Kirk-Othmer Encyclopedia of Chemical Technology.

(POLYHYDROXY)BENZENES

Polyhydric phenols with more than two hydroxy groups (ie, the three positional isomers of benzenetriol, the three isomeric benzenetetrols, benzenepentol [4270-96-6], and benzenehexol [608-80-0]) are discussed in this article. The benzenediols are catechol, resorcinol, and hydroquinone (see Hydroquinone, resorcinol, and catechol).

The following names of the benzenetriols have been used.

Common (trivial) name	CAS Registry Number	*Chemical Abstracts*	Other usage
pyrogallol (pyrogallicacid)	[87-66-1]	1,2,3-benzenetriol	1,2,3-trihydroxybenzene
hydroxyhydro-quinone	[533-73-3]	1,2,4-benzenetriol	1,2,4-trihydroxybenzene
phloroglucinol	[108-73-6]	1,3,5-benzenetriol	1,3,5-trihydroxybenzene 0.0pt1,98.0pt

The benzenetetrols, -pentol, and -hexol do not have trivial names, except for 1,2,3,4-benzenetetrol [642-96-6], which was named apionol in some of the older literature. The other two benzenetetrol isomers are 1,2,3,5-[634-94-6] and 1,2,4,5-benzenetetrol [636-32-8].

Derivatives of these compounds or their corresponding quinones are of widespread occurrence in nature. They are abundant in plants and fruits as glucosides, chromones, coumarin derivatives, flavonoids, essential oils, lignins, tannins, and alkaloids (see alkaloids; Coumarin; Lignin; Oils, essential). They also occur in microorganisms and animals. Many of these compounds have distinct properties and uses, eg, antibiotics (qv), plant-growth factors, insecticides, astringents, antioxidants (qv), toxins, sweeteners (qv), pigments (qv) and dyes, drugs, and many others (see Dyes and dye intermediates; Insect control technology; Pharmaceuticals). Developing uses for the benzenepolyols and derivatives appear particularly valuable in the pharmaceutical and agricultural chemical areas. The most recent applications of these compounds are as components of photosensitive compounds in high resolution heat-resistant photoresist compositions.

Identification, isolation, and removal of (polyhydroxy)benzenes from the environment have received increased attention throughout the 1980s and 1990s. The biochemical activity of the benzenepolyols is at least in part based on their oxidation–reduction potential. Many biochemical studies of these compounds have been made, eg, of enzymic glycoside formation, enzymic hydroxylation and oxidation, biological interactions with biochemically important compounds such as the catecholamines, and humic acid formation. The range of biochemical function of these compounds and their derivatives is not yet fully understood.

1. Pyrogallol

Pyrogallol **(1)** was first observed by Scheele in 1786 as a product of the dry distillation of gallic acid [149-91-7] (3,4,5-trihydroxybenzoic acid). Pyrogallol, which is of widespread occurrence in nature, is incorporated in tannins, anthocyanins, flavones, and alkaloids (1).

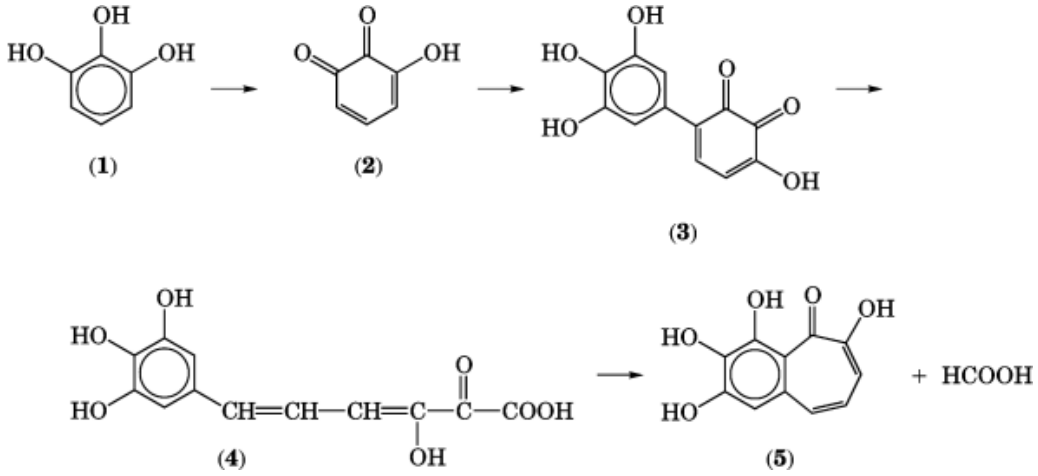
2 (POLYHYDROXY)BENZENES

1.1. Properties

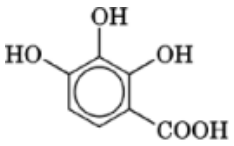
Pyrogallol (mp 133–134°C) forms colorless needles or leaflets which gray on contact with air or light. Its boiling point at atmospheric pressure with partial decomposition is 309°C; at 13.3 kPa (100 mm Hg), 232°C; and at 1.3 kPa (10 mm Hg), 168°C. When heated slowly, pyrogallol sublimes without decomposition; sp gr at 4°C, 1.453; heat of combustion, 2.673 MJ/mol (638.9 kcal/mol); solubility in parts per 100 parts solvent: 40 in water at 13°C, 62.5 in water at 25°C, 100 in alcohol at 25°C, 83.3 in ether at 25°C, slightly soluble in benzene, chloroform, and carbon disulfide. Pyrogallol is the strongest reducing agent among the benzenepolyols. Therefore, it is oxidized rapidly in air; its aqueous alkaline solution absorbs oxygen from the air and darkens rapidly. Sodium sulfite retards such oxidation.

Pyrogallol oxidized, which is obtained by the action of air and ammonia on pyrogallol, is a brownish black to black lustrous powder and is almost insoluble in water, alcohol, or ether but is soluble in alkalies. Hexahydroxybiphenyl [4371-20-4] (diphenylhexol), $(HO)_3C_6H_2C_6H_2(OH)_3$, is formed by mixing pyrogallol with barium hydroxide solution while air is passed through the reaction mixture. In solutions of hydrogen peroxide, pyrogallol oxidizes rapidly in the presence of catalysts, eg, colloidal suspensions of metals or metallic oxides, and luminescence occurs.

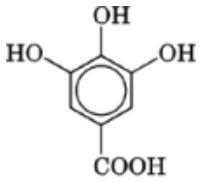
Purpurogallin **(5)**, a red-brown to black mordant dye, forms from electrolytic and other mild oxidations of pyrogallol **(1)**. The reaction is believed to proceed through 3-hydroxy-*o*-benzoquinone **(2)** and 3-hydroxy-6-(3,4,5-trihydroxyphenyl)-*o*-benzoquinone **(3)**. The last, in the form of its tautomeric triketonic structure, represents the vinylogue of a β-diketone. Acid hydrolysis leads to the formation of **(4)**, followed by cyclization and loss of formic acid to yield purpurogallin.



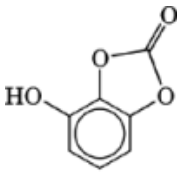
Methylation of **(1)** with methyl iodide or dimethyl sulfate in the presence of alkali gives 3-methoxy-1,2-benzenediol, 2,3-dimethoxyphenol, or 1,2,3-trimethoxybenzene (2). On heating with aqueous potassium bicarbonate, pyrogallol-4-carboxylic acid **(6)** and a lesser amount of gallic acid **(7)** are formed (3). Reaction of pyrogallol with phosgene (qv) in the presence of pyridine gives pyrogallol carbonate **(8)** (4). Bromination of this carbonate yields both 4-bromopyrogallol and 4,6-dibromopyrogallol. The direct bromination of pyrogallol in carbon tetrachloride produces 4,5,6-tribromopyrogallol, and with more bromine, 1,2,6,6-tetrabromocyclohexene-3,4,5-trione **(9)** is obtained (5).



(**6**)

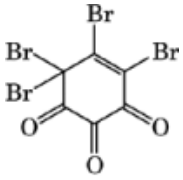


(**7**)



(**8**)

The formation of **(9)** is evidence for the ability of pyrogallol to react in keto forms. However, in contrast to phloroglucinol, pyrogallol does not react as a ketone with hydroxylamine.



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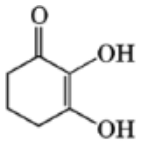


(**10**)

The hydrogenation of pyrogallol in ethanol at 100°C and 17 MPa (2400 psig), using a moist Raney nickel catalyst, results in a 60% yield of the γ-isomer, ie, *cis,cis*-1,2,3-cyclohexanetriol with only minor amounts of

the cis,trans-, ie, β-isomer, and the trans,trans-, ie, α-isomer (6). The hydrogenation of pyrogallol in water in the presence of 1 mol of alkali at 60°C and 7 MPa (1000 psig), with a Raney nickel catalyst, gives dihydropyrogallol [4337-36-4] **(10)** (7). Pyrogallol forms salts or chelates with many metals, some of which are used for identification in analysis, as pigments or lakes, eg, in inks (qv), or for medicinal purposes.

1.2. Manufacture and Synthesis

The commercial manufacturing process is based on Scheele's original procedure starting with crude gallic acid, which is extracted from nutgalls or tara powder. It proceeds according to the following equation:

$$C_6H_2(OH)_3COOH \longrightarrow C_6H_3(OH)_3 + CO_2$$

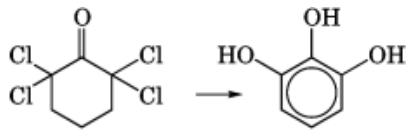
.

Gallic acid is heated with about half its weight of water in a copper autoclave until the pressure reaches 1.2 MPa (12 atm) and the temperature is 175°C. Steam and carbon dioxide are released but sufficient water is retained to maintain the pyrogallol as a liquid. The cooled solution is decolorized with animal charcoal and is then evaporated until the volatile pyrogallol distills into iron receivers. The solidified material is purified by repeated distillation, sublimation, or vacuum distillation at 200°C in the presence of dialkyl phthalates (8).

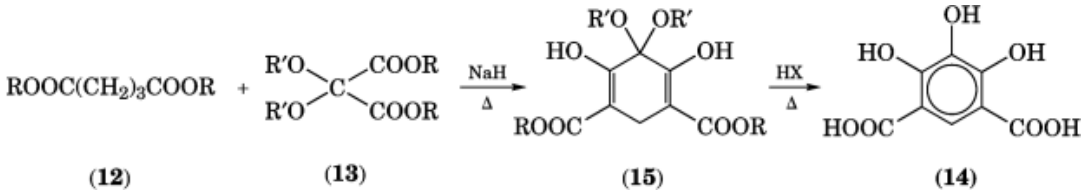
In 1981 Mallinckrodt was the only U.S. manufacturer of pyrogallol via decarboxylation of plant-derived gallic acid, but it has since ceased production. Harshaw Chemical (Europe) makes pyrogallol by the same process. Because of the continuing uncertainties of supply of plant materials for gallic acid–pyrogallol manufacture, and because of valuable uses for pyrogallol, there is much interest in the development of synthetic processes. Gallic acid **(7)** can be made, presumably in good yield, by the sodium alkoxide-catalyzed condensation of a tricarballylic ester with an acetal of mesoxalic ester, eg, dialkyl(ethylenedioxy)malonate, via substituted cyclohexane-1,2,3-triones (9).

