold for human use.

#### 5.1.1 Melatonin

The natural product melatonin **5** is found in animals and also in insects, microbes and some plants. Melatonin is mainly produced by the pineal gland in animals but it is synthesized throughout the body and readily passes through the blood–brain barrier. A diversity of biological responses is produced by the interaction of melatonin with its widespread receptors in body and central nervous system [6]. In addition to the well-documented role in regulating mammalian circadian rhythms, melatonin receptors are involved in modulating the immune system and bone growth among other processes [7]. The additional powerful antioxidant properties of melatonin are a potential bonus to those taking it for other reasons [6].



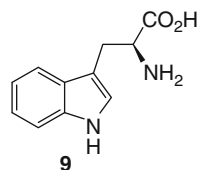
Melatonin still is available over-the-counter in the U.S. (since 1993), Canada and the United Kingdom but it is banned in many countries or is available only by prescription. U.S. sales in 2006 reached an impressive \$81 million and were rising. Numerous therapeutic benefits have been ascribed to taking melatonin supplements but it is used primarily to treat sleep disorders such as insomnia and to reduce jet lag ([http://www.webmd.com/sleep-disorders/circadian\\_rhythm\\_disorders](http://www.webmd.com/sleep-disorders/circadian_rhythm_disorders)).

### 5.1.2 Tryptophan

L-Tryptophan **9** is produced industrially by fermentation. It is an important feed additive, its primary use, and is part of a growing amino acid feed additive market that exceeded worldwide sales of \$3.4 billion in 2007. Its history as a dietary supplement is more sullied, although the toxicity concerns that were raised in 1989 and led to a ban in its use as a dietary supplement for several years may not have been justified (Scheme 11) ([http://thegormleyfiles.blogspot.com/2007\\_01\\_14\\_archive.html](http://thegormleyfiles.blogspot.com/2007_01_14_archive.html)).

L-Tryptophan is one of the essential amino acids in animals. In addition, it is the biosynthetic precursor to other important molecules such as serotonin (thus, melatonin) and niacin. Until 1989, L-Tryptophan was sold singly over-the-counter and as a constituent in dietary supplement combinations. One of several effects that ingesting L-tryptophan has on the body is an increase in serotonin levels. Partly because of this, L-tryptophan supplements commonly were used to treat premenstrual syndrome, as a sleep aid and as a natural antidepressant [8] (<http://www.webmd.com/vitamins-supplements/ingredientmono-326-L-TRYPTOPHAN.aspx?activeIngredientId=326&activeIngredientName=L-TRYPTOPHAN&source=3>).

In 1989, a large outbreak of eosinophilia-myalgia syndrome in the United States was associated with the use of L-tryptophan supplements. Supplement sales were immediately restricted in the US leading to an eventual world-wide ban in 1991 even though L-tryptophan continued to be sold as a feed additive in the US and was added to baby formula. The outbreak was eventually traced to product from a single Japanese manufacturer. Despite considerable effort, no contaminant was found nor did other hypotheses to explain the outbreak bear fruit. Other theories whereby L-Tryptophan itself or its metabolites could be the cause also are unproven. There remains no conclusive link between L-tryptophan and EMS. The FDA lifted, with some caveats, the ban on sales of dietary L-tryptophan in 2001 although importation still is restricted. It is again available in the US over-the-counter



**Scheme 11** L-Tryptophan

and by prescription. The uses to which it was put prior to 1989 are being rediscovered today, although still with some caution.

