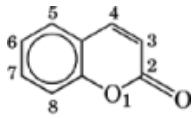
Kirk-Othmer Encyclopedia of Chemical Technology.

COUMARIN

Coumarin [91-64-5], 2*H*-1-benzopyran-2-one; 1,2-Benzopyrone, $C_9H_6O_2$ (**1**), is one of the most important aroma chemicals having unique characteristics not only because of its haylike bittersweet odor, but also because of its quality as a perfume fixative.



(**1**)

Coumarin is widely distributed in the plant kingdom but most of it has been produced synthetically for many years for commercial uses. In addition to its use in the perfumery, cosmetic, and related industries, coumarin has several other industrial applications. Formerly, large quantities of coumarin were used in the food industry mostly associated with vanillin for flavoring chocolates, baked goods, and in the confection of cream soda flavored beverages, but since 1954 its use in food has been suspended in the United States. In a statement of general policy under the Federal Food, Drug, and Cosmetic Act, foods containing coumarin are legally regarded as adulterated (1).

Coumarin is the parent substance of a large group of derivatives, many of which occur naturally and some of which are of economic significance.

1. Occurrence

Coumarin was first isolated by Vogel in 1820 by extraction from tonka beans (*Dipteryx odorata*) (2). It was subsequently identified in a large number of plants belonging to many different families. Its better known occurrences are in sweet clover (*Melilotus officinalis* and *alba*), woodruff (*Asperula odorata*), cassia (*Cinnamorum cassia*), melilot (*Melilotus officinalus*), lavender (*Lavandum officinalus*), and balsam of Peru (*Myroxylon pereirae*) (3, 4). Several reviews have been published on the distribution of natural coumarins and their biochemistry (5, 6).

2. Physical Properties

Coumarin is usually sold in the form of colorless shiny leaflets or rhombic crystals. Its ir (7), uv (8), Raman (9), and nmr spectra (10) are known. Physical constants appear in Table 1. Tables 2 and 3 give the solubility of coumarin in various water mixtures and solvents.

Table 1. Physical Constants of Coumarin

Constant	Value	Reference
mol wt	146.14	
mp, °C	71	(11, 12)
bp, °C		
at 100 kPa[a]	301.1	13
at 2.7 kPa[a]	170.4	13
at 0.7 kPa[a]	138.5	13
density at 100 °C, g/cm^3	1.178	14

[a] To convert kPa to mm Hg, multiply by 7.5.

Table 2. Solubility of Coumarin in Ethanol–Water Mixtures[a]

Ethanol, vol %	Solubility, g/100 mL soln. at			
	10°C	20°C	30°C	40°C
0	0.13	0.17	0.29	0.39
25	0.28	0.50	0.97	1.93
50	2.00	3.71	7.56	19.02
70	5.62	10.04	19.3	47.00

[a] Ref. 15.

Table 3. Solubility of Coumarin in Various Solvents[a]

Solvent	Solubility, g/100 g solvent	Temperature, °C
water	0.25	25
water	2.0	100
chloroform	49.4	25
pyridine	87.7	20–25

[a] Ref. 16.

3. Chemical Properties

The chemical properties of coumarin are those of the lactone of an α,β-unsaturated aromatic acid.

3.1. Hydrolysis

The lactone is easily hydrolyzed by alkalies to the corresponding salts of coumarinic acid or *o*-hydroxy-*cis*-cinnamic acid [495-79-4]. Coumarinic acid salts are odorless. Coumarinic acid and salts revert to coumarin upon acidification with inorganic acids. Alkaline fusion of coumarin yields salts of salicylic and acetic acids.

3.2. Hydrogenation

Hydrogenation of coumarin gives several different products depending on experimental conditions. Hydrogenation with a Raney nickel catalyst under moderate conditions yields 3,4-dihydrocoumarin [119-84-6] (17) but continued hydrogenation especially at higher temperatures leads to the formation of the saturated octahydrocoumarin [4430-31-3]. Hexahydrochroman [5655-24-3] and polymeric products can also be formed under more severe conditions (18). 3,4-Dihydrocoumarin is also obtained selectively by hydrogenation over a platinum sulfide catalyst (19). Hydrogenation with copper chromite catalyst at high temperature gives 3-(*o*-hydroxyphenyl)-1-propanol [1481-92-1] with a high yield (20).

3.3. Reduction

Coumarin is reduced to *o*-hydroxycinnamyl alcohol by reaction with lithium aluminum hydride (21). By reaction with diborane coumarin gives *o*-allylphenol [1745-81-9] (22).