Resorcinol can be hydroxylated with 50 wt % hydrogen peroxide in the presence of hexafluoroacetone at ca 60°C to give a mixture of pyrogallol and 1,2,4-trihydroxybenzene (10). The hydrolysis of 2,6-diamino-4-*t*-butylphenol with aqueous hydrochloric acid at 250°C for 8 h in a pressure reactor provides a 48% yield of pyrogallol and a 9% yield of 5-*t*-butylpyrogallol (11). Pyrogallol or 5-alkylpyrogallols can be prepared from 2,6-dibromophenol or 4-alkyl-2,6-dibromophenol by treatment with sodium methoxide. The 2,6-dimethoxyphenols produced are subjected to ether cleavage with dealkylation in the case of 4-*t*-butyl-2,6-dimethoxyphenol with aqueous 48 wt % hydrobromic acid to give pyrogallol in good yield (12).

2,2,6,6-Tetrachlorocyclohexanone **(11)** can be hydrolyzed with a base, eg, sodium acetate, to give pyrogallol in high yield and purity (13). The preparation of the starting material **(11)** by chlorination of cyclohexanone in the presence of collidine as the catalyst has been patented (14). The sodium hydride-catalyzed condensation of dialkyl glutarate **(12)** with a dialkyl dialkoxymalonate **(13)** to pyrogallol-4,6-dicarboxylic acid **(14)** by means of intermediate **(15)** has been patented (15); the dicarboxylic acid **(14)** is decarboxylated in methanol at 200°C under pressure to give pyrogallol.



(11) **(1)**



(12) (13) (15) (14)

Another synthesis of pyrogallol is hydrolysis of cyclohexane-1,2,3-trione-1,3-dioxime derived from cyclohexanone and sodium nitrite (16). The dehydrogenation of cyclohexane-1,2,3-triol over platinum-group metal catalysts has been reported (17) (see Platinum-group metals). Other catalysts, such as nickel, rhenium, and silver, have also been claimed for this reaction (18).

The first synthetic pyrogallol plant using hydrolysis of chlorinated cyclohexanol (2,2,6,6-tetrachlorocyclohexanone) was built by BFC Chemicals, Inc. (Muskegon, Michigan) and has been producing pyrogallol for the carbamate insecticide Beniocarb since 1982 (8, 19). Société Française Hoechst offers pyrogallol for sale in the United States (American Hoechst Corp.), and Japan is also a source of this chemical.

1.3. Grades and Specifications

Harshaw Chemical sells material from their overseas operation in four grades of pyrogallic acid: pure crystal, pure powder, resublimed, and technical grade. Depending on grade, pyrogallic acid is coarse and white to slightly yellow, having lustrous crystals with some smaller crystals. It may contain some black or brown specks, and has a characteristic odor. Its melting point is 131.5–135°C and maximum residue on ignition is 0.1%.

1.4. Analysis

Freshly prepared ferrous sulfate test solution produces a blue color in an aqueous solution of pyrogallol (20). Pyrogallol can be detected in amounts of ca 0.5 μg by the violet to orange color that results from the addition of phloroglucinol to ammoniacal pyrogallol. Pyrogallol reacts with osmium tetroxide [20816-12-0] to form a compound that is reddish violet in dilute solution and almost black in concentrated solution. This reaction is extremely sensitive and can be used to detect as little as one part pyrogallol in 2×10^6 parts water (21). Various other color tests for pyrogallol have been reported (22, 23). Derivatives used for the identification of pyrogallol are tris(phenylurethane), mp 173°C; tris-(3,5-dinitrobenzoate), mp 205°C; and tribenzoate, mp 90°C. Thin-layer chromatography is applicable to the detection of pyrogallol (24). Of the modern instrumental methods of analysis, liquid chromatography is particularly well-suited to the analysis of pyrogallol.

1.5. Health and Safety Factors

Pyrogallol is extremely toxic. Extensive exposure of the skin may cause discoloration, local irritation, eczema, or death if it is absorbed. Repeated contact with the skin may lead to sensitization. The principal symptom of poisoning attributable to pyrogallol is its effect on the red blood corpuscles which break down and lose their hemoglobin. The tremendous affinity of pyrogallol for oxygen of the blood has been shown in experimental animals, where complete removal of oxygen from the blood occurred as well as fragmentation and destruction of the erythrocytes. Severe pyrogallol poisoning also leads to degeneration of the liver and kidneys, and symptoms exhibited in such cases include urinary disturbance, headache, cyanosis, chills, vomiting, and diarrhea (25). A yeast test has proved useful in checking acute toxicity of a number of chemicals including pyrogallol (26). The effect of pyrogallol on algae has also been studied (27). Acute toxicity data include oral LD_{50} (rat) = 789 mg/kg, intraperitoneal LD_{50} (mouse) = 400 mg/kg, and oral LD_{50} (rabbit) = 1600 mg/kg (28).

1.6. Uses

The main commercial applications of pyrogallol are in pharmaceuticals (qv) and pesticides (qv). Pyrogallol is the oldest and one of the more versatile of the photographic developing agents in use (see Photography). Strong contrasts are possible with concentrated solutions, and soft delicate shades are achieved with more dilute solutions and lower alkali concentrations. However, because pyrogallol oxidizes readily, the yellow oxidation product stains the gelatin so that the useful life of a pyrogallol developer is short. Pyrogallol is relatively costly, quite toxic, and water soluble, therefore its removal from the environment has become important. Hydrogen peroxide-mediated photodegradation has been studied by flash photolysis/hplc techniques (29), as well as oxidation as pretreatment in wastewater discharge (30). Electrochemical oxidation has also received scrutiny (31). The ease of oxidation of pyrogallol is the basis for its use in fur and hair dyeing and as a chemical reagent for the estimation of oxygen. Pyrogallol has been used as part of analytical procedures, thus it is a component for a "screw-cap test" for fat-soluble vitamins (qv) (32). Pyrogallol is used to demonstrate chemiluminescence (33) and traces of chromium(III) are determined with a pyrogallol chemiluminescence system (34) (see Luminescent materials, chemiluminescence).

Scale-preventing coatings for polymerization reactors may contain pyrogallol or hydroxyhydroquinone condensed with amines (35–37). The use of pyrogallol and certain derivatives as stabilizers for photographic silver halide recording materials to improve storage stability and to reduce fogging has been patented (38). An improved synthesis of 5-bromopyrogallol-1,3-dimethyl ether by bromination of pyrogallol-1,3-dimethyl ether with *N*-bromosuccinimide in chloroform–ethanol has been disclosed; the product is an intermediate for photographic optical filter agents (39).

An adhesive with good peel strength and soldering tolerance for copper in printed circuits is based on a mixture of poly(vinyl butyral) and a modified melamine resin containing pyrogallol (40). A rubberized pyrogallol–formaldehyde adhesive improves the adhesion of rubber to nylon (41). Pyrogallol 1-methyl, 3-propyl or allyl ethers are useful in natural smoke-aroma compositions for food or tobacco (42). Pyrogallol-1,3-dimethyl ether imparts a bonito-like aroma to dried fish (43). Zinc or chrome-plated steel is treated with aqueous pyrogallol or gallic acid to improve the adhesion of a final alkyd or melamine resin coating (44). Glass fiber for reinforcement of cementitious products is protected from corrosion by a pyrogallol dip (45).

Certain natural products containing a pyrogallol moiety, eg, myricetin, are effective inhibitors of radical-chain reactions (46). Pyrogallol, as an antioxidant, is useful for preventing decomposition of alkali cellulose (47). A mixture of defatted rice bran and alkalized pyrogallol is useful in protecting foodstuffs from oxygen (48). Phosphite esters of 4,6-dialkylpyrogallol are effective heat- and light-stabilizers for plastics (49). The formation of deposits on reactor walls during vinyl chloride polymerization can be prevented by treating the reactor surface with a compound comprised in part of chelate-forming and free-radical chain-inhibiting groups, eg, pyrogallol (50). Pyrogallol can be used as a stabilizer to inhibit peroxide formation in dicyclopentadiene (51).

Many patents have been issued on the use of pyrogallol derivatives as pharmaceuticals. Pyrogallol has been used externally in the form of an ointment or a solution in the treatment of skin diseases, eg, psoriasis, ringworm, and lupus erythematosus. Gallamine triethiodide **(16)** is an important muscle relaxant in surgery; it also is used in convulsive-shock therapy. Trimethoprim (2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine) is an antimicrobial and is a component of Bactrin and Septra. Trimetazidine (1(2,3,4-trimethoxybenzyl)piperazine; (Vastarel, Yosimilon) is used as a coronary vasodilator. 1,2,3,4-Tetrahydro-6-methoxy-1-(3,4,5-trimethoxyphenyl)-9*H*-pyrido[3,4-*b*]indole hydrochloride is useful as a tranquilizer (52) (see Hypnotics, sedatives, anticonvulsants, and anxiolytics). Substituted indanones made from pyrogallol trimethyl ether depress the central nervous system (CNS) (53). Tyrosine- and glycine(2,3,4-trihydroxybenzyl)hydrazides are characterized by antidepressant and anti-Parkinson activity (54). 2-(ω-Dialkylaminoalkoxy)-3′,4′,5′-trimethoxychalcones are effective as antihypertensives (55). β-(3,4,5Trimethoxyphenyl)propionitrile was patented as a bactericide and a fungicide (56). Numerous

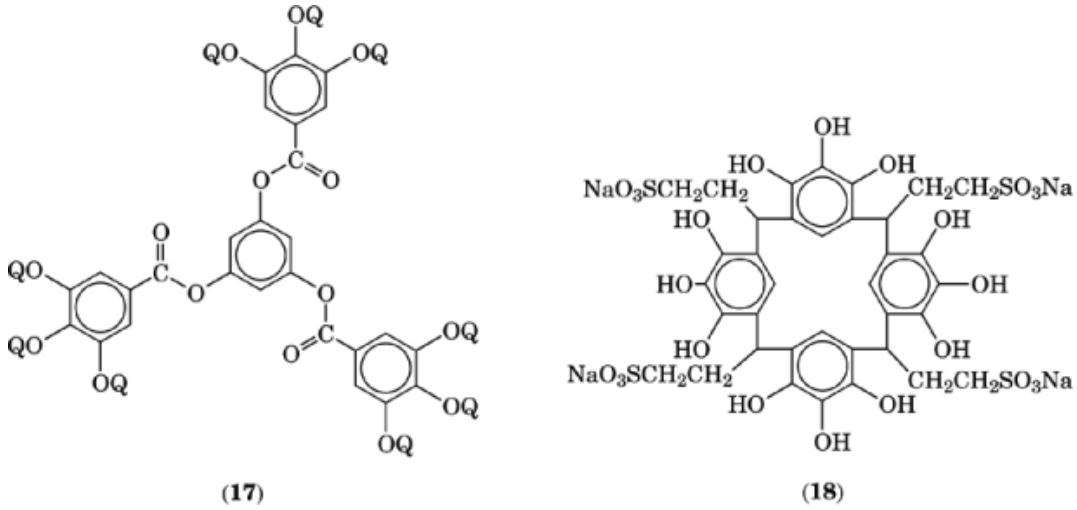
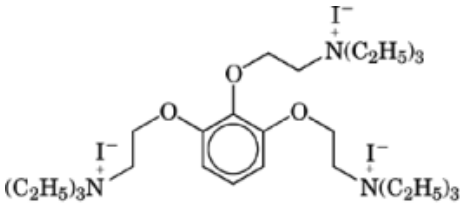


Fig. 1. Structures based on pyrogallol and phloroglucinol where $_{Q=C_{12}H_{25}}$.

