Raspberry Ketone

Application in flavors and fragrances and beyond

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Raspberry ketone (**F-1**) is found in raspberry, cranberry, blackberry, loganberry and sea buckthorn. In addition to its occurrence in the above mentioned fruits, raspberry ketone can be found also in Korean fir leaves, Korean pine needles, *Hedysarum thienum* and more.[1–3]

It has a berry, sweet, woody odor; a raspberry, ripe, jammy, seedy character; and a fruity, berry, raspberry and blueberry flavor with seedy, cotton candy nuances.[4] Raspberry ketone is applied in fruit and tobacco flavorings and in a wide range of heavy fruity compounds for cosmetic and alcoholic perfumery.[a]

Some ingredients with related structures used in the F&F industry are: raspberry ketone acetate (CAS# 3572-06-3), raspberry ketone methyl ether (CAS# 104-20-1) and zingerone (CAS# 122-48-5). (See **T-1**.)

Raspberry ketone is used in strawberry essence for fragranced candles and for ice cream flavor in concentrations of 2.4–4.2%. The concentration of raspberry ketone in these types of formulations is higher due to the use of propylene glycol as a solvent.[5]

Raspberry ketone is also used in preparing Chinese-style cigarettes. The molecule is diluted with water to 0.02–0.06% and added to cut tobacco. Raspberry ketone as a cigarette additive can increase oral sweet and damp taste and improve oral comfort.[6]

Another interesting application for raspberry ketone is as an insect attractant. Insect-attracting devices and substances have a variety of uses in research, agriculture, pest management and government agency-provided services. Insect-attracting substances are used in various types of lures and traps, both for monitoring the sizes and dynamics of insect populations as well as for killing insects that are harmful to agriculture, domesticated animals and human health. For example, raspberry ketone is used with methyl eugenol (CAS# 93-15-2) as a multi-component insect attractant. The effects of raspberry ketone on the mating success of male melon flies (*Diptera tephritidae*) confirms that cuelure (raspberry ketone acetate) and raspberry ketone (which are chemically related) have similar, short-lasting effects on mating success, and similar effects of subsequent capture probabilities.[7]

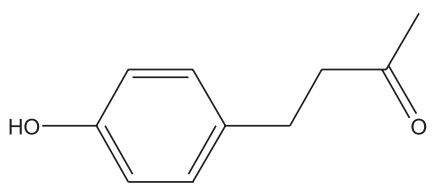
Raspberry ketone is active on an androgen receptor, which is activated by binding of either of the androgenic hormones testosterone (CAS# 58-22-0) or dihydrotestosterone (CAS# 521-18-6) in the cytoplasm, and then translocates into the nucleus. The androgen receptor is most closely related to the progesterone (CAS# 57-83-0) receptor and progestins in higher dosages can block the androgen receptor.[8] The effect of essential oils, such as ones containing raspberry ketone on an androgen receptor, was investigated using an MDA-kb2 human breast cancer cell[b] line for predicting potential androgen receptor activity. Among them, eugenol (CAS# 97-53-0) had the highest androgen receptor antagonistic activity with its IC50 (half maximal inhibitory concentration) value of 19 μM. Raspberry ketone, which has threefold higher anti-obesity activity (raspberry ketone has been applied in formulations for weight loss) than that of capsaicin (CAS# 404-86-4), also had androgen receptor antagonist activity with an IC50 value of 252 μM.[9,10]

Melanogenesis inhibition by raspberry ketone from *Rheum officinale* was investigated both in vitro in cultivated murine B16 melanoma cells and in vivo in zebra fish and mice. In B16 cells, raspberry ketone inhibited melanogenesis through

[a] Some of the information on occurrence and uses are taken from FRM 2001 and PMP 96 Databases of Perfumery Materials & Performance, Boelens Aroma Chemicals Information Services, The Netherlands.

[b] MDA-kb2 cells are human breast carcinoma cells that were stably transfected with a luciferase reporter gene that can be activated by compounds acting through either the androgen receptor or glucocorticoid receptor.

F-1. Raspberry ketone



Physical Data for Raspberry Ketone

Appearance: white crystalline powder

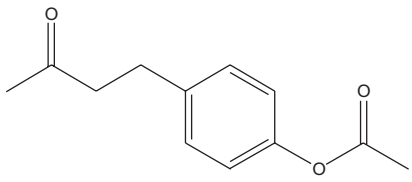
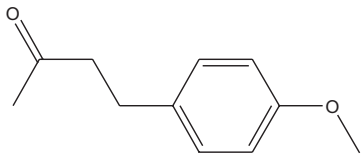
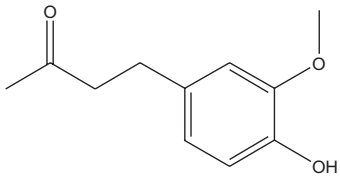
M.W.: 164.2