3.4. Bisulfite Reaction

Coumarin combines readily with sodium bisulfite solutions to form soluble sodium 3- or 4-hydrosulfonates (23). Coumarin can be regenerated by acidification and this method has been used for its purification.

3.5. Halogenation

Coumarin reacts with bromine under moderate conditions to give 3,4-dibromocoumarin [42974-18-5] (24). The 3-bromocoumarin [939-18-4] and 3,6-dibromocoumarin [58309-97-0] are formed under more drastic conditions (25). 3-Chlorocoumarin [92-45-5] is formed by reaction with chlorine in dichloroethane (26) or without solvent (27).

3.6. Oxidation

Coumarin is not readily oxidized by chromic acid but, by action of the Fenton's reagent, it is converted into 7-hydroxycoumarin (umbelliferone) [93-35-6] (28).

3.7. Sulfonation

Fuming sulfuric acid reacts with coumarin to give coumarin-6-sulfonic acid [27279-86-3] at moderate temperature and coumarin-3,6-disulfonic acid [69089-38-9] at higher temperature.

3.8. Nitration

Fuming nitric acid forms 6-nitrocoumarin [2725-81-7] (25).

3.9. Methylation

Methylating agents such as methyl sulfate and methyl iodide react with coumarin in the presence of sodium hydride to give methyl 2-methoxycinnamate [15854-58-7] (29).

3.10. Dimerization

A coumarin dimer is formed by prolonged exposure of coumarin to sunlight or uv radiation. Photodimerization is also catalyzed by boron trifluoride (30).

4. Methods of Preparation

Until the late 1890s, coumarin was obtained commercially from only natural sources by extraction from tonka beans and deer tongue. Then synthetic methods of preparation and industrial manufacturing processes were discovered and developed starting principally from *o*-cresol, phenol, and salicylaldehyde. Various methods can be used to obtain coumarin from each of these starting materials.

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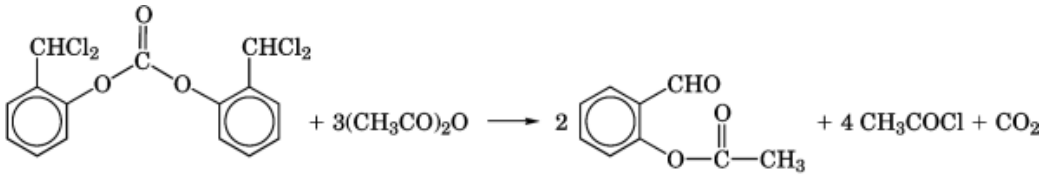
4.1. From o-Cresol

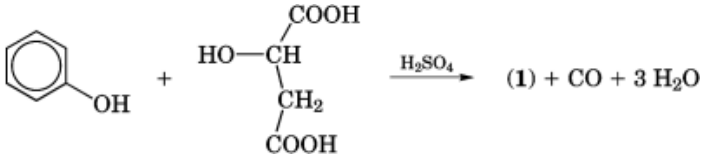
The Raschig method, starting with *o*-cresol [95-48-7], was discovered in 1909 (31). The hydroxyl group of *o*-cresol is first protected by a phosphate or, preferably, a carbonate (32) group and the methyl group is converted into a benzal chloride intermediate by dichlorination. The α,α-dichlorocresyl ester then reacts with an alkali acetate in an alkali fusion reaction (31) or with acetic anhydride in the presence of a metal catalyst such as cobalt oxide (33) to yield *o*-acetylsalicylaldehyde (**2**), acetyl chloride, and CO_2. Ring closure of *o*-acetylsalicylaldehyde [5663-67-2] with acetic anhydride gives coumarin and acetic acid.



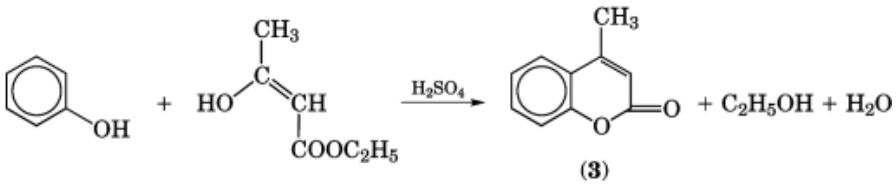
(**2**)

4.2. From Phenol

In the type of condensation discovered by von Pechmann in 1883, coumarin is formed by reaction of phenol [108-95-2] with malic (34), maleic, or fumaric acids (35–38) in the presence of concentrated sulfuric acid.



The Pechmann reaction has found extensive applications for the synthesis of numerous coumarin derivatives (39). Coumarin derivatives substituted in the pyrone ring can be obtained by condensing phenol with beta-ketoesters. For example, 4-methylcoumarin (**3**) is obtained with ethyl acetoacetate [141-97-9].