3,4,5-trialkoxycinnamamides are claimed to have therapeutic properties (57). Many *N*-alkyl, *N*-aminoalkyl-3,4,5-, or 2,3,4-trimethoxybenzylamines are useful therapeutic agents (58). Bendiocarb (2,2-dimethyl-1,3-benzodioxol-4-yl *N*-methylcarbamate) (Ficam) is used for the control of cockroaches, crickets, carpet beetles, earwigs, ants, silverfish, wasps, fleas, and bedbugs in foodstores and houses. Related benzodioxolyl and benzodioxepinyl carbamates have been patented as insecticides (59).



(16)

Pyrogallol has been cited for use in photosensitive compositions. It is used in the form of sulfonate esters of quinonediazides which hydrolyze when exposed to actinic light to liberate the acid which, in turn, catalyzes further reaction of novolak resins (60).

The synthesis and phase structure of a three-arms–nine-chain liquid crystal (**17**) based on pyrogallol and phloroglucinol has been reported (61), as has a complexing agent for amino acids in water (**18**) (62) (Fig. 1).

1.7. Derivatives

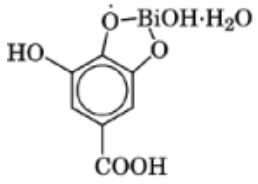
Gallic acid **(7)** is the most important derivative of pyrogallol. It is a colorless solid that crystallizes from water as the monohydrate and begins to dehydrate at ca 100°C. The anhydrous compound melts at 253°C with decomposition, its sp gr at 4°C is 1.694, and its dissociation constant at 25°C is 3.8×10^{-5}. It is soluble in alcohol and acetone, sparingly soluble in water, and insoluble in chloroform and benzene. Gallic acid darkens on exposure to light. It is manufactured by the chemical or enzymic hydrolysis of tannin from nutgalls (ie, gallnuts), Aleppo galls, or tara powder, ie, the ground seed pod of the Peruvian tree, *Coulteria tinctoria.*

Gallic acid is sold as the monohydrate or in anhydrous grades; bulk price in March of 1995 was listed as $28.67/kg.

Gallic acid has been used medicinally as a urinary astringent and internal antihemorrhageant and in veterinary medicine for the treatment of diarrhea (see Veterinary drugs). It is also used to manufacture pyrogallol by decarboxylation and as a plant-growth regulator (see Growth regulators, plant). The rates of decarboxylation of gallic acid in pyrogallol, catechol, and resorcinol have been studied. The reaction is first order and rate constants decrease in the above solvent order (63).

Gallic acid has traditionally been used with ferrous sulfate to make various types of inks, particularly the blue-black permanent-type writing inks. It is used in photothermographic reproduction processes, as a process chemical in engraving and lithography, as a developer in photography, and in tanning and fur- and hair-dyeing preparations (64). Miscellaneous applications of gallic acid include its use as a deflocculating, thickening, and sizing agent in the manufacture of wallboard; as a mordant in the manufacture of colored paper and fiberboard; as an analytical reagent for alkaloids, metals, and mineral acids; and in the manufacture of alizarin, thioflavine, and gallocyanine dyes.

Propyl gallate [121-79-9] is a food antioxidant made in the United States by Eastman Chemical Products, Inc.; it is used in synergistic combination with the antioxidants 4-methyl-2,6-di-*tert*-butylphenol (BHT) and butylated hydroxyanisole (BHA). The December 1995 price was ca $35.85/kg. Bismuth subgallate (gallic acid, bismuth basic salt) **(19)** is used as a dusting powder in dermatology. It is an ingredient in Bongast. Hexobendin (*N*,*N*′-dimethyl-*N*,*N*′-bis-[3-(3′,4′,5′-trimethoxybenzoyloxy)propyl]ethylenediamine; Reoxyl) **(20)** is a coronary vasodilator. Trioxazin (*N*-(3,4,5-trimethoxybenzoyl)morpholine), has been used as a tranquilizer. There has been considerable interest in amides of gallic acid trialkyl ethers as therapeutic agents (65).



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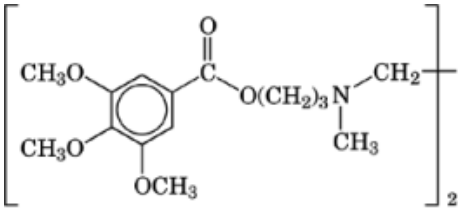
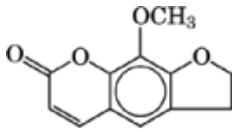


(20)

An ink composition containing a mixture of zinc diethyldithiocarbamate and bismuth subgallate changes color from white/yellowish to green when steam sterilized; thus the mixture is useful as a sterilization indicator in medicine (66) (see Chromogenic materials; Sterilization techniques). Alkyl gallates and gallic acid amides are useful stabilizers for aromatic amines (67). Gallic acid and its esters are adhesion promoters for cyanoacrylate adhesives (68) (see Acrylic ester polymers). The addition of 0.01–0.04 wt % gallic acid to gypsum-based building-panel formulations increases the resistance of these panels to collapse (69). Carbon steel can be made corrosion resistant by surface treatment with a gallic acid–chromite solution (70) (see Corrosion and corrosion control). The addition of small amounts of gallic esters to tin-ore flotation systems results in increased collection of tin (71) (see Flotation). Photographic silver halide emulsions can be stabilized with gallic acid or an alkyl gallate to

give long storage stability and to eliminate fogging (72). Alkyl gallates are useful components in latent-image printing inks which are developed with iron salts (73). Carbamate esters of gallic acid are useful fungicides (74).

The alkaloid reserpine [50-55-5], which is isolated from the roots of *Rauwolfia serpentina L.*, contains a gallate trimethyl ether moiety. Reserpine is used as an antihypertensive and a tranquilizer. A vinylogue of reserpine, rescinnamine [24815-24-5], is also an antihypersensitive (75). Methoxsalen [298-81-7] (8-methoxypsoralen; 7*H*-9-methoxy-furo[3,2-*g*][1]benzopyran-7-one) **(21)**, a furocoumarin that occurs in plants, eg, *Leguminosae* and *Umbelliferae*, is used in the treatment of vitiligo, as a suntanning promoter, and as a sunburn protectant. It is also available by synthesis (76).



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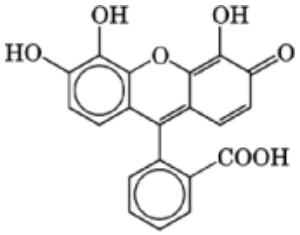

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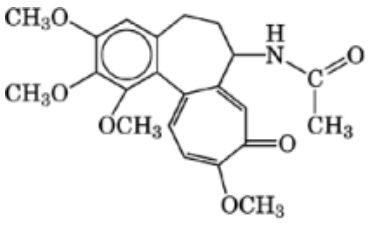
Gallein [2103-64-2] (pyrogallolphthalein, 4,5-dihydroxyfluorescein, tetrahydroxyfluoran; CI 45445) **(22)** forms greenish yellow crystals when anhydrous and red crystals in a 1:1.5 ratio with water. It is obtained by heating one part of phthalic anhydride with two parts of pyrogallol or gallic acid. Gallein is used as a sensitive indicator for acids, alkali hydroxides, and ammonia but not for carbonates. A dilute solution of gallein in 50% alcohol is used as a colorimetric reagent for determining phosphates in urine. Monophosphates give a yellow color, dibasic phosphates give red, and tribasic phosphates give violet.

Gallacetophenone [528-21-2] (4-acetylpyrogallol, 2,3,4-trihydroxyacetophenone; Alizarin Yellow C) forms gray leaf crystals or a yellow or brown powder, mp 173°C. It is slightly soluble in water, soluble in alcohol and in ether, and very slightly soluble in benzene. It is used medicinally as an antiseptic for skin diseases. It and other 4-acylpyrogallols are useful protective agents against harmful radiation (77) (see Radioprotective agents).

Mescaline [54-04-6] (2-(3,4,5-trimethoxyphenyl)ethylamine) is the active ingredient in mescal buttons (peyotl or peyote), which are the dried tops of the Mexican dumpling cactus *Lophopora williamsi*. Mescaline produces visual hallucinations on ingestion. Its possible use as a psychotomimetic drug in the field of mental health has been studied (see Alkaloids; Psychopharmacological agents).

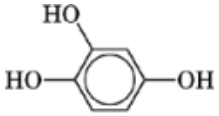
Colchicine **(23)** is a toxic substance occurring in *Colchicum autumnale*; it contains the nucleus of pyrogallol trimethyl ether. Colchicine has been used in the treatment of acute gout, and in plant genetics research to effect doubling of chromosomes.



(23)

2. Hydroxyhydroquinone

Hydroxyhydroquinone **(24)** forms colorless plates from diethyl ether when freshly prepared. It occurs in many plants and trees in the form of ethers, quinonoid pigments, coumarin derivatives, and complex compounds. Sponges from the coastal waters of Florida have been found to contain small amounts of 1,2,4-trihydroxybenzene and traces of 2,2′,4,4′,6,6′-hexahydroxybiphenyl **(25)** (78). The benzenetriol has also been isolated from tobacco leaves and tar from tobacco smoke (79). Hydroxyhydroquinone has strong reducing properties. Applications have been suggested in the synthesis of agricultural and photographic chemicals, drugs, and stabilizers.



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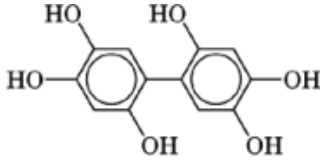
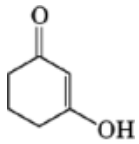


(25)

2.1. Properties

Hydroxyhydroquinone forms platelets or prisms (mp 140.5°C). The compound is easily soluble in water, ethanol, diethyl ether, and ethyl acetate and is very sparingly soluble in chloroform, carbon disulfide, benzene, and ligroin.

Hydroxyhydroquinone reacts as a typical oxidizable polyhydric phenol, but also undergoes certain keto-group reactions. In aqueous alkaline solution, it absorbs oxygen as effectively as pyrogallol. These solutions darken rapidly in the presence of oxygen, hydrogen peroxide, or potassium peroxysulfate, and produce a dark, humic acid-type precipitate. Mixing with excess bromine results in the formation of 2-hydroxy-3,5,6-tribromo-1,4-benzoquinone (80). Reduction with sodium amalgam produces dihydroresorcinol **(26)** (81). Condensation with aldehydes in the presence of sulfuric acid leads to the formation of 9-substituted 2,6,7-trihydroxyfluorones **(27)** (82).