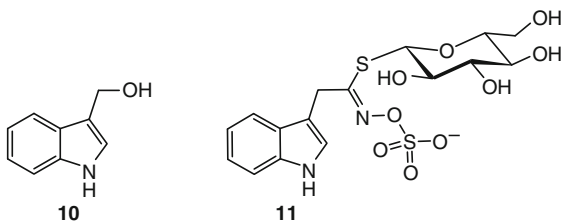
## 5.2 Nutraceuticals

Both dietary supplements and nutraceuticals are available without prescription as concentrated extracts or in pure form. Aside from that, the only statement that can be said with certainty with regard to the distinction between dietary supplements and nutraceuticals is that there is considerable disagreement. Either one can be considered a subset of the other depending on the forum. This point is quite aside from the also highly debated question of whether nutraceuticals are beneficial at all. Only for the purposes of this chapter, I define a nutraceutical as a natural product, plant or animal derived, which may be ingested in the belief of therapeutic benefit, but for which no cause-and-effect relationship has been established by rigorous clinical evaluation. Although the FDA monitors nutraceuticals to ensure that they are not overtly harmful, nutraceuticals remain a lightly regulated area of human medicine since the efficacy clinical trials that are mandated for prescription drugs generally are lacking in this area. However, the FDA is moving to more tightly regulate these products. The following examples are the noteworthy indole-derived nutraceutical products.

### 5.2.1 Indole-3-Carbinol

Indole-3-carbinol (I3C) **10** is a hydrolysis product of glucobrassicin **11**, both of which are found in high concentrations in cruciferous vegetables such as cauliflower (0.4 mg/g as the glucosinolate), broccoli and mustard greens (2.8 mg/g) [9]. The normal average dietary intake of **I3C** from these sources ranges from 20 to 120 mg/day (Scheme 12).

Studies have shown a correlation between diets high in cruciferous vegetables and the reduced incidence of several types of cancer [10, 11]. **I3C** has been proposed as one of the causative agents for these observations. The known estrogenic activity of **I3C** lends some support to this idea [12, 13]. However, there is some contradictory evidence from animal studies. Although **I3C** inhibited cancer



**Scheme 12** I3C and glucobrassicin

development in animals when given before or simultaneous with a carcinogen administration, cancer promotion was observed in other studies where **I3C** was administered after the carcinogen exposure [14–16]. Despite these conflicting indications, there is some clinical evidence that **I3C** may have utility as a cancer therapeutic agent. The results from a single, small clinical trial in women with biopsy-proven cervical intraepithelial neoplasia were encouraging. Roughly half of the women in the trial had complete regression of cancer after 12 weeks of daily 200 or 400 mg doses of **I3C** [17]. There are several other trials currently underway to examine the utility of **I3C** for general cancer prevention, as a follow-up therapy to prostate cancer patients who have undergone prostatectomy, for treatment of Lupus and to explore the antiviral activity of **I3C** (<http://clinicaltrials.gov/ct2/results?term=I3C>).

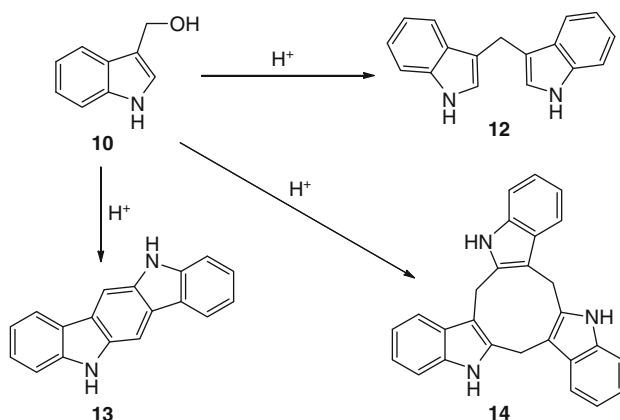
**I3C** supplements are sold OTC in pure form. There is no recommended daily requirement for **I3C** but there are some cautions for those taking supplements. There have been reports of skin rashes, tremors, nausea, and loss of balance during some of the clinical trials with **I3C** [18]. In addition, **I3C** has been shown to increase the activity of the liver enzymes CYP 1A1, CYP 1A2 and CYP 3A4 in rats, which raises the possibility of undesirable drug–drug interactions in humans [19].