(**3**)

Coumarin can also be formed by the reaction of phenol with diketene (40). Similarly, diphenols can react with hydroxycarboxylic acids or beta-ketoesters to give hydroxycoumarin derivatives. The reaction of resorcinol with malic acid produces umbelliferone (7-hydroxycoumarin) and its reaction with ethyl acetoacetate gives beta-methylumbelliferone (7-hydroxy-4-methylcoumarin).

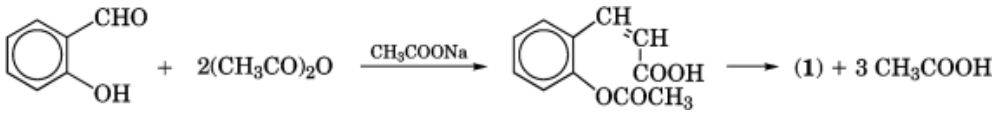
Phenol reacts with some acrylic acid derivatives to produce coumarin. With 3-ethoxyacrylic acid chloride, phenol gives phenyl ethoxyacrylate that cyclizes into coumarin on treatment with sulfuric acid (41). Coumarin is also formed by reaction of phenol with methyl acrylate in acidic medium and in the presence of air (42).

Hydroxycoumarins can be obtained by reaction of methyl acrylate [96-33-3] with diphenols in the presence of aluminum chloride followed by dehydrogenation with palladium on carbon (43).

4.3. From Salicylaldehyde

4.3.1. Perkin Reaction

Perkin first synthesized coumarin in 1868 by reaction of the sodium salt of salicylaldehyde with acetic anhydride (44) and it was found later that the reaction could be made from salicylaldehyde [90-02-8] itself by using sodium acetate as a catalyst, through the intermediary of *cis-o*-acetoxycinnamic acid [50363-92-3].

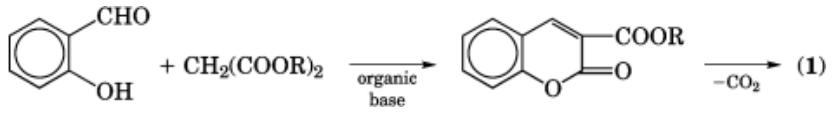


This reaction was also extended to other aromatic aldehydes for the preparation of α,β-unsaturated carboxylic acids. Several mechanisms of the reaction have been proposed (45). The most accepted mechanism involves the reaction of the aldehyde with the enol form of the acid anhydride which is promoted by the presence of the sodium salt or of another base. The resulting reaction product is then dehydrated into an unsaturated carboxylic acid.

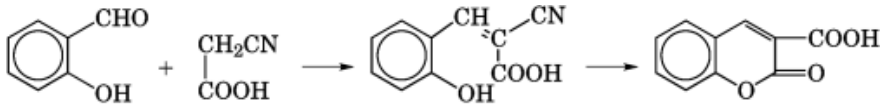
The Perkin reaction is of importance for the industrial production of coumarin and a number of modifications have been studied to improve it, such as addition of a trace of iodine (46); addition of oxides or salts of metals such as iron, nickel, manganese, or cobalt (47); addition of catalytic amounts of pyridine (48) or piperidine (49); replacement of sodium acetate by potassium carbonate (50, 51) or by cesium acetate (52); and use of alkali metal biacetate (53).

4.3.2. Knoevenagel Reaction

3-Substituted coumarins can be synthesized by the Knoevenagel reaction (54), which involves the condensation of *o*-hydroxyaldehydes such as salicylaldehyde with acetic acid derivatives containing an active methylene group such as acetoacetic acid, malonic acid [141-82-2], cyanoacetic acid, and their esters. Ammonia or organic bases such as pyridine, piperidine, and primary and secondary amines are used as catalysts (55). Removal of the substituted group in the 3-position by heating or hydrolysis can produce coumarin. Thus coumarin 3-carboxylic acid obtained by the condensation of salicylaldehyde with malonic acid (54) is decarboxylated into coumarin by heating to 290°C. The decarboxylation reaction can be done at a lower temperature and with a better yield in the presence of mercuric salts (56):



where R = H or C_2H_5. The coumarin 3-carboxylic acid [531-81-7] (**4**) is also obtained by hydrolysis of the cyano group resulting from the condensation of salicylaldehyde with cyanoacetic acid [372-09-8] (57).



