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Vanillin

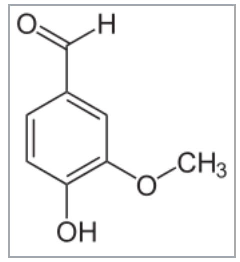
Vanillin is an organic compound with the molecular formula $C_8H_8O_3$. It is a phenolic aldehyde. Its functional groups include aldehyde, hydroxyl, and ether. It is the primary component of the extract of the vanilla bean. Synthetic vanillin is now used more often than natural vanilla extract as a flavoring in foods, beverages, and pharmaceuticals.

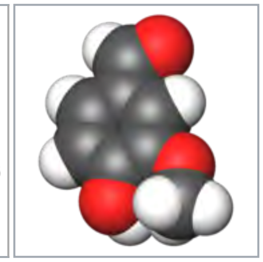
Vanillin and ethylvanillin are used by the food industry; ethylvanillin is more expensive, but has a stronger note. It differs from vanillin by having an ethoxy group ($-O-CH_2CH_3$) instead of a methoxy group ($-O-CH_3$).

Natural vanilla extract is a mixture of several hundred different compounds in addition to vanillin. Artificial vanilla flavoring is often a solution of pure vanillin, usually of synthetic origin. Because of the scarcity and expense of natural vanilla extract, synthetic preparation of its predominant component has long been of interest. The first commercial synthesis of vanillin began with the more readily available natural compound eugenol (4-allyl-2-methoxyphenol). Today, artificial vanillin is made either from guaiacol or lignin.

Lignin-based artificial vanilla flavoring is alleged to have a richer flavor profile than oil-based flavoring; the difference is due to the presence of acetovanillone, a minor component in the lignin-derived product that is not found in vanillin synthesized from guaiacol.[4]

Vanillin





Names	
Preferred IUPAC name	4-Hydroxy-3-methoxybenzaldehyde
Other names	Vanillin[1] Methyl vanillin[1] Vanillic aldehyde[2]
Identifiers	
CAS Number	121-33-5 (https://commonchemistry.cas.org/detail?cas_rn=121-33-5) ✓
3D model (JSmol)	Interactive image (https://chemapps.stolaf.edu/jmol/jmol.php?model=c1%28C%3DO%29cc%28OC%29c%28O%29cc1)
3DMet	B00167 (http://www.3dmet.dna.affrc.go.jp/cgi/show_data.php?acc=B00167)
Beilstein Reference	472792
ChEBI	CHEBI:18346 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=18346) ✓
ChEMBL	ChEMBL13883 (http

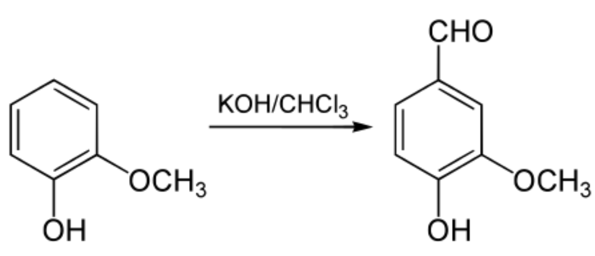
Contents

History

The oldest possible evidence of vanilla exploitation in the Old World dates from the second millennium BCE.[5]

Vanilla beans, called *tlilxochitl,* were discovered and cultivated as a flavoring for beverages by native Mesoamerican peoples, most famously the Totonacs of modern-day Veracruz, Mexico. Since at least the early 15th century, the Aztecs used vanilla as a flavoring for chocolate in drinks called *xocohotl*.[6]

Vanillin was first isolated as a relatively pure substance in 1858 by Nicolas-Theodore Gobley, who obtained it by evaporating a vanilla extract to dryness and recrystallizing the resulting solids from hot water.[7] In 1874, the German scientists Ferdinand Tiemann and Wilhelm Haarmann deduced its chemical structure, at the same time finding a synthesis for vanillin from coniferin, a glucoside of isoeugenol found in pine bark.[8] Tiemann and Haarmann founded a company Haarmann and Reimer (now part of Symrise) and started the first industrial production of vanillin using their process in Holzminden, Germany. In 1876, Karl Reimer synthesized vanillin (**2**) from guaiacol (**1**).[9]



1 **2**

Synthesis of vanillin by Reimer

By the late 19th century, semisynthetic vanillin derived from the eugenol found in clove oil was commercially available.[10]