### 5.2.2 Diindolylmethane

Animal studies have indicated that **I3C** primarily is a pro-drug [20, 21]. In the acid environment of the stomach, **I3C** is converted into several self-condensation products and one or more of these appear to be responsible for the intriguing biological activities ascribed to **I3C** [20]. The most prominent product is diindolylmethane (DIM) **12** (up to 20% of the product mixture). The indolocarbazole **13** (up to 6%) and trimer **14** also are generated. There are mixed in vitro results as to whether **13** overall is a cancer promoter or has cancer preventative effects [22–24]. Some in vitro studies indicate that the cyclic trimer **14** is a strong estrogen receptor agonist, suggesting that further research is warranted on the potential anticancer effects of **14** (Scheme 13) [25].

The potential of **DIM** as an anticancer agent that is predicted by in vitro assays has been reinforced by in vivo experiments. In animal models, **DIM** has shown efficacy in a similar range of carcinomas as **I3C** including prostate, breast, pancreatic, and colon cancers [26–29]. **DIM** induces apoptosis of cancer cells directly by several mechanisms and enhances the effectiveness of some cancer drugs. It also has antiproliferative effects in some cancer cell lines and exhibits protective activity against invasion of normal cells.

There are several clinical trials underway to investigate **DIM** as a cancer treatment therapy (see <http://clinicaltrials.gov/ct2/results?term=diindolylmethane>). In one completed study, a small group of women with a history of early-stage breast cancer were treated with **DIM** at 108 mg/day for 30 days. Urinalysis showed significant improvement in the levels of several key metabolite markers, but it is not yet known whether this encouraging result translates into a reduced risk of



**Scheme 13** Acid condensation products from **I3C**

breast cancer [30]. There also are reports of clinical trials investigating the antiviral and antibacterial effects of **DIM**.

Purified **DIM** supplements are available OTC although the preventative benefits of **DIM** supplements are unproven and largely unexplored. As yet, there have been no reports of **DIM**-related side effects from the clinical trials involving **DIM**. This contrasts with the documented side effects produced by **I3C** in some people and at some of the higher doses. In view of the wide range of activity of **DIM** on critical biological pathways and the, as yet, unproven cancer preventative benefit to healthy people, due caution would seem to be indicated before embarking on a regimen of **DIM** supplements.

## 6 Essential Oils

Essential oils are concentrated extracts or steam distillates of aromatic plants. Oils such as wintergreen or jasmine have been added to enhance the flavor and smell of food for centuries and are key components of perfumes. Chemical analysis of these oils reveals that the overall smell is due to complex mixtures of small molecules, many of which contribute to the smell of the oil. Indole and indolic compounds are common components of these mixtures. Natural jasmine oil typically contains about 2.5% indole. Over time, the increasing cost of raw materials and processing has led to efforts to produce simpler mixtures that would have the same sensory effect. Reasonable approximations of many of these oils can be made today with completely synthetic components. Despite these advances, the import/export market for natural essential oils in 2008 still was a respectable \$2.5 billion (See PDF download from [http://www.cnm.org/index.php?option=com\\_docman&task](http://www.cnm.org/index.php?option=com_docman&task)).

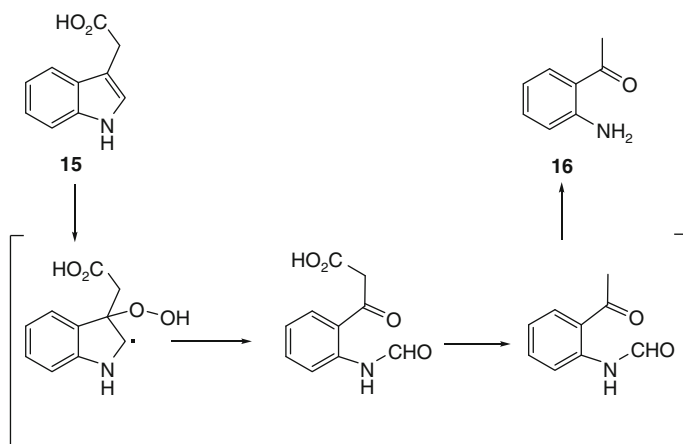
Indole and many of its derivatives have a relatively high vapor pressure well within the capability of the human nose to detect. Thus, an indole can affect the