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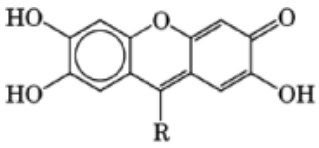
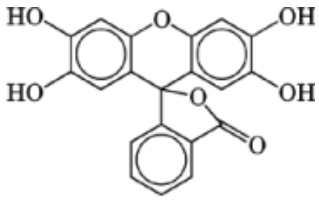


(27)

Condensation of hydroxyhydroquinone with ethyl acetoacetate gives 6,7-dihydroxy-4-methylcoumarin (83). Condensation with phthalic anhydride gives hydroxyhydroquinone phthalein **(28)** (84). Mild oxidants, eg, silver oxide, produce 2-hydroxy-*p*-benzoquinone. Reaction with ammonia or amines in aqueous solution at room temperature in the absence of air yields the corresponding 2,4-dihydroxyanilines. After prolonged heating with sodium bisulfite, an adduct containing 2 mol of sulfite is formed (85). Hydrogenation of hydroxyhydroquinone with a nickel catalyst in water or alcohol gives a mixture of stereoisomeric 1,2,4-cyclohexanetriols. Ethers or esters can be formed in the usual manner with alkylating and acylating agents.



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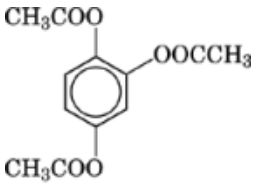


(29)

2.2. Synthesis

Hydroxyhydroquinone is not produced on a large scale, but many uses for it are being developed. The most convenient preparation of hydroxyhydroquinone is the reaction of *p*-benzoquinone with acetic anhydride in the presence of sulfuric acid or phosphoric acid. The resultant triacetate **(29)** can be hydrolyzed to hydroxyhydroquinone (86).

Hydroxyhydroquinone was first synthesized by the caustic fusion of hydroquinone (80, 87). The oxidation of aqueous alkaline solutions of 2,4- or 3,4-dihydroxybenzaldehyde or 2,4- or 3,4-dihydroxyacetophenone with hydrogen peroxide yields hydroxyhydroquinone (88). The oxidation of vanillin (qv) in this manner gives

2-methoxyhydroquinone. 5-*tert*-Alkyl-2-hydroxy-1,4-benzoquinone can be obtained in good yield by the oxidation of 4-*tert*-alkylcatechol with oxygen in methanolic potassium hydroxide (89). Reduction of the quinone yields the corresponding alkylhydroxyhydroquinone. Conversion of dilute aqueous solutions of 5-hydroxymethyl-2-furaldehyde and D-fructose under near-critical conditions leads to 1,2,3-benzenetriol in good yields (90). It is also a product, along with catechol and hydroquinone, in the oxidation of phenol (qv) in the presence of horseradish peroxidase (91). The acid-catalyzed oxidation of phenol with hydrogen peroxide in acetonitrile has yielded 88 mol %, based on H_2O_2 of 1,2,3-benzenetriol (92).

2.3. Analysis

Dilute aqueous solutions of hydroxyhydroquinone turn blue-green temporarily when mixed with ferric chloride. The solutions darken upon addition of small amounts, and turn red with additions of larger amounts of sodium carbonate. Derivatives used for identification are the picrate, which forms orange-red needles (mp of 96°C), and the triacetate (mp 96–97°C). Thin-layer chromatography and liquid chromatography are well suited for the qualitative and quantitative estimation of hydroxyhydroquinone (93, 94).

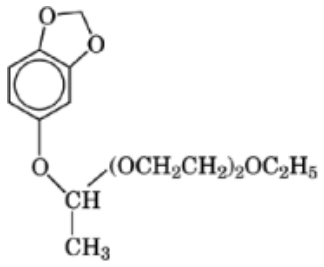
2.4. Health and Safety Factors

The LD_{50} of 1,2,4-trihydroxybenzene in mice after intracutaneous injection is 371 μg/g (95). Contact with hydroxyhydroquinone may blacken skin and fingernails. 1,2,3-Benzenetriol and other polyhydroxybenzenes have been found in water sources; when these react with chlorine and nitrite, derivatives having higher mutagenic potentials than their parent compounds, are formed. The mutagenicity of 1,2,3-benzenetriol is surpassed by that of hydroquinone but is greater than that of pyrogallol. The other di- and trihydroxybenzenes have been found to be nonmutagenic (96).

2.5. Uses

Hydroxyhydroquinone has been used in hair and mordant dyes, for healing plant wounds, and in corrosion inhibitors and adhesives.

Sesamex [51-14-9] (Sesoxane) **(30)** is a synergist of low toxicity, acute oral LD_{50} (rat) = 2000 – 2270 mg/kg, for pyrethrins and allethrin. 6,7-Dihydroxy 4-methylcoumarin has been offered as an antioxidant for phenolics and polymers, and as an anthelmintic. 2,4,5-Trihydroxybutyrophenone has been available as an antioxidant and light stabilizer for polyolefins, waxes, and foods. Isoflavones, eg **(31)**, have been patented as components of antioxidant compositions for foods and cosmetics (qv) (97).



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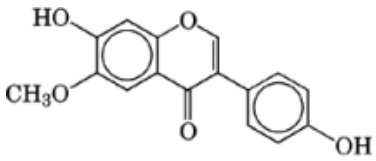
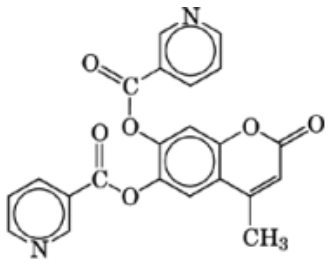


(31)

Hydroxyhydroquinone and pyrogallol can be used for lining reactors for vinyl chloride suspension polymerization to prevent formation of polymer deposits on the reactor walls (98). Hydroxyhydroquinone and certain of its derivatives are useful as auxiliary developers for silver halide emulsions in photographic material; their action is based on the dye diffusion-transfer process. The transferred picture has good contrast and stain-free highlights (99). 5-Acylhydroxyhydroquinones are useful as stabilizer components for poly(alkylene oxide)s (100).

4-Methylesculetol-6,7-dinicotinate **(32)** is useful as an antiinflammatory and vasodilator of low toxicity (101). The synthesis of asarone [5353-15-1] (2,4,5-trimethoxy-1-propenylbenzene), which is used as a tranquilizer, has been patented (102). It occurs in calamus root, *Acorus calamus L.*, and is a chemosterilant for insects (103). 6,7-Dihydroxycoumarin-4-methylsulfonic acid and its salts are useful in the treatment of capillary permeability and fragility and for protecting oxidizable metabolites and drugs against biooxidation (104). Certain chromones derived from hydroxyhydroquinone, eg **(33)**, and its salts, esters, and amides are valuable in the prophylactic treatment of asthma (105) (see Antiasthmatic agents). 2-Methoxy-6-multiprenyl-1,4-benzoquinones are intermediates in the microbiological synthesis of coenzyme Q compounds (106).



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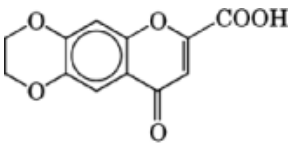
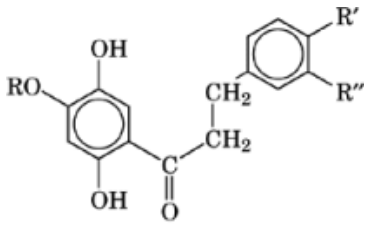


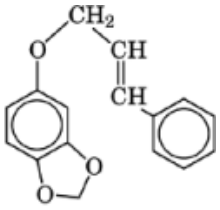
(33)

Dihydrochalcones (**34**, where R is D-glycosyl or the disaccharide neohesperidosyl) in conjunction with stevioside, a diterpenoid glycoside, are effective sweeteners (qv) for foods (107). Another series of trihydroxybenzene derivatives, namely 4-aryl esters and 4-carbonates with methoxy groups in the 1-position, are also sweeteners (108). 1,2,4-Triphenoxybenzene is an excellent high temperature heat-transfer agent, lubricant, hydraulic fluid, diffusion pump oil, and processing fluid (109) (see Lubrication and lubricants; Hydraulic fluids). 2,4-Dialkoxyphenols are antioxidants for a broad range of polymers (110).



(34)

Cinnamyl–sesamol ethers, eg **(35)**, are useful as insect chemosterilants (111). 3,4-Methylenedioxyphenyl-3-halo-2-propynyl ethers (**36**, X = halogen) are synergists for carbamate insecticides (112). Haloalkyl or haloalkenyl ethers, eg **(37)**, show acaricidal and insect juvenile hormone activity (113). The first total synthesis of gibberellic acid was from 2-methoxy-6-alkoxyethyl-1,4-benzoquinone, a derivative of hydroxyhydroquinone (114).



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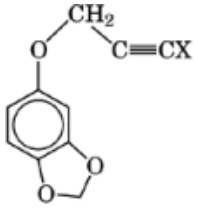

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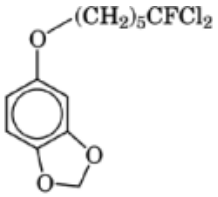
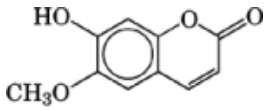


(37)

2.6. Derivatives

Scopoletin [92-61-5] (6-methoxyumbelliferone) **(38)** occurs, for example, in *Solanaceae* as a growth factor in plants. Primin [15121-94-5] (2-methoxy-6-pentyl-1,4-benzoquinone) is a skin irritant isolated from *Primula obconica*. Versicolin [4389-44-0] (1,2,4-trihydroxy-3-methylbenzene) is an antifungal antibiotic isolated from the cultural filtrate of a strain of *Aspergillum versicolor*. An epoxygeranyl ether **(39)** of 3,4-methylenedioxyphenol is an insect hormonomimetic. Rotenone [83-79-4] **(40)** occurs in many leguminous plants of the tropics and contains a hydroxyhydroquinone nucleus; it is used as an insecticide but is toxic to humans. Precocene-2 (2,2-dimethyl-6,7-dimethoxy-2*H*-chromene) is a chromene isolated from the bedding plant *Ageratum houstonianum*. It is an antijuvenile hormone and induces precocious metamorphosis in insects. It is expected to be developed as an insecticide (115) and a synthetic route has been reported (116). Maesanin **(41)**, isolated from berries of the *Maesa lanceolata* bush, has been claimed to kill gram-negative bacteria (117).