Synthetic vanillin became significantly more available in the 1930s, when production from clove oil was supplanted by production from the lignin-containing waste produced by the sulfite pulping process for preparing wood pulp for the paper industry. By 1981, a single pulp and paper mill in Thorold,

	s://www.ebi.ac.uk/chembldb/index.php/compound/inspect/ChEMBL13883) ✓
ChemSpider	13860434 (https://www.chemspider.com/Chemical-Structure.13860434.html) ✓
ECHA InfoCard	100.004.060 (https://echa.europa.eu/substance-information/-/substanceinfo/100.004.060)
EC Number	204-465-2
Gmelin Reference	3596
IUPHAR/BPS	6412 (http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=summary&ligandId=6412)
KEGG	D00091 (https://www.kegg.jp/entry/D00091) ✓
MeSH	vanillin (https://www.nlm.nih.gov/cgi/mesh/2014/MB_cgi?mode=&term=vanillin)
PubChem CID	1183 (https://pubchem.ncbi.nlm.nih.gov/compound/1183)
RTECS number	YW5775000
UNII	CHI530446X (https://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=CHI530446X) ✓
CompTox Dashboard (EPA)	DTXSID0021969 (https://comptox.epa.gov/dashboard/chemical/details/DTXSID0021969)

Ontario supplied 60% of the world market for synthetic vanillin.[11] However, subsequent developments in the wood pulp industry have made its lignin wastes less attractive as a raw material for vanillin synthesis. Today, approximately 15% of the world's production of vanillin is still made from lignin wastes,[12] while approximately 85% synthesized in a two-step process from the petrochemical precursors guaiacol and glyoxylic acid.[13][14]

Beginning in 2000, Rhodia began marketing biosynthetic vanillin prepared by the action of microorganisms on ferulic acid extracted from rice bran. At USD$700/kg, this product, sold under the trademarked name Rhovanil Natural, is not cost-competitive with petrochemical vanillin, which sells for around USD$15/kg.[15] However, unlike vanillin synthesized from lignin or guaiacol, it can be labeled as a natural flavoring.

Occurrence

Vanillin is most prominent as the principal flavor and aroma compound in vanilla. Cured vanilla pods contain about 2% by dry weight vanillin; on cured pods of high quality, relatively pure vanillin may be visible as a white dust or "frost" on the exterior of the pod.

It is also found in *Leptotes bicolor*, a species of orchid native to Paraguay and southern Brazil,[16] and the Southern Chinese red pine.

At lower concentrations, vanillin contributes to the flavor and aroma profiles of foodstuffs as diverse as olive oil,[17] butter,[18] raspberry,[19] and lychee[20] fruits.

Aging in oak barrels imparts vanillin to some wines, vinegar,[21] and spirits.[22]

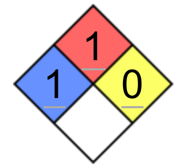
In other foods, heat treatment generates vanillin from other compounds. In this way, vanillin contributes to the flavor and aroma of coffee,[23][24] maple syrup,[25] and whole-grain products, including corn tortillas[26] and oatmeal.[27]

Chemistry

Natural production

Natural vanillin is extracted from the seed pods of *Vanilla planifolia*, a vining orchid native to Mexico, but now grown in tropical areas around the globe. Madagascar is presently the largest producer of natural vanillin.

InChI	
InChI=1S/C8H8O3/c1-11-8-4-6(5-9)2-3-7(8)10/h2-5,8H,1H3 ✗ Key: MWOOGOJBHIARFG-UHFFFAOYSA-N ✗	
InChI=1/C8H8O3/c1-11-8-4-6(5-9)2-3-7(8)10/h2-5,10H,1H3 Key: MWOOGOJBHIARFG-UHFFFAOYAS	
SMILES	
c1(C=O)cc(OC)c(O)cc1	
Properties	
Chemical formula	$C_8H_8O_3$
Molar mass	152.149 g·mol^{-1}
Appearance	White crystals
Odor	Vanilla, sweet, balsamic, pleasant
Density	1.056 g/cm^3[3]
Melting point	81 °C (178 °F; 354 K)[3]
Boiling point	285 °C (545 °F; 558 K)[3]
Solubility in water	10 g/L
log *P*	1.208
Vapor pressure	>1 Pa
Acidity (pK_a)	7.781
Basicity (pK_b)	6.216
Structure	
Crystal structure	Monoclinic
Thermochemistry	
Std enthalpy of combustion ($\Delta_c H^\ominus_{298}$)	−3.828 MJ/mol
Hazards	
GHS labelling:	
Pictograms	
Signal word	**Warning**

Hazard statements	H302, H317, H319
Precautionary statements	P280, P305+P351+P338
NFPA 704 (fire diamond)	
Flash point	147 °C (297 °F; 420 K)
Safety data sheet (SDS)	hazard.com (http://hazard.com/msds/mf/baker/baker/files/v2775.htm)
Related compounds	
Related compounds	Anisaldehyde Apocynin Eugenol Phenol Vanillyl alcohol

Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa).