(**4**)

Table 4. U.S. Production and Sales of Synthetic Coumarin

		Sales		
Year	Production, t	Quantity, t	Unit price, $/kg	Value, 10^3 $
1940	112	99	5.14	508
1946	163	149	5.51	822
1956	354	299	6.68	2000
1967	520	510	4.37	2221
1977	>544	>544	9.92	>5400
1990	>500	>500	15.43	>7700

4.4. Other Methods

Several other methods have been published, including cyclodehydrogenation of oxocyclohexane propionate (58); dehydrogenation of 3,4-dihydrocoumarin obtained by the Baeyer-Villiger oxidation of 1-indanone (59); and the dehydrogenation reaction can be made with sulfur (60) or in the vapor phase with a metal oxide catalyst (61).

5. Purification and Shipment

In order to be suitable for perfumary uses, synthetic coumarin must be treated to a high degree of purity. Normal purification processes include fractional distillation under high vacuum and crystallization from suitable solvents such as methanol or ethanol. Additional treatments have been proposed prior to distillation including heating with 10–20% concentrated sulfuric acid, neutralizing, and washing with warm water (62); dissolving in 80% concentrated sulfuric acid and treating with an oxidizing gas (63); and treating with aqueous sodium hydroxide under reflux, separating the organic layer, and washing (64).

Coumarin has also been purified by vacuum azeotropic distillation with polyhydroxy alcohols such as triethylene glycol (65). Purification by zone melting techniques has been described in several publications (66–68).

Commercial coumarin is packaged in polyethylene bags and shipped in fiberboard drums. Coumarin is stable in storage and does not require any special handling precautions.

6. Economic Aspects

Data on the production, sales, and value of synthetic coumarin were published by the U.S. Tariff Commission until 1967 (Table 4). Later data are not available because the number of producers dropped to three or fewer. In 1992, Rhone-Poulenc was the only coumarin producer both in the United States and in Western Europe. Commercial quantities of coumarin have also been produced in China and, to a lesser extent, in the former Soviet Union.

7. Specifications

An ir spectrum for identification of coumarin was published by the Scientific Section of the Essential Oil Association of the United States (EOA).

Manufacturers' specifications for commercial coumarin are (69)

Appearance: crystalline powder
Color of molten product: 70 Hazen maximum
Odor: characteristic
Melting point (capillary): 68–70°C
Assay: 99% minimum

8. Health and Safety

The acute and subchronic toxicity of coumarin have been well described. The oral LD_{50} in the rat has been reported to be 293–680 mg/kg (70, 71) but no adverse effects have been observed at doses up to 250 ppm for 90 days in the diet of rats; liver damage was noted at 2500 ppm. A subchronic oral toxicity study of coumarin administered was conducted for the National Toxicology Program (NTP) in 1981 (72). The results of this study, conducted for 13 weeks using gavage doses from 19 to 300 mg/kg/d, indicated significant decreases in body weight gain and dose-related changes in clinical pathology parameters indicative of hepatic injury at the two highest dose levels, 150 and 300 mg/kg/d. Increased liver weight and a histopathologic diagnosis of toxic hepatitis were reported at these two dose levels.

In contrast, the chronic toxicity and potential carcinogenicity of coumarin have been surrounded by scientific debate. Since 1954, coumarin has been classified by the FDA as a toxic substance and its use in foods was banned (1). In a two-year rat study reported in 1967 (73), no effects were observed at 1000 ppm in the diet, but growth retardation and hepatic toxicity (cholangiofibrosis, bile duct proliferation, and focal hepatic necrosis) were reported at 2500 and 5000 ppm. A chronic study in 1973 (74) in which cholangiocarcinomas were reported in rats fed doses of 5000 and 6000 ppm in the diet was inadvertantly interpreted as two separate studies during a review of the International Agency for Research on Cancer (IARC) in 1976 (75), leading IARC to classify coumarin as a carcinogen. Further, the interpretation of the histopathologic findings as neoplastic in the 1973 study (74) was questioned in 1979 (76). In 1987, IARC reclassified coumarin as a Group 3 chemical, indicating limited evidence of carcinogenicity in animals and insufficient evidence in humans (77). A more recent chronic study which included an *in utero* exposure phase resulted in hepatoxicity but no dose-related increase in tumors following two-year administration of 2000 ppm in the diet of rats (78). A two-year gavage study in rats and mice has been conducted for the NTP, although data are not yet available.