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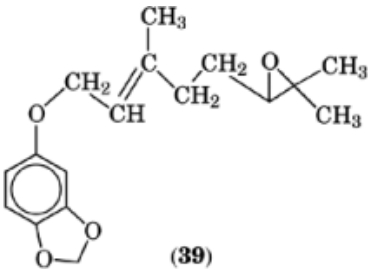

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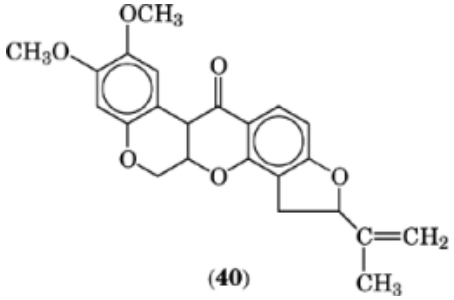

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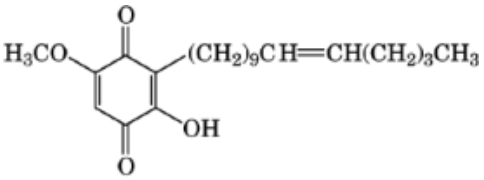


(41)

3. Phloroglucinol

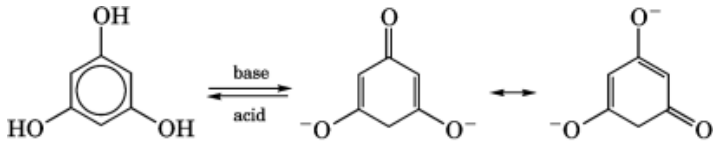
Phloroglucinol **(42)** is a colorless and odorless solid which is only sparingly soluble in cold water (82). It was discovered in 1855 in the hydrolysis products of the glucoside phloretin, which was obtained from the bark of fruit trees. Phloroglucinol occurs in many other natural products in the form of derivatives such as flavones, catechins, coumarin derivatives, anthocyanidins, xanthins, and glucosides.

There has been much interest in improved synthetic processes for phloroglucinol and in natural product-derived food sweeteners, each of which are characterized by a phloroglucinol nucleus in the structure. Phloroglucinol is of low toxicity, but complex natural products containing a phloroglucinol moiety range in biological properties from antibiotic and antimitotic to potently carcinogenic. Dose–effect relationships of these natural products can be beneficial or harmful. Some of the applications of phloroglucinol derivatives are patterned after the natural product model.

3.1. Properties

Phloroglucinol forms odorless, colorless, sweet-tasting, rhombic crystals which tend to discolor on exposure to air or light. The dihydrate loses its water of crystallization at about 110°C (mp 113–116°C on quick heating); the anhydrous material melts at 217–219°C when heated rapidly. Phloroglucinol sublimes at higher temperatures with partial decomposition. The heat of combustion of phloroglucinol is 2.59 MJ/mol (618 kcal/mol); $K_1 = 4.5 \times 10^{-10}$ at 25°C. It is soluble to the extent of 1 part in 100 parts water at 25°C, 10 parts in 100 parts ethanol at 25°C, and 296 parts in 100 parts pyridine; it also is soluble in ether. Phloroglucinol is a mild reducing agent, eg, it reduces Fehling's solution. In aqueous alkali, it is slowly oxidized by air.

Although most of the physical and chemical properties of phloroglucinol characterize it as a polyhydric phenol, in many cases it reacts in a tautomeric keto form or as the β-triketone, 1,3,5-cyclohexanetrione. This tautomeric triketone has never been isolated; however, phloroglucinol dianion has been shown by ^{1}H-nmr spectroscopy to exist as the ketone **(43)** (118). The rapid hydrogen–deuterium exchange of phloroglucinol in weakly alkaline solutions may be evidence for this ketone-enolate tautomerism (119).



(42) **(43)**

Based on this tautomerism, certain addition and replacement reactions at the hydroxyl or keto groups can be effected easily as with certain reactions of resorcinol and 2-naphthalenol. Thus, phloroglucinol forms a trioxime with hydroxylamine (120); it forms mono-, di-, and triaddition compounds with sodium bisulfite (121); it undergoes the Bucherer reaction with ammonia at room temperature (122) to give at first phloramine (5-amino-1,3-dihydroxybenzene) and eventually 3,5-diaminophenol. Displacement of the hydroxyl groups with aromatic amines is possible at higher temperatures (123). Alkylation with a methyl halide in alkaline media leads to the formation of 2,2,4,4,6,6-hexamethylcyclohexane-1,3,5-trione (124). Cyanoethylation in the presence of sodium methylate gives 2-(2-cyanoethyl)phloroglucinol (125). Sodium borohydride reduces phloroglucinol to resorcinol (126). Halogenation in anhydrous solvents yields halogenated cyclohexane-1,3,5-triones. The reaction of phloroglucinol with potassium cyanide in the presence of sulfuric acid yields the cyanohydrin of dihydrophloroglucinol which gives γ-resorcyclic acid [99-10-5] (3,5-dihydroxybenzoic acid) on treatment with concentrated hydrochloric acid (127).

Etherification with diazomethane gives phloroglucinol trimethyl ether (128). With dimethyl sulfate at pH 8–9, the mono-, di-, or trimethyl ether can be obtained (129). Friedel-Crafts acylation with acid chlorides and aluminum chloride in carbon disulfide gives the nuclear monoacylated phloroglucinols in good yield (130) (see Friedel-crafts reactions). The reaction of phloroglucinol with excess acetyl chloride yields phloroglucinol triacetate. The Gatterman reaction of phloroglucinol with hydrogen cyanide and hydrochloric acid gives 2,4,6-trihydroxybenzaldehyde; similarly, with zinc cyanide the dialdehyde of phloroglucinol can be formed (131). The Hoesch reaction of phloroglucinol with nitriles yields the corresponding ketones; eg, reaction with benzonitrile in the presence of hydrochloric acid yields phlorobenzophenone. Phloroglucinol couples readily with aryldiazonium salts to give di- and triazo compounds. Phloroglucinol reacts readily in the presence of alkaline or acid catalysts with aliphatic and aromatic aldehydes to give various condensation products, which often are colored. The reaction of phloroglucinol with phthalic anhydride gives phloroglucinol phthalein (132). The Perkin condensation of 2,4,6-trihydroxybenzaldehyde with sodium acetate and acetic anhydride, and the Pechmann reaction of phloroglucinol with ethyl acetoacetate in the presence of sulfuric acid yield coumarin derivatives. The Lewis acid-catalyzed reaction of phloroglucinol with olefins or alkyl halides gives nuclear alkylation products; eg, reaction with ethylene and catalyzed by $FeF_2{\cdot}BF_3$ and HF gives triethylphloroglucinol [2437-88-9] (133). Alkylphloroglucinols can be prepared by Clemmensen reduction of acylphloroglucinols. The catalytic hydrogenation of phloroglucinol gives a mixture of the stereoisomeric cyclohexane-1,3,5-triols. The hydrogenation of phloroglucinol in the presence of a rhodium-on-alumina catalyst gives cyclohexane-1β,3β,5β-triol in good yield (134). Aqueous alkali bicarbonate or carbonate reacts with phloroglucinol at 20°C to give phloroglucinolcarboxylic acid (135). 2,4,6-Trinitrosophloroglucinol is obtained by reaction of phloroglucinol with nitrous acid in acetic acid (135).

3.2. Manufacture and Synthesis

The only commercial process in use in the United States through the 1970s involved the oxidation of 2,4,6-trinitrotoluene (TNT) with dichromate in sulfuric acid to 2,4,6-trinitrobenzoic acid. This was followed by the reduction of the nitro groups to amino groups with iron and hydrochloric acid with simultaneous decarboxylation to give 1,3,5-triaminobenzene. Acid hydrolysis at ca 108°C gave phloroglucinol in ca 75% yield (136). The process involved some explosion hazard in the initial stages. Phloroglucinol is no longer made in the United States because of the problem with waste disposal involving acid liquors and iron, chromium, and ammonium salts. The largest producer using the process based on TNT is Océ-Andeno BV (the Netherlands) (137).

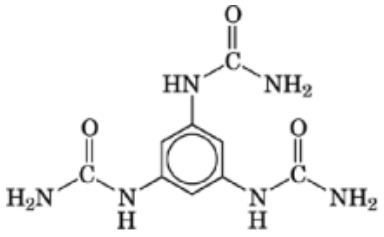
An improved version of the amine hydrolysis process involves catalytic hydrogenation of 1,3,5-trinitrobenzene or 2,4,6-trinitrobenzoic acid in acetone solvent (138). Acid hydrolysis of 2,4,6-triaminobenzoic acid has been improved by addition of copper catalyst and gives phloroglucinol in 80% yield (139).

The reaction of 1,3,5-tribromobenzene with excess sodium methoxide in methanol–*N*,*N*-dimethylformamide and in the presence of a catalytic amount of cuprous iodide gives ca 90% yield phloroglucinol trimethyl ether (1,3,5-trimethoxybenzene). The latter is hydrolyzed with 35 wt % hydrochloric acid at room temperature to give a 90% yield of phloroglucinol (140–142).

Preparation of phloroglucinol or its monomethyl ether by reaction of a halogenated phenol with an alkali metal hydroxide in an inert organic medium by means of a benzyne intermediate has been patented (142). For example, 4-chlororesorcinol reacts with excess potassium hydroxide under nitrogen in refluxing pseudocumene (1,2,4-trimethylbenzene) with the consequent formation of pure phloroglucinol in 68% yield. In a version of this process, the solvent is omitted but a small amount of water is employed (143).

Phloroglucinol can be obtained from 1,3,5-triacetylbenzene by conversion to the tris-oxime which is subjected to a Beckman rearrangement in trifluoroacetic acid to give 1,3,5-triacetamidobenzene. The latter undergoes hydrolysis in aqueous hydrochloric acid to give phloroglucinol in 88% yield (144). A modification of this process has also been patented (145). Another patented process starts with the chlorination of benzene-1,3,5-tricarboxylic acid triamide to the tri-*N*-chloroamide, which reacts with ammonia to produce

1,3,5-triureidobenzene **(44)**; the latter is hydrolyzed with aqueous mineral acid to give phloroglucinol in 94% overall yield (146). Phloroglucinol also has been prepared in high yield from hexachlorobenzene by reaction with sodium isopropylate in an aprotic solvent to give trichlorophloroglucinol triisopropyl ether **(45)**. The latter is dechlorinated with sodium to phloroglucinol triisopropyl ether, followed by ether cleavage (147). Another process involves hydrolysis of an ether of triacetic acid δ-lactone **(46)** with aqueous hydrochloric acid to give phloroglucinol in good yield (148).



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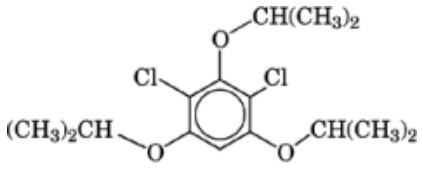

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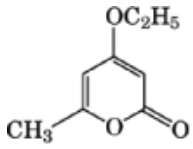


(46)

Much work on the hydroperoxidation of triisopropylbenzene to make phloroglucinol, similar to the process of phenol from cumene, has been reported (149–155). The shortest route is based on readily available 4-chlororesorcinol. World production of phloroglucinol is estimated to be in excess of 200 metric tons annually (156).

3.3. Grades and Specifications

Two grades of phloroglucinol, ie, grades 2 and pure, are offered in the United States by Haake, Inc., who resell material made by Fisons (Table 1). The product discolors slowly on exposure to light.