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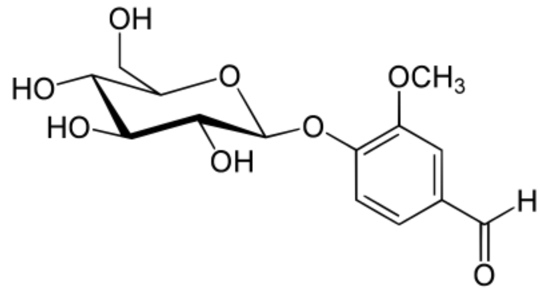
Infobox references

As harvested, the green seed pods contain vanillin in the form of its β-D-glucoside; the green pods do not have the flavor or odor of vanilla.[28]

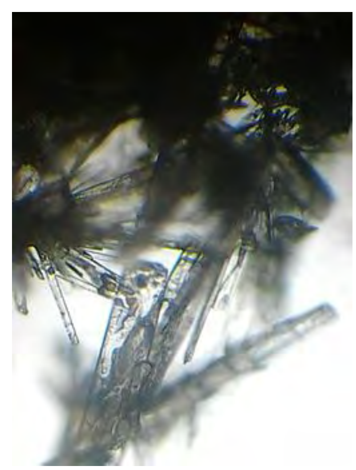


β-D-glucoside of vanillin

After being harvested, their flavor is developed by a months-long curing process, the details of which vary among vanilla-producing regions, but in broad terms it proceeds as follows:

First, the seed pods are blanched in hot water, to arrest the processes of the living plant tissues. Then, for 1–2 weeks, the pods are alternately sunned and sweated: during the day they are laid out in the sun, and each night wrapped in cloth and packed in airtight boxes to sweat. During this process, the pods become dark brown, and enzymes in the pod release vanillin as the free molecule. Finally, the pods are dried and further aged for several months, during which time their flavors further develop. Several methods have been described for curing vanilla in days rather than months, although they have not been widely developed in the natural vanilla industry,[29] with its focus on producing a premium product by established methods, rather than on innovations that might alter the product's flavor profile.

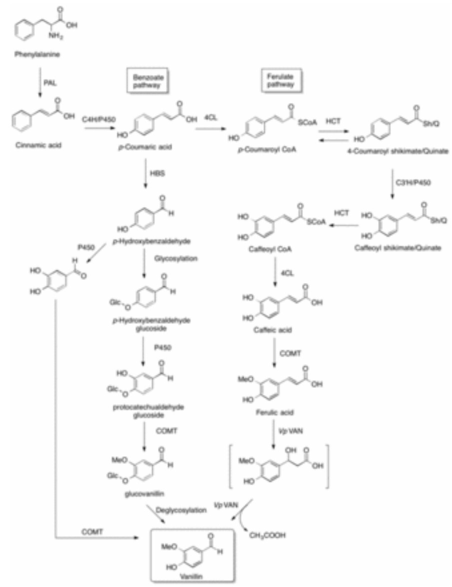
These green seed pods contain vanillin only in its glucoside form, and lack the characteristic odor of vanilla.