flavor of food or contribute to the aroma of a perfume. Whether the smell is sensed as pleasant or odiferous, of course, varies from person to person but it also is highly concentration and substituent dependent. For example, the main component responsible for the odor of feces is skatole, 3-methylindole. At high concentrations, indole has a similar smell, but indole generally is perceived as having a sweet aroma at low concentration. Many indole derivatives are perceived as having floral scents.

## 6.1 Flavor Enhancers

Indoles are found naturally in many foods, some contributing to both the smell and taste while other indoles such as tryptophan provide nutritional value. Indole and skatole, in particular, are important components that affect the flavor and smell of foods such as green tea, coffee, cooked vegetables, whole grains, uncured meat, shellfish, and fresh fruit [31]. This can be useful to the analytical chemist. The amount of indole along with several other volatile flavoring compounds in the different types of tea is characteristic of that variety. In order to aid customs agents and tea vendors, a gas chromatographic method has been proposed to distinguish between the tea varieties [32].

The presence of indole or an indole derivative in a food is not always desirable. Some white wines develop an off-flavor described as “...floor polish like...” within a few months of storage [33]. The chemical responsible for this unpleasant flavor was identified as 2-aminoacetophenone **16** in 1993 [34]. Reported in a series of papers over the next 10 years, researchers traced the ultimate source of this agent to indole-3-acetic acid **15** that was present in the grapes before harvesting! Indole-3-acetic acid itself is derived from another indole: L-tryptophan. The proposed mechanism for this transformation is shown in Scheme 14 [35].



**Scheme 14** Mechanism for conversion of indole-3-acetic acid to 2-aminoacetophenone

The authors present evidence that the process begins after sulfite is added to halt the fermentation. Superoxide radicals are formed with concomitant oxidation of sulfite to sulfate. Pyrrole cleavage followed by decarboxylation gives the formamide that spontaneously hydrolyzes to the observed end product **16**. With this understanding, vintners have made a considerable effort to prevent this process from tainting their product. Significant portions of symposia have been devoted to just this topic ([http://www.oenology.de/texte/symp\\_02\\_engl/symp02\\_4\\_engl.html](http://www.oenology.de/texte/symp_02_engl/symp02_4_engl.html)). Although **16** can be a serious problem in white wines, the pathway for its generation is blocked by the greater amount of phenolic radical scavengers present in red wines.

## 6.2 *Perfumes*

While the public disclosure of food additives is government-mandated, the exact ingredients and ingredient ratios in perfumes are closely held secrets even today. However, two lines of evidence indicate that indole and its derivatives still are crucial components in many perfume formulae and that additional novel indole additives are being sought. Experts reviewing new perfumes often refer to the "...jasmine indoles..." and "...floral indoles..." in their discourses (<http://www.mimifroufrou.com/scentedssalamande>). A recent application describing the floral scents of *N*-carboxy esters of indole is but one example of the numerous recent patent applications which attests to the continuing interest in finding indole derivatives having new and novel aromas (see UA20090036690A1).

## 7 *Summary*

Centuries before the structure of indole was known, many of its derivatives were important commercial products. Ancient textile dyes and perfumes are but two of the markets described above in which indole has had a rich history. Indoles continue to impact both of these markets today. The use of indoles has expanded into facets of agriculture, animal health and the relatively new areas of dietary supplements and nutraceuticals. These are all commodity markets, distinct from the explosion of medicinal uses that have been discovered for indole-containing substances.

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