3.4. Analysis

The following analyses for reagent-grade phloroglucinol are suggested: insolubles in alcohol, dissolve 1 g in 20 mL alcohol and a clear and complete solution results, mp 215–219°C; residue on ignition, ignite 1 g with 0.5 mL sulfuric acid, resulting in a residue which weighs not more than 1 mg (0.1 wt %); diresorcinol, heat a

Table 1. Grades and Specifications of Phloroglucinol Dihydrate[a]

Property	Grade 2	Pure
mp, °C	215–219	217–221
appearance	off-white to buff powder	off-white to cream powder
loss at 105°C, wt %	20–24	20–24
sulfated ash, wt %	0.20 max	0.1 max

[a]CAS Registry Number [6099-90-7].

solution of 100 mg in 10 mL acetic anhydride to bp, cool the solution, and superimpose it on 10 mL sulfuric acid. No violet color appears at the zone of contact of the liquids.

With ferric chloride, phloroglucinol in aqueous solution gives a bluish violet color, which reddens on addition of a few drops of ammonia. With furfuryl alcohol and hydrochloric acid, phloroglucinol gives a greenish black precipitate. Derivatives of phloroglucinol that are used for identification are the tris(phenylurethane) (mp 190–191°C), tris(3,5-dinitrobenzoate) (mp 162°C), tribenzoate (mp 173–174°C), and picrate (mp 101–103°C). The instrumental methods of analysis are applicable, especially gas chromatography, with possible derivatization, and liquid chromatography.

3.5. Health and Safety Factors

Phloroglucinol has low toxicity by ingestion. Prolonged severe overexposure may disrupt the thyroid function. High dust concentration may cause respiratory irritation; the product is irritating to eyes and skin. Toxicity data include LD_{50} oral (rat) = 5800 mg/kg; LD_{50} percutaneous (rat) = 2600 mg/kg; TC_{50} for 48 h (rainbow trout) = >2000 mg/L; Ames test = negative.

3.6. Uses

Two of the principal commercial applications of phloroglucinol, ie, in the diazotype copying process and textile dyeing processes, are based on the ability of each mole of phloroglucinol to couple rapidly with 3 mol of diazo compound. The azo dyes (qv), which are produced, give fast superior black shades. Phloroglucinol also is used in resins and adhesives, as a plastics component or additive, as an intermediate for hydraulic fluids, as a rubber additive, as a photographic chemical, and as a starting material for priming compositions.

Phloroglucinol is listed in the *Colour Index* as CI Developer 19. It is particularly valuable in the dyeing of acetate fiber but also has been used as a coupler for azoic colors in viscose, Orlon, cotton (qv), rayon, or nylon fibers, or in union fabrics containing these fibers (157). For example, cellulose acetate fabric is treated with an aromatic amine such as *o*-dianisidine or a disperse dye such as *p*-hydroxyphenylazo-2-naphthylamine and the amine diazotizes on the fiber; the fabric is then rinsed, freed of excess nitrite, and the azo color is developed in a phloroglucinol bath at pH 5–7. Depending on the diazo precursor used, intense blue to jet-black shades can be obtained with excellent light-, bleach-, and rubfastness.

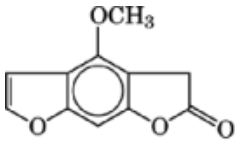
The condensation on the fabric of 1-amino-3-iminoisoindolenines or 2-amino-5-iminopyrrolenines with phloroglucinol, preferably in the presence of metal salts and solvents, yields fast dyeings in brown shades (158). Metallized azo dyes derived from phloroglucinol yield fast dyeings on leather (qv) or silk (qv) (159).

The diazotype duplicating and copying (white printing) processes are methods for making positive, direct copies of written, drawn, or typed material (160). A light-sensitive diazonium compound is coated onto a sheet of supporting material such as paper. The tracing to be copied is placed on this light-sensitive sheet and exposure to a suitable light source is made. Where not protected by the lines of tracing or drawing, the diazonium compound decomposes with loss of nitrogen and loss of the ability to form azo compounds by coupling. The copy develops by coupling of the remaining diazonium compound with, eg, phloroglucinol. Both wet and dry

processes are used. In the wet process, the sensitized paper contains only the diazo compound and, after exposure, development is effected by means of a dilute aqueous solution of phloroglucinol. Dry processes are more complicated and employ ammonia, heat, or ir radiation for development (161, 162).

The use of phloroglucinol and its derivatives as developer for light-sensitive planographic plates and for other photographic purposes has been described (163–167).

Cyclohexane-1α,3α,5α-triol (*cis*-hexahydrophloroglucinol, α-phloroglucite) is a starting material in Woodward's synthesis of prostaglandin F2α and F3 α (168) (see Prostaglandins). C_1–C_3 alkyl ethers of phloroglucinol are administered as urethral and gastrointestinal antispasmodics (169). 5-Methoxypsoralen **(47)** is made from phloroglucinol and is effective in the treatment of psoriasis (170). 3-Pyrrolidinobutyrylphloroglucinol increases the blood flow of the femoral artery in dogs and inhibits blood platelet aggregation in rats (171). *O*-Substituted (+)-cyanidan-3-ols (**48**, R = alkyl, acyl, or sulfonyl) have been patented as antihepatitis agents (172). Acylated phloroglucinols are bactericides (173). Other acylated phloroglucinols are useful as fungicides (174). Substituted 1-(2,4,6-trihydroxyphenyl)-1,2-propanediones prevent liver damage in mice (175). Phloroglucinol-3,5-dimethyl-1-(2-amino-3-hydroxybutyryl)ether is characterized by antiarrhythmic activity (176). 2,4-Diacylphloroglucinols were patented as compounds with pronounced anthelmintic activity (177). Phloroglucinol mono- and di-(2-chloroethyl) ethers have antispasmodic or tranquilizing activities (178). 2-(3,5-Dialkoxyphenoxy)ethylamines have antispasmodic, choloretic, sedative, and vasodilating effects (179). 2-Dimethylaminoethyl-2,4,6-trimethoxybenzoates and similar esters are useful as spasmolytics and in relieving indigestion (180). Bis-chromonyl compounds derived from phloroglucinol are valuable in the treatment of asthma (see Antiasthmatic agents) (181).



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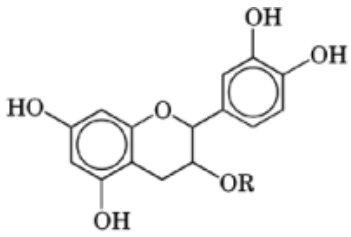


(48)

2,4,6-Trihydroxypropiophenone is useful in cosmetics, as it protects the skin from sunlight (182). Diphenylated acylphloroglucinols and their preparation have been patented as intermediates for bitter-flavoring agents for beer (183). There has been considerable development of dihydrochalcone glycosides and their metal salts as artificial sweeteners (qv) for foods (184) (Fig. 2). Quaternary ammonium salts of these dihydrochalcones are used as sweet-tasting bactericides, especially in dental compositions (185) (see Quaternary ammonium compounds). The parent dihydrochalcone (**49**, R, R′ = H) is useful as an artificial sweetener (186). Another dihydrochalcone such as (**49**), wherein R′ is H (ie, a phloroglucinol ring) and the other ring is a 4-substituted pyrogallol, is an antiulcer agent (187).

Diacetylphloroglucinol and its homologues have been prepared and found to be inhibitors of the herpes virus (188). Syzygiol **(50)**, a skin tumor promotion inhibitor, has been prepared from phloroglucinol (189). The

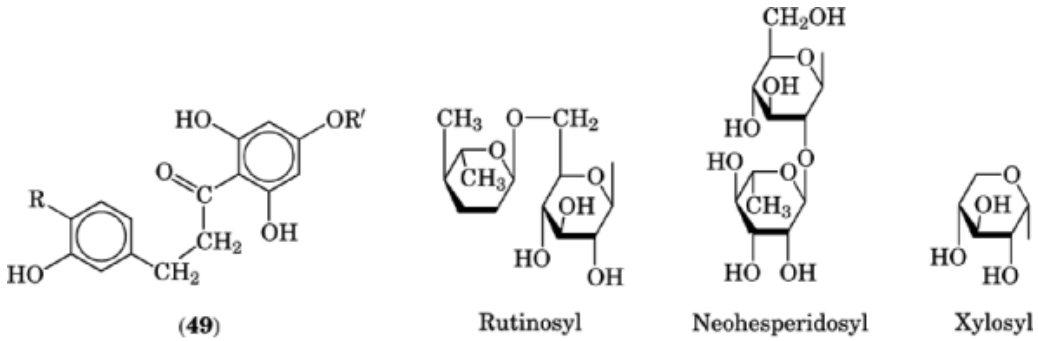
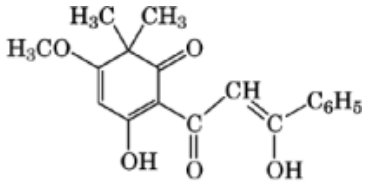
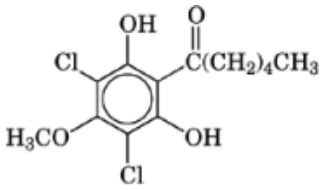


Fig. 2. Dihydrochalcone glycoside (**49**), where $_{R=H}$, OH, or O–alkyl and $_{R'=glucosyl}$, rutinosyl, neohesperidosyl, or xylosyl.

first natural morphogen (cell-differentiation agent) **(51)** has also been identified as a phloroglucinol derivative (190).



(**50**)



(**51**)

Phloroglucinol or certain of its simple derivatives in conjunction with an organic phosphite are improved heat stabilizers for vinyl chloride polymers and copolymers (190). 1,3,5-Tris(benzoyloxy)benzene was patented as an uv light stabilizer for polyolefins (191). Thermoplastic polycarbonates are produced by the polycondensation of a dihydric phenol and a carbonyl halide in the presence of phloroglucinol (192). Polybutadienes containing two terminal allylic halide groups per unit can be vulcanized in the presence of an inorganic base with phloroglucinol (193).

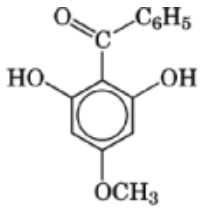
Alkanoyl esters of phloroglucinol, eg, phloroglucinol trisheptanoate, are high temperature–resistant lubricants and high performance fluids (194). An aqueous solution of phloroglucinol (or of several of its simple derivatives) is used as a corrosion-resistant coating on galvanized sheet (195). The alkali or ammonium salts of 2,4,6-trihydroxy-1,3,5-benzenetricarboxylic acid and 2,4,6-trihydroxy-1,3,5-benzenetrisulfonic acid are sequestering agents useful for synthetic detergent formulations (196, 197).

Phloroglucinol can be used in place of silver iodide for cloud seeding to modify weather conditions (198). A nutrient medium containing cytokinin, auxin, and phloroglucinol improves rooting of cuttings from woody plant material (199). Reagent-grade phloroglucinol is used as a sensitive analytical reagent for the detection

and estimation of aliphatic and aromatic aldehydes; carbohydrates, eg, pentoses, pentosans, glycuronic acids, galactoses, and galactans; lignin (qv); and hydrochloric acid.