Vanillin crystals extracted from vanilla extract

Biosynthesis

Although the exact route of vanillin biosynthesis in *V. planifolia* is currently unknown, several pathways are proposed for its biosynthesis. Vanillin biosynthesis is generally agreed to be part of the phenylpropanoid pathway starting with L-phenylalanine,[30] which is deaminated by phenylalanine ammonia lyase (PAL) to form t-cinnamic acid. The para position of the ring is then hydroxylated by the cytochrome P450 enzyme cinnamate 4-hydroxylase (C4H/P450) to create *p*-coumaric acid.[31] Then, in the proposed ferulate pathway, 4-hydroxycinnamoyl-CoA ligase (4CL) attaches *p*-coumaric acid to coenzyme A (CoA) to create *p*-coumaroyl CoA. Hydroxycinnamoyl transferase (HCT) then converts *p*-coumaroyl CoA to 4-coumaroyl shikimate/quinate. This subsequently undergoes oxidation by the P450 enzyme coumaroyl ester 3'-hydroxylase (C3'H/P450) to give caffeoyl shikimate/quinate. HCT then exchanges the shikimate/quinate for CoA to create caffeoyl CoA, and 4CL removes CoA to afford caffeic acid. Caffeic acid then undergoes methylation by caffeic acid O-methyltransferase (COMT) to give ferulic acid. Finally, vanillin synthase hydratase/lyase (vp/VAN) catalyzes hydration of the double bond in ferulic acid followed by a retro-aldol elimination to afford vanillin.[31] Vanillin can also be produced from vanilla glycoside with the additional final step of deglycosylation.[28] In the past *p*-hydroxybenzaldehyde was speculated to be a precursor for vanillin biosynthesis. However, a 2014 study using radiolabelled precursor indicated that *p*-hydroxybenzaldehyde do not synthesise vanillin or vanillin glucoside in the vanilla orchids.[31]

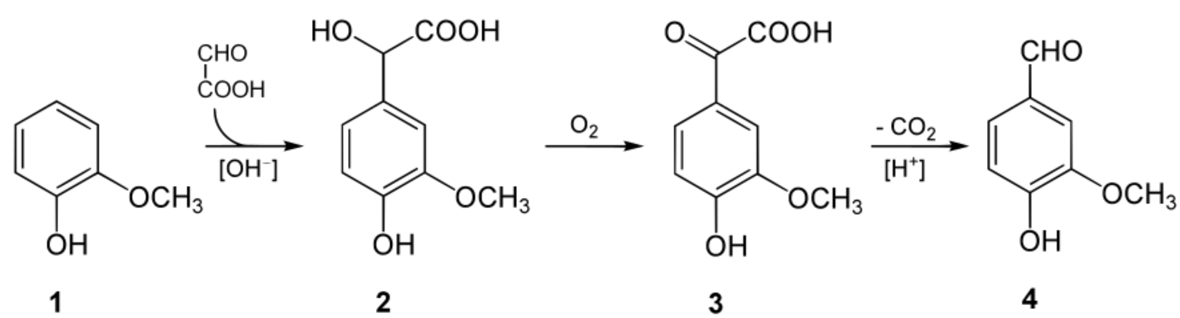


Some of the proposed routes of vanillin biosynthesis

Chemical synthesis

The demand for vanilla flavoring has long exceeded the supply of vanilla beans. As of 2001, the annual demand for vanillin was 12,000 tons, but only 1,800 tons of natural vanillin were produced.[32] The remainder was produced by chemical synthesis. Vanillin was first synthesized from eugenol (found in oil of clove) in 1874–75, less than 20 years after it was first identified and isolated. Vanillin was commercially produced from eugenol until the 1920s.[33] Later it was synthesized from lignin-containing "brown liquor", a byproduct of the sulfite process for making wood pulp.[11] Counterintuitively, though it uses waste materials, the lignin process is no longer popular because of environmental concerns, and today most vanillin is produced from the petrochemical raw material guaiacol.[11] Several routes exist for synthesizing vanillin from guaiacol.[34]

At present, the most significant of these is the two-step process practiced by Rhodia since the 1970s, in which guaiacol (**1**) reacts with glyoxylic acid by electrophilic aromatic substitution.[35] The resulting vanillylmandelic acid (**2**) is then converted by 4-Hydroxy-3-methoxyphenylglyoxylic acid (**3**) to vanillin (**4**) by oxidative decarboxylation.[13]



Wood-based vanillin

15% of the world's production of vanillin is produced from lignosulfonates, a byproduct from the manufacture of cellulose via the sulfite process.[11][12] The sole producer of wood-based vanillin is the company Borregaard located in Sarpsborg, Norway.

Wood-based vanillin is produced by copper-catalyzed oxidation of the lignin structures in lignosulfonates under alkaline conditions[36] and is claimed by the manufacturing company to be preferred by their customers due to, among other reasons, its much lower carbon footprint than petrochemically synthesized vanillin.

Fermentation

The company Evolva has developed a genetically modified microorganism which can produce vanillin. Because the microbe is a processing aid, the resulting vanillin would not fall under U.S. GMO labeling requirements, and because the production is nonpetrochemical, food using the ingredient can claim to contain "no artificial ingredients".[37]

Using ferulic acid as an input and a specific non GMO species of *Amycolatopsis* bacteria, natural vanillin can be produced.