Although no quantitative data were presented, rabbits dosed orally and dermally with coumarin showed similar patterns in the urinary excretion of coumarin metabolites (79). Metabolism of coumarin when fed to animals and humans occurs essentially by hydroxylation at all 6-ring positions, although the 7-position appears to be the primary site for many species. In addition, the heterocyclic ring may be opened to yield *o*-hydroxyphenylacetic acid and *o*-phenoxyphenylacetic acid. The 7-hydroxycoumarin is much more prominent in humans (79%) and baboons (60%) than in rats ($<1\%$), rabbits (12%), and dogs (3%) (76, 80). The species difference in the metabolism of coumarin may have important toxicologic implications. *In vitro* data demonstrate that the predominant metabolite in rats, *o*-hydroxyphenylacetic acid, inhibits glucose-6-phosphatase in the liver, whereas coumarin and its principal metabolite in humans, 7-hydroxycoumarin, were inactive in this *in vivo* glucose-6-phosphatase inhibition assay (81). Available data from *in vivo* studies suggest that the degree of susceptibility to the hepatotoxic effects of coumarin is strongly correlated with the inability of the exposed species to make 7-hydroxycoumarin, ie, those species with the least ability to hydroxylate at the 7-position have the greatest degree of hepatoxic response (76). It is therefore possible that humans could be less susceptible than the rat to the hepatotoxic action of coumarin.

9. Uses

Because of its unique sweet note and stability, coumarin has long been recognized as an important raw material in the fragrance industry (see Perfumes). It is widely used in hand soaps, detergents, lotions, and perfumes at concentrations usually extending from 0.01 to 0.8%. It is normally associated in perfumery with herbaceous odors and enters in the formulation of fern (Fougere) and Chypre-type fragrances. It is used as an odor enhancer to achieve a long lasting effect when combined with natural essential oils such as lavender, citrus, rosemary, oak moss, etc (see Oils, essential). Coumarin is used in tobacco to enhance its natural aroma. It is also applied in large quantities to give pleasant aromas to household materials and industrial products or to mask unpleasant odors (see Odor modification).

In other fields, coumarin has a significant use in the electroplating industry, mostly in the automotive area, to provide high polished quality to chrome plated steel (see Electroplating) but this use is presently declining. Coumarin and some of its derivatives have been tested in pharmacology for treatment of schizophrenia (82), or of microcirculation disorders and angiopathic ulcers (83), and also for treatment of high protein edemas in animals (84).

10. Derivatives

A large number of coumarin derivatives have been identified in plants and many of them have been synthesized and studied for their physiological activity. Only a few are mentioned here because of their economic significance.

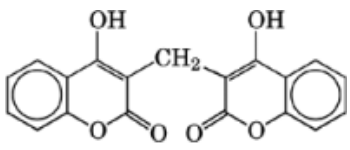
3,4-Dihydrocoumarin [119-84-6] is prepared by catalytic hydrogenation of coumarin. It is also used in the perfumery industry for its haylike odor. It is less powerful than coumarin but its higher solubility in alcohol may make it preferable in some applications. It has GRAS status and can be used as a food flavor ingredient with a sweet caramel-like taste. The U.S. market for dihydrocoumarin is estimated at 50 t/yr at a price of $34/kg. The U.S. producers are Givaudan and Arsynco.

3-Methylcoumarin [2445-82-1] and 6-methylcoumarin [92-48-8] have some use in the perfume industry. The 6-methyl derivative is permitted in flavor compositions.

4-Hydroxycoumarin [1076-38-6] can be synthesized by cyclization of acetyl methyl salicylate. It is a coumarin metabolite occurring in spoiled hay. Derivatives of 4-hydroxycoumarin such as dicoumarol [66-76-2], warfarin [81-81-2], cyclocoumarol [518-20-7], ethylbis–coumaracetate [548-00-5], and bis-4-hydroxycoumarin [25892-93-7] are synthetic blood anticoagulants (see Blood, coagulants and anticoagulants).

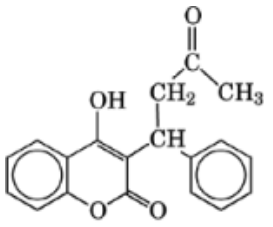
7-Hydroxycoumarin [93-35-6], known as umbelliferone, occurs naturally in gum resins of umbelliferae and is an important coumarin metabolite. It is readily manufactured from resorcinol and maleic or fumaric acid. Umbelliferone and β-methylumbelliferone are used as fluorescent brighteners.

Dicoumarol [66-76-2] (**5**) was isolated from spoiled sweet clover hay. It is prepared synthetically by reaction of 4-hydroxycoumarin with formaldehyde (85). It is used in anticoagulant therapy often associated with heparin.



(**5**)

Warfarin [81-81-2](**6**) is prepared by the Michael condensation of benzylidene acetone with 4-hydroxycoumarin (86). It is used as a rodenticide (see Poisons, commercial) and in anticoagulant therapy.



(**6**)

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