3.7. Derivatives

Many derivatives of acylated phloroglucinols that bear a benzene ring substituent or an ether or glycoside linkage occur in nature. Examples are cotoin [479-21-0] **(52)** in coto bark and conglomerone [480-25-1] **(53)** in *Eucalyptus conglomerata*.



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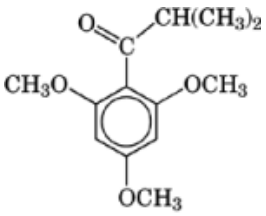
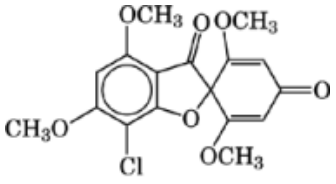


(53)

Griseofulvin [126-07-8] **(54)** contains the phloroglucinol nucleus. It is an important oral antifungal agent in humans and animals, elaborated by certain strains of *Penicillium*. One synthesis of griseofulvin is based on the appropriately substituted phloroglucinol (196). Uvaretin [58449-06-2] **(55)**, which is extracted from *Uvaria acuminata*, inhibits lymphocytic leukemia (200).

Aflatoxins B are fungal metabolites and are produced by *Aspergillus flavus*. There are several related products; all contain a phloroglucinol segment in their structure and all are extremely toxic and carcinogenic, eg, aflatoxin B **(56)** (201).

The bioflavanoids (vitamin P complex) are substances which maintain the small blood vessel walls. The substances are widely distributed among plants, eg, all citrus fruits, and have been used medicinally to decrease capillary permeability and fragility.



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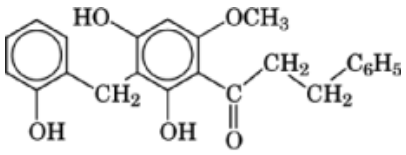
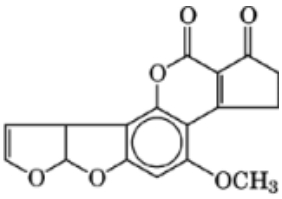
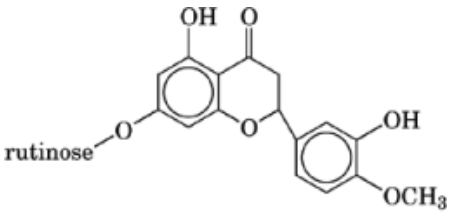


(**55**)

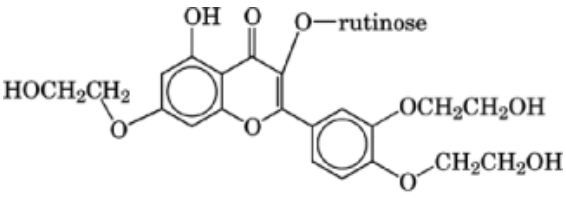


(**56**)

Hesperidin [520-26-3] (hesperetin(7-rhamnoglucoside or 7-rutinoside)) **(57)** contains a core structure of phloroglucinol. A relative of this series is troxerutin [7085-55-4], which is a component of Paroven **(58)** and is used in the treatment of venous problems.



(**57**)

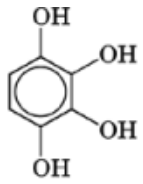


(**58**)

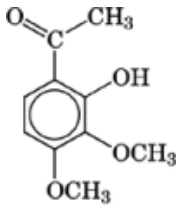
4. Benzenetetrols

4.1. 1,2,3,4-Benzenetetrol

1,2,3,4-Tetrahydroxybenzene or apionol **(59)** forms needles from benzene (mp 161°C). It is easily soluble in water, diethyl ether, ethanol, and glacial acetic acid and is sparingly soluble in benzene. It has been identified as one of the many constituents of wood–vinegar distillate (202).



(**59**)



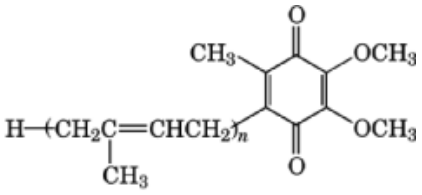
(**60**)

1,2,3,4-Benzenetetrol is best prepared by the hydrolysis of 4-aminopyrogallol hydrochloride (203). Its 1,2-dimethyl ether (bp 160–170°C at 203 kPa (2 atm)) can be prepared by the oxidation of gallacetophenone-3,4-dimethyl ether **(60)** with hydrogen peroxide or with potassium peroxysulfate (204, 205). The oxidation of pyrogallol-1,2-dimethyl ether with potassium peroxysulfate gives the 2,3-dimethyl ether of 1,2,3,4-benzenetetrol, ie, 1,4-dihydroxy-2,3-dimethoxybenzene (mp 84–85°C) (206). Similarly, the oxidation of 2,3,4-trimethoxybenzaldehyde with peracetic acid affords 2,3,4-trimethoxyphenol in 95% yield (207). Formylation of pyrogallol-1,2-dimethyl ether by methyl chloromethyl ether in the presence of titanium tetrachloride followed by reduction and then oxidation by nitrosodisulfonate gives 2,3-dimethoxy-5-methyl-1,4-benzoquinone (208). This product also can be obtained by formylation of 3,4,5-trimethoxytoluene with dimethylformamide and phosphorus oxychloride, treatment with hydrogen peroxide, and oxidation (209). A procedure based on gallic acid has also been reported (210). γ-Irradiation of gallic acid in aqueous solution in the presence of hydrogen peroxide and oxygen gives 2,3,4,5-tetrahydroxybenzoic acid in good yield, and similar treatment of 5-nitropyrogallol gives 2,3,4,5-tetrahydroxynitrobenzene (211).

4.1.1. Derivatives

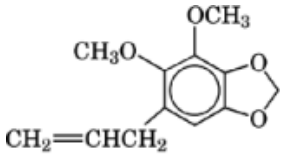
The most important derivatives of 1,2,3,4-benzenetetrol are the ubiquinones, eg, coenzyme Q, which are dimethoxytoluquinones with polyisoprenoid side chains **(61)**. They occur in plants and animals. Mice with hereditary muscular dystrophy have a deficiency of coenzyme Q in their heart and hind leg muscles. Therapeutic administration of coenzyme Q [1339-63-5] produces physical improvement and a significantly prolonged lifespan (212). Coenzyme Q also has been used to treat deafness when administered either orally or parenterally (213).

The preparation of coenzyme Q usually involves either 2,3-dimethoxy-5-methylbenzoquinone or hydroquinone as the starting material. Treatment of the hydroquinone with geranyl bromide followed by oxidation affords (**61**, $n = 2$) (214). A facile and efficient preparation of ubiquinone-10 (**61**, $n = 10$) has been developed (215).

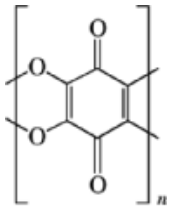


(**61**)

Fumigatin [484-89-9] (3-hydroxy-2-methoxy-5-methyl-*p*-benzoquinone) is isolated from metabolism of *Aspergillus fumigatus* and is used as an antimicrobial. 5-Allyl-1,6-dimethoxy-2,3-methylenedioxybenzene (dillapiole) **(62)** is a synergist for pyrethrum. Derivatives have been prepared and evaluated (216).



(**62**)



(**63**)

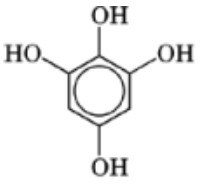
Derivatives of ubiquinones are antioxidants for foodstuffs and vitamins (qv) (217, 218). Ubichromenol phosphates show antiinflammatory activity (219). Chromanol compounds inhibit oxidation of fats and can be used in treatment of macrocytic anemias (220). Monosulfate salts of 2,3-dimethoxy-5-methyl-6-substituted hydroquinone have been reported to be inhibitors of lipid oxidation in rats (221). Polymers based on chloranilic and bromanilic acid have been prepared and contain oxygenated quinones **(63)**, which are derived from 1,2,3,4-benzenetetrol (222).

4.2. 1,2,3,5-Benzenetetrol

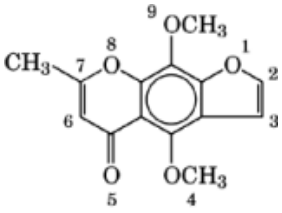
1,2,3,5-Tetrahydroxybenzene **(64)** forms needles (mp 165°C) from water. The compound is easily soluble in water, alcohol, and ethyl acetate and is insoluble in chloroform and benzene. In aqueous potassium bicarbonate solution sparged with carbon dioxide, 1,2,3,5-benzenetetrol yields 2,3,4,6-tetrahydroxybenzoic acid (mp 308–310°C dec).

1,2,3,5-Benzenetetrol has been prepared by the hydrolysis of 2,4,6-triaminophenol with dilute hydrochloric acid and by heating aqueous solutions of $<0.2\ M$ 2,4,6-triaminophenol at >130°C (223–225). The acid hydrolysis is improved by copper (226). 1,2,3,5-Benzenetetrol also has been prepared in 46% overall yield by the nitration of hydroquinone diacetate at low temperature to 2,6-dinitrohydroquinone acetate, followed by reduction to the corresponding diamine hydrochloride with tin and hydrochloric acid. The diamine hydrochloride

is hydrolyzed to the tetrol with 1 wt % hydrochloric acid at 155–160°C (224). Hydrogenation of 2,6-dibenzoyloxy-*p*-benzoquinone over Pd–C gives a 90% yield of 1,2,3,5-tetrahydroxybenzene (227).



(**64**)

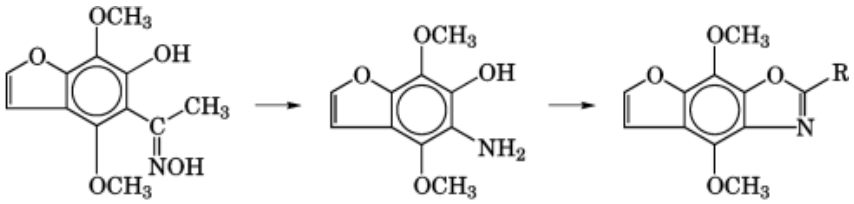


(**65**)

4.2.1. Derivatives

Oxidation of pyrogallol trimethyl ether with nitric acid, followed by reduction in acetic anhydride and treatment of the product with aluminum chloride, affords 3,6-dihydroxy-2,4-dimethoxyacetophenone (228). 3,4,5-Trimethoxyphenol (antiarol) has been prepared by treatment of 3,4,5-trimethoxyacetophenone with peracetic acid and in 75% yield from 3,4,5-trimethoxybenzoic acid by conversion to the azide, decomposition of the azide, and hydrolysis of the resulting amine (229, 230). In contrast, treatment of 3,4,5-trimethoxybenzaldehyde with peracetic acid affords 2,6-dimethoxybenzoquinone as does oxidation of 4-hydroxy-3,5-dimethoxybenzaldehyde with peroxides (231, 232).