Biochemistry

Several studies have suggested that vanillin can affect the performance of antibiotics in laboratory conditions.[38][39]

Uses

Butter-vanilla flavoring

The largest use of vanillin is as a flavoring, usually in sweet foods. The ice cream and chocolate industries together comprise 75% of the market for vanillin as a flavoring, with smaller amounts being used in confections and baked goods.[40]

Vanillin is also used in the fragrance industry, in perfumes, and to mask unpleasant odors or tastes in medicines, livestock fodder, and cleaning products.[13] It is also used in the flavor industry, as a very important key note for many different flavors, especially creamy profiles such as cream soda.

Additionally, vanillin can be used as a general-purpose stain for visualizing spots on thin-layer chromatography plates. This stain yields a range of colors for these different components.

Vanillin–HCl staining can be used to visualize the localisation of tannins in cells.

Manufacturing

Vanillin has been used as a chemical intermediate in the production of pharmaceuticals, cosmetics, and other fine chemicals.[41] In 1970, more than half the world's vanillin production was used in the synthesis of other chemicals.[11] As of 2016, vanillin uses have expanded to include perfumes, flavoring and aromatic masking in medicines, various consumer and cleaning products, and livestock foods.[42]

Adverse effects

Vanillin can trigger migraine headaches in a small fraction of the people who experience migraines.[43]

Some people have allergic reactions to vanilla.[44] They may be allergic to synthetically produced vanilla but not to natural vanilla, or the other way around, or to both.[45]

Vanilla orchid plants can trigger contact dermatitis, especially among people working in the vanilla trade if they come into contact with the plants sap.[45] An allergic contact dermatitis called **vanillism** produces swelling and redness, and sometimes other symptoms.[45] The sap of most species of vanilla orchid which exudes from cut stems or where beans are harvested can cause moderate to severe dermatitis if it comes in contact with bare skin. The sap of vanilla orchids contains calcium oxalate crystals, which are thought to be the main causative agent of contact dermatitis in vanilla plantation workers.[46][47]

A pseudophytodermatitis called **vanilla lichen** can be caused by tiny mites.[45]

Ecology

Scolytus multistriatus, one of the vectors of the Dutch elm disease, uses vanillin as a signal to find a host tree during oviposition.[48]

See also

- Phenolic compounds in wine
- Other positional isomers:
  - Isovanillin
  - *ortho*-Vanillin
  - 2-Hydroxy-5-methoxybenzaldehyde
  - 2-Hydroxy-4-methoxybenzaldehyde
- Benzaldehyde
- Protocatechuic aldehyde
- Syringaldehyde

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2. CID 1183 (https://pubchem.ncbi.nlm.nih.gov/compound/1183) from PubChem.
3. Haynes, William M., ed. (2016). *CRC Handbook of Chemistry and Physics* (97th ed.). CRC Press. p. 3.310. ISBN 9781498754293.
4. According to Esposito 1997, blind taste-testing panels cannot distinguish between the flavors of synthetic vanillin from lignin and those from guaicol, but can distinguish the odors of these two types of synthetic vanilla extracts. Guaiacol vanillin, adulterated with acetovanillone, has an odor indistinguishable from lignin vanillin.
5. Linares, V.; Adams, M. J.; Cradic, M. S.; Finkelstein, I.; Lipschits, O.; Martin, M. A. S.; Neumann, R.; Stockhammer, P. W.; Gadot, Y. (June 2019). "First evidence for vanillin in the old world: Its use as mortuary offering in Middle Bronze Canaan" (https://www.sciencedirect.com/science/article/abs/pii/S2352409X18307557). *ScienceDirect*.
6. MexicanVanilla.com. "Mexican Vanilla - A History" (https://mexicanvanilla.com/pages/history-of-vanilla). *MexicanVanilla.com*. Retrieved 2022-06-14.
7. Gobley 1858.
8. Tiemann 1874.
9. Reimer 1876.

10. According to Hocking 1997, synthetic vanillin was sold commercially in 1874, the same year Tiemann and Haarmann's original synthesis was published. Haarmann and Reimer, one of the corporate ancestors of the modern flavor and aroma manufacturer Symrise, was in fact established in 1874. However, Esposito 1997 claims that synthetic vanillin first became available in 1894 when Rhône-Poulenc (since 1998, Rhodia) entered the vanillin business. If the former claim is correct, the authors of the latter article, being employees of Rhône-Poulenc, may have been unaware of any previous vanillin manufacture.
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