Melting point: 82°–84°C

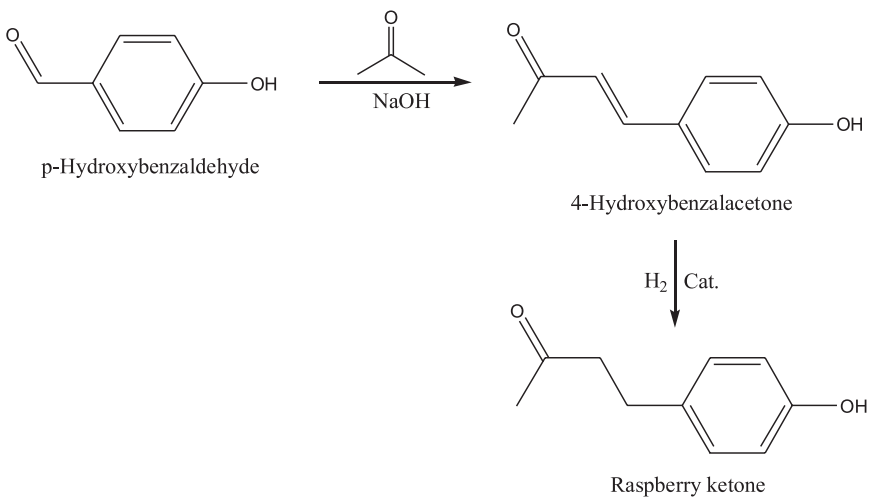
Flash point: >200°F TCC

LogP (o/w): 0.94 (estd.)

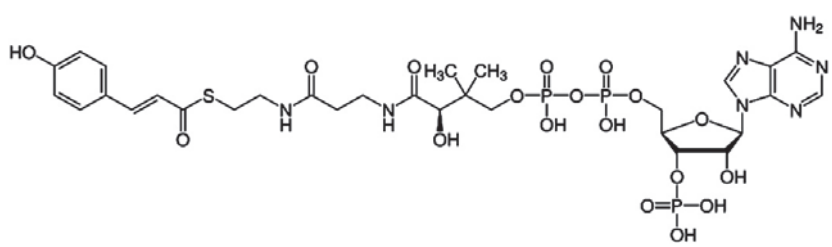
T-1. Raspberry ketone-related materials

Derivative	Structure	Organoleptic properties
Raspberry ketone acetate 4-(p-Acetoxyphenyl)-2-butanone (cuelure)		Sweet aromatic, somewhat fruity, raspberrylike
Raspberry ketone methyl ether p-Anisyl acetone		Fruity, raspberrylike on dilution; floral, woody, ionone, raspberry, spice and berry
Zingerone 4-(4-Hydroxy-3-methoxyphenyl)-2-butanone		Sweet aromatic, vanillalike and slightly spicy

F-2. The synthesis of raspberry ketone



F-3. Coumaroyl-CoA



a post-transcriptional regulation of tyrosinase gene expression. In zebra fish, raspberry ketone also inhibited melanogenesis by reduction of tyrosinase activity. In mice, application of a 0.2% or 2.0% gel preparation of raspberry ketone applied to the mice's skin significantly increased the degree of skin whitening within one week of treatment. In contrast to the widely used flavoring properties of raspberry ketone in perfumery and cosmetics, the skin-whitening potency of raspberry ketone has been demonstrated. Based on these findings, raspberry ketone would appear to have high potential for use in the cosmetics industry.[11]

The synthesis of raspberry ketone starts from p-hydroxybenzaldehyde, which is condensed with acetone in aldol reaction, to give 4-hydroxybenzalacetone as an intermediate. This intermediate is further hydrogenated in the presence of a catalyst to obtain the target molecule as described in **F-2**.

Raspberry ketone is an important compound for the flavor industry, and so the demand for the natural material is growing considerably. However, this product is highly expensive. Extraction of pure raspberry ketone is usually 1–4 mg per Kg of raspberries.[12] The molecule is biosynthesized in

plants from coumaroyl-CoA (CAS# 119785-99-8), a compound used in the production of chalcones and a key compound in the flavonoid and stilbenoid biosynthesis pathways in plants (**F-3**).[c]

Natural raspberry ketone can be prepared also by biotechnological methods of aromatic compounds, *e.g.* by *Escherichia coli* (ATCC 86963) whole cells, specifically by 2-deoxyribose-5-phosphate aldolase.[13]

Enhanced commercial appeal and value are indeed conferred upon the materials produced in this manner because they can be labeled natural products, thus receiving increased consumer preference. However, a major problem faced in this area is the occurrence of adulterations of these expensive natural materials with readily available nature-identical products of petrochemical origin. The measurement of the ^{13}C and ^{14}C content may be a useful tool to verify the non-petrochemical origin of a substance. However, these methods do not guarantee against the transformation of natural precursors by non-natural synthetic methods.

The site-specific natural abundance deuterium distribution of raspberry ketone can be obtained through a variety of methods and also through ^{2}H-NMR spectroscopy. This technique provides a means of distinguishing between the natural molecule, which is bio-generated from 4-hydroxybenzalacetone obtained from 4-hydroxybenzaldehyde of extractive botanical origin and acetone produced by sugar fermentation, and other raspberry ketone samples obtained in non-natural methods.[14]

[c] *http://biocyc.org/META/new-image?type=PATHWAY&object=PWY-5393*

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