Many 1,2,3,5-benzenetetrol derivatives are used medicinally. For example, khellin [82-02-0] **(65)**, which is a naturally occurring benzopyranone, is used as a coronary vasodilator and bronchodilator (233). Derivatives of khellin are effective local anesthetics and antiarrythmics (234). Similarly, amine derivatives **(68)** that are prepared from khellinone oxime **(66)** exhibit hypnotic, sedative, anticonvulsant, antiinflammatory, cardiac analeptic, diuretic, and antiulcerous activity (235) (see Analgesics, antipyretics, and antiinflammatory agents).

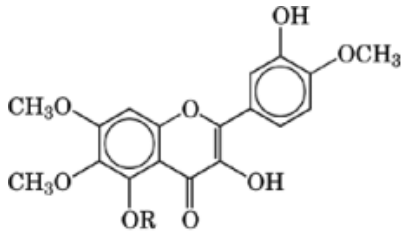


(**66**) (**67**) (**68**)

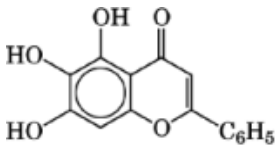
Eupatin (**69**, R = H) and Eupatoretin (**69**, R = CH_3), which are isolated from thistle perennials, show moderate cytotoxicity against human carcinoma of the nasopharynx (236). Baicalein **(70)** salts exhibit antiallergic

and antiinflammatory activity. 3,4,5-Trimethoxyphenoxyacetamides are hypotensives and diuretics and are useful for controlling arrhythmia during anesthesia (237).

2,6-Dimethoxy-*p*-benzoquinone is a naturally occurring antiinflammatory (238). 3-Alkyl derivatives of it have also been prepared (239).



(**69**)



(**70**)

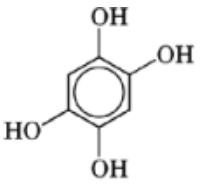
4.3. 1,2,4,5-Benzenetetrol

1,2,4,5-Tetrahydroxybenzene **(71)** forms leaflets from glacial acetic acid (mp 215–220°C). It is easily soluble in water, ethanol, and diethyl ether but is not quite as soluble in concentrated hydrochloric acid and glacial acetic acid. Ferric chloride produces a precipitate of 2,5-dihydroxy-1,4-benzoquinone (137). The same compound also is produced by aeration of the alkaline solution. Aeration of its acid solutions precipitates a black quinhydrone.

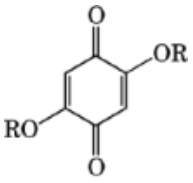
1,2,4,5-Benzenetetrol is obtained by the reduction of 2,5-dihydroxyl-1,4-benzoquinone, which is readily made by oxidation of hydroquinone dissolved in strong aqueous sodium hydroxide with hydrogen peroxide, with stannous chloride and hydrochloric acid or by catalytic hydrogenation (240). Etherification with methyl iodide in the presence of base gives the tetramethyl ether of 1,2,4,5-benzenetetrol (mp 103°C). Several partial ethers, halo, and amino derivatives of 1,2,4,5-benzenetetrol are obtained by reduction of the appropriately substituted 1,4-benzoquinones. For example, 4,5-dimethoxy-1,2-benzoquinone is obtained by reaction of pyrocatechol with lead dioxide and sodium methoxide in methanol (241).

The saturated derivative of maesarin **(41)**, dihydromaesarin, has been synthesized and showed activity as a bacteriocide and antitumor agent (242).

Phosphorus derivatives of 1,2,4,5-benzenetetrol **(71)** are effective antiwear and antioxidant additives for lubricating oils and also have flame-retardant properties (see Flame retardants; Lubrication and lubricants) (243). Bis(cyclic acetals) derived from 1,2,4,5-benzenetetrol are used in perfume and fragrance compositions (244) (see Perfumes). Polyamides for use as tire cord are stabilized against thermal degradation by incorporation of 2,5-dihydroxybenzoquinone (245). Reaction of 2,5-dialkoxy-*p*-benzoquinones with diamines give polyaminoquinones of good heat and chemical stability (246). Intermediates in dyestuff manufacture and especially dioxazine dyestuffs and auxiliaries are prepared from (**72**, R = $C_1 - C_5$ alkyl or allyl) and its derivatives (247). Derivatives of **(72)** are reported to be useful as antifogging and stabilizing agents for photographic silver halide emulsions (250). Compounds, eg **(73)**, possess moderate activity against Walker carcinosarcoma and leukemia (248). Redox polymers have been prepared from *p*-benzoquinonediols and diisocyanates (249).



(71)



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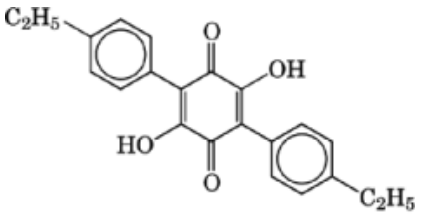
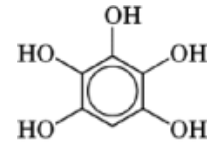


(73)

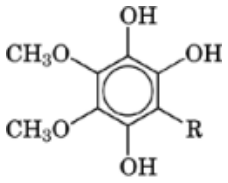
5. Benzenepentol

Benzenepentol [4270-96-6] (pentahydroxybenzene) **(74)** has been prepared by boiling 2,4,6-triaminoresorcinol diethyl ether with water, followed by ether cleavage with HI (251). The product is very soluble in water but sparingly soluble in organic solvents. Benzenepentol prepared by hydrolysis of 4,6-diaminopyrogallol hydrochloride is sparingly soluble in water, easily soluble in diethyl ether, ethanol, and ethyl acetate, and insoluble in benzene (252).

Ethers of benzenepentol have been obtained by Dakin oxidation of the appropriately substituted acetophenone. Thus, the oxidation of 2-hydroxy-3,4,6-trimethoxyacetophenone and 2-hydroxy-3,4,5-trimethoxyacetophenone with hydrogen peroxide in the presence of alkali gives 1,2-dihydroxy-3,4,6-trimethoxybenzene and 1,2-dihydroxy-3,4,5-trimethoxybenzene, respectively; further methylation of these ethers yields the pentamethyl ether of benzenepentol (mp 58–59;degC) (253). The one-step aromatization of myoinositol to produce esters of pentahydroxybenzene is achieved by treatment with carboxylic acid anhydrides in DMSO and in the presence of pyridine (254) (see Vitamins). 6-Alkyl- or alkenyl-2,3-dimethoxy-5-hydroxy-1,4-hydroquinones **(75)** and benzoquinones **(76)**, where $R = C_{10} - C_{50}$ alkyl or alkenyl, are coenzyme Q antagonists and antioxidants for fats and oils (255). Several naturally occurring flavenoids derived from pentahydroxybenzene have been synthesized (256–258).



(74)



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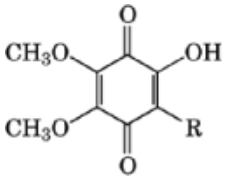


(76)

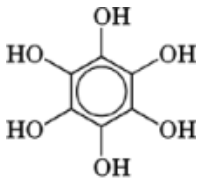
6. Benzenehexol

6.1. Properties

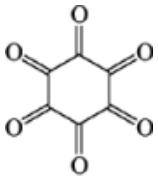
Benzenehexol [608-80-0] (hexahydroxybenzene) **(77)** forms snow-white crystals when freshly prepared and collected in an inert atmosphere. Benzenehexol of good purity does not melt up to at least 310°C. It is sparingly soluble in water, ethanol, diethyl ether, and benzene. It readily reduces silver nitrate solution and is oxidized by air in sodium carbonate solution to tetrahydroxy-*p*-benzoquinone. Triquinoyl **(78)** is obtained from oxidation with concentrated nitric acid. Catalytic hydrogenation gives inositols, ie, stereoisomeric cyclohexanehexols, and quercitols, ie, cyclohexanepentols, although the hydrogenation of benzenehexol with platinum oxide catalyst at 50–55°C yields phloroglucinol **(42)** (259, 260). On evaporation of benzenehexol with potassium carbonate, the potassium salt of croconic acid **(79)** forms by a benzilic acid-type rearrangement from quinonoid intermediates.

6.2. Synthesis

Benzenehexol is available only from laboratory reagent suppliers. The simplest laboratory preparation involves the aeration of the glyoxal–bisulfite addition product in sodium carbonate solution at 40–80°C, isolation of the sodium salt of tetrahydroxybenzoquinone, followed by acidification to obtain the free tetrahydroxy-*p*-benzoquinone in about 8% yield; the latter is reduced with stannous chloride in boiling dilute hydrochloric acid solution to benzenehexol **(77)** in 77% yield (261). A similar procedure affords dipotassium rhodizonate **(80)** in good yield (262).



(77)



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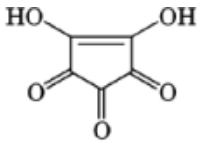

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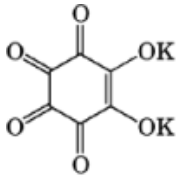


(80)

The oldest method of preparation of benzenehexol involves the reaction of molten potassium with carbon monoxide to give the potassium salt of the hexol; the free phenol is obtained by neutralization of the salt with dilute acid (263). This reaction has been reinvestigated and improved (264).

A simple synthesis of tetrahydroxybenzoquinone by methoxylation–hydrolysis of chloranil has been reported (265). Similarly, tetraaryloxybenzoquinones have been prepared from chloranil and alkali salts of phenols (266).

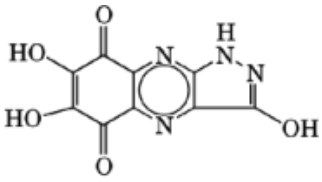
6.3. Analysis

Benzenehexol gives a violet color with ferric chloride. Derivatives which can be used for its identification are the hexaacetate (mp 205°C) and the hexabenzoate (mp 313°C).

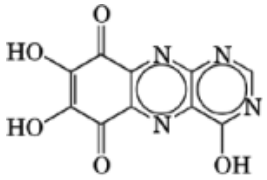
6.4. Derivatives

A considerable number of compounds that contain the benzenehexol structure possess therapeutic activity. Esterification of benzenehexol with a pyridinecarbonyl chloride gives the corresponding hexaesters, which are

antiatherogenics (267). Tetroquinone [319-89-1] (tetrahydroxy-*p*-benzoquinone) is administered orally for the treatment of keloids. The dipotassium salt of rhodizonic acid **(80)** is useful as a remedy for diabetes mellitus (262). Compounds, eg **(81)** and **(82)**, which are derived from rhodizonic acid, are useful as antiinflammatory agents and diuretics (qv) (268).



(81)



(82)

Inositols, ie, hexahydrobenzenehexols, are sugars that have received increasing study and are useful in the treatment of a wide variety of human disorders, including vascular disease, cancer, cirrhosis of the liver, frostbite, and muscular dystrophy (269). Myoinositol esters prepared by reaction with lower fatty acid anhydrides are useful as liver medicines and nonionic surfactants; the aluminum and ammonium salts of inositol hexasulfate are useful anticancer agents (270). Tetraaryloxybenzoquinones are intermediates in the preparation of dioxazine dyes (266, 271). The synthesis of hexakis(aryloxy)benzenes has also been published (272).

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